CRITICAL CARE MEDICINE REVIEW NOTES

Jon-Emile S. Kenny M.D.

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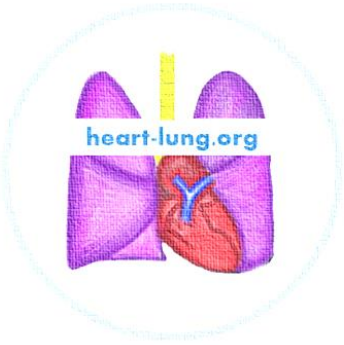
Esteemed reader,

I compiled these notes while studying for the ABIM Critical Care Medicine Board examination. These notes were made from a number of fairly recent resources including SCCM lectures, SEEK questions, ACCP study guides and, of course, *pulmccm.org*. I cannot guarantee their correctness in content, grammar, and spelling; nor are these notes peer-reviewed. *They absolutely should not be used as a resource for patient care.* They should be used for board exam preparation; that is all I will use them for as well. This is not my heart-lung physiology text. Please *share* these review notes *freely*. *#FOAMcc*

Happy Studies,

Jon-Emile



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1. CRITICAL CARE CARDIOLOGY

CARDIAC RESUSCITATION

The quality of CPR is associated with survival to discharge for in-house arrest. It is *not* the application of an AED, which has been studied. 40% of chest compressions in house are of insufficient depth, there is a long period of time during codes when health care providers are not actually on the chest. *Compressions should be hard and fast [to Bee Gee's stay'n alive] 100 per minute, 2 inch depth*. There should be minimization of time off the chest even for pulse checks and defibrillation. It is CPR that matters, 2 minutes of CPR interspersed with defibrillation, 1 mg epinephrine every 3-5 minutes or 40 U of vasopressin. *Atropine is no longer a part of PEA.*

Avoid hyperventilation as this can reduce cerebral perfusion via alkalemia and more importantly cause dynamic hyperinflation.

Previously, the brain injury [apoptosis, excitability, edema, etc.] induced by ischemia re-perfusion was thought to be treatable. The Feb. 2002 NEJM article with 137 patients in each arm, enrolled *witnessed, shockable* cardiac arrest patient s with ROSC but still not following commands. Patients were randomized to therapeutic *hypothermia target 32 to 34 celsius over 8 hours*, held at that temp for 24 hours and then passively re-warmed over 8 hours. A meta-analysis of the three largest trials [380 patients] showed an odds ratio of 1.7 for favourable neurological outcome. The largest of the three trials selected patients who were resuscitated within 60 minutes with a shockable rhythm, comatose, and not in shock. Cooling was done within 2 hours of the event.

Therapeutic hypothermia [TH] is commonly associated with coagulopathy, hyperglycemia, bradycardia and hypovolemia – the latter on account of the cold diuresis. There is an increased risk of infection following TH and altered drug metabolism.

However, skeptics noted the *lack of blinding to treatment allocation in the above studies*. Further, in the biggest of those hypothermia studies, a large number of patients in *the usual care group* developed *fever* which is associated with worse outcomes after cardiac arrest. So it was thought that perhaps TH simply had to *accomplish fever reduction* to improve outcome.

So the big one came out in NEJM November 17, 2013 [*950 patients in 3 years, 80% vfib, 12% asystole, 8% PEA, and randomized the patients to celsius 33 or 36 ASAP* for 28 hours and then fever reduction for 72 hours]. After *72 hours*, a neurologist blinded to initial treatment allocation recommended withdrawal or continued care based on standardized criteria, with withdrawal recommended only for known predictors of a terrible outcome [e.g., refractory status epilepticus; Glasgow motor score 1-2 with bilateral absence of N20 peak on median nerve SSEP]. CPC more than 2 or Rankin more than 3 was defined as severe disability. *There was no difference in death or disability between the two groups [i.e. 33 versus 36 degrees] even in the 80% shockable group*.

Temperature should be maintained at 36° C or below after out-of-hospital cardiac arrest. Despite its physiologic rationale and evidence of benefit in prior smaller studies, *targeted temperature management below 36° probably does not improve outcomes after out-of-hospital cardiac arrest of any type.* Because average human core temperature is 37° C, maintaining temperature continuously at or below 36° C still would require cooling in almost all patients.

In a related vein, in 2013 JAMA, 100 patients with bacterial meningitis were randomized to 32-34 degrees or standard care and this trial was stopped early for a 20% absolute *risk increase* in mortality!

What about the prognosis following cardiac arrest? What is the *false positive rate for diagnosis of poor neurological outcome*? We should strive for zero. *Pupillary reaction to light has a false positive rate of 0-31% at day one*. At *day three*, no pupillary reaction has a *false positive rate for poor outcome of zero*. So absent pupillary response at day three is important information. The absence of corneal reflex is similar at 72 hours. What about posturing? Similar at 72 hours. All of this data was generated during an era of no therapeutic hypothermia and the reason why neurological assessment for continued care in the aforementioned trial took place at 72 hours.

So what has a perfect specificity for determining poor neurological outcome? There is a review in the Lancet – *day 3 absent motor, absent pupillary response and abnormalities in somatosensory evoked potentials*. SSEP occurs when the median nerve is stimulated. Bilateral absence is poor neurological prognosis from NEJM article in 2009. Day 1-3 there is nothing great to help. *You must wait at least 72 hours and you must wait for analgesia to wear off*. This is important with TH because there is alteration of sedation and analgesia metabolism with hypothermia – it will stay longer. There is no clear answer as to when the patient may wake up, but anecdotally up to one week as the effects of hypothermia wear off and sedation is cleared, though this will be less important as TH is used less with the results of the Nov. 2013 NEJM trial.

Prognosis after a first cardiac arrest occurring in the ICU is poor. An observational study of almost 50,000 such arrests showed an *overall survival to hospital discharge of 16%*. Requiring vasopressors *prior to the arrest* was a major discriminator in outcome:

Only 10% of patients *on pressors prior to arrest* survived to discharge, and only *4% overall were discharged home* [the others went to rehab or long-term acute care].

Among those with *PEA/asystole despite pressors, only 1.7%* were able to perform their own activities of daily living at the time of discharge.

People with ventricular fibrillation or tachycardia *not requiring pressors* prior to arrest did much better: 40% survived, 20% went home, and 17% had good neuro outcomes.

CONGESTIVE HEART FAILURE

About 50% of the mortality with heart failure is sudden, the other half is slow progression. There are stages of heart failure described in 2001 [ACC/AHA] where stage A is those patients *at risk*, B [structural disease without symptoms] is NYHA I, stage C [current or prior symptoms] corresponds to NYHA II and III and stage D is NYHA IV.

NYHA Class IV heart failure has a 60% mortality at one year. In acute, severe heart failure a poor prognosticator is: *hypotension*. Hypernatremia and polycythemia are not. Hypotension is defined as a systolic below 115 mmHg. Other bad prognoses: *hyponatremia, CAD, high BUN or creatinine, low EF, elevated BNP or troponin, anemia, diabetes*.

Precipitants of ADHF? 25% excess salt and fluid intake, 25% noncompliance with medications, and 16% from adverse medication effects [e.g. new CCB, NSAID, steroids, glitazones and ethanol, new anti-arrhythmics]. The rest are acute medical causes such as ischemia, PE, HTN, valve dysfunction, arrhythmia. There are extra-cardiac causes as well – sepsis, infection, renal failure, thyroid, new anemia.

Flavors of Myocardial Dysfunction

There are different kinds of myocardial dysfunction to consider – hibernating, stunned myocardium, sepsis, myocarditis, etc. *Stunned myocardium* occurs when there is ischemia that relates to a wall motion abnormality, but *when blood flow resumes, there is a persistent WMA that lasts from hours to days*. The patient must be supported during these time – consider stress cardiomyopathy as an example of stunned myocardium. The patient may present with all the signs and symptoms of ischemia and heart failure with *stress cardiomyopathy*. There must be no coronary stenosis to explain the disease *and WMA do not* correspond to single coronary distribution. There may be STE and big T wave inversions.

Recognize *Takotsubo cardiomyopathy –* the major complications of this are mechanical in nature, heart failure, shock and arrhythmia. It presents exactly like a STEMI, or at least it can, but angiogram is normal and there is apical hypokinesis on the LV gram, this invariably resolves by 2 months. *Some argue against* the use of inotropes or catecholamines in these patients as they catechols be the cause; they argue that IABPs should be used. This disease usually happens in post-menopausal women and has a mortality rate of 0-8% in house.

Hibernating myocardium is due to chronic ischemia without infarction. There will be a WMA that lowers ejection fraction. If the occlusion is reversed, *the ejection fraction will return to normal*. What kind of revascularization? In the CAST trial, those with a low ejection fraction who *got CABG* did better. The STITCH April 2011 NEJM looked at chronic heart failure patients [EF less than 35%] with bypass surgery [versus medical therapy] and there was improved death from cardiac causes, hospitalization [not overall death] with CABG. Based on CAST and STITCH, improving hibernating myocardium by revascularization can improve NYHA class, exercise tolerance, cardiac performance and maybe survival.

With *myocarditis, patients typically get better themselves*, not good data but prednisone likely improves EF by 5% but only if there is *cellular infiltrate on biopsy*. There is improved exercise tolerance and cardiac performance.

Treatment Modalities for Heart Failure

Treatment should improve quality & quantity of life; some meds do one or the other or both.

What about diuretics? There is no difference in continuous infusion versus bolus - Felker et al in NEJM 2011 [DOSE trial]. However high dose seemed to improve global assessment of symptoms – high dose is *double their outpatient dose*. There was no difference in creatinine, readmission, no cardiac performance change, there is no survival benefit shown.

What about vasodilators? V-HEFT trial was original hydralazine with isosorbide versus prazosin versus placebo. The hydral-nitrate group had a *mortality benefit*.

Nesiritide is a formulation of BNP which was *initially* derived from pig brain. It antagonizes the renin-angiotensin axis and comes from the ventricles of the heart – it is released in response to high ventricular volume and pressure. It causes diuresis & *vasodilation*. It causes a drop in filling pressure, blood pressure and increases cardiac output. It lowers filling pressure compared to nitroglycerine and diuretics. But nesiritide doesn't significantly improve clinical end-points in O'connor et al. NEJM 2011 – *it might improve dyspnea*. There is no effect on death [*does not increase mortality*] and re-hospitalization.

ACE inhibitors do everything! Consensus in NEJM 1987 was quite impressive in terms of mortality benefit for severe, symptomatic systolic heart failure. Angiotensin II blockers are likely as good.

The addition of ARB to ACEI may improve in some patients [CHARM trial].

NEJM - RALES in 1999 improved mortality in severe heart failure with spironolactone, but overall few of the patients in RALES were on chronic beta-blockers as it was not an entirely accepted therapy at the time of enrollment for that trial. *Juurlink NEJM -2004 ICES database review showed excess hyperkalemia hospitalization and deaths after RALES*. Eplerinone [less gynecomastia] can reduce mortality following MI with LV dysfunction, in systolic heart failure with mild symptoms EMPHESIS-HF also reduced mortality [NEJM 2003], and there is an increase in potassium as well. It improves cardiac performance.

What about inotropes? In the 1980s, patients who had the highest norepinephrine levels did the worst. Chronic use of inotropes – will worsen mortality – *dose-dependent decrease in survival*. They should only be used when nothing else works.

Both US carvedilol [NEJM 1996] and the MERIT-HF [lancet 1999] trial showed survival benefit with beta-blockers in low EF [carvedilol and XL-metoprolol, respectively] and Copernicus in 2001 [very low EF patients getting carvedilol].

Digoxin reduces hospitalizations, reduces *symptoms* in the Digitalis investigation group [DIG - NEJM 1997].

What about anti-arrhythmic therapy? The MUST trial NEJM 1999 showed benefit with defibrillator – *addition of medical anti-arrhythmia worsens mortality [similar to afib trials RACE and AFFIRM]*. SCD-HEFT showed that *amiodarone does not increase mortality* compared to placebo, but ICD improves survival for sure – especially those with LVEF less than 35% [also MADDIT 1 &2 trials].

If there is LBBB and QRS more than 120 ms, and depressed LVEF with symptoms, the patient can begin CRT therapy – *BiV pacing to try to improve electromechanical association*. The COMPANION trial in NEJM showed that CRT in patients with NYHA III-IV HF with an EF of less than 35% and a wide QRS improved a combined end-point of mortality and hospitalization compared to standard care. All-cause mortality by itself was *only lowered in the CRT plus AICD group*. CRT does *not* increase myocardial oxygen demand and is associated with *reverse remodeling* of the myocardium with an improved LVEF. CRT also: improves stroke volume, dyspnea [functional class], mitral regurgitation, and lowers Ppao.

How about VADs? Eric Rose et al. NEJM 2001 [REMATCH trial] in late class IV heart failure showed improved survival [ARR 25% in death] using pulsatile flow or pusher plate. Continuous flow VAD, however, is better per Slaugther 2009 NEJM.

Heart transplant? Hearts are limited resources. The one year survival is 85-90%, 10 year survival is about 50% for heart transplant. Many get to NYHA I and II with transplant.

The ESCAPE study looked at the use of pulmonary artery catheters in heart failure, there is no mortality benefit, but perhaps better hemodynamics.

ST-ELEVATION MYOCARDIAL INFARCTION

With *STEMI, about 50% of people just drop dead*, without crushing chest pain preceding the event. It is common for there to *be minimal or no coronary stenosis seen on an angiogram* prior to there being ACS. Yet, there *is abnormal flow* on angiography *in more than 90% of patients with STEMI* [60% with TIMI *zero or total occlusion*, 13% with TIMI 1 or penetration but no distal perfusion, and 19% with TIMI 2 flow or complete penetration, but delayed perfusion].

What are the *clinical events* associated with plaque rupture? Clearly many, but documented:

shoveling snow, earthquakes, bad traffic, watching stressful sporting events [e.g. the Leafs or the Canucks], respiratory tract infections, waking up in the morning. *There is evidence to suggest that the influenza vaccine reduces MI risk! So vaccinate patients with coronary disease*.

ECG AND STEMI

There may be profound, dynamic ECG changes in a matter of minutes – from t wave inversions to STE. With confirmed MI [NSTEMI or STEMI], *up to one third did not have chest pain*. When there is no chest pain, patients are treated differently and this may triple their mortality.

A 12 lead ECG must be performed immediately in the ED that is within 10 mins, this is class IB because *the artery must be open within 90 mins*. [STREAM – NEJM 2013 showed that a strategy involving early fibrinolysis with *bonus tenecteplase* and contemporary anti-thrombotic therapy offers similar efficacy as primary PCI in patients with STEMI who present within 3 hours of symptom onset and who could not undergo primary PCI within 1 hour of first medical contact].

If the first ECG is non-diagnostic and suspicion is high, repeat ECG should be performed within 15-30 minutes and this too is class IB evidence.

STE has a differential diagnosis; LVH, hyperK+, Brugada syndrome *can all present with STE*. Q waves are present within 6 hours in about 50% of STEMI patients, and this is a poor prognosis. *29% of trans-mural MIs did not have Q wave, 28% of sub-endocardial MIs [non-transmural] MIs did have Q waves, so it is neither sensitive nor specific for trans-murality [based on MRI study in 2004]*, but the probability of Q waves does increase as the MI size and number of trans-mural segments increased.

Recognize that *characteristic symptoms for coronary occlusion plus a new LBBB pattern means that a patient should receive lytics or go to the cath lab emergently*. The LBBB is known to obscure the normal patterns of ischemia on the ECG *and LBBB patients tend to have a worse prognosis during coronary ischemia*, so there is more to be gained by revascularization. *Wenkebach* is *not* a classic finding in coronary ischemia, but rather pathological changes in the AV node [though it can accompany right coronary ischemia, this should also present with ST changes in the inferior leads]. *Complete heart block* is less commonly a result of coronary ischemia. Long runs of Vtach will certainly obscure STEMI, but if the runs are short, then the interceding ECG should still detect current of injury.

Recognize *cerebral T waves on an ECG*. Consider a patient with a hypertensive internal capsule hemorrhage with an ECG with deep, inverted T waves in the precordial leads. These are known to occur following head bleeds, and sometimes ischemic strokes. They are thought to be the result of massive sympathetic discharge. *Classically, Wellen's sign is biphasic T waves* in the precordium, though it can present symmetrically.

Note that *left circumflex occlusion is commonly silent on a 12 lead* ECG [distal circumflex marginal artery]. This may lead to rupture of the anterolateral papillary muscle in days after the infarction. The presence of a normal ECG with pulmonary edema should prompt evaluation for lateral coronary disease. If a PAC were placed, one would see tall V-waves. Importantly, on the ddx of tall v waves is ventricular septal rupture, but this would give a 5 mmHg step up of oxygen saturation on the PAC [see below].

TREATMENT MODALITIES FOR STEMI

Three doses of SL NTG of 0.4 mg may be given every 5 minutes for a total of 3 doses after which IV NTG should be considered.

In the patient with *STEMI*, there should be *dual anti-platelet therapy and heparin begun*. *If thrombolysis* is *given*, standard of care is *not to give GPIIBIIIA*. For STEMI, morphine is still IC for analgesia, all NSAIDs should be stopped at presentation IC. IIIC evidence says that NSAIDs *should not even be started* during hospitalization.

ISIS-2 trial 160 mg of ASA had a 23% reduction in mortality. In patients with *STEMI, clopidogrel does reduce mortality* regardless of whether reperfusion is received – it should be continued for 14 days. Unless there is CABG planned, then clopidogrel should be *stopped 5 days prior to OR*.

Anticoagulation should be used for at least 48 hours, but up to 8 days *even with reperfusion therapy*. The guidelines favor LMWH compared to UFH. In STEMI, for every 100 patients treated with LMWH there are 15 less non-fatal MI, 7 less urgent revascularizations, 6 fewer deaths but 4 more non-fatal bleeds [no increase in ICH].

Pooled analysis of *ECG and fibrinolytic therapy* showed that per 1000 patients, *49 lives were saved if baseline ECG showed LBBB, 37 saved with anterior STE, 8 saved if inferior STE and 14 harmed/died if ST depression on baseline ECG*. Indication for fibrinolysis is *symptoms within 12 to 24 hours* and STE in 2 contiguous leads or new or presumed new LBBB. Prior ICH, known cerebral vascular lesions, ischemic stroke within 3 months, suspected aortic dissection, active bleeding excluding menses, significant head or facial trauma or neurosurgery within 3 months *are the absolute contraindications to fibrinolysis*. The relative contraindications are: systolic more than 180, diastolic 110, prolonged [10 minutes] CPR, major surgery [including eye surgery] or internal bleeding such as GI/GU bleed within one month, non-compressible vascular punctures [e.g. recent trans-venous pacemaker in subclavian vein], pregnancy, and current use of anti-coagulants. If you can't re-perfuse an artery within 90 minutes with STEMI, you should give a fibrinolytic, *there is a direct correlation between the number of leads with elevation and the benefit of fibrinolytic*, in fact, and there is little benefit if only 2-3 leads have STE, but it is still recommended.

What about *GPIIBIIIA in STEMI*? It is a 2B recommendation, the benefit is uncertain based on 2009 guidelines. It is *reasonable to start these drugs at the time of PCI*, so this is really the call of the interventionalist. Abciximab is a long-acting GPIIbIIIA inhibitor, so it should never be given prior to potential bypass surgery. Abiciximab is *not* cleared by the kidneys, but eptifibitide and tirofiban are.

The mortality benefit of primary PCI compared with onsite fibrinolysis was *nullified* when the time delay to primary PCI was more than *2 hours*.

Fibrinolytic therapy in STEMI should be infused when an anticipated delay to performing primary PCI is more than 120 minutes of first medical contact [FMC]; FMC defined as the time at which *the EMS provider* arrives to the patient.

If someone gets fibrinolysis, what is the benefit for rescue PCI? This is the *TRANSFER-AMI trial* and there seems to be *clinical benefit for transfer immediately to cath lab following lysis* [up to 6 hours post lysis]. Those going to a non-PCI facility should receive lysis or immediate transfer for PCI, the decision depends upon the mortality risk, lysis risk, duration of symptoms on presentation, time required for transport. *Those patients best suited for transfer are*: more than 4 hours after symptoms, high risk lesions or features [e.g. shock, see below], high bleeding risk. For patients going for PCI, AC should be initiated, *do not use fondaparenux as it can cause catheter clotting*.

Know the *SHOCK trial [NEJM 1999]*. In patients presenting with *STEMI and cardiogenic shock*, emergent *revascularization* [either PCI or emergent CABG] provided a *mortality benefit* compared to *thrombolysis*. Of those who did survive, the vast majority [more than 80%] were

NYHA 1 or 2 at one year. The *minority of patients in the SHOCK trial presented with hypotension to the hospital*, but go on to do so within 24 hours. Further, 25% of patients from the SHOCK registry lacked pulmonary congestion on examination [recall, all of these patients were in cardiogenic shock].

No trials support the use of IABP in acute myocardial infarction with shock *[in fact, the IABP-SHOCK2 trial in NEJM 2012 refutes its value*], though it is often done. In the original SHOCK trial, the patient's in the medical arm could not be re-vascularized until 54 hours after the event. The 30 day mortality was no different between the two arms [47 versus 56% mortality]! However, the 6 month mortality was significant [50 versus 63%]! While there was mortality non-significant mortality reduction at 30 days, in *patients under 75 years*, it was significant at 30 days.

Based on the SHOCK trial, cardiogenic shock is an AHA class I indication for *emergent revascularization*. Nitrates, beta-blockers and ace inhibitors are generally avoided in cardiogenic shock because they can exacerbate hypotension.

Oral BB should be started in the first 24 hours, unless there are concern for shock, pulmonary edema, elderly, more than 12 hours of symptoms, bradycardia or heart block, reactive airway disease. ACEI should be started if LVEF less than 40% or with DM, CKD, HTN.

Right Ventricular Infarction

Hypotension with acute inferior MI should prompt right sided precordial leads. *RV infarction may show shock with clear lungs,* elevated venous pressures, Kussmauls sign, and 'square root sign' on PAC [see below].

Look for tall R waves in the anterior pre-cordial leads. The patient will present with hypotension, bradycardia and an absence of pulmonary congestion. There will be STE in right sided leads, depressed RV function on TTE. *RV infarction* is seen in *30% of patients with inferior MI* and is clinically significant in about 10% of those with inferior MI.

The *treatment* is maintaining RV preload, inotropic support, reperfusion. *Diuretics should not be used*. IABP *is an* effective option in RV infarction. Sometimes pacing to maintain AV synchrony is needed, cardioversion for SVTs.

Reperfusion typically results in RV improvement in days. Nitroglycerin should not be given to hypotensive patients, or suspected RV infarction, nor patients who have received PDEI in 24-48 hours. With *administration of lytics*, the blood pressure remains low, *but the heart rate increases*. Volume infusion should be considered to improve preload. Streptokinase itself can cause some hypotension, but this is much less likely with tPA.

Mechanical Complications of Stemi

Recognize *mechanical complications post infarction*. Pra, RV diastolic, PA diastolic and pulmonary artery occlusion pressure [Ppao] all elevate and are within 5 mmHg of each other with tamponade secondary to cardiac rupture. Post-infarction rupture is different from *hemorrhagic pericarditis*, which may occur in the setting of thrombolysis. *Hemorrhagic pericarditis is not the result of a ruptured muscular wall. It can be treated with needle decompression*, but this often clogs, and sometimes a surgical window is required.

The most difficult ddx in the setting of equalized cardiac pressures is that of an RV infarction secondary to right coronary occlusion which *can also raise Pra, Prv, and Ppao* [via ventricular interdependence] but in the setting of a known LAD lesion, rupture would be more likely.

Other considerations are: *VSD which would display an oxygen step up of 5 mmHg from the RA to the RV*.

Another option would be *papillary muscle rupture of the posterolateral leaflet*, but this would be presented with a murmur, crackles and *tall V waves*. Consider this in a patient 48 hours post inferior MI with sudden onset, bilateral pulmonary edema with low output. There may be no audible murmur. An inferior infarction can cause rupture or the posterolateral papillary muscle as it has a single blood supply and is susceptible to ischemia the most. The murmur is often absent because of equalization of pressures.

In each of the mechanical complications of MI, the mortality is very high. Surgical mortality is about 50% for VSD [worse with inferior ischemia] and papillary muscle rupture and there are case reports of surgical survival in patients with free wall rupture. Medical mortality approaches 90% in all forms.

NON-ST SEGMENT ELEVATION MYOCARDIAL INFARCTION

Ischemic chest pain may involve an occlusive thrombus or non-occlusive thrombus and these clinical scenarios can be detected by the ECG as STEMI and NSTEMI, respectively. *Unstable angina* is the term for ischemic chest pain *without ECG change and no biomarker* elevation.

Consider an *NSTEMI patient on dialysis with recent history of TIA/stroke* – all of the following are contraindicated: prasugrel, LMWH, eptifibitide and fibrinolysis. Recall that with ST segment depression there is harm with the administration of fibrinolysis. There is an increased risk of ICH absolute of 2.3% in those with a history of stroke or TIA. Too many patients in the US on dialysis received the contra-indicated medications: LMWH and eptifibitide – this increased the risk of death.

What about *anti-platelets*? Those at medium to high risk and in whom an initial invasive strategy is chosen, the patient should receive ASA immediately. For ASA, the dose doesn't seem to matter, but less is more in terms of bleeding. Plavix reduces the risk of *composite end point* by 2.1% in the CURE trial – NEJM 2001. Whether or not patients will not receive a cath, Plavix should be started ASAP [600 mg per CURRENT OASIS 7 – NEJM]. Recall that some PPIs are metabolized by CYP2C19, omeprazole and Plavix moves through that CYP – *the data about this is totally mixed*. It is probably OK to use clopidogrel and PPIs concomitantly, but often patients don't really need the PPI.

The choice of the second anti-platelet agent to be added to ASA includes: as above, clopidogreal *before or at time of PCI*, an IV GPIIBIIIA *before or at time of PCI*, or prasugrel *at the time of PCI*. *Fondaparinux should not be used* if going to the cath lab because of catheter thrombosis.

Anti-coagulation should be added ASAP with presentation. When invasive strategy is chosen, the patient should get either LMWH, UFH or bivalirudin. In a patient *with renal failure*, or CrCl less than 30 ml/min, *fondaparinux is contra-indicated*, LMWH can be used, but it must be dose-adjusted. UFH may be used. The general dose of UFH for ACS is a loading dose of 60 U/kg bolus and maintenance of 12/Kg/hr for PTT of 50-70. Fondaparinux is 2.5 mg SQ once, but cannot be used if CrCl is less than 30. It should not be given if going to the cath lab. Bivalirudin is OK with a history of HIT.

What about *CCB*? There is old evidence from the late 1980s, in patients with pulmonary edema by CXR or exam, *diltiazem can worsen outcome*. But, a CCB can be used over a BB if the patient has a normal LVEF and is not in failure as a means to minimize myocardial oxygen demand.

An *ACEI* should be given *within 24 hours in NSTEMI in patients with pulmonary congestion or depressed LVEF* unless there is hypotension or contraindication to that class of medication. Patients with NSTEMI and a low EF should be

strongly considered for cardiac catheterization. This is essentially a risk stratification; an LV gram should be considered in all NSTEMI patients.

What is best in NSTEMI, conservative or invasive management? There is evidence to *suggest improvement with an invasive approach if there is baseline troponin elevation or ST segment change*. A meta-analysis showed that there was no difference between invasive and conservative strategies in low risk patients. What about *early versus late invasive* intervention in ACS – the TIMI risk score and GRACE risk score were used and again, *those at high risk benefitted from early intervention, not low to moderate*. This is Mehta NEJM 2009. If there is recurrent angina, elevated troponins, new ST depressions, HF, instability, prior CABG, PCI within 6 months, high TIMI or GRACE score, reduced LVEF – the patient should receive an early invasive approach.

Recognize and treat *Prinzmetal or variant angina*. The classic picture of this is abrupt onset [at rest] chest pain with inferior ST elevations that completely resolve with resolution of chest pain. It is typically in leads II, III and avF and PVCs are common. *Variant angina may produce all of the complications of plaque rupture*. The gold standard for diagnosis, really, is coronary angiogram, but even patients with variant angina may have pre-morbid, severe coronary obstruction. The treatment of this disease involves selective coronary vasodilators [*nitrates and calcium channel blockers*]. It is argued that patients should *not* get beta-receptor selective beta-blockers because this may lead to unopposed alpha stimulation which might make things worse. Variant angina may cause bradycardia if the right coronary is involved [from AV node ischemia]. Again, the clue is the ECG with transient ST elevation without infarction. On angiography, ergonivine [which stimulates both alpha receptors and serotonin receptors] may be infused at very low dose, but some clinicians think that this is dangerous.

BRADYCARDIAS & PACEMAKERS

The sinus node is spontaneous. The AV node introduces AV delay to allow mechanical coupling of atrial systole and ventricular systole – this is the PR interval. The AV node is also protective, if atrial fibrillation develops, it prevents ventricular fibrillation.

The His-Purkinje, by contrast, is very, very rapid – this gives rise to synchronous ventricular contraction. There are subsidiary pacemakers down the conduction system which can give rise to escape beats which can be narrow complex if junctional or above AV node, but become progressively slower down the pathway. Junctional escape must be clarified as there are different implications e.g. junctional escape with sinus arrest versus junctional escape with complete heart block.

Describe first what the underlying bradycardia is. Sinus bradycardia is common and usually benign – at night, *during sleep there can be very long pauses in young healthy athletes*.

It is common to see comorbid atrial fibrillation and sinus node disease [*tachy-brady*] as the pathophysiology for the two is essentially the same, also medications used can do this.

Following *conversion from atrial fibrillation* there is quite commonly a long pause/asystole before the sinus node recovers. The pause may be alarmingly long, but these patients often do well without a pacemaker.

Second Degree Heart Block

A prolonged PR interval is much less pathological compared to a patient with *pathological AV block*. *Type I AV block* tends to occur in the AV node; there is intermittent failure of the AV conduction system. There is *progressive PR prolongation prior to complete block*. When there is 'grouped beating' of the RR intervals on the ECG, think of Wenckebach. It is usually not

progressive, usually does not need a PPM and common causes include drugs, vagal tone, inferior infarction; it resolves with atropine and exercise.

Type II AV block is due to block in the His-Purkinje system and is characterized by a stable PR prolongation prior to AV block; this is typically the result of block below the AV node, tends to be progressive *and frequently needs* or should require a PPM. It is often caused by conduction disease, anterior infarction and *worsens* with atropine and exercise.

Recognize *Mobitz II heart block following an anterior AMI*. A patient will have bradycardia, normal blood pressure but chest pain. There is grouped beating. This is Mobitz II and requires a PPM. *Adams-Stokes attacks* can commonly occur with *Mobitz II block* as it frequently progresses to high degree AV block *with syncope*. By contrast, *Mobitz I may complicate inferior MI, but typically does not progress to high degree block* and resolves with atropine. Type II usually occurs in the setting of an *anterior infarction* and is commonly associated with permanent pacemaker dependence and pump failure. Anatomically, type I [mobitz] is an AV node phenomenon whereas type II is the result of destruction to the His-Purkinje system. This is also why atropine is not effective in speeding up the heart rate.

Always assess the *sinus rate* – if slow at the time of AV block, it *suggests* that there may be high vagal tone. There will be a slowing of the sinus node and then block. That may be caused by pain or suctioning.

Third Degree Av Block

Complete heart block is more severe His-Purkinje disease and a result of structural heart disease. Remember that AV dissociation is a generic term – it occurs with ventricular tachycardia – so describe the bradycardia first 'complete heart block *with* AV dissociation.' In complete heart block there is no association between atrial and ventricular activity.

Consider a patient with *first degree AV block*, *LAFB*, and *RBBB* who then gets complete heart block. There is *no slowing of the sinus rate* prior to block. This is a serious situation.

But heart block, in reality, is more muddy than the aforementioned, that is, 2:1 AV block or high-grade AV block. *The level of block is important*.

2:1 AV block is a failure of AV conduction with every other beat, *so PR prolongation is difficult to detect on the ECG*. In this situation, clues for Mobitz I versus II: If the QRS is very wide, it is more likely Mobitz II, check the rhythm strip for times when conduction is better to determine if PR prolongation occurs prior to block.

High grade AV block may also be called intermittent third degree and occurs when more than one P wave blocks in a row. The level of block can be determined as above. There will be intermittent AV conduction in high grade block.

The difference between high degree AV block and complete heart block is that the latter reveals a *complete dissociation* between atrium and ventricles, i.e. both p waves and QRS complexes should march out perfectly but in a mutually exclusive fashion. If there is *any irregularity to the ventricular rhythm*, then *there is some conduction*, unless there are PVCs during the complete block.

Recognize that Lyme myocarditis may present with complete heart block. The patient will also present with dyspnea, Bell's palsy and bad headaches. There may not be a history of stage I Lyme [erythema migrans], but there likely will be arthritis. *4-8% of patients with Lyme disease have some element of myocardial involvement*. The Ddx here includes: mycoplasma perimyocarditis which could certainly present like a stage II Lyme disease involving the heart,

however, it is not associated with oligoarticular arthritis, nor cephalalgia to the extent that Lyme does. Bullous myringitis and erythema migrans can be seen with mycoplasma perimyocarditis. Stage III lyme disease [recurrent oligoarthritis] is more difficult to eradicate than stage II [even with meningeal involvement].

Treatment of Bradycardia and Heart Block

ACLS – if bradycardia, look for cause, get IV access, determine symptoms. First give 0.5 mg atropine, then consider IV infusion of epinephrine or dopamine. Trans-cutaneous [TC] pacing is useful, but often not tolerated. *Must confirm capture mechanically [feel the pulse, observe on art line/plethysmography]*. TC rate may be set at 60/min initially and dialed up if perfusion remains inadequate. The usual initial dose is 2 mA above the dose that induces "capture."

PPMs – the first letter is the chamber that is paced, the second letter is the chamber sensed and the third is the response to sensed event. The sinus rate can be an indicator of the degree of stress upon the patient, so if there is block with high sinus rate, this is concerning as the patient is having an adrenergic response to this conduction disease.

Placing a magnet over a dual chamber PPM will cause it to become DOO, that is, pace both chambers in sequence at 70 bpm, if it's a single chamber pacer, a magnet *will make it VOO*.

On the boards, after EP lab intervention [e.g. PPM placement], especially with hypotension & chest pain, it's usually perforation and tamponade until proven otherwise.

As an aside, left atrial-esophageal fistula can occur following an *afib ablation*. There can be stroke-like symptoms given *food emboli and bacteremia* - risk is less than 1 per 1000. Fever post device could be a sponge in the pocket. If someone has a dual chamber pacer, modern pacers can detect atrial fibrillation and stop tracking the atrial rhythm. Old pacers will revert to VVI after a long period for example 8 years or so. *This may precipitate heart failure*.

A pacing stimulus on a T wave can rarely lead to ventricular fibrillation. *Making the pacer more sensitive [to detect a smaller R wave] can prevent this [so the PPM can recognize the R wave*].

SUPRAVENTRICULAR TACHYCARDIA

Pathophysiology

There are 3 mechanisms of tachy-arrhythmias for both the atria and ventricles. *1. Re-entry [most common]* for example scar-based monomorphic VT post-MI, or atrial flutter. *2. Abnormal automaticity* – an example would be sinus tachycardia or MAT and *3. Triggered activity* which is frequently a drug-effect for example, torsades de pointe, digoxin toxicity. Triggered activity occurs from a DADs or EADs [delayed or early after-depolarizations].

The most common is *re-entry*, either macro re-entry or micro-re-entry. Monomorphic Vtach is a macro re-entry typically around a scar. What is re-entry? Most of the heart is homogeneous, with similar conduction velocities and refractory periods. But the introduction of a scar can increase heterogeneity or dispersion of depolarization and repolarization within the myocardium - producing areas of rapid and slow conduction. If a pre-mature beat blocks in one limb and re-enters through the slow pathway that is now repolarized then re-entry has begun.

Atrial flutter is a macro-re-entry about the tricuspid valve. AV re-entry can occur about the AV node. Vtach is about a scar. The drugs given tend to *change the refractory periods*. The shock applied during a defibrillation causes a synchronous depolarization at once *to eliminate the re-entrant circuit*.

Supraventricular Tachycardia

SVT is usually 100-260 bpm. It can be narrow or wide depending on underlying bundle disease, rate-dependent aberrations or pre-excitation [e.g. WPW].

PSVT means sudden onset, sudden offset. The primary re-entrant mechanisms of PSVT are AVNRT [65%], AVRT [30% - about half of these have pre-excitation like WPW, the other half have a concealed pathway found on EP study] and lastly about 5% have AT. *Thus, the AV node is a critical part of the re-entry in AVNRT and AVRT, but not AT. Blocking the AV node [e.g. adenosine] with AT will not terminate the rhythm*.

In *AVNRT*, the p wave is usually within the QRS or slightly thereafter. In *AVRT*, the p wave typically comes after the QRS as they are depolarized in series. WPW describes a patient with both pre-excitation on ECG *and* symptoms. This is the difference between pattern and syndrome. There is a short PR with delta wave which is the slurred upstroke of the QRS [the pattern].

The acute treatment of these rhythms *depends on symptoms*. Adenosine is great for AVNRT, AVRT, 6-18 mg bolus is given rapidly. If a patient is stable with termination of PSVT with 6 of adenosine, but then back in one hour, what is the next step? A higher dose of adenosine will not lead to prevention of recurrence, the best next step would be to *use a drug that blocks the AV node over a longer period of time such as a CCB or BB.*

Recognize that in a patient on a methyl-xanthine [e.g. aminophylline] *adenosine will not be effective because of antagonism effects*. For example, a patient admitted for an asthma exacerbation is treated with aminophylline and develops what appears to be an orthodromic SVT. *The correct answer is to give verapamil [not adenosine] because the patient is on a methyl-xanthine*. Beta-blockers are not as effective at treating SVT as CCB and adenosine are. BB should generally be avoided in acute exacerbations of OVD. *Lower doses of adenosine should be considered for patients who: are on dipyridamole, have a heart transplant or who receive the drug through a central line*

Multifocal Atrial Tachycardia

Treat *multifocal atrial tachycardia.* Consider a patient with pneumonia, a COPD exacerbation [treated with a methylxanthine], and rapid MAT. Treatment is *with amiodarone*. The patient has a number of Ashmann's beats in his ECG. MAT is associated with theophylline use, but also more prominently, pulmonary disease. The treatment of MAT *is to treat the cause* [stop theophylline, treat respiratory disease]; if treating the PNA and COPD does not slow the rate, you should medically treat the MAT.

Amiodarone is a type III anti-arrhythmic with modest beta-blocking properties. It has been shown to *slow and convert MAT*. DC cardioversion, by contrast, is most effective for *re-entry type* arrhythmias such as atrial fibrillation and atrial tachycardia and most types of ventricular tachycardia. *MAT is an automatic* arrhythmia, so DC cardioversion will not be as effective. Similarly, MAT will not respond to digitalis as it is an automatic arrhythmia. Lidocaine tends to suppress only ventricular arrhythmias, so it would not be as effective. Calcium channel blockers could be considered, but they will likely cause hypotension more than amiodarone.

Atrial Flutter and Fibrillation

What about *atrial flutter*? It is almost always a right atrial rhythm. Typical flutter has a constant flutter wave morphology in the inferior leads. The mechanism is a single re-entrant mechanism. Right atrial stretch/disease can lead to flutter. It is easy to ablate. It passes through an area near the IVC and tricuspid valve or isthmus-dependent atrial flutter, type I flutter. But there is also scar-based atrial flutter, valve surgeries can result in

left atrial flutters. The crista terminalis is a natural barrier between smooth and trabeculated portions of the right atrium. *Upright in V1, down in lead II is typical for classic flutter*. In V1, large amplitude fibrillation waves can be confused with flutter.

Atrial fibrillation or a disorganized atrial activity is the most common arrhythmia is the world. *Paroxysmal* = spontaneous conversions, *persistent means that there is some attempt* to convert the patient and *permanent means that there have been failed attempts at conversion*. There can be *asystole* from adenosine [rare] there can be *pause-dependent* polymorphic *VT* from adenosine [rare], so try to avoid adenosine if you are sure that the rhythm is atrial fibrillation. Atrial fibrillation and flutter themselves uncommonly cause shock, it is usually some other co-morbid disease that is the reason for the shock such as MI, tamponade or sepsis.

The focus in the ICU should be immediate rate control *as well as AC*! Digoxin is less effective in states of high sympathetic tone, but when given in high doses, digoxin can be helpful. *Cardioversion must be synchronized*. A shock on the upslope of the T wave is the most sensitive time of the cardiac cycle to cause a ventricular arrhythmia. *Synchronization times the shock with the QRS* which is the portion of the cardiac cycle most likely to correct the rhythm. *Sometimes the defibrillator auto-corrects to unsynchronized cardioversion following an initial shock*.

Medical conversion is best carried out by ibutilide [60% effective] but when a patient is unstable, the correct answer is electricity. IV ibutilide can be effective [1 mg over 10 mins, followed by 1 mg thereafter – it can cause QT prolongation]. Ibutilide is also helpful immediately after an electrical cardioversion, or if too much electricity is required to cardiovert, but this is less problematic with biphasic cardioverters.

Paroxysmal atrial tachycardia with block is classic for digitalis toxicity. *Dronedarone is known to cause liver injury* [Multaq is dronedarone], transplant has been required in this situation, but it is very rare. Get baseline and repeat liver enzymes. Flecainide is usually associated with HA, neuro, ventricular pro-arrhythmia, propafenone can cause metallic taste, both are IC, sodium channel blockers. Defetilide is class III, can prolong QT. Sotalol is partially a beta-blocker.

AF with WPW is badness, the risk of death chronically is 0.1% per year. AF with WPW, if hemodynamically unstable is treated with synchronized shock, *IV procainamide is the sodium channel blocker of choice*. Could consider Ibutilide or amiodarone, but there is no data there. *Never* give CCB or BB.

Anticoagulation

When using a drug or shock to cardiovert a patient, there is a high risk of stroke; it is not caused by the shock, it is caused by the conversion to sinus rhythm. If the AF is less than 48 hours in duration, cardioversion is OK. After a couple of days, then you need to think about anticoagulation. If longer than 48 hours, then 3 weeks OAC pre cardioversion, then 4 weeks post. *If the patient has a TEE and there is no clot, the patient still needs 4 weeks of OAC post cardioversion as it is the stunned myocardium that increases the risk of thromboembolism*. If the patient cannot receive AC, there is no point to getting TEE.

In a low CVA risk patient with AF, it is reasonable to hold AC for one week without heparin.

VENTRICULAR TACHYCARDIA

Ventricular tachycardia is at a rate of 100-120 bpm with three of more consecutive beats at that rate. There is a slow spread through the

ventricles and the *dysrhythmia may be monomorphic or polymorphic*.

Monomorphic is commonly scar-based VT, RV outflow tract [RVOT-VT] can occur idiopathically.

Polymorphic VT can look like Vfib, but polymorphic VT displays gradual change in the size of the QRS. If it turns about a point and, technically, if the patient has a long QT at baseline, this is known as *Torsades de Pointe, as this is a clinical syndrome.*

If a patient has VT *more than 30 seconds it is sustained* or, if there are symptoms despite being less than 30 seconds it is also sustained in nature.

Wide complex QRS tachycardia has a differential. Obviously it can be VT, but also SVT with aberrancy [rate-dependent aberration, or pre-existing bundle], it could be antidromic AV re-entry, ventricular pacing [if the pacing stimulus is small and not seen on the monitor], drug or electrolytes, artifact, or even ST elevation if seen in only one lead. Patient movement, infusion pumps, loose electrodes, etc. can all look like Vtach. *Following Vtach, there tends to be a pause, if there is no pause, it may be artifact*. Usually with artifact, there are QRS complexes marching through the artifactual waves.

By contrast, a long pause, followed by a PAC, followed by a wide-complex tachycardia is most *likely Ashman phenomenon*. Recall that the right bundle has a slightly longer refractory period than the left. Further, the refractory period of the bundle is directly related to the length of the preceding beat. So if there is a long depolarization, there will be a longer refractory period. If, during this longer refractory period, premature supraventricular activity occurs [e.g. a PAC or an afib beat], then it will hit the right bundle during its refractory period and have right bundle configuration [wide-complex morphology]. If this occurs during rapid afib, this can look a lot like V-tach. So if the patient has just had a long pause, followed by a narrow complex beat and then wide-complex tachycardia in a RBBB pattern, this is an excellent way to distinguish V-tach from SVT with aberrancy.

Differentiating VT from SVT with aberrancy is also aided by considering the clinical context, like if the patient came in with prior MI, heart failure, has an AICD, etc. worry more about VT. *The rate and hemodynamic stability can be misleading; always treat as VT if uncertain*.

Ask yourself if it looks like RBBB or LBBB? The best lead is V1. *If looks like typical RBB or LBB, it's probably aberration*. A sharp R wave just prior to the wide S wave is strongly suggestive of LBBB pattern. *If there is a notching within the wide S wave, it is more suggestive of VT*.

The Brugada criteria first looks for precordial concordance; if all the R waves are in the same directions in V1-V6, it strongly suggests a ventricular source [VT] but if they are up in V1 and down in V6, this suggests RBBB, or if down in V1 and up in V6 - LBBB. *If the beginning of the R wave to the nadir of the S wave is short, then likely PSVT, if long, likely VT*. AV dissociation is also VT. But these rules are not perfect, there can be pre-cordial *dis*cordance and there still may be VT, especially if there is *AV dissociation* or the presence of *fusion* or *capture* beats.

In a wide complex tachycardia of uncertain etiology, *the use of adenosine is reasonable to differentiate the two [VT versus SVT with aberrancy], if the patient is stable*. Be very wary of WPW with pre-excitation, though.

As in the preceding section, the treatment of WPW-associated atrial fibrillation is procainamide. This will present as a young patient with a heart rate above 200. The ECG may reveal a wide complex with a RBBB pattern with precordial concordance. *It is unusually irregular, however*. The accessory pathway of WPW does *not have decremental conduction*. The treatment is to slow this pathway with procainamide. *Digoxin* is reported to decrease

the refractory period of the accessory pathway, and *therefore increase the ventricular rate*. Lidocaine has also been reported to increase the ventricular rate in WPW. Substitutes for procainamide here are amiodarone, ibutilide and sotolol.

What about *VF*? The etiology is likely *multiple re-entrant wavelets within the ventricles*, it is life-threatening. The use of drugs is for Vfib is amiodarone 300 mg or lidocaine 1 mg/kg, vaso 40 U, epi 1 mg. Lidocaine blocks both activated and inactivated sodium channels, it cannot be given orally, but mexilitine can be. *Lidocaine may be more effective during active ischemia*. Amiodarone is a class III agent, it blocks potassium and inactivated Na channels, as well as alpha, beta and calcium channels. It has iodine attached to it, so can affect the thyroid, with prolonged half-life. 200 mg per day is usually afib, 400 mg is for VT. Liver, thyroid, lung, ophtho side-effects. Even though it prolongs the QT, *it rarely leads to Torsades, probably because of its trans-mural stabilization effects*.

Remember that *lots of drugs prolong QT and predispose to Torsades*. Methadone is one, many antibiotics, antifungals, anti-psychotics. *The treatment of torsades is magnesium and speed up the heart rate*.

The treatment of long QT syndrome either congenital [channelopathies, usually potassium channels] or drug effect is treated with IV magnesium. Standard treatment with long QT is beta-blocker potentially with AICD.

The shocking lead of an AICD can be seen in the RV. If a patient is having afib and getting multiple shocks as a result. *A magnet will suspend all tachycardia therapies* – thus it will also prevent shocking Vfib. If a magnet is placed over a pacemaker it will change to DOO or VOO, that is, an asynchronous pacing mode.

HYPERTENSIVE EMERGENCY

Severe hypertension with new or progressive end-organ dysfunction. This *requires immediate* reduction in blood pressure. There is no specific blood pressure which defines an emergency.

The *brain, heart and kidney* should be evaluated immediately – check for mental status, neuro deficits, retinal changes, consider CT scan and drug screen.

Consider chest pain, dyspnea, rales, S3 or pulse deficits, a new murmur [e.g. aortic dissection], ECG, CXR, biomarkers and TTE can all help triage.

For the kidneys evaluate urine output, hematuria, BUN/Cr, lytes, UA, CBC [e.g. uncommon, but MAHA]. Consider drugs, pheo, MAOI, clonidine withdrawal, pre-clampsia.

The treatment of hypertensive emergency is to *lower the MAP by 15-[20]-25%*. The systolic pressure can vary quite a bit so don't rely on it that, nor diastolic. The goal is to stop and reverse end-organ injury while simultaneously preventing iatrogenic complications by correcting too rapidly.

Cerebral blood flow tends to *remain constant between a MAP of 50 to 150*, but in chronic hypertension, the curve is shifted rightwards, so lowering MAP too much can impair organ perfusion.

AGENTS

Which medication to use? Must consider pre-existing conditions. Titratable, potent and safe drugs that are parenteral are ideal initially, then start oral agents within 12-24 hours.

Nipride is an arterial and venous vasodilator. It requires the ICU for very close BP monitoring, 0.3-1.0 mcg/kg/min. There is cyanide toxicity. *Labetolol* can be bolus or infusion. It is mostly a beta-blocker, but some alpha [6-7:1 is the ratio of beta-to-alpha effects]. *Nitroglycerin* is a venodilator. Over 100 mcg is more of an arterial effect. *Nicardipine* is a systemic and coronary

vasodilator with minimal negative inotropic effects. It is hepatically cleared, so watch for liver and older people. *Clevidipine* is a very short-acting arteriolar dilator. There is little change in heart rate or cardiac output. It is metabolized by tissue-esterases which is nice though it is fairly expensive. *Fenoldopam* is a dopamine 1 receptor agonist which increases renal blood flow, with no toxic metabolites; it can lower potassium from increased renal blood flow. *Esmolol* is a cardioselective beta-blocker without vasodilating effects. *Hydralazine* has a long duration and variable effect – there may be precipitous drops in BP – there is also reflex tachycardia; in many ICUs hydralazine is falling out of favor for these reasons. *Enalaprilat* is low potency with variable response in emergencies.

DISEASES

Hypertensive encephalopathy is treated with *nipride, labetolol, nicardipine, nitroglycerine, clevidipine, fenoldopam*. PRES may be seen in these cases.

Nitroglycerine is usually the right answer for hypertensive emergency with *acute coronary syndrome*, may also consider labetolol, esmolol, nicardipine, nipride. What about the treatment of *acute heart failure*, with systolic dysfunction? NTG, nicardipine, labetolol [with caution], nipride should be tried, remember that diuresis may be touchy is there is a small cavity from LVH, and in many instances, these patients are actually volume down in hypertensive emergencies from a pressure natriuresis.

What about an acute *aortic dissection*? The correct answer is labetolol to a *target of 100/70*. Nipride should never be used alone during a dissection, there must always be a beta-blocker to lower the aortic dP/dt. Recognize and treat a *Stanford type-A thoracic aortic dissection*. The patient will present with severe hypertension and chest pain. The CT angiogram will demonstrate a monster aorta with an intimal flap. *Notably 10-20% of CXR with dissecting aortic aneurysms do not have a widened appearance*. Surgical outcome is better than medical therapy for Stanford type-A dissection, whereas *medical therapy is better for Stanford B*. Some of the latter patients may need surgery if the diameter of the aorta is excessive [more than 5 cm], if there is ongoing ischemic symptoms or if BP cannot be controlled.

What about *head bleeds*? See section on hemorrhage in neurology section, but briefly. INTERACT 1 trial lowered to systolic of 140, and this *lowered hematoma growth* [INTERACT 2 did not find this result though]. The guidelines are blurred, consider baseline BP, age, ICP, cause of bleed. If ICP is high, reduce the MAP, but keep CPP high – certainly above 55. Goal is *MAP of 110* versus 130 mmHg if the ICP is high. The agents often used are labetolol, *nicardipine*, nipride, NTG, esmolol, hydralazine, enalaprilat.

What about *SAH*? The patient *will need nimodipine and pain treatment*. Shoot for systolic less than 160 with beta-blockers or nicardipine IV. *Ischemic stroke*, the systolic *must be less than 185/110 if tPA to be administered*. All others, the BP is 220/120 goal. CHHIPS study is looking to treat systolic more than 160 in ischemic stroke. *Perioperative hypertension* requires pain relief, nitroglycerin, nicardipine, clevidipine, labetolol, nipride.

Excess catecholamine states, phentolamine is the boards answer. The choice is always alpha blocker before beta-blocker.

Hypertensive urgency is severe hypertension, but no acute end-organ injury. The blood pressure should be lowered over 24 hours. Usually just give them back their home meds PO – no need for ICU level care.

HEMODYNAMIC MONITORING

Central pressure monitoring involves central venous pressure [CVP] and pulmonary artery occlusion pressure [Ppao].

Principles of Measurement

The *phlebostatic axis* is an attempt to find the left or right atrium – the nipple line at mid chest – once zeroed, the patient should not really be moved. The system must be opened to atmosphere at that point. The CVP is measured following the a-wave which is *the first positive deflection following the ECG p wave*. For the CVP the a-wave usually follows P wave *but precedes* the QRS. For the Ppao, the a-wave follows the QRS and the v-wave follows the ECG T wave.

Find the a-wave at end-expiration. One method is to take the top of the a-wave and the bottom of the a-wave and divide by 2. So if the top of the a-wave is 12, and the bottom is 6, then the average is 9. *End-expiration is most difficult to find when the patient is triggering the ventilator*. This typically requires a bedside assessment while looking at the patient and looking at the CVP tracing and ventilator waveforms.

There are clear limitations to the use of pressure as a surrogate for preload and it *really shouldn't be done*. What about echocardiographic measures? *The LV end-diastolic area [LVEDA] has been used as a surrogate for preload and fluid responsiveness, but is an equally poor predictor*.

What about *continuous cardiac output*? There are pulse-contour analysis devices such as PICCO, LiDCO, or Flotrac. The former two use measures of cardiac output [e.g. thermodilution or lithium dilution] to calibrate while flotrac does not – *they use the area under the arterial pulse-pressure curve as a surrogate for stroke volume*. Esophageal Doppler monitoring may also be used. Systolic and pulse pressure variation may be used as markers of fluid responsiveness – but with a plethora of caveats.

Pattern Recognition From the Pulmonary Artery Catheter

Pulmonary artery occlusion pressure is an [admittedly poor] estimate of LV filling. *The pulmonary artery catheter must be in West Zone III physiology*. Zone II and I physiology will result in faulty measurements. It will measure airway pressure in these states.

PEEP tends to *decrease* the LV trans-mural pressure as a consequence of decreased LV filling – this occurs despite PEEP increasing *the absolute value* of the Ppao.

The *PAD-PCWP gradient is important*. The normal gradient should be less than 5 mmHg. If greater, it suggests that there is a true increase in pulmonary vascular resistance. Use of the PVR should be largely abandoned [IMHO] in the care of ICU patients.

Overwedging occurs when the balloon or PAC tip is stuck up against the vessel wall and the tracing slowly shoots up over time. Pulmonary artery rupture may also occur. There will be hemoptysis and blush on angiogram. The treatment is embolization. Risk factors for rupture are long-term steroids, PAH, older age, balloon hyperinflation, cardiac manipulation, hypothermia.

Thermodilution curves - if there is high CO there is a very quick up and down thermodilution curve – the low temp gets there faster and goes away faster, the opposite is true for low CO [there is an *inverse* relationship between the thermodilution AUC and cardiac output]. The thermodilution cannot be reliably used in patients with tricuspid regurgitation. Further*, in low output states, the cold injection may be diluted in the warm cardiac tissue* and therefore *give a falsely small area under the curve* [and therefore high cardiac output]. Potential problems with thermodilution measurement of cardiac output may also result from technical factors [such as variation in

injectate temperature, volume, or rate of injection] or from physiologic factors such as arrhythmias or respiratory variation. Variability in calculations of cardiac output by thermodilution is estimated at approximately 10%; *thus, changes in cardiac output should generally be on the order of 15% to be regarded as valid.*

May have a board question on a patient with a recent MI with sudden worsening, especially after thrombolysis *with tall v waves on the PA tracing*. It may be confused with the dicrotic notch of the pulmonary artery tracing. Do not confuse with a dampened waveform. The cause is acute papillary muscle rupture, the treatment is surgery with balloon pump.

The 4th day following an acute MI, there is hypotension with a loud systolic murmur with a step-up in the right ventricle, say from 60 to 70 mmHg. *This is a VSD*.

The *square root sign* occurs in the setting of *constrictive pericarditis* and is the result of the right ventricle filling against a stiff pericardium [the plateau portion of the square root sign following the v wave].

Recognize electrical alternans on an ECG and anticipate the pressure waveform on a PAC. The PAC data will have nearly equal Pra, Ppao and PAD. The patient *with tamponade will have a dramatic x decent because of the enhanced systolic filling of the right atrium*, and a diminished y decent because of the lack of a pressure differential between the RV and RA at the onset of systole. The patient may also have pulsus paradoxus.

Differentiate *traumatic tricuspid valve rupture* from constrictive pericarditis on ECG and RAP tracing. Consider a patient in a car accident with hemopericardium that was drained. One month later he presents with dyspnea and LE edema. The ECG reveals right atrial enlargement, and the RAP tracing depicts tall v waves, with prominent x and y descents; this is traumatic TR.

Be able to *calculate the VO2* if given cardiac output, hemoglobin, mixed venous and arterial oxygen saturations. O2ER = VO2/DO2; and DO2 = Hb [grams per LITRE – Canadian units] x 1.39 x cardiac output. Thus VO2 = O2ER [i.e. the difference between arterial PaO2 and mixed venous PvO2] x [1.39Hb x CO]. If the arterial PaO2 of 0.99, the mixed venous of 0.50, the Hb of 120 g/L and CO of 3. The VO2 becomes 245.

In very simple terms, generally: severe hemorrhage results in low filling pressures, pneumococcal sepsis results in low filling and high index. AMI will result in high wedge, low index and low PAD-PCWP. RV infarction will result in a low index, normal wedge and elevated CVP.

IABP Waveforms

Understand IABP waveform analysis. The ideal timing of the IABP is *to inflate at the onset of diastole* [the dichrotic notch on the pressure waveform] around the ECG t wave and then *deflate right before the following systole* which, on the pressure waveform, is right before systolic upstroke or right before the QRS on the ECG. Balloon inflation can be too late [well after the dichrotic notch] which limits the coronary perfusion and peripheral perfusion effects, or it may be too early [before the dichrotic notch or before the QRS] which increases afterload. Conversely, the balloon may deflate too early [well before the next upstroke in arterial blood pressure or well before the QRS] which will impair diastolic perfusion. The balloon may also deflate too late which occurs when it deflates into the next systole [seen when the balloon deflation occurs well past the upstroke of the next beat and well past its QRS]. In the latter situation, when the balloon does deflate, there is a diminutive arterial pulse with dichrotic notch. This essentially afterloads the heart [deflation too late is physiologically akin to inflation too early]. Importantly, *to diagnose these problems, you must change the IABP to 1:2 or 1:3 and analyze*

the native and augmented pressure waveforms with the ECG.

SHOCK BASICS

Shock is a profound and widespread reduction in the effective delivery of oxygen and other nutrients to tissues which leads first to *reversible* and then, if prolonged, *irreversible* cellular injury.

In all types of shock there is an activation of the SIRS response. Some of this may be a result of poor gut perfusion and endotoxin release in all forms of shock. Neutrophils, endothelial cells, macrophages, etc. are all activated and there is microvascular, tissue and organ dysfunction.

Effective tissue perfusion is determined by: cardiac performance, vascular performance, arterial pressure and cellular function. The third-order arterioles are the principle determinant of vascular resistance, these arterioles are 20-35 micrometers in diameter.

The cardiac [Starling] function curve is shifted not just by contractility. For example, increasing the afterload [e.g. giving vasopressin] also shifts the cardiac function curve down and to the right. In patients with systolic dysfunction, increasing the vascular resistance will diminish the stroke volume.

Auto-regulation is important. Between a MAP of 50 and 150, the blood flow to an organ is essentially unchanged. Autoregulation physiology may be disturbed in shocked states.

The use of the pulmonary artery catheter can be helpful in the differential diagnosis of shock and can be tested on the boards. The PAC is in decline because there is little benefit in mortality, but no significant increase in mortality. There was likely overuse of the PAC in less-sick patients. Most monitoring methods show no mortality effect. In the RCTs that studied PAC, the patients who the physician thought would benefit from a PAC were NOT randomized [i.e. they were placed into the PAC group]. *The PAC must be measured correctly, interpreted correctly and applied correctly*.

VASOACTIVE AGENTS

The hemodynamic response to *dobutamine* is to *increase cardiac output, heart rate, decrease SVR* and *lower* filling pressures. It is a synthetic derivative of isoproterenol. It has affinity for beta1 and beta2 receptors. It will also augment coronary blood flow. As it has a propensity to lower systemic vascular resistance, so this may cause hypotension in sepsis or hypovolemia. *Levophed* is more of a vasopressor than an inotrope, but has some cardiac effects. *Epinephrine* has both very potent alpha [vasopressor] and beta [heart rate, contractility, vasodilatory] effects. Epi may cause bronchodilation as well.

Dopamine increases renal blood flow and urine output, but when used routinely [ANZICS trial in Lancet] there is no effect on renal function.

Vasopressin [AVP] directly stimulates smooth muscle contraction [V1a]. Concentration of AVP is depressed in septic shock. In certain shock states it results in an impressive rise in blood pressure. It *decreases cardiac output* and may produce myocardial ischemia. Patients in the *VASST trial* [NEJM 2008] with myocardial ischemia were excluded. Additionally, AVP will raise pulmonary artery pressure, filling pressure. In '*low dose*' vasopressin [i.e. contemporary dosing from the VASST trial], there is an *increase in splanchnic blood flow* and urine output. Whereas in higher doses [when used to treat severe GI hemorrhaging] AVP lowers splanchnic blood flow, but these doses were related to an unacceptably high risk of myocardial ischemia and digital ischemia.

Nitric oxide antagonists also increase blood pressure, but decrease survival in septic shock.

There was worsening heart failure and pulmonary hypertension.

Types of Shock

Hypovolemic shock – *there is decompensated shock at 25% blood loss.* At *10% loss* there can be a totally normal blood pressure. With less than *20% blood volume lost* there can be cool extremities, increased capillary refill, diaphoresis, collapsed veins and anxiety. With moderate blood loss *[20-40%] of the blood volume* there is the addition of *tachycardia*, tachypnea, oliguria and postural changes. Then in severe blood loss [*more than 40%* of the blood volume] there is *hemodynamic instability*, marked tachycardia, hypotension and AMS.

There is older data suggesting delayed resuscitation with fluids with penetrating trauma is beneficial [Mattox NEJM -1994] – see chapter 9 for details.

Moving to *extra-cardiac obstruction* such as tamponade there can be a very slow accumulation of fluid that has minor hemodynamic effects, but a small, but rapid accumulation can be fatal. The *causes of pericardial effusion* are usually idiopathic or malignant [about 20% each], iatrogenic causes are 18%. Infectious cause are less than 10% and renal failure is less than 3 percent. *Beck's acute cardiac compression triad* is 1. Hypotension 2. A small quiet heart and 3. a rising systemic venous pressure. Note that this triad is often absent in medical patients.

Cardiogenic shock is most often due to acute MI or a mechanical abnormality. Sometimes you will get an RV infarction on the boards [see RV infarction above]. The vast majority of cardiogenic shock is due to LV pump failure. There is 40% or more loss of the LV function. Killip class IV is cardiogenic shock, and class III is overt pulmonary edema [clinically, radiographically]. Only 25% were in shock at presentation in the SHOCK registry, and the remaining 75% developed shock within 24 hours. In the GUSTO trial 11% were shocked on presentation. So cardiogenic shock develops in front of you.

What agent to use in cardiogenic shock? Based on the SOAP II trial, norepinephrine is a good choice. Balloon pumping by diastolic augmentation is frequently tested on the boards in terms of timing or inflation and deflation. The SHOCK trial by Hochman et. al showed that revascularization was better than thromobolysis not at 30 days, but at 6 months and one year, there was a difference. Revascularization saves more lives than lytics, ASA, beta-blockers and ACEI in myocardial infarction. The SHOCK trial performed revascularization within 18 hours of presentation.

2. CRITICAL CARE PULMONOLOGY

AIRWAY BASICS

If a patient needs a patent airway, the patient needs to be intubated. This applies for frequent suctioning, GI bleeding with frequent emesis [though intubation needn't be routine in GIB], aspiration risk, etc. Clearly for work of breathing and gas exchange, intubation is required. There are case reports of patients who cannot be intubated [e.g. severe, severe head and neck burns] and such patients *have received ECMO*.

In patients *capable of protecting* their airways with an upper GIB, retrospective studies have shown that patients who were *prophylactically intubated* had a *much higher* risk of aspiration pneumonia following the procedure. There was a suggestion of increased mortality in the intubation group as well. Nevertheless, *massive* bleeding and/or an inability to protect the airway should prompt intubation prior to endoscopy.

An airway scenario on the board exam may be *hereditary angioedema*. Consider this in a patient who has a first degree relative with similar symptoms of tongue swelling, lip swelling and upper airway edema. Additionally, these patients often present with predominant abdominal symptoms because of *peri-colonic edema*. Complement cascade is activated in these patients for unclear reasons and the *C4 level is typically abnormally low*. There is an autosomal dominant inheritance pattern of C1 esterase inhibitor deficiency such that *the complement cascade is readily activated*. There *should not* be urticarial lesions. There is frequently some precipitating agent or event such as a minor dental procedure, trauma, etc. *Antihistamines, epinephrine and steroids in the setting of hereditary angioedema have an unpredictable effect*. Attenuated androgens may help restore C1E1 levels. The use of FFP may replace C1E, but it also replaces other complement factors which may prolong the attack. In Europe, purified C1E inhibitor is available. Intubation in these patients may be challenging.

How to *verify tube placement during intubation*? The most important is direct visualization of the tube passing between the vocal cords, also: no air during gastric auscultation, bilateral breath sounds, reservoir bag compliance, bag movement, condensation, *carbon dioxide in exhaled gas*. *During cardiac arrest, there will be no carbon dioxide in exhaled gas*. If carbon dioxide returns, resuscitation is adequate.

Mallampati oral pharynx score correlates with airway grade *somewhat*. *Malampatti I* means full view of oropharynx [OP] and this correlates with *grade I* airway [fully see both cords between epiglottis and arytenoids], *Mallampatti II* can see OP, but uvula touches back of tongue and a *grade II* airway means that a portion of the cords may not be seen. *Mallampatti III* is loss of uvula with portion of OP seen, *Grade III* airway is no cords seen, space seen between arytenoids and epiglottis. *Mallampatti IV* is tongue completely occludes OP, no cords seen with *Grade IV* airway.

PREPARING TO INTUBATE

Needed? laryngoscope, always have oxygen, always have suction, medications for hypotension and cardiac arrest. You must be able to bag valve mask the patient.

Sniffing position is key, a little reverse Trendelenburg can help. Mask ventilation must be mastered. There is evidence to suggest lower lip mask ventilation improves mask ventilation – *essentially nasal versus oral bag ventilation* can help truly ventilate the patient.

There is a mortality of up to 3% during an emergent airway. The long term survival of emergent airways is 45-55%, induction can cause cardiac arrest. Pre-oxygenation is less effective in emergent airways. In healthy adults you have many minutes of apnea time.

The Intubation

After three attempts, there is a very high risk of hypoxemia, there is a 25% chance of a surgical airway, 50% have gastric aspiration, 2% cardiac arrest rate. Persistent attempts are correlated with poor neurological outcome. After 2 attempts, the 3 time must be the charm.

Gum elastic bougie can help obtain an airway, *as well* more muscle relaxants and narcotics as this likely decreases complications; an experienced attending decreases complications.

Cricoid pressure can decrease the lower esophageal tone! There is no standard practice for RSI, it is not clear that it prevents aspiration, it is done for medical-legal reasons, and it is what you do for board exams.

Induction agents include: propofol 0.5-1.5 mg/kg, etomidate 0.1-0.2 mg/kg, etc. LMA? Can be helpful, but not the right answer if a patient is vomiting. Videolaryngoscopy requires practice, perhaps maybe more than direct laryngoscopy.

Recognize differences in pseudocholinesterase levels and activities. If a patient receives a bolus of succinylcholine for intubation and has not moved in two hours. The patient may have a genetic abnormality in pseudocholinesterase *activity*. Succinylcholine is a molecule very similar to acetylcholine. *It is a depolarizing paralytic and is rapidly degraded [within minutes] by pseudocholinesterase* which is present in the synapse and the serum. If the patient is deficient in this enzyme, succinylcholine will last for quite some time. While *levels* of pseudocholinesterase may alter succinylcholine metabolism to a mild degree, the real question is *activity level* as genetic mutations can severely impair the enzyme's ability to degrade succinylcholine despite normal levels of the enzyme.

Following the Intubation

About 4% of emergent intubations in the ICU are complicated by *right mainstem insertion*. Orotracheal intubation is associated with more ETT movement and can be 'tongued' much better by the patient as compared to nasotracheal intubation; the latter is more associated with sinusitis. If there is a rapid drop in blood pressure and jump in heart rate, then think tension pneumothorax. Mucous plugging of the endotracheal tube could produce similar results, so suction should always be tried.

What about *post-intubation hypotension*? It had a 6-10% incidence with both etomidate and midazolam! It is essentially ubiquitous and you can expect it in a good portion of all patients. Always be ready with fluids and a vasopressor stick.

Etomidate - one dose can be associated with adrenal suppression for 48 hours or longer in trauma patients. There was *no* difference between ketamine and etomidate in terms of intubation outcome/hypotension. In terms of adrenal function, ketamine was better – etomidate has more adrenal dysfunction [Lancet 2009] but there was no difference in intubating conditions. Ketamine was better in terms of mortality, but *not* statistically significant. Ketamine has several active metabolites, it *can increase ICP*.

BASICS OF OXYGENATION

Generally, mode, tidal volume, rate, and other settings have modest effects on PaO2. In the ARDS Network tidal volume trial, *smaller tidal volume was associated with a decrement in the ratio of PaO2 to FIO2* [156 vs 178], despite the improved mortality!

Oxygenation & Peep

FIO2 less than 0.6 is considered nontoxic. There is some experimental evidence that injured lung may be *more resistant to oxygen-induced injury*. Try to limit exposure to concentrations less than 0.6 for less than 24 h; instead *use PEEP*, diuresis, positional maneuvers, or inhaled vasodilators.

Clinical trials addressed the potential role of higher PEEP. While each failed to demonstrate enhanced survival, all showed a trend in that direction. *Liberal PEEP typically uses PEEP above 12, but limits end-inspiratory plateaus to less than 30-35 cm H2O*. The ARDSNet trial targeted a PaO2 of 55 to 80 using different PEEP-FiO2 tables [conservative versus liberal]. On day 1 the differences in PEEP were 8-9 versus 14-15, but the trial was stopped early for futility [*same length on the ventilator, same mortality*]. The Canadian LOVS trial and European ExPress trial were both larger [983 and 850 patients, respectively] which showed similar outcomes.

The *stress-index* has been advocated to titrate PEEP. Normally the airway opening pressure rises linearly *during constant flow, volume-controlled ventilation* because respiratory system mechanical properties [compliance and resistance] do not vary much over the tidal range. If compliance increases late during tidal inflation [suggesting that lung is being recruited], the pressure-time display will be *convex [rounded] upward* (stress index < 1): more PEEP is likely to be helpful. If the pressure-time display is *concave [scooped] upward*, compliance is falling as lung is being over-distended. Perhaps PEEP should be reduced.

When the inflation *pressure-volume [PV] curve* of the respiratory system is obtained under high flows [*above 0.1 L/s*] [note, *normal ventilator flows are given in liters per MINUTE e.g. 60 L/min*] the inspiratory PV curve represents *dynamic conditions* and therefore the shape of this curve cannot speak to lung recruitment as lung recruitment is a static parameter. In addition to the static characteristics of the lung, a dynamic PV curve also includes inadvertent PEEP and the resistive components of the intubated respiratory system. This *cannot provide accurate* data as to where PEEP should be set [e.g. above the lower inflection point] because this inflection point [under dynamic conditions] *represents more than a simple recruitment threshold*.

The most valuable piece of data from a *dynamic PV curve* of the respiratory system is the upper inflection point which, if it flattens, suggests that the lungs stiffen [compliance decreases] at high lung volume [*similar to the stress index*]. The problem with this information is that it is unknown if this worsens outcome or if modifying it improves outcome.

Under dynamic conditions, *nothing reliable* may be obtained *from the deflation curve* because airway pressure is determined by expiratory flow and the resistive elements of the lung and ventilator tubing [and PEEP valves]. The only way the deflation curve can provide meaningful information is if the ventilator tube is intermittently occluded to allow the Paw to equilibrate with the alveolar pressure. *Therefore, the difference between the two curves does not say anything about the hysteresis properties of the lungs [under dynamic conditions]*.

Mean Airway Pressure

In addition to FIO2 and PEEP, *the mean airway pressure affects recruitment and oxygenation*. High-frequency oscillatory ventilation (HFOV), inverse ratio ventilation (IRV), and airway pressure release ventilation (APRV) are various ways to raise mean airway pressure.

BASICS OF VENTILATION

Carbon dioxide tension is determined by the balance between its production and alveolar ventilation. The latter is controlled by the

ventilator via *minute ventilation*. Carbon dioxide is also eliminated during HFOV through various incompletely understood mechanisms [e.g. Taylor Dispersion].

Pressure Versus Volume-Preset Ventilation

Preset, here, refers to the variable that the clinician wants to keep constant [i.e. pressure versus volume]. As below, the *mode* of ventilation refers to the *types of breaths* that the ventilator allows. A breath is composed of a *trigger*, a *limit* [or target] and a *cycle* variable. Volume preset ventilation [e.g. VACV or 'assist-control'] is *flow-limited* and *volume-cycled* while pressure-preset ventilation is *pressure-limited* but either *flow-cycled* [pressure support – PS] or *time-cycled* [PACV or 'pressure control'].

Pressure-preset modes, in theory, makes lung protective ventilation simpler by elimination of the need to repeatedly determine Pplat and periodically adjust the VT. During use of pressure-preset modes, the patient also has greater control over inspiratory flow rate which may improve comfort.

Several features of pressure - preset modes have *raised concern that lung protection cannot be assured*. Most importantly, a safe level of maximal alveolar pressure is not known. Moreover, *unless the patient is fully passive, the trans-pulmonary pressure cannot be controlled or known using pressure-preset modes*. A final limitation is that pressure-preset modes *do not* allow ready determination of the respiratory system mechanical properties.

CONVENTIONAL MODES OF MECHANICAL VENTILATION

Physiological Considerations

The pressure-volume curve of the lung is sigmoidal, over-distension at high volumes, atelectrauma at low volumes.

Total lung capacity is a trans-pulmonary pressure of about 30 cm H2O. Is it the reduction in the plateau pressure or tidal volume that benefits the lung? Remember *that tidal volume best reflects trans-pulmonary pressure* whereas plateau pressure *does not*. People who play wind-instruments generate *more than 100 cmH2O in their airways* when playing the instrument, but this does not cause lung injury, because their *trans-pulmonary pressure* [i.e. lung volume] *is normal* as they play their instrument.

Understand *time-constants.* The compliance of the respiratory system [in the passive patient] multiplied by the airflow resistance is the time-constant [TC] and multiples of TC is the time it takes for the lung to deflate by 67%, 90%, 95%, and 99%. Consider a patient with a respiratory system compliance of 20 *mL/cm H2O* and a resistance of *10 cm/1000mL/s*. How long would it take the lung to empty by 99%? The time constant is 0.2 seconds. Thus this lung would empty 99% of its inspiratory volume in [0.2 x 4 = 0.8 seconds]. This is important to know for the development of intrinsic PEEP.

What about cardiac function effects? ITP tends to retard venous return. ITP increases from spontaneous to assisted ventilation to controlled ventilation; in sick lungs it is assumed that perhaps 0.25 to 0.33 of the airway pressure makes it to the pleural pressure [*grossly oversimplified*]. If intravascular volume is low, high ITP can impair venous return, if intravascular volume is high, LV afterload reduction predominates.

Basic Breaths

Control breaths are *triggered by the ventilator*, *assist breaths are triggered by the patient*. When patient-mediated, the trigger can be a pressure trigger or flow trigger. The flow trigger *used to be more sensitive*, but now with fancy microprocessors, the pressure trigger is just as good. Many ventilators have both pressure and

flow triggers sensing systems working simultaneously. *Target* [or limit] and *cycle* are the two *other* variables [in addition to trigger] that determine the type of breath.

Volume-preset breaths classically deliver a constant flow [*flow-limited*] and volume [*cycled*] and airway pressure varies. If you set volume, you have total control over minute ventilation. By contrast, *pressure-preset* breaths have a set pressure [pressure-limited] and set inspiratory time [time-cycled] and flow and volume vary. The nice thing about pressure-preset ventilation is that the flow is variable and the patient *may be more comfortable if the patient is triggering the breaths*.

How do you *cycle* a breath? There may be a set volume [volume-preset breaths, i.e. VC and VA], time [pressure-preset breaths, i.e. PC and PA] or flow reduction threshold [pressure support].

There are five *basic breaths* of mechanical ventilation [VC, VA, PC, PA, PS]. The combination of these breaths determines the *mode of ventilation* [below].

Volume Assist-Control Ventilation [VACV]

VACV is also known as 'assist control' or 'volume control.' It is the mode used in the ARMA trial demonstrating reduced mortality in patients with ALI and ARDS; respiratory mechanics can be measured readily.

The clinician sets the minimum respiratory rate and tidal volume. The patient may go above this depending on how often they are triggering assisted breaths.

When high inspiratory effort continues during the ventilator-delivered breath, the patient may trigger a second, superimposed (''stacked'') breath (rarely a third, as well) – aka 'flow-starvation' as noted by negative deflections in the pressure tracing.

Patient effort can be increased [if the goal is to exercise the patient] by *increasing the magnitude of the trigger or by lowering VT* [which increases the rate of assisting]. *Lowering f at the same VT generally has no effect on work of breathing* when the patient is initiating all breaths.

The mode of VACV is composed of VA and VC breaths.

Synchronized Intermittent Mandatory Ventilation

In the passive patient, SIMV cannot be distinguished from controlled ventilation in the ACV mode.

The difference occurs when the patient triggers a breath.

If the triggering effort comes in *a brief, defined interval before the next mandatory breath* is due, the ventilator will deliver *the mandatory breath ahead of schedule* to synchronize with the patient's inspiratory effort [no different from an ACV-assisted breath].

If a breath is initiated *outside* of the synchronization window, *VT, flow, and I:E ratio are determined by patient effort and respiratory system mechanics*, not by ventilator settings. The spontaneous breaths tend to be of small volume and are highly variable. Most ventilators today add pressure support to these 'additional' breaths.

SIMV has been shown to prolong weaning in various RCTs.

SIMV can be composed of PA and PC breaths *or* VA and VC breaths with or without additional PS breaths.

Pressure Assist-Control Ventilation [PACV]

PACV is also known simply as 'pressure control.' In the *passive patient*, *ventilation* is determined by f, the inspiratory pressure increment (Pinsp-PEEP), I:E ratio, *and the time constant of the patient's respiratory system*.

In patients without severe obstruction (i.e., time constant not long) *given a sufficiently long TI, there is equilibration between the ventilator-determined Pinsp and alveolar pressure (Palv) so that inspiratory flow ceases*. In this situation, VT is highly predictable, based on pressure difference and the mechanical properties of the respiratory system (Crs).

In the presence of severe obstruction or if TI is too short to allow equilibration between ventilator and alveoli, VT *will fall below that predicted based on Pinsp and Crs*.

It is typically the case during PACV that alveolar and ventilator pressures do not equilibrate either at end-inspiration or at end-expiration. *Thus the maximal inspiratory alveolar pressure is generally less than the set inspiratory pressure on the ventilator and the end-expiratory pressure exceeds the set expiratory pressure* (i.e. there is auto-PEEP).

The *active patient* can trigger additional breaths by reducing the airway opening pressure (Pao) below the triggering threshold, raising the I:E ratio. The inspiratory reduction in pleural pressure combines with the ventilator Pinsp to augment the trans-pulmonary pressure and the VT. *This point leads many intensivists to be skeptical regarding the ability of PACV to ensure lung-protective tidal volumes in patients with ALI and ARDS*!

Pressure Support Ventilation

Non-invasively, pressure support is known as BiPAP. Once a breath is triggered, the ventilator *attempts to maintain Pao [airway pressure or airway occlusion pressure] at the physician-determined Pinsp*, using whatever flow is necessary to achieve this. Eventually flow begins to fall as a result of *either cessation of the patient's inspiratory effort* or *increasing elastic recoil of the respiratory system as VT rises*. The ventilator will maintain a constant Pinsp until inspiratory flow falls an arbitrary amount (eg, to 25% of initial flow) or below an absolute flow rate.

Because patients' respiratory system time-constants vary widely [so that the time for flow to fall to 25% varies widely], *many patients have to actively work to turn off* the inspiratory pressure, raising the work of breathing.

Especially in patients with exacerbations of COPD, *a threshold well above 50% is often* necessary to minimize this unintended expiratory work.

Respiratory system mechanical parameters cannot be determined readily on pressure support because the ventilator and patient contributions to VT and flow are not represented by Pao. That is, *because PS is flow-cycled [or, similarly in PC, time-cycled],* inspiration ends *before proximal airway pressure* equalizes *with alveolar pressure*; thus *measured airway pressure will not correspond to alveolar pressure*. Accordingly, these important measurements of Pplat, Ppeak-Pplat, and autoPEEP are measured during a brief, daily switch from PSV to volume-preset ventilation.

A potential advantage of PSV is improved patient comfort and, for patients with very high drive, reduced work of breathing compared with volume-preset modes.

LESS CONVENTIONAL MODES OF VENTILATION

How does *APRV* fit into this scheme? It is actually a pressure-limited reverse ratio IMV. It provides a prolonged breath to a set pressure [P-high]; it is time-cycled and *allows spontaneous breaths to occur* [IMV]; with a long I time and short E time [reverse ratio] the spontaneous breaths occur during the inspiratory phase [i.e. during P-high]. *The most effective* way to *increase minute ventilation* in APRV is to *decrease the time at P-high or T[high],* which increases the frequency of

breaths [causes more frequent cycling between Phigh and Plow]. Plow should almost always be zero [i.e. don't add traditional 'PEEP']. The rapid mahcine *expiration – inspiration* cycling of APRV creates auto-PEEP.

Understand the physiology *of inverse ratio ventilation*. The mechanism of improved oxygenation is most likely the development of intrinsic PEEP which occurs as a result of the very short expiratory time [as above in APRV]. This tends to *increase mean airway pressure*, but *reduce peak airway pressure*. As long as IRV and extrinsic PEEP lead to the same end-expiratory lung volume [i.e. the same end-expiratory trans-pulmonary pressure], the effects on oxygenation should be the same. There may be *decreased dead space* ventilation because of the prolonged inspiratory time [to allow for gas mixing] but this effect is likely modest at best.

Understand *the basics of HFOV*. The *pressure swings* in the trachea [compared to the alveolus] are *relatively* large. This occurs at a frequency of 150-900 cycles per minute. The relationship to alveolar pressure is that the pressure swings in the alveolus are as frequent, but completely blunted, i.e., *the mean pressure in the alveolus is the same as the mean in the proximal airway/trachea*, it's just that the pressure in the alveolus, compared to the trachea, is totally damped. Because each tidal breath is much lower than dead space, the mechanism of gas exchanged is clearly *NOT convective*. Carbon dioxide clearance is improved by *increasing the pressure amplitude* as opposed to frequency. The mechanisms at play are: coaxial flow, Taylor dispersion [gas mixing beyond a moving wave-front], molecular diffusion and pendeluft mixing. Which mechanism is most important is not clear, and they probably all play some role depending upon the patient underlying pathophysiology. When non-convective forces are at play, *alveolar ventilation is determined by the frequency multiplied by the amplitude [squared]*, thus increasing the amplitude has the greatest effect on CO2 elimination. Increasing mean airway pressure *does not* help with CO2 elimination, though it can with oxygenation. Changing the bias flow [the continuous flow of gas in the circuit which is oscillated] has small effects on CO2, but not nearly as much as the frequency or amplitude. The diameter of the airway can also affect CO2 clearance, *so creating a cuff leak can also lower PaCO2*. The ultimate physiological benefit of HFOV is that tidal pressure, volume and atelectasis swings are reduced. HFOV *from the perspective of the alveolus* is best described as 'CPAP with wiggle' meaning the pressure is elevated, with *small deflections about this mean*.

There are feedback controls available – for example *PRVC* on the Servovents [a.k.a. auto flow – on the Drager, also known as VC+], in an attempt to mesh the best of both worlds. It is a *pressure preset* [pressure-limited, time-cycled] mode that will vary the pressure limitation up and down based on the compliance of the respiratory system and the measured volume achieved. It is like having a little RT in your machine changing the pressure to get the right tidal volume.

ASV or *adaptive support ventilation* is only available on the Hamilton. It adjusts tidal volume for you using feedback to minimize ventilator work; further, it alters the I:E ratio to minimize air-trapping. This is a fancy, algorithm-based mode of ventilation whereby the clinician sets the minute ventilation, PEEP and fraction of the minute ventilation supplied by the ventilator. The ventilator then supplies some 'test breaths' and calculates resistive and elastic work of breathing and sets its own tidal volume and respiratory rate to minimize work and such that *there is always 1 inspiratory time constant to 3 expiratory time constants*. Clinically, ASV has been compared to physician preferences and when the clinician preferences are high lung volumes, ASV tends to select lower lung volumes

with higher respiratory rates. When low compliance situations exist, ASV tends to select higher tidal volumes than the recommended 6 cc per kg. ASV may help weaning when compared to older weaning methods, but not yet compared with newer SBTs.

New feedback controls – PAV and NAVA. *Proportional assist ventilation* – with a bigger effort, there is an increased flow [like pressure assist or pressure support], but also *more pressure* in an attempt to unload the muscles of respiration. So it responds with *flow AND pressure*. The downside is that if the effort drops, your MV drops, there are no minimums with PAVS, so the patient must be awake and cooperating. *There may be a waveform case of PAV on the boards*. Consider a patient receiving MV with *varying pressure and flow* based on *effort [estimated from esophageal pressure tracing]*. PAV or proportional assist ventilation calculates inspiratory resistance and compliance from a test breath. It monitors inspiratory flow demand, calculates the work of breathing [i.e. pressure requirements for desired flow and volume] and applies a set 'proportion of required pressure. It is *compared to power steering on an automobile*. The driver selects the distance to turn wheel and the system supplies pressure to reduce effort. Like the automobile driver, the patient must be reliable.

What *about NAVA*? It short-circuits the normal pathway between the generation of the trigger and the ventilator. It uses direct diaphragm contraction as the trigger. The greater the EMG-diaphragm contraction, the greater the breath. The studies are small and observational. There was a recent great study on NAVA and cardiopulmonary interaction in the Critical Care Medicine September 2014; it showed that right ventricular performance is less impaired during *NAVA compared to PSV*. Proposed mechanisms are preservation of cyclic intra-thoracic pressure changes characteristic of spontaneous breathing and limitation of right-ventricular outflow impedance during inspiration, regardless of the NAVA level.

INTRINSIC PEEP, SYNCHRONY AND LIBERATION

Intrinsic Peep or Auto-Peep

What *about intrinsic PEEP [PEEPi]*? What determines PEEPi? Minute ventilation, I:E ratio, & time constant. In volume control ventilation, peak and plateau pressures go up with PEEPi. In pressure control ventilation, what happens is that *tidal volume and flow decrease with PEEPi [this can be exceptionally important during PRVC as tidal volume falls with PEEPi, the ventilator can respond by increasing the pressure delivered].* Classic sign of air-trapping - expiratory flow does not return to baseline.

To fix PEEPi, you can fix one of the three determinants – decrease tidal volume [or RR], improve I:E, reduce time-constants. The best bang-for-your-buck is usually to lower the tidal volume and/or RR. *Reducing the respiratory rate will prolong the E time* and mitigate the air-trapping. Adding PEEPe will not fix the problem unless it is a triggering problem [below].

Think of air-trapping in a patient with COPD with a rising PaCO2. The effect is to increase intra-thoracic pressure and the classical signs are increasing Paw in VACV, decreasing Vte in PACV and *incomplete expiratory flow*. There may also be decreased blood pressure and high dead space with increasing PaCO2. There will be a case of COPD with increasing PaCO2 and decreasing BP and the correct answer is to reduce the RR, Vte or disconnect the circuit. In a passive patient, PEEPtot may be measured at end-expiration.

What are the other consequences of PEEPi? Well, *the circuit pressure must fall* prior to an *assisted [patient-triggered] breath*; PEEPi adds a threshold load in this situation as it raises the

circuit pressure. Put your hand on the chest and eye the ventilator. If there is effort and no breath, this is a classic sign of high trigger threshold load. You can remove the PEEPi, *or add PEEPe [extrinsic PEEP]* to lower the trigger threshold. The breath rate might increase because of the increased trigger sensitivity – *don't be alarmed*; you've done the right thing.

Ventilator Synchrony

What about *synchrony*? The response of the ventilator lags behind patient effort during both inspiration and expiration. This causes 'fighting' and increased sedation. Look at the assisted [patient-triggered] breath pattern and compare it to a control breath waveform [if there is one]. Look to the pressure graphic, it may have a negative deflection! Sometimes flipping to a pressure-preset mode can improve synchrony. PAV and NAVA have theoretical appeal.

Ineffective triggering is seen in patients with airway obstruction and auto-PEEP and is *the most common* cause of ventilator asynchrony in the ICU. There is a drop in airway pressure and a small increase in inspiratory flow, but no breath delivery. This is due to PEEPi as above, and is treated as described above.

Recognize double-triggering [DT]. The second most common cause of ventilator asynchrony. DT is seen in patients with very *high respiratory demand with a short inspiratory time*. There is a very brief expiratory phase noted, [less than half the duration of the preceding inspiratory time] and there is a second breath delivered. The drop in airway pressure in early expiration triggers another breath.

Auto-triggering is seen when there are frequent drops in airway pressure that trigger breaths [usually caused by a leak] and seen during low respiratory rates. Auto-triggering [whether pressure or flow is the trigger] *can be caused by cardiac oscillations*. This phenomenon has been studied in cardiac surgery patients who tended to have larger hearts, larger cardiac output and therefore larger effects on intra-thoracic pressure tracings. The clue is typically cardiac oscillations noted in both the pressure and flow tracings with followed by rapid [usually less than one second] breaths delivered by the ventilator. A *leak in the ventilator circuit, water in the ventilator circuit, hiccups or chest tube are other causes* of auto-triggering.

Recognize *flow-starvation [or flow asynchrony] on the ventilator*. Consider a patient who is dys-synchronous with the ventilator on VACV and the pressure waveform shows low [scooped out] Paw with negative inspiratory deflections. The flow is constant at 45 L/min and there is a *consequent long inspiratory time*. There is an 'intervention' and the next waveform bundle reveals normal pressure waveforms that are higher and higher flow rate. The EEP level of the Paw has not changed*, but the inspiratory time is shorter confirming the intervention was to make the ventilator deliver higher flow rates*. Note that flow starvation may result in double triggering as described above.

Liberation from the Ventilator

What about *discontinuation of the ventilator*? What is the best way to liberate? Pressure support? SIMV? The one that worked the best is a *technique that doesn't wean* – the daily spontaneous breathing trial technique. SBT should be *30*-120 minutes [see Tobin's editorial in the Blue Journal 'The Myth of Minimal Ventilator Settings' early 2012].

SBT via pressure support or T piece is equally effective based on the trials and 30 minutes versus 2 hours of SBT are equally effective. Note that there is data in COPD patients who *failed* T-piece and *then were immediately extubated and placed on NIPPV* that showed improved weaning outcomes. Other data reveals that patients assigned to a weaning protocol did better than

those who did not receive a protocol. Measures of respiratory muscle pressure, vital capacity, etc have been used to predict extubation success, *but they are rather poor indicators.*

When to consider vent discontinuation? There must be a reversal of ARF, the PF ratio must be above 150-200, PEEP less than 8, FiO2 less than 0.4, pH more than 7.25, minimal inotropic support, reliable inspiratory efforts. Once SBT passed – *cough is essential*, cough velocity must be more than 1 L/sec. Some perform the white card test – does a goober hit a card with cough? Also consider suctioning frequency [if more than every 2 hours probably too much]. *Less important than cough is actually gag reflex*, cuff leak and alertness. *Evidence favors excessive secretions [suctioning every 1-2 hours] as most likely to predict extubation failure*, above and beyond that of altered sensorium. In conclusion one of the most important factors, is the ability to *cough and clear secretions*.

The use of a cuff leak to predict *post-extubation stridor* is contentious with one study showing that a returned volume within 110 cc of the tidal breath predicted post-extubation stridor. The risk factors for post-extubation upper airway obstruction are: female, trauma, repeated intubations, and length of intubation duration.

There are conflicting data regarding *the use of steroids prior to extubation*. The risk of post-extubation laryngeal edema is variable [2-22%] and the rate of *reintubation is less than 5%*. It can be difficult to predict which patients will have this problem. Female gender and traumatic injury increase the risk of post-extubation laryngeal edema. In one trial *patients were indiscriminately* given 80 mg of MP 12 hours prior to a planned extubation and there was less clinically significant laryngeal edema and less re-intubation due to laryngeal edema [*8% versus 4%*]. Some don't believe these results. One more recent trial gave steroids only to patients who had a reduced cuff leak [the difference between the inspiratory and expiratory volume should be *more than 10%* of the tidal volume or 110 cc] but their cutoff was less than 24% of the total tidal volume and this resulted in reduced edema and reintubation [*30 versus 8%* - these numbers still seem high to me].

The Kress trial looked at *daily sedation vacations* and found that *mechanical ventilation was reduced by 2 days, ICU time by 3.5 days and benzodiazepine doses were cut in half* [not true for propofol]. The amount of self-extubations was *not* different between the two groups. However, *the ABC trial in Lancet, 2008* showed that those patients awakened and given an SBT *did self-extubate more, but there was no difference in re-intubation rate*. Continuous infusion of sedatives tends to provide a more steady state concentration in the blood than bolus dosing.

Why does someone fail an SBT? Search for causes, try again in 24 hours – in the meantime there is little benefit to changing settings.

Recognize *that a Passy-Muir [PM] valve can cause asphyxia and respiratory arrest if used in conjunction with a cuffed tracheostomy*. It makes exhalation impossible. Removal of the PM valve should always be attempted first if this is a consideration [rather than drop the cuff] because the internal diameter of an un-cuffed or deflated tracheostomy can still obstruct the airway. Only *removing the PM valve* will be fail-safe. The incidence of aspiration has been shown to decrease with the use of a Passy-Muir valve [compared to tracheostomies without a PM valve, *not* compared to no tracheostomy] because it may promote normal expiration during gluttation. *There is also reduced secretions and improved cough with the Passy-Muir as compared to standard tracheostomies*. Air escaping through the nose and mouth likely contribute to secretion evaporation, as well as the improved cough response. In patients who are unable to be fully liberated from mechanical ventilation, they must

be able to clear secretions, have an adequate cough, have normal mentation and be hemodynamically stable before being candidates for a PM valve.

ARDS

ARDS must be of an *acute onset*. The old definition of ARDS required a PF ratio of less than 200 [less than 300 was acute lung injury]. There must also have been bilateral CXR infiltrates and there should have been no evidence of LA hypertension.

The *new, Berlin Criteria* get rid of ALI and define mild [300-200], moderate [200-100] and severe [less than 100] ARDS by PF ratio. Also, acute *requires 7 days* of symptoms onset or less and there is *no need to absolutely rule out elevated left atrial pressure* by any means – other criteria such as PEEP and pulmonary compliance, etc. *did not predict clinical outcome*.

Primary [or pulmonary] ARDS tends to be patchy, *less PEEP* responsive [see Blue Journal Gattinonni article 1998]. If it does not evolve to SIRS/MODS then the outcome is better than secondary ARDS. Secondary [or extra-pulmonary] ARDS occurs from severe hypotension, pancreatitis, abdominal sepsis – tends to be *more diffuse, more PEEP responsive*, but somewhat worse outcomes.

The initial indices of oxygenation [PF ratio, etc.] are NOT related to ARDS mortality. In fact, in the ARDSNet trial, initially the patients with the *lowest PF ratios* tended to have *the best outcomes*. The most common cause of death is worsening MODS and sepsis. Any non-pulmonary organ dysfunction, *especially liver as well as the failure to improve after 7 days of treatment* were negative predictors of survival.

So there is a disconnection between physiology and outcomes. ARDSNET improved outcome, but made gas-exchange worse! Small tidal volumes resulted in worse gas exchange and worse compliance [perhaps from increased atelectasis] – *until the third day* – and then things get better. There is clearly respiratory acidosis with small tidal volumes. There is some evidence that respiratory acidosis *helps cell injury*. Perhaps by unloading oxygen from hemoglobin.

The mortality rate for ARDS has decreased since the early 80s [above 60% or so] to mid-30% now in early 21st century. There has been *no reduction from 1994 to 2006*! Sepsis is the main disease in ARDS/ALI. It is a disease of old people with pneumonia – which is probably why mortality has plateaued. In 80 year olds, there is a 50% survival rate in ARDS.

A portion of patients who survive long bouts of ARDS, suffer *from chronic critical illness* [generally defined as respiratory failure lasting weeks – see Blue Journal concise clinical review 2010] and require tracheostomy and LTAC placement. In these patients: *most are not* freed from mechanical ventilation [reported liberation rates: 30 - 50% and if success is achieved, it's almost always within 60 days]; at *the end of one year*, *fewer than half will be alive* [32 - 52%]; and *12% will be alive and independent*.

How can ARDS be treated? Unfortunately, there is very little to be done other than blocking manifestations to buy time for the patient to improve. The most important thing to do is *not* to make things worse. Appropriate infection management as quickly as possible is very important, as well as surgical intervention/source control where present. Minimize transfusions, minimize excess fluids, and reduce aspiration risk.

Treatment

What has failed in ARDS? Anti-endotoxin antibodies, NSAIDS, anti-TNF, ketoconazole, lysophylline, PGE. Why is there so much failure? It may have been that the human spectrum of ARDS is exceptionally heterogeneous, so drugs or therapies in a very specific animal population

with a certain pulmonary insult or in small clinical trials may not be applicable to all patients with ARDS.

It is known that in ARDS there are pulmonary microthrombi and a couple of large sepsis trials have looked at APC [xigris] which were initially positive, have now fallen out of favor.

When does one use *steroids in late ARDS*? There is no right answer, some people do it. It was once thought that ARDS would respond to high dose steroids [3-4 grams per day] it seemed to make things worse in trials in the early 1990s. Then steroids in ARDS seemed to *get patients off the ventilator 2 days early*, but many went back and there was no change in mortality. The steroids were weaned off very quickly, so is it that they were tapered off too quickly or did the patients have too much myopathy? The answer is unknown.

What about *immune-nutrition*? The addition of combinations of arginine, glutamine, nucleotides, omega 3 fatty acids of feeding formulae. There seemed to be a reduction in infectious complications [2001 JAMA]. Then there were three RCTs since 1998 *all three were positive* – ARDS patients came off the ventilator and had a mortality benefit. By the mid-2000s it was essentially a recommendation with grade A evidence.

The *ARDS Net OMEGA trial from CCM 2009* and stopped for futility with more than 500 patients [more than all three of positive trials combined]. The *control group* in the ARDS NET OMEGA trial had *no fat*, only carbs. In the three positive trials, the control groups all had omega 6 fatty acids [did this cause harm?] as O6 fatty acids are known to be pro-inflammatory. The answer isn't known.

So how do we buy time in ARDS then, if we cannot mitigate the mediators? Recall the hysteresis curve – not too high [volutrauma] not too low [atelectrauma]. Keep the *tidal volumes low* – keep the [usually estimated] trans-pulmonary pressure less than 30 cm H2O [assuming normal chest wall compliance]. In the seminal ARDSNet trial [ARMA] the respiratory rate was higher in the *physiologically normal* tidal volume group [i.e. 6 cc/kg Vte group]. Also in this group, PaCO2 were higher, plateau pressures lower, *PF ratios and static compliance were lower*; but most importantly, the mortality was also lower in the 6 cc/kg group. The NNT was 10. Patients on the lower tidal volume were off the ventilator earlier. The ARDSNet [ARMA] trial revealed an ARR of 9% for those patients who received both a volume-limited [5-7 cc/kg IBW] and pressure-limited [Pplat less than 30 cm H2O] approach with ARDS.

While *there is a direct correlation between plateau pressure and mortality*, in the ARDSNet [ARMA] trial, the incidence of pneumothorax was *neither related to end inspiratory nor end expiratory airway pressure [probably because this is once removed from the trans-pulmonary pressure]*. In normal lungs, tidal capacity is reached at a *trans-pulmonary* pressure of about 30-35 cm H2O so this is used as the upper limit for the plateau pressure; *but it is tidal volume or volutrauma that is the culprit, not barotrauma*. Interestingly, very low tidal volumes with extra-corporeal carbon dioxide scavenging did not show benefit on mortality.

What is more important, plateau pressure or tidal volume? *Even when the plateau pressure is kept less than 30, keeping the tidal volume as low as possible seems to confer mortality benefit*. CCM review – patients without any ALI at outset, there was a dose-response relationship between tidal volume received and the progression to ALI. Basically the dictum should be that *no Pplat is safe* and keep volumes low.

PEEP AND ARDS

Increasing PEEP is an attempt to recruit atelectatic, consolidated lung. Too much PEEP

however, will augment right ventricular afterload as well as increase the risk of lung fracture. The average reduction in cardiac output with PEEP can be 13%.

What's the best PEEP? There were three big trials that addressed this. The ALVEOLI trial [part of the ARDS Network] was the American trial in NEJM [2004], LOVS was Canadian in JAMA [2008], EXPRESS was French in JAMA [2008], 2300 patients in total. All three RCTs in high versus low were *negative for high PEEP* in terms of *survival*. The details are these: the *intervention group was 4-6 cm H2O above the control*. Interestingly, *survival was higher* in the EXPRESS *trial for high PEEP in ARDS* [not ALI]. There are more recent trials showing *that if* the lung can be recruited, there *is benefit* to high PEEP. In some patients, high PEEP [high teens] there will be harm, in others, there may be benefit. Overall, the trend *suggests high PEEP is better*. The Canadian trial was the largest in 2008 with almost 1000 patients. The meta-analysis in JAMA 2010, found that *high PEEP does reduce mortality in sicker patients* [lower PF ratio], whereas the *high PEEP in ALI [PF 200-300] patients seemed to do worse with high PEEP*. If the lung injury is less severe, the high PEEP may harm the good lung. In the pooled-analysis, however, higher PEEP seems to only improve PF ratio.

The use of PEEP to keep the lungs above their lower inflection point has been advocated to reduce atelectotrauma, but *these measurements are difficult to make accurately and studies have been inconclusive* [see discussion above].

Understand *patent foramen ovale*. Autopsy studies have shown an incidence of *20-30% of all people may have some degree of PFO*. If a patient is given 10 cm of PEEP, there is no change in cardiac output, a decrease in PaO2 and an *increase in calculated shunt fraction, think PFO*. PEEP per se *should reduce* shunt fraction as it increases alveolar ventilation. In theory, excessive PEEP can increase dead space and then redirect flow causing venous admixture and potentially shunt but this is a modest effect at best.

Adjunctive Therapies in ARDS

When you are failing on maximal ventilator management, what is the next best step? *APRV* does recruit lung & improves PF ratio. It is also known upside down SIMV, or comfortable PCIRV. The long I time can recruit alveoli. There is little evidence to suggest that it improves outcome.

HFOV is basically CPAP with 'wiggle' in the alveolus. The wiggle causes CO2 and oxygen movement up and down the tracheobronchial tree. A 2010 meta-analysis from 6 peer reviewed studies showed reduced mortality, less barotrauma, PF ratio improves. But this does not include the most recent NEJM article which *suggested harm* [see Slutsky commentary NEJM spring 2013]. This mode of ventilation should now generally be avoided in ARDS.

What about *ECMO*? CESAR, 180 patients with severe ARDS and there was a suggestion of improvement with ECMO but this trial had many methodological problems.

What about keeping the lungs dry? The *FACCT trial* [NEJM 2006] showed that there was no increased shock, no increased renal failure, but over two days alive and off the ventilator. *The FACCT protocol can only be instituted when the patient is stable and no longer in shock.* Specifically, the FACCT trial looked at conservative fluid versus liberal as well as central venous versus PAC. *PAC versus CVC arm showed that there was no difference in management utensil*. In the conservative arm there was less fluid and more Lasix. The net fluid balance in the conservative arm was less than the liberal arm. There was *CVP separation [8 versus 11-12]; in the PAC arm Ppao was 13 versus about 16.* Tidal volume the same, but PEEP and respiratory rate were slightly lower in the conservative [Lasix]

arm. *Again, there was no difference in mortality, there were 2.5 days fewer alive and off ventilator in conservative arm and more time out of ICU by about 3 days*. In the group that got less fluid and more Lasix, there was less CNS dysfunction [? Less sedatives or less cerebral edema?] All other organs the same.

What about *paralysis*? Papazian in NEJM 2011. *24 hours of paralysis*, and then 3 weeks later there is a mortality benefit. How can this be? The reason is not known. Does paralysis improve synchrony? Decrease the trans-pulmonary pressure and improve mortality in ARDS? Be wary, however; consider a patient with ARDS getting PACV, *triggering all breaths*. With NMB, there is volume loss on following breaths. There is loss of spontaneous effort, not bronchospasm, mucus plugging or tension pneumonthorax. In pressure assisted ventilation, if the patient is working with the ventilator and the patient's contribution is removed, the patient will lose volume and Mve.

What about *esophageal balloon monitoring*? Consider a patient with obesity with high Pplat, but *end-inspiratory esophageal* pressure is 17 cm H20 [normal less than 5 at end-inspiration] & Pplat is 37. What to do? Just leave it alone. The trans-pulmonary pressure is only 20 at end-inspiration [37 minus 17]! *At Duke, they raise their Pplat to BMI. That is, if BMI is 40, Pplat can go to 40!*

Understand *basic effects of prone positioning*. The time-course of when to prone a patient is not known. Proning a patient typically results in an immediate improvement in the PF ratio, but the effect may be delayed as well. *There is no relation between the severity of ARDS and the degree improvement in PF ratio when a patient is placed in prone*. Sometimes the beneficial effect of prone may reverse as the abnormal ventral areas of the lung shift anteriorly. Prone positioning doesn't change perfusion of the lung much, but *closing volume is likely reduced* in the dorsal lung units when compared to the supine position. In 60-75% of patients with ARDS, prone positioning improves the PF ratio. In animal models, pronation has been shown to protect against the development of lung injury, but this unknown in humans. *The time when to flip someone and when to return to supine is not known nor is the frequency of flips known*. Prone does increase the risk of new pressure sores on the ventral position of the body. In a 2001 study by Slutsky, the prone position for *7 hours per day* for 10 days had no effect on mortality, but did improve mortality in the most severe ARDS. *However, the PROSEVA trial in May 2013 showed that in patients with a PF less than 150, prone for 16 hours per day, every day, for up to 28 days or longer*, improved mortality. This resulted in a 17% absolute risk reduction in mortality for the prone position. A meta-analysis in the CMAJ this past summer echoed these findings especially the 16 hour rule.

What about iNO? *iNO selectively dilates well-ventilated portions of the lung to improve VQ and this improves oxygenation*. It also tends to lower physiological dead space for a similar reason and *carbon dioxide elimination is improved* but this effect is seen only in patients with a pre iNO value of *PaCO2 more than 50 mmHg*. There is no change in overall mortality. At small doses the risk of Met-Hb is low. iNO at high inhalational levels increase the risk of methemoglobinemia. *Increasing from 20 ppm iNO to 80 ppm will not improve mortality, shorten ventilation time or increase the PF ratio*. *20 ppm is basically the maximal dose with little effect above that level*, certainly not 80 ppm. At 80 ppm there is an elevated risk of methemoglobinemia or nitrogen dioxide toxicity. In 75% of patients receiving iNO [with ARDS] there will be a modest improvement in their PF ratio. The average increase in the PF ratio is 16 mmHg. There may be a higher risk of renal replacement in patient on iNO. It is argued that routine use of iNO in ARDS patients should not be done.

Continuous lateral rotational therapy was developed in the late 60s and employs special beds that can only be rented and not purchased. The *rotation is 40 degrees in each direction* and studies [all funded by the bed makers] have shown numerous beneficial effects though no large, rigorous trial has been performed.

NON-INVASIVE POSITIVE PRESSURE VENTILATION

What feature of NIV with pressure supported breaths causes the most problems? *Flow cycling causes the most problems*. Pressure support delivers a flow to a pressure target. When the flow reaches a minimum value, the *breath terminates based on flow cycling*. The problem occurs because *of the leaks* inherent in facemasks and particularly bad if the patient *has a BPF* [common board scenario]. So breath delivery will be prolonged. Sometimes triggering mechanism may not be as sensitive. There is *no set inspiratory time with pressure support*.

Pressure support ventilation with variable flow [like NIPPV] tends to interact with the patient a little better. Comparatively, pressure-ACV allows a back-up rate and allows inspiratory time selection. Having control of the I-time will allow the clinician to address a leak. By contrast, NIPPV or PS, which gives variable flow control, and the patient controls I-time. The interface is important, the larger the mask can cause more problems in terms of leak.

The strongest evidence base for NIV is with AECOPD; Asthma has been disappointing. If a COPD patient can protect the airway, but fails an SBT, *NIV can be attempted*. Two general scenarios – one, you failed to correctly predict that a patient would be liberated from invasive ventilation, should the patient be re-intubated or tried on NIV? There is data to support the use of NIV in the COPD population. This jives with the data about NIV pre-intubation. But if the patient cannot protect their airway, cannot cough or clear secretions, then – back to el tubo.

Patients must be monitored closely while on NIPPV. *Improvement in PaCO2 and pH within 30 minutes to 2 hours predicts success* [avoidance of intubation and death]. A *higher level of consciousness* at presentation also predicted success in one trial.

There is some evidence for failed extubations and heart failure. The end-point is typically avoiding intubation. Pulmonary edema has fairly good evidence in terms of CPAP – it improves gas exchange and prevents intubation [C3PO Trial in NEJM]. The addition of inspiratory support during pulmonary edema seemed to make people more comfortable, but there was suggestion that this may increase MI risk, but this was probably a fluke; therefore, BiPAP is an effective form of therapy during pulmonary edema.

What about acute hypoxemic RF [e.g. PNA, early ALI]. There isn't much data supporting its use here. NIV does seem to prevent intubation in the transplanted and immunocompromised for some unclear reason.

What about NIV in the chronically hypercapneic patients? The thought is letting the respiratory muscles 'rest' at night with NIV. Studies show that the PaCO2 is lowered during the day, but there are little good clinical data otherwise [this goes for neuromuscular, sleep disordered breathing, chronic COPD].

Starting NIPPV. Start low, titrate inspiratory pressure to patient comfort, can start with 5-10 cm H2O of PS. Don't go above 20 cm H2O, this blows open gastro-esophageal junction. Titrate PEEP [EPAP] per triggering and patient effort. PEEPi can be detected with an esophageal pressure probe, and inspiratory threshold load can be seen. NIV requires additional time from the RT, not really the RN. The first 8 hours of NIPPV requires 100 minutes to establish a

rapport between the patient and the ventilator. The complications of NIV are: leak, discomfort, eye irritation, drying, congestion, gastric insufflation, hemodynamic compromise.

LIFE-THREATENING ASTHMA

Life-threatening asthma [LTA] is defined as: respiratory arrest, need for MV, pH less than 7.3 from retention, LOC. Ultimately as a result of intense airway spasm & mucous congestion.

How many people die of asthma in the US every year? There are about 5000 deaths [ARDS is more than 100,000]. There are 1.5 million ED visits for asthma each year in the US. About one in 5 are admitted and 4% of those admitted require ICU level care. African-Americans have twice the average mortality rate and ED/inpatient asthma care and account for 50% of the total cost of asthma.

There is *rapid onset LTA* [type 2] where people essentially die within 2 hours. Slower onset [type 1] is more than 2 hours in presentation.

Asthma Treatment

Bronchodilators – IV or inhaled? MDI or nebulization? *Properly aerosolized beta-agonists are better than IV*. An MDI versus a nebulizer are *equally effective if the patient can work with the MDI/spacer*. Remember that proper MDI use requires expiration to FRC, inhalation of the drug via a spacer *to TLC* and *holding for 10 seconds*. High volume nebulizers can deliver higher doses with *tidal breathing*. The standard dose by nebulizer is several fold higher than the MDI, so the patient can breathe tidally, *the efficiency is therefore quite low*, but the patient can breathe slowly.

What about dosing? Continuous usually requires 5 mg per hour. There is suggestion that continuous is slightly better – the patients should be closely monitored.

What about anti-cholinergics? There is reduction in hospitalization, improved PEFR and reduced costs with the use of inhaled anti-cholinergics.

The use *of steroids* – they work; multiple studies have shown steroids to be beneficial especially in severe asthma. IV or PO? They both have equal effects – the bias is to give it IV, *but the literature shows that the oral form kicks in at the same time as IV*. What about steroids by MDI? This method is possible if the patient can cooperate by MDI as described above [holding for 10 seconds].

What about the use of *oxygen*? It is helpful if low, but the PaCO2 can rise as it does in COPD [BMJ. 2010 Oct 18;341]. Target saturations in the low 90s. The reason for the worsening hypercapnia is due to: *respiratory muscle fatigue, diminished minute ventilation from hypoxic drive, worsening VQ mismatch from release of hypoxic vaso-constriction, and the Haldane effect*. The biggest contributor is the VQ mismatching. The *release of the hypoxic drive to breath is a small and transient reason for CO2 retention* in these patients. There may be a board's question where a CO2 retainer is given zolpidem for sleep. It is *not* the ambien that is causing the carbon dioxide retention.

Magnesium blocks muscle contraction, there is a Cochrane review favoring IV magnesium in severe asthma.

What about the use of *mechanical ventilation* for the patient failing the aforementioned therapies? There are special asthma problems on the ventilator – avoid VILI. With airway obstruction there is heterogeneity of time-constants, and therefore there may be over-distension of normal parts of the lung. Therefore, treat like ARDS to prevent over-distension. There is the problem of PEEPi as well. All the pressures in the chest will rise with PEEPi. This will cause the plateaus to rise. It increases the triggering load [see above discussions].

A *respiratory acidosis rarely causes a lot of harm*, and there is some literature to suggest that it may improve outcome. It's OK to have a respiratory acidosis if it protects the lung. So sacrifice some minute ventilation.

Triggering dys-synchrony can be visualized by a delay between the drop in the esophageal pressure and airway pressure. What is the *normal delay* between the *pleural pressure* and *airway pressure*? *It moves at the speed of sound [MACH1] – super fast*. So pleural and airway pressure should drop at exactly the same time. The application of extrinsic PEEP will not change the total PEEP, but it will help the trigger load.

What about *heliox*? It is a low-density [but high viscosity] gas compared to air and it may reduce PEEPi. It has never been shown to improve outcomes. It will foul the monitors as most monitors are calibrated for air/oxygen and it's unpredictable. *Heliox will decrease the output of nebulizers* because of a decrease in particle size and therefore inhaled mass of the nebulized drug. *Flow or dose of nebulizers must be increased when combined with heliox* to maintain the same nebulized output. The reduced *density* of helium will convert some turbulent flow to laminar flow [via Reynolds number] and also reduce the driving pressure required to move turbulent airflow itself. These latter effects likely *increase the deposition of drug delivery* via inhalation and improved gas exchange. Interestingly, carbon dioxide diffuses better through helium than air which aides in carbon dioxide excretion. There is evidence in spontaneously breathing patients with severe airflow obstruction [COPD] that there are clinical benefits with heliox [even though the viscosity of Heliox is greater than air]. *The greatest improvement in flow [reduction in effective airway resistance] occurs with a helium concentration of 40%, and flow increases linearly to helium of 80%*. Most departments have heliox-oxygen mixtures in 40-60% concentration for hypoxemic patients [higher FiO2]. If the patient is not hypoxemic [e.g. a central airway obstruction] then a 20% O2-80% He mixture may be used.

One last mechanical ventilation issue. *Aerosols are retarded by the endotracheal tube*. There needs to be extra-dosing/very high doses in the mechanically ventilated patient. The MDI may be used if the patient on the vent is paused, but there still needs to be more than 2 puffs, probably 6-10 puffs. Also, make sure the MDI is in the inspiratory limb so it's not exhaled away.

Outcomes of Life-Threatening Asthma

Type 2 [rapid] needs more steroids, fewer hours of MV, *lower* death rate. Slow or type I is the opposite. If you are young and intubated for asthma, six year mortality is quite low, but if you are older survival is only 60%.

PULMONARY EMBOLISM

Basics of Diagnosis & Risk

Stasis, vessel wall injury and hypercoagulability are Virchow's triad – flying over an ocean in economy class, compared to business or first, there is an *increased risk of clot*.

What is the relationship between temperature and PE? The *vast majority of patients [86%] are typically without fever*, once above 103 degrees, PE was found in less than 2%.

What about the ECG? A *new RBBB is concerning especially in a hypotensive patient* – other features include: S1Q3T3, right axis deviation, most common feature is sinus tachycardia.

On CXR, a wedge-shaped pleural-based infiltrate is known as *Hampton's Hump*, there may be atelectasis with parenchymal densities, enlarged right descending PA [marker of PH], decreased vascularity, cardiomegaly, but also *normal in up to 25%*.

Troponin levels, BNP levels do correlate with severity of RV dysfunction. Negative troponins are a powerful predictor of survival; so is a negative BNP. *In contrast to a positive troponin, a positive BNP does not predict poor outcome*. In a patient *without underlying* cardiopulmonary disease, *50-60% of the pulmonary vasculature must be occluded before pulmonary hypertension arises*, this is why there may be a totally normal RV on echo and by ECG. So a normal right heart on TTE does not rule out PE, it may suggest PE, or it may diagnose or exclude alternative etiologies. RV dilation, RV HK, shift of the IV septum, dilated PAs, dilated IVC may be seen on TTE. *If there is hypotension from PE, there must be RV findings*.

A normal ABG does not rule out a PE. 38% of angiographically documented PE, had *completely normal ABG*.

The d-dimer [latex agglutination is the old one] the new rapid ones are useful *if the d-dimer is not elevated*.

The use of end-tidal CO2 may be helpful is there is a sudden, abrupt drop in ETCO2 which suggests an acute PE – from the loss of cardiac output; successful thrombolysis of the PE will result in an increase in ETCO2.

Ventilation perfusion scans are of good value in non-intubated patients with a normal CXR. Looking for large, segmental defects in perfusion [6 view study is what is needed]. Most V/Q scans are of intermediate probability.

Computed tomography of the lung has multiple names [e.g. CAT scan, CT scan, CT angiogram, spiral CT, helical CT, multi-detector CT]. The CT scan *may detect clots into the segmental arteries*. The sub-segmental arteries are more difficult to see, but clots can be there as well. Treatment of sub-segmental PE is a controversial topic. Negative studies are negative when combined with other clinical /imaging parameters. PIOPED II evaluated CT angiogram, if angiogram positive then treat, if negative, but high clinical pre-test probability then there is diminished predictive power.

A negative bilateral LE US does not rule out PE. A majority of patients with PE by CT have negative LE ultrasounds.

27% of patients had CT angiogram contra-indications [high creatinine is the most common cause]. PIOPED III looked at MRA/MRV for PE – it is technically inadequate for the diagnosis of PE. Very short breath hold, new MRI technology may improve this.

Treatment

It is safe to withhold treatment is there is a low pre-test probability and the d-dimer is negative. AC with heparin should be used for at least 4-5 days as transitioned to Coumadin regardless of the INR [*the INR will become therapeutic prior to Coumadin protection*].

100 mg of tPA IV over 2 hours is the dose for treatment of PE if using thrombolysis. Indications for tPA is persistent hypotension, severe, persistent hypoxemia maybe. There is expert opinion for front loading a patient who is actively dying – that is front load with 40-60 mg and then the other half over 2 hours.

The *use of half-dose for sub-massive PE is still controversial*. Based on the small *MOPPETT II* trial, it may improve long-term RVSP by TTE. The [ACCP] 2012 consensus guidelines suggest systemic tPA in sub-massive PE patients only if there is a high risk of developing into massive PE [a grade 2C suggestion based on low quality evidence/expert consensus]. There have been a couple of recent trials including: *TOPCOAT [U.S.]* which is a much smaller study compared to *PEITHO* [*European* - 12 times larger with 1,000 patients]. In TOPCOAT there was no mortality benefit as also seen in the PEITHO study, but the sample size was too small to make definite conclusions about mortality or bleeding risk. The

follow up was little longer (90 days vs 30 days in PEITHO), but it *difficult to recommend systemic tPA in sub-massive PE unless patients are in impending hemodynamic collapse*.

Mechanical disruption or surgical interventions may be considered, when the patient has contraindication to medical thrombolysis.

The IV septum can be compressed during PE. The IV septum may be used as a marker of fluid resuscitation. Keep the aortic diastolic pressure adequate which is the coronary pressure head to the right heart. Inotropes should be used, *less fluids [limit 500 cc to 1L]*. Always think about filter placement, upper extremity clot is felt to be less of a problem for hemodynamic instability.

When *IVC filter*? Contra-indications to AC, onset of bleeding, ongoing clots, hemodynamic instability in patients who will not be given tPA. *Patients with filters should be anti-coagulated when possible*; returning to an active life-style is important as filters increase DVT risk. Also, retrievable filters should be considered. 40-120 days may make removal difficult.

In calf-vein thrombosis, only AC if there are symptoms. If no symptoms, and no longer term risk, probably no treatment, consider serial US exams. For upper extremity thrombus it is now recommended to provide AC! *Not necessary* to remove catheter, as you can treat through the catheter. The patient may ambulate with PE/DVT, unless there is symptomatic DVT, then this should resolve prior to ambulation.

COMMUNITY-ACQUIRED PNEUMONIA FOR THE BOARDS

The CAP pathogens tend to be somewhat esoteric on the board examination; CXR findings can be too.

Recognize that the *bulging fissure sign* is not pathognomonic for klebsiella and that antibiotic coverage should not be tailored based on radiographic findings. Consider a patient with severe sepsis; broad spectrum antibiotics should remain until the patient improves. The bulging fissure sign is most commonly seen in klebsiella pneumonia, but can commonly be seen in streptococcal pneumonia as well. Further *it has been reported in acinetobacter infection as well as TB, H flu and Yersinia pestis!*

RSV

RSV has significant morbidity and mortality in elderly and transplant patients. There is one serotype with two subtypes A/B. RSV is highly seasonal and reinfection is exceptionally common. Fomites are the way it is transmitted and there are hospital and ICU outbreaks.

Individuals can be infected more than once during the same virus outbreak. The *DFA or EIA for RSV is not very sensitive*. The rapid antigen test is terrible in adults, the culture is slightly better [40-65% sensitive] but takes days. Antigen tests of the upper respiratory tract can be negative while BAL positive. RT-PCR has high sensitivity.

Severe disease may occur in immunosuppressed patients like lung transplant or bone marrow suppression; early treatment of URI may prevent progression to viral pneumonia. *Secondary pulmonary co-infection with bacteria un-commonly occurs with RSV*.

In selected adults, *ribavirin may be helpful, Immunotherapy with IVIg may be helpful*. But, inhaled ribavirin is a challenge to deliver and IVIg is expensive and has not been shown to change outcome.

INFLUENZA

Influenza can be spread by large droplets within 6 feet. Certainly hand contact. Aerosol from NIPPV may spread influenza. Incubation is 1-4 days, *virus shedding may occur 24 hours prior to symptoms and through days 5-10 of symptoms*.

There may be prolonged shedding in severe disease especially in those with co-morbidities, those on steroids, and immunocompromised hosts who *may shed for weeks to months*.

About 25% of patients with influenza develop pneumonia, fever is nearly ubiquitous. Influenza itself can uncommonly cause shock. The RT PCR for influenza is the most rapid and most specific. All means of testing can detect A and B types. *Rapid tests are immunoassays* that are positive or negative, but sensitivity and specificity are not great. Sensitivities range from 10-80%! Specificities much better 90-95%. *So a negative RIDT does not exclude influenza*.

Rimantadine is not effective against B influenza. Zanamavir gets both types. *Oseltamivir and Zanamivir are the treatments of choice*. 300 elderly patients with influenza in Canada. Those who went to the ICU had a 50% mortality. *Early use of oseltamivir and early ED visit improved outcomes*.

Do steroids work in the severely ill with influenza? There were 5 studies done retrospectively with many confounding factors that *favor not giving steroids*. Primary influenza pneumonia and secondary bacterial pneumonia are the big complications.

Pregnant women and obese patients are at risk for complications as well as the common causes for bad outcome [e.g. old, cardiopulmonary disease, co-morbidities]. Mortality in 2009 H1N1 pandemic was 17%, 39% if on ventilator. Shock was also quite common. The *pandemic influenza stains affect the entire tracheobronchial tree* [1918 H1N1 and 2009 H1N1], but the seasonal influenza does not do this.

Fungal Pneumonias

Recognize and treat *blastomycosis*. The scenarios will often describe a persistent pneumonia unresponsive to multiple rounds of antibiotics with a specific geographic locale. Consider a *patient in Chicago* with pulmonary and CNS symptoms. There is little on history, however, to differentiate blastomycosis from histoplasmosis other than blasto's penchant for the CNS [as well as skin and bones]. *Blasto* clues are often *skin lesions or infection of one's dog*. Blasto itself in the early days was known as 'Chicago disease.' Stiff neck is rarely seen in fungal meningitis and this total clinical picture is somewhat consistent with TB, though the rapid progression of symptoms argues against it. Blastomycosis and Histoplasmosis *do not* cause peripheral eosinophilia and blasto is a budding yeast. Blastomycosis is asymptomatic in 50%. It is treated with *itraconazole and amphotericin* depending on severity. One answer option may be caspofungin for treatment, *but echinocandins are not adequate for the treatment of endemic fungi or aspergillus*. Caspo should really be reserved for bad candidemia. Further caspo does not enter the CSF.

Histoplasmosis is without symptoms in more than 95% but can cause a plethora of symptomatic syndromes including acute and chronic pneumonia, acute and chronic disseminated disease, fibrosing mediastinitis and cavitary pneumonia. Like blasto, histo is treated with itraconazole or amphotericin depending on severity.

Sporotrichosis causes dermatitis in immuocompetent patients and pulmonary and disseminated disease in immunocompromised patients. Pulmonary sporotrichosis usually causes upper lobe cavitary disease [so too can blasto and histo].

Another scenario may be a patient who has traveled throughout Southern Ontario, Tennessee and Alabama [blasto], Iowa and Ohio [histo] and Arizona/California [cocci] and develops bilateral pulmonary infiltrates and respiratory failure after being given a course of prednisone. If there is peripheral eosinophilia and/or large spherules on lung biopsy, these

clinch the diagnosis of *coccidioidomycosis*. Cocci is typically asymptomatic, but can cause a CAP like picture. Up to one-third of CAP syndromes in endemic areas are actually due to this endemic mycosis. Asians and African Americans have a higher risk of disseminate coccidioidomycosis. Cocci is treated with fluconazole or ampho depending on severity. It does not respond to echinocandins.

Tuberculosis

Fun facts: the rate of TB in the UK is about 4 times that in the US, surgery may be used as an adjunct for resistant TB and HIV is the most important risk factor for progression of latent to active TB.

1.7 million people die each year in the world from TB. In the UK there is much easier travel from high risk populations. Sick patients with TB in the ICU have a very high mortality – they die of multiple organ failure and shock. Note that disseminated TB in the ICU can present with 'gram positive rods' in the blood, because TB is well-known to enter the blood [that's how it disseminates] and it is a gram positive rod.

The normal response of the body is to *form a granuloma with central caseous necrosis* and this sits in a precarious balance and is altered by nutrition, immune state, drugs, HIV, etc.

'*HIV is the fuel on the fire of tuberculosis*.' HIV patients can't really form granuloma and have higher burden in the airway, they cavitate and collapse into the lung. HIV is the most important risk factor in the US for progression to active disease.

Culture is the gold standard for diagnosis - AFB smear provides an indication of infectiousness, and *TST and IGRA cannot distinguish between active and latent disease*. The TST depends upon degree of induration. The QFT gold depends on lymphocytes from host reacting to known antigens of TB. IGRAs are likely better in those who received BCG. In *active TB*, the TST and IGRA are only about 70% sensitive.

50-80% of active TB have positive smears. Traditional cultures take 3-8 weeks, broth can grow 1-3 weeks. Molecular probes can be applied to any tissue. They have very *high specificity* but sensitivity varies with burden of organisms. What about the use of nucleic acid amplification [NAA] tests? Always use the NAA tests in conjunction with a smear. *If both positive, this is very predictive*. If NAA positive but smear negative, presume TB pending culture if *2 or more NAA positive*. If NAA negative, smear positive, this is likely a false negative NAA due to *sputum inhibitors that prevent NAA amplification*. If *both* NAA and smear negative, it's hard to say. *NAA detects 50-80% in smear negative but culture positive*. Basically a single negative NAA is not definitive to exclude TB if there is a moderate to high clinical suspicion.

The initial *therapy* is 4 drugs IRPE. Second line therapies are serious. *MDR-TB resistant to at least IR, XDR-TB resistant to IR, any quinolone and at least one injectable [amikacin, kanamycin, capreomycin]*. The highest rates of these bad bugs are in the former Soviet Union and China.

Legionella

This often occurs in outbreaks or after returning from an enclosed space such as a cruise. Legionella comes from the environment and may affect normal and abnormal hosts. There are *16 serotypes* and 70-90% of disease are from serotype 1. The gram stain has polys but no organisms.

Culturing L. pneumophilla requires non-routine media, urine antigen may persist for days after anti-microbial therapy is begun, *only serotype 1 [70 or so % or L. pneumophilla] is detected by the urinary antigen test*, but importantly, once the urine test is negative, a full treatment course must still be undertaken.

Who should be tested? Enigmatic pneumonias, compromised hosts, during outbreak, those who fail treatment with beta-lactam, travel history within 2 weeks and nosocomial PNA of unknown etiology. *Antigenuria is 60-95% sensitive and highly specific*. *Nosocomial outbreaks are 50-60% sero-group 1 [as opposed to travel where it is essentially all serotype 1]*. Azithro, *levoflox* or moxiflox are therapies. There is data to support levofloxacin as superior to azithromycin; there is an increasing incidence of azithromycin failure in legionella.

Anthrax

Anthrax is a disease of herbivores, and transmission to humans by contact with infected animal or animal part. Bacillus anthracis was previously very common in livestock *before a vaccine was developed by Louis Pasteur*. Human disease is consequently rare save for areas of the world where vaccine is rare. It is a gram positive rod, non-motile. *Human infection is cutaneous, GI or inhalational*.

Cutaneous anthrax occurs when the spores get under the skin with a 20-30% death rate. Cutaneous anthrax begins as small papules that progress to deep ulcers and then eschars, there is regional lymphadenopathy. In 2009 there was an outbreak in Scotland from *cutaneous heroin injection*. These people died quickly in resistant shock with huge fluid requirements. *GI anthrax* is from ingestion of contaminated meat. GI is more lethal with severe inflammation and necrosis of the gut – 50-100% mortality.

Inhalational Anthrax is more of a bioweapons concern. The incubation period can be up to one month. When inhaled spores cause disease, lots of badness happens. The spores are transported to the local lymph nodes where the toxins are produced. This leads to hemorrhage, lymphedema, systemic unrest, shock and death. *Hemorrhagic mediastinitis and pleural effusion are the most common thoracic manifestations, with CXR demonstrating a wide mediastinum*, but a fairly normal parenchyma. Those patients who progress to shock frequently have non-cardiogenic pulmonary edema [ARDS picture] as well as meningeal signs with meningeal hemorrhage being common. Bronchospasm is not reported.

The *mortality is 100% untreated and 90% treated*. There is no risk of person-to-person transmission so standard isolation is required. *Pulmonary anthrax does not require respiratory isolation*, because it is contracted by spore inhalation from the environment. Health care providers do not require PEP, spores are very hardy in the environment and are not inactivated by drying or sunlight.

The therapy is cipro or doxy plus one or two additional agents [rifampin, chloramphenicol, clinda, *pen or amp or vanc*, imi, clarithro], consider steroids for *severe edema or meningitis*. The vaccine should be administered subcutaneously at diagnosis and 2 and 4 weeks later. Post vaccination Ig is available for anthrax when documented. Typically those prophylactically vaccinated are in the army.

The Plague

What about the plague? It is caused by Y. pestis. The plague is common in the SW of the US and transmitted by fleas. Bubonic plague has a 15% mortality. It is a *small gram negative coccobacilli with a safety pin appearance*. Bubonic plague presents with a cervical bubo, petechiae if it progresses to septicemic plague; blood cultures must be specifically looked for in the microbiology lab. Bubonic plague can progress to pneumonic plague.

Pneumonic plague does not require many organisms to get sick. 70% mortality, *there is person-to-person transmission so the patient should be in respiratory isolation*. Person-to-

person droplet transmission is *a less* common means of contracting pneumonic plague.

Bubonic plague differential is staph, strep, glandular tularemia, cat scratch disease. *Pneumonic plague* differential is anthrax, tularemia, meliodoidosis, CAP, flu, hantavirus, hemorrhagic leptospirosis. *Septicemic plague* differential is also broad – gram neg, meningococcus, RMSF, TTP.

Treatment requires streptomycin, gentamicin or doxy, cipro, chloremphenicol, *patient must be in respiratory if pneumonic plague considered* and for these patients, health care providers *require* post-exposure prophylaxis with doxy, cipro, chloramphenicol, TMP. Health care workers *do not need IVIg PEP*.

DAH SYNDROMES

The definition of massive hemoptysis varies between 100 and 600 cc of BRB per day, but most accept 200 mL in 24 hours. The management includes airway stabilization with intubation if needed, cough suppression, coagulation correction, sometimes antibiotics and localization with a bronchoscopy or *CT scan with angiography*. These patients often take a kidney hit from all of the dye that they receive to localize and coil the bleeding. Setting them up for dialysis might be indicated pre-emptively. There are multiple, multiple causes of hemoptysis.

Recognize that *heart failure [especially from mitral stenosis] can present with significant hemoptysis*.

Consider a patient admitted with insidious onset of dyspnea and then is intubated as his hemoptysis worsens. An ECG reveals RVH with LAE and CXR shows Kerley b lines with mediastinal haziness and lower lobe infiltrates, large pulmonary arteries and a straight left heart border. There is also a *double density sign with splayed carina both suggesting an enlarged LA.*

The diagnostic test is a TTE because this patient has mitral stenosis. *This patient was found to have DAH on BAL, but this is due to rupture of hypertensive pulmonary veins rather than capillary inflammation*. The difference between mitral stenosis and pulmonary veno-occlusive disease would be the size of the left atrium. In North America, severe MS is often due to subclinical, childhood rheumatic fever which progresses insidiously over decades. Other causes of DAH should be considered much less likely given the degree of cardiopulmonary abnormality on CXR and ECG. It would be quite strange to see this picture in a patient with ANCA-positive vasculitis or catastrophic APLS or inhaled cocaine all of which may present with DAH. *Isolated pulmonary capillaritis which is a small vessel capillaritis confined to the lungs can only be detected by surgical lung biopsy*.

Recognize that *smoking crack* can cause diffuse alveolar hemorrhage. Consider a young patient with sudden onset disease and hemoptysis. The CXR reveals bilateral alveolar infiltrates in the lower lobes. There is a slight 19% *peripheral eosinophilia*. A big clue is melanoptysis – coughing up soot – in these board questions. Importantly the UA is normal, which essentially rules out the pulmonary renal syndromes. As an aside, crack is extracted from cocaine via an ether solution. It is called crack because it pops when you heat it.

Understanding Goodpasture's syndrome [GPS]. Consider a young patient who smokes who presents with hemoptysis and nephritic syndrome on a UA. The anti-GBM antibody is positive and so too is p-ANCA. It is important to note *that the absolute value of the GBM antibody does not correlate with disease severity*, though its level can be followed to measure treatment. A subgroup of patient's with GPs syndrome also have positive p-ANCA and these patients are more likely to have multi-organ involvement. The trigger for GPS is unknown, but the original

syndrome was described following *influenza infection*. Hydrocarbon exposure may also increase this risk, especially smoking. *GPS has been known to relapse with resumption of smoking*. Hemoptysis is the most frequent presenting symptom though there are exceptions – some present only with renal symptoms – and *most patients on presentation have an active urine sediment*. Renal biopsy is the gold-standard for diagnosis *and linear staining is seen* as opposed to the granular staining seen in other nephritic diseases. The treatment for GPS is plasmapharesis, cyclophosphamide and steroids. This is dropped mortality to less than 20%.

Recognize that negative pressure pulmonary hemorrhage [NPPH] can mimic DAH. Consider a patient who receives anesthesia via an LMA and then goes into respiratory distress in the recovery room with hypercapnia and blood in the LMA and then ET tube. His CXR shows patchy consolidation much more in the right with volume loss and a *bronchoscopy shows blood everywhere with increasing blood on lavage*. He likely developed NPPH trying to breathe around a misplaced LMA. Intubation corrected this. *Pulmonary capillary stress fracture occurs in thoroughbred horses and can occur in human athletes*. *During exercise*, the trans-capillary pressure can reach *35 mmHg in people*!

VENTILATOR WAVEFORM SCENARIOS

Recognize pressure assist control ventilation based on the ventilator waveforms. There is a machine and patient triggered, pressure-targeted [there is a 'square wave' pressure waveform] and *time-cycled* [*each breath is the same length*] breath. Note that flow and volume are varying.

In the *patient-triggered breath*, *flow increases* to maintain the square-wave pressure. Also note that the *value of flow at which the breath cycles varies* meaning that it is cut short based on the time-cycle. The mimic of this mode would be volume control with volume/flow-limited ventilation, but with a clinician-set decelerating flow waveform. In this situation, *the flow will not vary* and there will *not* be a square-wave pressure tracing.

There are variations of pressure-targeted mechanical ventilation. One such variation is known as PRVC, auto-flow or volume control plus which essentially allows the ventilator to *alter inspiratory flow and pressure* to achieve a given volume. When this physiology is applied to pressure support it is known as 'volume support.' Another variation of PACV is known as BiLevel, BiPhasic or Airway pressure release ventilation which allows for spontaneous breaths on top of a prolonged inspiration.

Consider a COPD patient who is switched to pressure support with dropping volumes and dyspnea, what to do? With *airway obstruction, and pressure support, the pressure target is hit quickly*. Then as flow gets passed the obstruction, it tapers slowly. So breaths become very long and there is air-trapping. Shorten the I-time [also true with NIPPV].

Recognize auto-PEEP. The presence of expiratory flow prior to machine inflation indicates dynamic hyperinflation and intrinsic PEEP. Since intrinsic PEEP occurs with increases in airway resistance and/or rapid respiratory rates, sedation and paralysis is a good therapeutic choice. Additionally, decreasing airway resistance with medications, increasing rather than decreasing inspiratory flow rates to allow more time for exhalation (ie, decreasing I:E ratio) would also work.

Understand pulmonary mechanics and waveforms including the esophageal pressure [Pes] tracing. The patient has developed pulmonary edema with high peak pressure. You must know that this high peak pressure is the result of poor pulmonary compliance and therefore a high plateau pressure. Then you are also given *Pes so you can differentiate the effects*

of poor chest wall from poor pulmonary compliance. A high Pplat in the setting of a high Pes means that chest wall compliance is impaired. Whereas as high Pplat with an unchanged Pes means that pulmonary compliance is worsened [e.g. pulmonary edema].

Understand ATC on the ventilator. What ATC is doing is trying to achieve a smooth, pressure, square wave. But the resistance of the tube adds to this such that a square wave at the tube opening may be more triangular in the proximal trachea. It calculates the pressure waveform distortion based on the length and resistance of the endotracheal tube. It is done to add comfort.

OTHER PULMONARY BOARD EXAM SCENARIOS

Understand *leukocyte larceny*. The patient has a WBC count of nearly 300K and a PaO2 in the 30s. Normally, placing an ABG on ice will inhibit oxygen consumption by thrombocytes and leukocytes, but in extreme values, even rapid placement on ice cannot inhibit oxygen consumption. The only way to accurately measure PaO2 is to add an inhibitor of oxygen consumption such as potassium cyanide or NaF. The former is better studied. Heparin must be added as well.

Recognize and treat *methemoglobinemia*. The patient receives topical cetacaine for a TEE and has falling oxygen saturations to the mid-80s. *Her membranes are cyanotic and ABG reveals blue blood with a PaO2 over 100 mmHg*. She needs IV methylene blue. When ferrous iron on Hb is oxidized to the ferric state, the Hb curve is shifted leftwards such that *tissue hypoxemia can be profound as the Hb will not unload oxygen*. Other agents can cause Met-Hb as well *including dapsone, primaquine, and nitrates including iNO*. The incidence of Met-Hb may be as high as 1 per 1000 TEEs that use benzocaine. Pulse oximetry is totally inaccurate when measured oxygen saturation in the setting of Met-Hb and *typically reads in the mid-80s*. Iatrogenic met-Hb can lead to abrupt, profound symptoms including cyanosis, convulsions and death. Congenital forms of Met-Hb can lead to asymptomatic cyanosis. The *dose of methylene blue is 1-2 mg per kg IV over a few minutes*. Excessive methylene blue can worsen symptoms and produce hemolysis [especially those with G6PD deficiency]. Methylene blue further impairs pulse oximetry to detect oxygen saturation so it should be discarded.

Recognize and treat tropical pulmonary eosinophilia. The patient is a young woman from India and is recently diagnosed with asthma, though she continues to be short of breath. She has enhanced bronchovascular markings on CXR and lower lobe mottled opacities. She has a marked leukocytosis 33K with a *prominent peripheral eosinophilia*. Stool for O and P are negative twice, and *IgE is markedly elevated and ABPA titres are negative*. She likely has been sensitized to either W. bancrofti, Brugia malayi, Brugia timori which are parasites that live in Africa and Southeast Asia. Mosquitos are the vectors and the larvae travel via the lymphatics to the pulmonary system and cause congestion and eosinophilia. *There are 6 diagnostic criteria for TPE*: 1. Residence in an endemic area 2. Insidious onset over weeks to months 3. Prominent evening symptoms 4. Marked peripheral eosinophilia 5. Markedly elevated IgE and 6. elevated anti-filarial antibody. The treatment is that of asthma and diethylcarbamazepine [150 PO BID for 3 weeks].

Understand the treatment of *decompression sickness complicated by arterial air embolism*. The patient ascends too quickly from 20 feet below when he is frightened. He does so against a closed glottis. During the rapid ascent, *the nitrogen bubbles expand*, and when done so against a closed glottis, the alveoli rupture and cause barotrauma. Further, this patient also has

a headache, seizes and then has decerebrate posturing indicating that *the air also entered his pulmonary veins and then traveled to the left heart and brain*. Treatment of central arterial air embolism classically involves putting the patient in the left lateral decubitus position and in trendelenberg to 'trap the air bubbles in the right atrium' but this technique is questioned. Hyperbaric therapy with 100% oxygen should certainly be considered to reduce the amount of air within the vasculature.

Treat *fusobacteria necrophorum infection*. The patient presents with a pharyngitis and then progresses to *liver abscesses and iliac crest inflammation*. From this you are supposed to know that this is Lemaire's Syndrome which is characterized by pharyngeal infection, septicemia with rigors 4 to 5 days after the local infection, lateral neck tenderness and swelling, metastatic abscesses (especially to the lung), suppurative arthritis, jaundice, and renal failure. *F. necrophorum is a gram negative anaerobe that requires treatment with prolonged clindamycin, surgical incision, and anticoagulation*. The pathogenesis is unclear but involves an inciting pharyngeal infection of the pharyngeal or peritonsillar space, septic thrombophlebisits and metastases to various organs – commonly the pleural space, kidneys, liver and bone. It usually occurs in very young people. Overwhelming septicemia and death can rarely occur.

3. CRITICAL CARE NEPHROLOGY

ACUTE KIDNEY INJURY

There are various means of classification of AKI. There is the *RIFLE classification* [Risk – increase Cr by 1.5-2 x or oliguria for *6 hours*, Injury – increased Cr by 2x or oliguria by *12 hours*, Failure – increase in Cr by 3 x or *oliguria for 24* hours or *anuria for 12* hours, Loss – which is persistent AKI with complete loss of kidney function for more than 4 weeks, ESKD which is complete loss for more than 3 months]. But there is also *AKIN stage 1-3* which are kind of similar but should be within 48 hours because the AKIN only applies to acute kidney injury. AKIN stages 1-3 correspond to the 'RIF' of RIFLE.

Classic Framework and Urinary Indices

The classical framework is *pre-renal, post-renal and intra-renal*. Note that *pre-renal does not mean hypovolemic; it means 'salt-avid physiology'* which may occur in any state of fluid balance.

The 3 key tools beyond the history are: a renal US, UA and urinary indices. In pre-renal disease, the UA should be bland with maybe hyaline casts [Hyaline casts are formed by Tamm Horsfall protein]. In ATN, there may be tubuloepithelial cell casts or muddy brown casts or coarse granular casts. By contrast, if there are lots of RBCs, RBC casts, WBCs [*sterile* pyuria] and especially *WBC casts* – think of AIN.

In one study the density of muddy-brown casts was used to predict ATN. In the *absence of granular casts per LPF, the likelihood of ATN is very, very low. If more than 5 per LPF, the likelihood is very high for ATN*. So muddy brown casts are very helpful for diagnosing ATN. This study then went on to describe a sediment score. The higher the sediment score, the worse the AKI stage. The sediment score was based on RTE [renal tubular epithelial cells] per HPF, and number of granular casts per LPF.

Consider a patient with AKI in the ICU with a creatinine bump on pip-tazo, valsartan and plavix; there were 20-25 WBC with *minimal protein and blood*. This is likely an *interstitial nephritis*. The UA is benign with valsartan and Plavix can cause a micro-angiopathy in the kidney.

Urinary indices are helpful but have caveats – FeNa and FeUrea. *The clinically valuable urinary electrolytes lie in the patient with oliguria [without CKD], first presenting to the hospital*. When you start looking at patients in whom there have been interventions [including saline infusion], or in patients who are not oliguric then the value of these indices *are greatly degraded*.

FeNa cutoffs are 1 and 3%, FeUrea is 35 and 50% for pre-renal physiology versus intra-renal physiology as the culprit for AKI.

Drug-Induced Kidney Disease

The spectrum of drug-induced kidney disease within the ICU is wide. Systemic capillary leak with pre-renal azotemia may occur, there may be *changes in intra-renal blood flow* [e.g. ACEI, ARB, NSAIDs including COX2, tacrolimus, vasopressors, contrast, exenatide].

There may be *direct glomerular injury* from NSAIDs, gold, penicillamine, captopril, pamidronate, all interferons or microangiopathy from ticlopidine, Plavix, OCP, gemcitabine, mitomycin C.

Tubulointerstitial injury may be a consequence of *direct toxicity*, classically this is contrast, aminoglycosides [AGs] – a cumulative effect after 5-7 days of AG therapy, vancomycin, amphoB, pentamidine, cisplatin, tenofovir, bisphosphantes, *osmotic nephropathies* such as hetastarch, IVIG, mannitol, *but also AIN* such as beta-lactams, quinolones, sulfonamides, vancomycin, *PPIs – may be the most common cause of AIN,* allopurinol, diuretics.

Crystal deposition can occur from MTX, acyclovir, indinavir, atazanavir, sulfadiazine, TMP-SMX. *Acyclovir toxicity* tends to present with neurological depression and renal failure with *needle-shaped crystals*. Acyclovir neurotoxicity usually presents within 24 to 72 hours of initiation of the drug; signs include changes in cognition, level of consciousness, action tremor, multifocal myoclonus, asterixis, hallucinations, and delusions. Seizures may occur and the dysfunction can progress to coma [usually with an abnormal electroencephalogram]. The treatment is cessation of the drug and use of *hemodialysis* [effective because of limited protein binding of the drug and its low molecular weight, 225 Daltons] which shortens the duration of toxicity. By contrast, *uric acid nephropathy may be seen* in a recurrent multiple myeloma patient, just started on salvage chemotherapy with AKI. Normally, uric acid nephropathy doesn't occur unless serum levels are well above 15, but para-protein nephropathy from myeloma can cause uricosuria which raises the risk. The real kicker is the *presence of rhomboidal or rosette-shaped crystals* in the urine which are uric acid [note, uric acid is needle-shaped in arthritis!] The treatment is rasburicase.

RP fibrosis from methyldopa can lead to urinary obstruction.

Cholesterol Emboli

Recognize cholesterol embolic phenomenon. Consider a patient with an infrarenal stent placed for a AAA and two weeks later develops profound weakness, fluid overload and a creatinine over 12 and a potassium of almost 8. There may be *livido reticularis and peripheral blood eosinophilia* [more than 80% have eosinophilia]. This embolization can occurs days to weeks following the manipulation of the aorta. *Anticoagulation in these patients has been associated with accelerated atheroembolism and should not be used*. There is no role for thrombolysis in the treatment of atheroembolism, but in thromboembolism of the kidneys, within 6-12 hours there may be a role. The prognosis of atheroembolic disease is quite poor. Less than 50% who require dialysis recover renal function and mortality at one year is 22-80%.

Hepatorenal Syndrome

Type 1 is the acute, fulminant form, classically with a precipitating factor. *Type 2* is a smoldering, insidious type Cr 1.5-2.5 range that doesn't change much. The diagnosis requires a *Cr more than 1.5* or GFR less than 40, *no shock, lack of improvement after stopping diuretics and with plasma expansion, no nephrotoxins*, *no proteinuria, & no obstruction*.

Classic type I HRS typically has a urine Na less than 10, oliguria, hyponatremia. *Lack of infection is no longer a criteria as infection is the most common precipitant*, other triggers include large volume paracentesis without albumin, aggressive diuresis, GI bleeding, new liver insult [e.g. ethanol, hepatitis].

How is *HRS managed*? Albumin replacement often with invasive monitors, liver transplant if eligible. Vasoconstrictors +/- TIPS. Systemic vasoconstrictors are often tried – midodrine with octreotide – but the data is marginal. There is reasonable evidence that IV infusions of NE are helpful, the best evidence is vasopressin and terlipressin [not available in the US].

Prevention of HRS is important - teat SBP in the patient with cirrhosis and ascites promptly! The patient should receive antibiotics that are renally dosed because of AKI. *Patients with SBP, who also have a serum creatinine >1 mg/dL, blood urea nitrogen >30 mg/dL, or total bilirubin >4 mg/dL should receive 1.5 g albumin per kg body weight within 6 hours of detection and 1.0 g/kg on day 3*.

Evaluate acute kidney injury in the setting of decompensated cirrhosis with large ascites. Consider a patient who was aggressively diuresed but his creatinine continued to rise. His urine sodium is 38 with blood and trace protein in the UA. *Hepatorenal syndrome is diagnosed when the patient is removed from diuretics for 2 days and receives 1 gram per kilogram per day of albumin and there is no improvement in creatinine*. Urine sodium should not be used to differentiate HRS from pre-renal azotemia because their physiologies are essentially identical. Further, diuretics given in house raise urine sodium. Large volume paracentesis should be tried only after albumin is given. Octreotide and midodrine can be tried to treat HRS after the diagnosis is made, but firstly albumin must be administered to rule out a hemodynamic culprit.

Managing AKI in the ICU

Most cases of AKI in the ICU have no specific intervention. There are general supportive measures: avoiding further injury, adjust medication doses, manage nutrition, electrolyte and acid-base balance, correction of anemia and coagulopathy.

The most common cause of AKI in the ICU is ATN. Therefore *intelligent use* of diuretics is required. Remember that GFR only applies to the steady state, so *acutely changing creatinine cannot be used to calculate a GFR*, it could be much less than 10 for example is the creatinine increases from 1.0 to 2.0, even if the MDRD GFR is calculated as much higher.

What is the *'intelligent use'* of diuretics in AKI? The PICARD study suggest that *mortality may be worse with diuretics*. High dose diuresis can lead to deafness by 4x. Use diuresis if the patient is volume overloaded but do not waste time delaying other interventions. With 200 mg of Lasix + thiazide [or Lasix drip 10-80 mg per hour], the patient should make urine within 30 minutes or so. If not, the patient may need dialysis.

Dialysis for AKI in the ICU

What are the indications for dialysis? Clinical uremia, diuretic resistant volume overload, intoxications, refractory electrolytes, acidemia. Questions about dialysis in AKI – early versus late, continuous versus intermittent and the intensity of dialysis [i.e. the dose of dialysis].

Timing of dialysis is difficult to know. If there is a BUN over 150, the patient *should be* dialyzed, but this is very old data. What about subtle differences, like a BUN more than 80 for a few days? Early is probably better. The problem is, what defines early? Some use time to BUN or creatinine elevation, some use time of admission. Based on timing of admission to ICU, late dialysis *based on number of days did worse [late = more than 5 days]*. The answer is still somewhat unclear.

What about *modality*? Continuous [CRRT] versus intermittent [iHD]. iHD has good-to-excellent, solute control depending on how often it is done. iHD provides more rapid solute clearance and there is hemodynamic instability *only* if volume is removed. In terms of CRRT, CVV*HDF* has excellent solute control and greater solute clearance than CVV*HF*. Remember that *hemofiltration* is convective clearance of solutes while *hemodialysis* is diffusive clearance of solutes. The continuous modalities offer precise volume management, and better hemodynamic stability, but he disadvantages are that CRRT demands a different dialysis machine that

requires special fluids and training plus the need for anticoagulation.

SLED is sustained low efficiency dialysis [or EDD extended daily dialysis], it is a conventional iHD machine run over 7-8 hours, sometimes every day. *SLED/EDD versus CVVH is quite comparable, but need for AC is the same*. Acute PD is not used in the US. It is less precise than CVVHDF and typically used only for patients who are on PD as an outpatient.

There is still much debate about modality, but what is known is that *CRRT is superior to peritoneal dialysis* in acute, infection-associated renal failure [mortality rate of 47 versus 15%] – a study in Vietnam in 2002 NEJM. *There is little, good-quality evidence supporting the use of iHD over SLED, EDD or CRRT.* There are conflicting meta-analyses as to the benefit or not of CRRT.

Is there a mortality effect? There were 3 meta-analysis and the RR for *CRRT modalities versus iHD shows no consistent effect on mortality, recovery of renal function or development of chronic kidney disease*. There was much less HD instability in patients on continuous modalities. The MAP was 5 mmHg higher in the continuous group. *In patients receiving continuous modalities there is a much better fluid removal over a period of days*. Fluid overload is associated with worsened outcome.

Good scenarios for CRRT – liver failure [cerebral edema effect], hypotension, severe volume overload, and excessive volume intake that is obligatory [i.e. from IV infusions].

Dialysis dose and AKI outcomes. Remember the *dose is how much dialysis* – is more, better? The truth is unclear. The two best papers – Palevksy and Belloma in NEJM 2008 and 2009 *did not show a benefit to more dialysis* – in the RENAL and ATN studies. One trial [Schiffl – NEJM 2002] showed an improved survival in *daily dialysis* compared to *every other day*, though this trial is criticized because the dosing was less than optimal.

Another trial looked at dosing in CRRT and found an improved survival when comparing an effluent of *20 cc/kg/hr to 35 cc/kg/hour, BUT NOT improvement when comparing 35 to 45 cc/kg/hour [i.e. optimal effluent of 35 cc/kg/h]*

So the summary is: IHD or CRRT as per preference, intensity iHD 3 times per week as long as kt/V [i.e. the dose] is more than 1.2 per session.

Contrast Nephropathy

The prevention of contrast nephropathy [RCIN] is far from clear, but evidence suggests the use of *normal saline*, potentially IV NAC and the use of iso-osmolar radio-contrast may reduce the incidence. In *small trials*, ACEIs have been shown to *be protective*!

Risk factors include ESRD, heart failure, diabetes, and NSAID use. There is little study on this topic, *but normal saline is superior to oral hydration* and *normal saline is superior to half-normal saline* for the prevention of RCN.

The rate is 1 cc/kg/hour for 6-12 hours before and after the contrast load. The addition of Lasix to saline infusion is detrimental, *however*, there is no evidence that stopping chronic Lasix in a patient will protect the kidneys when trying to prevent RCIN. Fenoldapam is a selective, peripheral dopamine agonist with effects of renal blood flow, but an RCT showed that it did not prevent RCIN. Low-osmolar [non-ionic] contrast agents seem to prevent RCN compared to the classical ionic ones. Prophylactic hemodialysis to prevent RCN made things worse.

ELECTROLYTES IN THE ICU

Hyponatremia [Excess Free Water]

Pathophysiologically, hyponatremia should really be considered '*hyper-aquemia*' or an excess of free water. The diagnosis should focus on why the patient has too much free water.

How to approach *hyponatremia*? 1. Is it *real* 2. Is *water* excretion appropriate and 3. Is *ADH* secretion appropriate?

Is this *real*? Look to the *serum osmolality*. If it is normal or high, consider pseudo-hyponatremia, uremia, transpositional hyponatremia from glucose, mannitol, or glycine. Each increase in serum glucose by 100, above 200 mg/dL lowers Na by 1.6. If the *serum osms are low*, then it is 'true' hyponatremia.

Is *water excretion* appropriate? Look at urine osms or specific gravity [if you multiply the last two digits of the specific gravity by 30, this approximates urine osmolality]. If urine osmolality is less than 100 [spec gravity between 1.003 and 1.004], the patient is appropriately urinating free water [ADH activity is low]. Reset osmostat rarely lowers urine osms below the high 120s. If urine osms are high, then ADH release is high.

Then *ask volume status*. *'Appropriate' ADH release occurs when the patient is volume down*. If the patient is volume down, then look to the urine sodium, if it is low, then there are non-renal volume loses, if high, consider renal loses such as diuretics, adrenal insufficiency, cerebral salt wasting should be entertained which occurs following craniofacial injuries. If the patient is hypervolemic, then the ADH is maladaptive and this is fairly obvious from the clinical examination. Euvolemia is the most difficult situation. If urine osms are high*, SIADH*, renal failure, hypothyroid, isolated glucocorticoid deficiency [anecdotally rare, but one paper suggested up to 30% of SIADH is actually isolated glucocorticoid deficiency]. If urine osms are low, consider polydipsia, reset osmostat even if patient appears euvolemic – consider sending serum uric acid to help distinguish SIADH [SIADH results in hyperuricosuria which lowers serum uric acid level].

ADH is stimulated in response to multiple disorders and physiological stimuli – pain, nausea/vomiting, malignancies, pulmonary disease, CNS disorders. Drugs affect water metabolism, drugs have multiple mechanisms – *ADH analogues* like DDAVP, oxytocin; *increased ADH secretion* by drugs [nicotine, anti-psychotics, certain anti-depressants, carbamazepine]; *increased renal sensitivity* to ADH [NSAIDS]; drugs that cause hyponatremia by *unknown mechanisms* such as haloperidol, SSRIs, MDMA, PPI.

How is excess free water *treated*? The etiology, rapidity and volume status are important. If hypovolemic and no symptoms, always give NS. If euvolemic or hypervolemic and *no symptoms, free water restrict*. If *mild symptoms,* give saline & furosemide ['poor man's hypertonic saline'] or just furosemide [depending on volume status], and consider V2 antagonists [though V2 antagonists are rarely the answer in the boards]. If symptoms are *severe* [i.e. neurological in nature], the answer is hypertonic IV. *A 100 cc bolus of 3% will safely increase the Na by 2-4 mEq/L in most patients*; another rule of thumb is that *in general, a bolus of 1 mL/kg [or by hourly infusion] of 3% saline will raise the serum sodium by 1mEq/mL*. Regardless, very close monitoring is important.

AVP receptors – V1a is vascular smooth muscle cells & myocardium; V2 is the renal collecting duct. V2 antagonism induces a brisk loss of free water. Conivaptan is a mixed antagonist, all others are pure V2. Conivaptan is only available IV.

Consider a woman with GERD, depression, and *confusion for 2 days*. Spontaneous UOP is 50 ml/hour. Serum sodium is 116. Urine osms high. On the boards, fluid restriction is *never appropriate with CNS symptoms*. The answer is 3% saline IV. The brain defends itself from excess water by increasing intra-cellular sodium, potassium and idio-osms. The acute response is

mostly sodium and potassium. A large portion of idio-osms are generated by 74 hours. This is what dictates acute and non-acute. If you don't know how long it has been, rapid correction can lead to CPM. The patient *should not increase more than 10-12 in 24 hours or 18 in 48 hours*. Rapid achievement over 2-4 hours of 2-4 mEq/L is safe and advisable. Caution is advised with patients who may develop a brisk water diuresis [i.e. superimposed ADH secretion from hypovolemia].

"CPM" can be extra-pontine, so it is not called CPM anymore. It is now *called osmotic demyelination syndrome [ODM]*. It rarely occurs in patients whose serum is more than 120 mmol/L. It typically develops after an initial improvement in mentation - *potentially by weeks*. There can be focal motor deficits, *quadriparesis*, paralysis, *respiratory depression*, pseudobulbar palsy, coma, up to 33% extra-pontine. MRI with hyper-intense lesions on T2, non-enhancing. Those with: ethanol abuse, malnutrition, hypokalemia, elderly women on thiazides, burns, liver transplant are at *excess risk for ODM*.

Consider a patient with cirrhosis who loses lots of ascites through and abdominal incision and presents over two weeks with worsening hypotension and *new hyponatremia to 103*. He received hypertonic saline and *corrects 12 mEq over the course of 4 hours*. Alcoholics and cirrhotics are particularly susceptible to ODM because of their inherently low intra-cellular osmolality. What's interesting is that *despite his diuresis and rapid correction of serum sodium* [presumably due to release of ADH and free water diuresis], *his urine osmolality is shockingly high [above 500]* suggesting that there is SIADH. However, the urine osms are high because the *kidneys start to dump urea that accumulated in the pre-renal state*, so even though the osmolality of the urine is high, it is essentially free water. *He still needs free water replacement to prevent his serum sodium from jumping too quickly*.

Consider a schizophrenic with a tonic-clonic seizure, Na 116, urine osms 92, plasma osms 240. He is making about 120 cc per hour. *Schizophrenia should raise concern for SIADH, and polydipsia*. His urine sodium of 35 suggests that he is not volume down, he's making good urine and he is diluting the urine quite well; this patient has polydipsia. With *reset osmostat*, this degree of low Na is rarely achieved.

Hypernatremia [Free Water Deficiency]

Pathophysiologically, hypernatremia should really be considered '*hypo-aquemia*' or a deficiency of free water. The diagnosis should focus on why the patient has too little free water.

Hypernatremia is very common in the ICU and almost always the MD's fault. It has a negative prognostic value. It is the combination of *a loss of drive for free water, loss of access to free water* and *hypotonic fluid loses* [e.g. fever, NG suction, increased MVe, mechanical ventilation, urinary concentration defects such as DI, diuretics, solute diuresis from glucose, mannitol, urea, TPN].

How to *manage hypo-aquemia*? *Give back free water!* The patient needs replacement for what is lost *and* also for ongoing loses. If the patient is hypovolemic, give saline back, *also give free water*. If the patient is hypervolemic, *give free water*. *It is a fallacy to withhold or 'limit' free water in a patient who is volume overloaded*. In *one liter* of free water, *less than 150 mL* stays in *the intra-vascular space.* This will *not* contribute to vascular congestion, but it will *replenish* the *intra-cellular* free water *deficiency*. Further, free water replacement will help mitigate *thirst*, which is one of the *most unpleasant experiences* recalled by *ICU survivors*.

In patients who are hypervolemic *and* hypernatremic [common in the ICU], there are *two separate* problems to be addressed. *1.* the hyper*volemia* is due to excess total body *sodium content* [treat with *sodium restriction* and Lasix]

and *2.* The hyper*natremia* is due to *free water deficiency* [treat the calculated free water deficit with enteral free water flushes *or* D5W IV].

Special circumstances of hypernatremia include DI – which requires DDAVP replacement, but this uncommon outside of the neurosurgical population.

Tonicity balance? This is a physiological/rational approach to determining the treatment fluid for dysnatremic patients. The *tonicity is the amount of sodium and potassium* in *the infusion* fluid as well as the sodium and the potassium *coming out* of patients. If the input tonicity is more than the output tonicity, then serum sodium will increase. If the input tonicity is less than the output tonicity then the serum sodium will drop. There are fancy formulae for this approach.

Hypokalemia

Low serum potassium is a combination of intake problems, excretion problems and trans-cellular shifts [which is only an acute issue].

B2-adrenergic agents shift potassium into cells, re-feeding can shift potassium into cells and alkalosis can as well, but the latter is a mild effect.

You can use the *TTKG* to narrow the differential for hypokalemia. Note that *the urine is the numerator of the TTKG*; so the TTKG is a measure of renal potassium excretion. The lower the TTKG, the more potassium avid are the kidneys. If the patient is hypokalemic and the TTKG is *more than 2*, then the beans are wasting too much potassium.

If the patient is *hypertensive* and there is *renal K+ wasting* based on the TTKG, then the patient should be checked for aldosterone and renin activity. If both the renin *and* aldosterone activities are high [a ratio less than 10] then the patient is: *on a diuretic, has CHF, reno-vascular HTN, malignant HTN, renin-secreting tumors*, these entities are known as *secondary hyper-aldosteronism*. Note that these work-ups are often initiated in search for renin-secreting tumors, or renal artery stenosis etc*. but that being on a diuretic can mimic this physiology*. If there is high aldosterone activity with a suppressed renin activity, this is primary aldosteronism. If both low aldosterone and low renin occurs, then consider the patient is on exogenous mineralocorticoids, has Cushing's syndrome, has lots of licorice intake, or other weird things like Liddle and Geller syndrome.

Other hypoK+ pearls: always treat magnesium too [JASN Oct. 2007 v.18; p.2649]. Be aware of hypokalemia as a part of re-feeding syndrome - low phosphate may occur too. Be very wary of the kaleriuretic effect of bicarbonate. Sometimes patients have a metabolic alkalosis and the clinician plans of using acetazolamide. If the patient is also hypokalemic, *then there can be a pronounced reduction of potassium*. If you dump bicarbonate through the kidneys, you will dump potassium like crazy. This can also be a problem if *giving bicarbonate for contrast nephropathy or in patients with DKA* [typically discouraged in both].

Hyperkalemia

Like, low serum potassium, a high concentration of serum potassium is a combination of intake problems, excretion problems and trans-cellular shifts [which is only an acute issue].

Shifting potassium out of cells is known to occur in critically ill patients – low insulin states, solvent drag in hyperosmolar states and *mineral acidosis* [NOT organic acidoses e.g. lactic and keto-acidosis]. Further, *cellular destruction causes hyperkalemia*, not increased 'cellular turnover.' *Also*, during the clotting process, cells leak their contents such that *whenever electrolytes are measured from serum [as they usually are], the potassium levels are slightly higher than when measured from plasma [0.2 to 0.4 mEq higher]*.

This becomes a problem *only* when there is a *wild* elevation in WBC or in platelet count [serum potassium may be 1-2 mEq higher from cellular leak]. In this situation one can try rapidly separating plasma from cells and measuring the electrolytes.

In terms of problems with potassium excretion, if the patient is hyperkalemic and the TTKG is less than 6, then the beans are holding onto K+ too avidly; this is almost always a drug-effect. ACE, ARB, aldactone, *trimethoprim which has an amiloride-like* effect, BB can do it, heparin IV and SQ and LMWH are also common, but forgotten culprits, others are succinylcholine, ketoconazole and digitalis toxicity.

As above, trimethoprim acts like amiloride – a potassium sparing diuretic. Amiloride blocks the *apical* distal nephron sodium channel which decreases the trans-membrane voltage and *favors potassium retention within the cell*. Studies have shown that the administration of high dose *trimethorprim raises serum potassium by 0.5 to 1 mEq in general* with case reports of significant elevations. The latter may occur in patients with hepatic disease as the liver clears trimethoprim

How is high *K treated*? First, to treat severe, high potassium is to control cardio-toxicity [calcium chloride IV], then shift potassium into cells [beta-agonists, insulin] and then remove the potassium [diuresis, kayexelate, and hemodialysis]. These three things occur in concert. The kayexelate story is interesting because of *the FDA warning regarding* kayexelate crystal formation in the gut causing necrosis; in one series this complication was noted in *2 of 117* [roughly 2%] patients given kayexelate. The sorbitol may be the culprit. Consider only using kayexelate for a potassium above 6.

HYPERCALCEMIA

What causes hypercalcemia in the ICU? Usually malignancy [multiple mechanisms including PTH-rp secretion, bony involvement, excess vitamin D synthesis]. Consider also thiazides, rhabdomyolysis recovery and immobilization. When do you suspect Milk-Alkali syndrome? This can be seen with very high calcium levels in 'fitness & vitamin enthusiasts' or those taking fist-fulls of Tums for various reasons. The most common cause in the ICU is, however, malignancy.

Patients with mild to moderate hypercalcemia often have primary hyperparathyroidism, but this is not typically an indication to be in the ICU. Moderate to severe is frequently malignant but may also be milk alkali syndrome. If the calcium is high, check a PTH to make sure that PTH is appropriately suppressed.

Treatment: There may be normal or high phosphate, metabolic alkalosis, and certainly AKI. PTH and 1,25 D levels are usually suppressed, management is supportive – saline and removal of the source. Generally, treatment involves sodium-containing hydration and this promotes calciuresis. Loop diuretic should be used *sparingly* if at all but *only when volume replete*. *Steroids* can be used if there is a granulomatous process driving the calcium from excess vitamin D production. *Calcitonin has a rapid tachyphylaxis*, but it is good because it acts quickly, especially when hypercalcemia is quite severe. Bisphosponates IV are important, zoledronic acid is typically used. Hemodialysis is last resort.

Recognize and treat calciphylaxis and systemic calcinosis. There may be a scenario set up like a pulmonary renal syndrome. However, the patient has chronic renal failure [on peritoneal dialysis] and presents with bilateral infiltrates, hypoxemia and *lower extremity raised, violaceous lesions*. Notably the stem does not state that the lesions are biopsied and the *parathyroid hormone level is given as normal, despite a fairly high serum calcium.* Further, collagen vascular &

immunogenic work up is entirely normal. *The skin lesions are the calciphylaxis and are thought to be the result of calcium deposition into superficial arteries that then necrose*. These lesions are typically *not biopsied* as they rarely heal. *Systemic calcinosis is the calcification of the organs*. The lungs may certainly be involved. The alveolar-septal walls are often filled with granular and linear calcific deposits – these findings may also be seen in pulmonary vessels and airways. *The bone scan is the best diagnostic procedure here*, though it does have poor sensitivity and false positives can occur in lymphoma. The best treatment is prevention. In ESRD, it is important to keep the *calcium phosphate product less than 70*. Corticosteroids and immunosuppressants should *be avoided*. Mortality is high, usually secondary to sepsis.

Hypocalcemia

It is quite common in the ICU with many causes, probably sepsis is the most common cause followed by provision of blood products. There is a physiological hypoparathyroidism of sepsis.

There is little data to suggest that replacement is beneficial and some data [in animals] that it makes things worse. *Calcium should be replaced if there is instability, seizures, tetany*, or essentially any symptoms. Calcium gluconate or chloride can be used [the latter having 3 x more elemental calcium – usually requiring a central line]. *Post para-thyroidectomy* may result in '*hungry bone syndrome*' especially in patients with end-stage renal disease and prolonged, refractory secondary hyperparathyroidism. *A calcium drip* may be needed in this situation.

Like hypokalemia, with hypocalcemia, you cannot correct it until hypomagnesemia is also corrected.

Hypomagnesemia

Hypomagnesemia is typically caused by diuretics and ethanol abuse, nutritional deficiency, but also aminoglycosides, ampho B, but also *PPIs* that is a mixed mechanism *[it is probably from dumping mag into the bone]*!

You can do a FEMg – in those without renal loss it will be *less than 4%,* if more then it may be renal dumping. Replacing with IV or PO Mg. Amiloride, triamterene and spironolactone will *also raise* magnesium levels.

Hypophosphatemia

Hypophosphatemia can be evaluated by a *FEPO4*, with the cutoff *being 5%*. *The kidneys will hold on to phosphate when there is trans-cellular shift* of phosphate [e.g. insulin secretion, respiratory alkalosis, re-feeding, hungry bones, sepsis], *but also decreased intestinal absorption* [e.g. phosphate binders, calcitriol deficiency].

FEPO4 will be high [more than 5%] in hyperparathyroidism, Fanconi syndrome, and osmotic diuretics or solute diuresis – the latter being very common in the ICU.

Causes of severe hypophosphatemia seen in the ICU are – ethanol withdrawal – chronic depletion, and re-feeding syndrome with D5; DKA which is from losses and pH shifts; TPN with re-feeding; acute respiratory alkalosis, correction of chronic respiratory acidosis, and the diuretic phase of severe burns. Perhaps *the most common cause is respiratory alkalosis*. Usually, if the PaCO2 goes back up, the hypophosphatemia will also reverse.

ACID-BASE IN THE ICU

Metabolic Acidosis

There are 5 basic mechanisms of metabolic acidosis – *renal acid excretion problems* such as renal failure or distal RTA, *renal loss of bicarbonate* such as a proximal RTA, an *extra-renal loss of bicarbonate* that is in excess of the kidney's ability to regenerate bicarb [e.g. diarrhea, pancreato-biliary fistulae, pancreas transplants, ileal conduits], *increased generation*

of metabolic acid in excess of the renal ability to regenerate bicarb [e.g. lactate, d-lactate, ketoacids, HCl, cationic and sulfated aminoacids, toxic ingestions], and *lastly 'dilution' acidosis* which is the result of *excess chloride* [see Stewart approach below].

Anion Gap Acidoses

What are the causes of a *high anion gap* – added anions, but also consider hypoK+, hypoMg++, hyperPO3, hyperSO4 [mediators of AG in renal failure which can get up to 20 or so], hyper-albuminemia. If AG is *more than 25- 30, it is almost always an organic acidosis*. The clinically *important anion gap acidoses can be remembered by:* KULT *[ketones, uremia, lactate and toxic alcohols*].

What about the causes of a low AG? This is important in hypo-albuminemia because the patient's expected AG will *drop by about 2.5 for each decrease in albumin by 1 g/dL*. Other causes of a low AG are cationic paraproteinemia, hypoPO4, hyper: Ca, K, Mg, Li intoxication, and severe hypernatremia.

Toxic Alcohols

Remember that the *osmolal gap* is the difference between measured and calculated serum osms. If it is more than 10, there's an unmeasured osm floating around. If this is in conjunction with a metabolic acidosis, then the culprits are *ethylene glycol, methanol, ethanol, propylene glycol, formaldehyde and paraldehyde*. If there is not a metabolic acidosis, but only an osmolal gap, think about: mannitol, glycine, sorbitol, maltone [IgG infusion], isopropyl alcohol [rubbing alcohol – *will also give you ketones as acetone*] and pseudo-hyponatremia.

With toxic alcohol ingestion, the cause of the osmolal gap is different from the cause of the anion gap. With *ethylene glycol*, the osmolal gap is ethylene glycol, and the AG is *glycolic, oxalic and hippuric acids*. With *methanol*, the OG is from methanol, but the AG is from formic and lactic acids. With *propylene glycol*, the OG is from propylene glycol, but the AG is from *L and D lactic acids*.

Where does *ethylene glycol* come from? Anti-freeze and other solvents. There is typically CNS depression early with HTN and this is followed by acidemia, CV collapse and renal failure from oxalate crystals in the urine. The diagnosis is made by a high AG with high OG. Leukocytosis is common. The treatment of ethylene glycol, prevent further metabolism with fomepizole and increase the conversion of glyoxalate to glycine with pyridoxine and thiamine. Then you want to remove toxic metabolites with iHD or PD – *this is recommended only when there are neurological changes, renal failure or severe acidemia*. Charcoal hemoperfusion is not indicated for the treatment of ethylene glycol toxicity.

Consider a patient who presents following a suicide attempt with obtundation, renal failure, *rhomboid crystals* in the urine and a combined osmolal and anion gap. *The combination of a combined osmolal and anion gap is [in clinical reality] limited to propylene glycol, ethanol, ethylene glycol and methanol*. The presence of oxalate crystals in the urine clinches it for ethylene glycol toxicity. Hemoperfusion is only indicated when the molecule of interest cannot be dialyzed. This is common in very large molecules, those that are highly protein bound or those with a high volume of distribution ['tissue-bound']. There are complications with charcoal hemoperfusion so this is not ideal. As in all toxic ingestions, GI decontamination with activated charcoal should be instituted immediately once airway protection is established [within one hour of ingestion]. *The major toxicity in ethylene glycol ingestions is not due to the parent compound but is due to its metabolites glycoaldehyde and glycolic* acid. This metabolism may be inhibited by the administration of either IV ethanol (loading dose, 0.6 g/kg, followed by a continuous infusion

titrated to maintain a blood level of 100 to 200 mg/dL) or 4-methylpyrazole (fomepizole, 15 mg/kg loading dose, followed by 10 mg/kg q12h). Although ethanol has been the standard treatment for ethylene glycol ingestions, *ethanol's kinetics are unpredictable, patients must be rendered intoxicated, and it may predispose to hepatotoxicity and hypoglycemia*. 4-methylpyrazole is a more specific inhibitor that is not associated with these toxicities, but it is substantially more expensive. Although it is only approved for the treatment of ethylene glycol intoxication, 4-methylpyrazole is likely to be beneficial in the treatment of methanol intoxication as well. *Hemodialysis is indicated when the ethylene glycol concentration is > 50 mg/dL. In patients being concomitantly treated with IV ethanol, the rate of ethanol infusion must be increased to compensate for enhanced clearance by dialysis.*

Other high AG/OG acidosis is *methanol and propylene glycol*. The latter is from IV lorazepam drips. 10 mg/hour for more than one day results in a lactate acidosis and renal failure. They often need dialysis.

Consider a patient with ethanol abuse, pH 7.2//24//100, AG 31, serum ketones 1:4, lactate 3.5. UA with granular casts and *calcium oxalate crystals*. The patient has a high AG and high osmolal gap as well. When both gaps are present it means either that the toxic alcohol ingestion is caught early, or there is *co-ingestion with ethanol which slows the metabolism of the toxic alcohol*. Methanol or ethylene glycol are the common causes from the community.

Non-Anion Gap Acidoses

The *urine AG* measures ammoniagenesis. *The normal urinary anion gap is negative* because there are unmeasured urinary cations [mostly ammonium] getting rid of daily acid intake. In other words, the *urinary chloride normally exceeds the sum of the urinary sodium and potassium*. This normal concentration of ammonium is in the 30 mEq range [from our acidic protein intake]. When a metabolic acidosis from bicarbonate loss occurs, the distal nephrons work to excrete more acid in the form of ammonium such that the urinary gap becomes *more negative* [50 mEq or more negative].

If there is *systemic acidosis* with a *negative serum anion gap*, *hyperchloremia* and the *urinary gap is positive*, then the distal nephrons are behaving badly and there is *either a type 1 or 4 RTA* in the works. The difference between the latter is usually potassium level as *type 4 RTA* occurs in the setting of aldosterone resistance such as diabetes [where renin and angiotensin levels are low], ACEI, NSAIDS, heparin, and various adrenal abnormalities so there is commonly hyperkalemia. *Type 1 RTA ['distal']*, by contrast, occurs in the setting of lupus, active hepatitis, Sjogren's syndrome and hypergammaglobulinemia.

Type 1 [distal] and type 2 [proximal] RTA both classically have hypokalemia. Urinary pH is generally unhelpful when making the distinction between the aforementioned because it is regulated by multiple other factors, though an 'alkaline' pH in the setting of systemic acidosis, in general, supports the diagnosis of an RTA.

Type II RTA occurs from proximal nephron bicarbonate wasting, if you give bicarbonate, they dump bicarbonate, but *they can acidify* their urine. Type II RTA, therefore, also has a negative urinary anion gap [like gut bicarbonate loss], because the distal nephrons can still generate ammonium.

As an aside, *type III RTA* was once used to refer to the condition of a combined Type I and Type II RTA [an inability to generate ammonium in the distal nephron and an inability to resorb proximal bicarbonate, respectively]. That's when you consult nephrology [JASN: Aug. 2002 vol. 13; p2160].

ICU RTA causes [type I – autoimmune, ampho B, transplant rejection, sickle cell disease, volume depletion], [type II or proximal, renal bicarbonate wasting – multiple myeloma, acetazolamide use, Sjogren's, transplant rejection] and [type IV or aldosterone deficiency or resistance for example from ACEi, NSAIDs, heparin, aldactone].

Why should acidosis be *treated*? HD stability, myocardial performance, arrhythmias, and chronically muscle catabolism. *The treatment of metabolic acidosis is to treat the cause*. Sodium bicarbonate can be used for patients with diarrhea, renal failure, etc. If the patient is on TPN, acetate and lactate and citrate should be titrated. Dialysis may be needed.

Metabolic Alkalosis

Metabolic alkalosis occurs from the loss of hydrogen for example from NG suction, antacids, renal proton loss from diuretics, mineralocorticoids, hypercalcemia, post-hypercapnia compensation, low potassium or re-feeding. There may be retention of bicarbonate from administration of sodium bicarbonate or milk-alkali. There may be metabolism of organic anions from massive transfusion or recovery from organic acidosis. Or there may be contraction alkalosis from chloride loss.

In the proximal tubule bicarbonate is reabsorbed [facilitated by hypokalemia, hypercapnia and volume contraction], in the distal nephron bicarbonate is regenerated [facilitated by hypokalemia, hypochloridemia, hyperaldosteronism] – these factors *maintain* the metabolic alkalosis.

Metabolic alkalosis should be treated because of hypoventilation, reduced oxygen release from Hb, hypokalemia, hypocalcemia, muscular and cardiac complications. Correct *the generating and maintaining factors*. In the hypovolemic patient sodium and potassium should be infused. It corrects volume contraction, it lowers renin and aldo activity, corrects Cl depletion, corrects K depletion, and increases GFR. *The use of acid is rarely needed [0.1N HCl]*, one also could consider giving acetazolamide, spironolactone, amiloride. Lastly, dialysis or CVVH.

Consider a patient with cryptic metabolic alkalosis. The *history and physical is paramount*. In patients with*out* a history of hypertension, it is almost always surreptitious use of diuretics or induced-vomiting. However for board exams the patient is usually hypertensive with stigmata of uncontrolled hypertension such as AV nicking on retinal exam, suggesting hyperaldosteronism. The urinary chloride can help differentiate hyperaldosteronism from diuretic use. *Diuretics initially increase urinary chloride*, but then with hypovolemia the urinary chloride level falls [many hours after last dose]. Hyperaldosteronism [e.g. Conn's Syndrome] presents with *urinary chloride* that is high [*above 25*]. If the patient's urinary chloride is high and has not received a diuretic recently, the patient likely has hyperaldosteronism.

Consider a patient aggressively diuresed for heart failure with Na 142, K 3.7, Cl 86, CO2 40. *7.57//41//78*. He is still with edema. What to do, spironolactone or acetazolamide? The preference is spironolactone, not use acetazolamide because the patient is already hypokalemic and this will worsen with acetazolamide administration. Aldactone has a better synergistic effect with Lasix and aldactone also *results in acid retention*. The patient has a mixed metabolic and respiratory alkalosis which is the most common acid-base problem of treated heart failure.

Mixed Disorders

What about the *gap/gap* or *delta gap*? In a simple disorder, the *increase in AG* should match *the drop in the measured venous bicarbonate mEq for mEq*. Making this comparison is the gap-gap. If the AG increased more than the drop in

bicarb, then there was a *pre-existing metabolic alkalosis* – i.e. the measured venous bicarbonate is too high as compared to the elevated anion gap.

Remember, when determining the change in AG, you must correct for albumin. So if the AG is 25 with a normal albumin, it means that there are 13 'excessive anions' that must be accounted for – *assuming a normal AG of 12*. The 13 cryptic anions must be matched by a drop in venous bicarbonate. Thus, assuming a normal bicarbonate of 25, the measured venous bicarbonate should be 12-14. If the measured value of bicarbonate is much higher, there is a pre-existing metabolic alkalosis, if the measured bicarbonate is much lower there is a pre-existing *non-gap acidosis*.

A common board scenario is the *triple acid-base question*. Consider a young patient with IDDM, with pneumonia [respiratory acidosis], DKA [AG metabolic acidosis], and vomiting for one week [metabolic alkalosis]. How is this approached? Find the primary disorder – there is acidosis with a low bicarbonate and a PaCO2 below 40 mmHg, but Winter's Formula [1.5 bicarbonate + 8 (+/-2)], shows that the PaCO2 is too high. Thus there is a metabolic [AG] and respiratory acidosis. But applying the gap-gap will reveal that the measured bicarbonate is too high for the increase in anion gap, thus there is a metabolic alkalosis [from puking].

Brief Overview of the Stewart Approach to pH

What is the mechanism of post-fluid resuscitation metabolic acidosis? *It is a narrowing of the strong ion difference* based on the Stewart model.

Note that if you add normal saline [154 Na, 154 Cl] to the plasma [average Na & Cl around 140 and 105, respectively], the excess chloride in the NS relative to the serum chloride will *increase the serum chloride out of proportion to the increase in serum sodium*. In other words, the difference [i.e. the strong ion difference] between sodium and chloride will narrow. This will favor more protons dissociated into the plasma, and *less bicarbonate* anions [to maintain electro-neutrality] and therefore a more acid pH. This is often explained as the NS 'diluting' away the bicarbonate but, per the Stewart approach, the bicarbonate is disappearing per its dissociation constant in order to maintain electroneutrality [as the negatively charged chloride increases].

Common Board Acid-Base Scenarios

Board exam scenarios – *additive disorders* – metabolic acidosis *plus* respiratory acidosis which presents with *severe* acidemia, low bicarbonate [from cryptic lactate] and increased PaCO2 – e.g. cardiac arrest.

There may be metabolic *plus* respiratory alkalosis – *severe* alkalemia with high bicarbonate and low PaCO2 – e.g. vomiting with hepatic failure, or treated acute heart failure.

There may be *counterbalancing disorders* where the pH is near normal. Consider respiratory acidosis with metabolic alkalosis with variable acidity – high bicarbonate, high PaCO2 for example acute on chronic lung disease *and* CHF treated with diuretics.

Respiratory alkalosis and metabolic acidosis variable acidity with low bicarbonate and low PaCO2 – for example chronic renal failure with GNR sepsis.

There could be an anion gap metabolic acidosis and metabolic alkalosis with variable acidity, variable bicarbonate, variable PaCO2. *The increase in the AG will exceed the decrement in bicarbonate*. There is classically shock with lactic acidosis [or DKA] and *superimposed vomiting*.

Then there are *triple disorders* such as respiratory acidosis, metabolic acidosis and metabolic alkalosis – chronic lung disease with DKA and

vomiting [as above patient] and respiratory alkalosis, metabolic acidosis and metabolic alkalosis for *example ASA overdose in a patient receiving diuretics*.

There may be a *combined gap, non-gap* metabolic *acidosis* in a burn patient. The patient has an albumin of 2, an anion gap of 15 and a measured venous bicarbonate of 8. *His predicted anion gap is only 5 because* of his low albumin which means that his measured anion gap of 15 leaves 10 anions unaccounted for. If his gap-gap is 10, his measured venous bicarbonate should be 15, *but it is 8* which means that there is a bicarbonate wasting process as well. He is hyperchloremic with lactic acidosis.

Recognize inconsistent an uninterpretable data in acid-base. Consider a patient with a venous bicarbonate of 13 and an AG of 27. Further, the PaCO2 is 40 – this would be both a *metabolic and respiratory acidosis* and the pH should be rather low. However the pH listed is normal. In the presence of an anion gap acidosis with a bicarbonate that low, the pH could only be normalized if the PaCO2 is lowered substantially. Even if this patient were a chronic retainer, at a pH of 7.40 and a PaCO2 of 40, the venous bicarb should be in the mid-20s [because the chronic retainer would chronically raise their bicarb such that an anion gap acidosis of 27 would bring the measured bicarbonate down to the mid-20s]. Therefore, this data is wrong.

4. CRITICAL CARE GASTROENTEROLOGY

SEVERE ACUTE PANCREATITIS

The goals of this section are to recognize common presentations and etiologies or pancreatitis, describe the staging roles of CT scans, when to use IAP monitoring, when to use early enteral feeding, when to use antibiotics, and define when intervention is important.

The common *causes of acute pancreatitis are alcohol, gallstones, trauma and hyperlipidemia*. Only about 10-20% have life-threatening course. The death is from complications and typically occur *less than 7 days or more than two weeks* [two peaks of critical illness]. The real morbidity and mortality occurs in a small group of the severe pancreatitis. *World-wide the number one cause of severe pancreatitis is gallstones, in the U.S. it is alcohol*.

There is no real definition of severe pancreatitis, but be wary of: APACHE II more than 8, three or more Ranson's criteria, and acute pancreatitis plus local complications.

Acute pancreatitis is a lot like sepsis with a lot of IL1, IL6 and TNF. Symptoms occur and patients *present to the ED prior to the peak of cytokine production*. There is a window of time between cytokine production and end-organ dysfunction. Presentation to the ED typically occurs in the first 12 hours, maximal cytokine production typically occurs around 24 hours, and *end-organ badness flares around 60 hours*. Therefore there is not more than 60 hours for one to prevent end-organ dysfunction with intervention.

ENZYMES

Renal failure can falsely elevate amylase. The initial amylase is typically 3x normal [80 is usually normal] but *can be normal in up to one third*. The pancreas may be burned out, the patient may be late in presentation.

Both amylase and lipase can be measured, there is no reason to measure both after a procedure. Trigs, glucose, LDH, calcium, liver enzymes should also be measured. Procalcitonin may predict co-morbid infections, but not certain.

The *severity assessment* is via the Ranson's Criteria. *At admission* – Age, WBC, blood glucose, AST, serum LDH and again at *48 hours* [48h criteria are essentially about fluid requirements].

There is a simple bedside score – five easily obtained measures such as serum urea more than 9, age more than 60, mental status disturbed, SIRS, pleural effusion. If *more than 3 then consider severe acute pancreatitis*.

IMAGING

What does the CT scan tell you or what are the classical indications for scanning? The following should *prompt a CT scan*: if the diagnosis is in doubt, severe clinical pancreatitis, high fever with leukocytosis, Ranson more than 3, APACHE more than 8, lack of improvement at 72 hours, or acute deterioration after improvement.

The single best way to prognosticate severe acute pancreatitis? *CT scan with IV and oral contrast with more than 50% necrosis*. This comes from Balthazar. A is a normal pancreas, B is focal or diffuse enlargement of the pancreas, C is B but *with peri-pancreatic inflammation*, D *is single fluid collection*, E is *two or more fluid collections and/or gas*.

What are the data between Ranson and Balthazar in terms of infection and mortality? *Balthazar* is *probably better in terms of prognosis for both*

mortality prognosis and infection. The data is from the early 1990s.

Organ failure in necrotizing pancreatitis - the most common organ to fail in response to pancreatitis is the respiratory system [35%], followed by CV in the 20% range, GI just below that, hepatic and renal about 15%. Balthazar did refine the scoring from letter grade to points [A0, B1, C2, D3, E4, with percent necrosis as the addition] from 2002 and this is the CT severity index. *7-10 on the CT severity index is a bad prognosticator*.

What about an *ultrasound*? Gallstones should be suspected in *all patients* and therefore *all patients* need an US and biochemical tests to assess the common bile duct; endoscopic US may also be helpful.

Management

Management issues require identification and severity assessment, patients must be assessed for risk of rapid deterioration [e.g. elderly, obese, ongoing volume requirements, substantial necrosis]. Consider intra-abdominal pressure [IAP] elevation, and pain control – such as systemic *or* epidural analgesia [*there was no difference between the two groups in one study*].

The lungs are typically the first system to fail, there is diminished FRC. These patients require lots of fluids, sometimes up to 500 mL per hour. There is a *23% incidence of acute renal* failure as well.

What *about IAH and compartment syndrome [ACS] in pancreatitis.* Elevated intra-abdominal pressure [IAP] is roughly 12 *mmHg*, but ACS usually defined at 20-25 mmHg with organ dysfunction. There is still a large proportion of patients requiring abdominal decompression after 10 days. UOP, MAP, etc. tend to improve after decompression. If decompression *occurs beyond 7 days*, there is a low survival percentage. Intra-abdominal hypertension [IAH] and ACS are rare in mild disease; thus, measure IAP in all patients with severe acute pancreatitis [APACHE more than 7, MODS more than 2], if IAP more than 18 *mmHg* on first assessment, then this should be monitored continuously.

IAH management is to consider limiting crystalloids, decompress stomach, consider fluid drain, and consider surgical intervention.

A patient with jaundice and severe acute pancreatitis should have an ERCP within 24 hours of presentation – absolutely. The key is the presence of jaundice. *Severe acute pancreatitis without signs of obstruction then urgent ERCP is not needed*. This is based on 7 RCTs of ERCP, 3 of which were methodologically sound. Overall complications no difference, mortality no difference, no effect on predicted severity.

A new patient with severe, *acute pancreatitis* a *fever*, *elevated WBC* should receive which *antimicrobial therapy*? A popular clinical practice is to place such patients on a carbapenem such as imipenem, *but there is no clear benefit from this practice*. The Isenmann trial and Dellinger trials were the latest and best [cipro/flagyl and merrem] and showed no difference in outcome. The fever, white count and systemic unrest are a result of severe pancreatic inflammation and not infection per se.

The practice of antimicrobial therapy for severe, acute pancreatitis comes from Pederzoli in 1993 which gave imipenem - 70 some patients and the study was criticized methodologically.

What about *probiotics*? Lancet 2008 looked at 298 patients. There was no benefit to probiotics and suggestion of harm.

Patients with severe acute pancreatitis [SAP] can get lipids to their hearts' content. *They should get early enteral nutrition. There is suggestion that total enteral nutrition has a lower mortality*.

It takes a long time to get organized necrosis. *When* should *intervention* be considered? If an FNA is positive [i.e. infected necrosis or pancreatic abscess], if the diagnosis is uncertain [rare with CT], if there is persistent biliary pancreatitis, or a concurrent surgical problem such as ischemic enterocolitis.

An FNA is performed in the majority of patients – if an FNA is positive for infection, intervention was done [*surgical*] still those people have a very long length of stay. There are many forms of intervention here, classically it was surgical. It was previously felt that early intervention with debridement would be beneficial, but this is totally wrong. *Now, the idea is to never operate on these patients as mortality will increase*.

There was an RCT in NEJM 2010 which used a minimally invasive approach. *Complications and death were lower when the initial approach was percutaneous drainage*. At MGH, the vast majority of patients had lots of gram negatives, but usually polymicrobial. AGA recommendation is to *always perform an FNA prior to intervention*.

Recognize and treat severe, *hypertriglyceridemia-induced pancreatitis*. Consider a young woman with type II DM with severe pancreatitis and SIRS who is intubated for declining mental status. Her triglycerides [*trigs*] *are above 6000*. This type of pancreatitis is relatively rare as a cause [less than 4% of causes] but can occur in patients with *trigs above 1000*. Triglycerides this high are usually the result of some genetic disorder or lipid metabolism [of Frederickson]. As an important aside, a triglyceride level of more than 500 can cause a falsely low amylase level [to confound the diagnosis of pancreatitis], but lipase should be elevated. Recall that on the endothelial cells of muscle and fat, lipoprotein lipase degrades triglycerides into FFA and glycerol. Importantly, *heparin and insulin* activate lipoprotein lipase and *lower serum triglyceride levels*, so these therapies *are an important part of treating severe hypertriglyceridemia*. The dose of heparin should be prophylactic dose because there is fear of hemorrhage into the inflamed pancreas. If heparin and insulin do not lower the triglyceride content quickly, plasmapharesis can be tried. It is important to avoid propofol in these patients and consider co-morbid hypothyroidism.

In Summary

What are the conclusions? Identify risk factors by severe disease – CT staging too. IAP monitoring should be considered in the most ill. EBM does NOT support ABx, there is no role for ERCP in patients without jaundice, no role for early necresectomy. A positive FNA should have drain. Less invasive drainage is favoured.

GI BLEEDING IN THE ICU

GI mucosal and motor dysfunction is common in the ICU. Bleeding adversely affects outcome and increased LOS by 8 days and mortality by 1-4x or so.

Stress-related mucosal damage may develop within 24 hours in the majority of ICU patients [depending on how this is defined]. Deb Cook looked at this in 1994 and in 2001 – there was an increase in mortality when ICU-related bleeding occurred. *How is the disease defined*? Endoscopic evidence is highly sensitive. Endoscopically, this is seen as multiple subepithelial petechiae, which progress to superficial erosions. Most occur in the fundus – it looks like skinning your knee on the concrete. An isolated lesion in the proximal stomach is usually a vascular malformation and not-stress related, they tend to not be localized vascular lesions.

While clinically *evident* ICU bleeding occurs *in 5-25% of ICU patients* [i.e. coffee grounds in NG, melena, hematocheezia], what should be used is clinically *important* GI bleeding. What is this? HD instability, measured decrease in Hb, or need for blood transfusion [2 U]. *The natural history of this disease is 1.5%!*

Mechanism

Gastric acid secretion, mucosal blood flow diminution, duodenal reflux [bile and bile salts are very caustic to the stomach]. All must be somewhat present.

In critical illness, splanchnic *hypo-perfusion* results in insults *to all 4 protective mechanisms of the gastric mucosa*: reduction of bicarbonate, reduced blood flow, decreased motility and acid back diffusion. Free radicals are also important. Prostaglandins accelerate healing, have direct cytoprotective effects, and increase blood flow.

Gastrin, histamine and acetylcholine all facilitate gastric acid secretion [remember basic pathophysiology cartoon] via activation of the proton-potassium pump. The target pH of the stomach is what? *The pH is 1-2 normally*! It's essentially a sterile lumen. Get *the pH above 4 to prevent stress ulcers*.

There are only two risk factors in the Cook study that were significant – *mechanical ventilation for more than 48 hours and coagulopathy*. Notably, hypotension was *not quite* significant. The multiple regression odds ratio for bleeding was *15.6 for mechanical ventilation, 4.3 for coagulopathy, 3.7 for hypotension* [NS], and 2.0 for sepsis [NS] as well as other NS risks. *There were 847 patients who were high risk [MV, coagulopathy]; 31 of them had clinically important bleeding [above – drop in BP, need for pRBC] and 2 of the 1405 low-risk patients had clinically important bleeding [3.7 versus 0.1%].*

So, the most important risk factor for stress related mucosal injury is MV for more than 48 hours! H. pylori is not really a risk for stress ulcer bleeding in the ICU from a few observational studies.

Prevention

How do we prevent stress ulcer bleeding? What is the best preventative therapy? The data suggests that *continuous infusion of H2 blockers is the best prevention*! This is an old, old study, but convincingly, infusion was required to get the gastric pH more than 4. H2-blockers have many drug-drug interactions; summarizing 10 RCT, H2 blockers *by infusion*, are better than placebo by about 50%.

What about immediate release powder with bicarbonate for oral suppression versus cimetidine continuous infusion – there was *no* difference in bleeding, gastric pH or PNA!

In 1997 *PPI* versus *H2* versus *sucralfate*, 67 patients *no* difference. *Sucralfate* has a mechanical effect, does not alter pH, it was not *better* than H2 blockers, *but it is better than placebo for prevention*.

What about *H2 blockers versus PPI*. The pH was higher with high dose PPI, but *no difference* in GI bleeding [continuous H2 infusion versus high dose PPI]. PPI is a pro-drug that is inactivated by protons. They work only on activated pumps, so they are *not* instantly acting drugs. *The max effect takes 3-4 days!* The *enteric coating of the PPI is critical*, the PPI *must* be in the enteric capsule; otherwise, they are inactivated by acid.

PPIs have some 2C19 and 3A4 effects. There is a genetic polymorphism to the metabolism of this drug. In Asians, there are slow metabolizers and have an extended half-life. There shouldn't be important clinical effects from this.

In clinical practice, *PPI is commonly supported over H2 blocker* [Conrad 2005 CCM] – they used a definition of a positive NG aspirate – *PPI had a lower risk of positive NG aspirate, but no difference in overt bleeding* [the Cook definition] nor was there a difference in pH.

CCM 2010 meta-analysis showed that *PPI has no important advantage in either clinically important bleeding or the development of PNA.* H2 blockers are cheaper, *considered the standard*.

CCM 2013 meta-analysis found that in critically ill patients, *proton pump inhibitors seem to be more effective* than H2 blockers in preventing clinically important *and* overt upper gastrointestinal bleeding. The robustness of this conclusion *was limited* by the trial methodology, differences between lower and higher quality trials, sparse data & possible publication bias. *No* observed *difference* between drugs in the risk of pneumonia, death, or ICU length of stay.

Paul Marik looked at enteral feeding [CCM 2010]. His analysis showed that *there was no benefit to H2 blockers while using enteral nutrition, nor was there a difference in PNA overall*. However, PNA risk may increase in those who receive *both* enteral feeding and H2 blockers. It is still felt that enteral *feeding is not* a substitute for stress ulcer prophylaxis until further study confirms this.

Peptic Ulcer Disease & Conclusion

Prevention of stress-related *mucosal injury* is not the same as active peptic *ulcer* bleeding – PPIs are held as the standard for treatment of GI ulcer-related bleeding. PPIs enhance healing, decrease rebleeding and reducing surgery.

Conclusions – stress ulcers do occur, but they are *uncommon* and in patients *with known risk*. H2 blockers are efficacious, *PPI have not been studied as well in the realm of prevention*. PPI will increase pH. Enteral nutrition is not a substitute. Patients with peptic ulcer bleeding require PPI prior to endoscopy and this will change the stigmata of bleeding, rebleeding and need for surgery is reduced with PPI for ulcer bleeding; it is unclear if H. pylori is a cause of stress-related mucosal injury when identified.

GI BLEEDING IN CIRRHOSIS

Consider a cirrhotic with melena, large esophageal varices and *red wale sign*. What is the most important management step?

70% of cirrhotics have varices; there is a varix development rate of *6% per year of cirrhosis*. Not every patient with varices will bleed, *but 30% will*. Variceal bleeding commonly requires at least 4 units of pRBCs, and in a sizeable percentage of patients the pRBC requirement can be dozens of units.

Initial Approach

The initial approach to the bleeding cirrhotic should be to *assume it's variceal in nature*. About *50% of variceal bleeds stop spontaneously*. The risk of bleeding relates to variceal size [LaPlace's law] and endoscopic stigmata. The red wales sign are little red blebs that put the patient at *high risk for re-bleed*. The overall risk is directly related to liver insufficiency. Currently, *in house* mortality is 20%; 'twas 30-40%, 20-30 years ago. There is *still a 30-50% one year mortality after the first bleed*, if there is additional renal failure, or other organ failure, then the risk of in house mortality goes way, way up.

There is a good body of literature as varices are fairly common. *Antibiotics* have a *survival* benefit. *Endoscopy* will lower bleeding risk and re-bleeding risk, but interestingly *no survival benefit*. *Vasoactive drugs* reduce transfusions and bleeding, non-selective beta-blockers reduce bleed and rebleed. Sucralfate and rFVIIa have no data, *PPI have no data, but are suggested as many patients have multiple reasons for bleeding*. 25% of patients will have non-variceal causes of bleeding. So strongly consider PPI. Can consider tranexamic based on the CRASH-2 trial [in trauma patients, not GIB], but in upper GIB with modern anti-ulcer treatment, there was no significant difference in outcome [Cochrane 2012].

Pathophysiology

There is too much pressure in the portal circulation via prehepatic, hepatic, and posthepatic causes. *Prehepatic* would be thrombosis of portal vein; varices develop, but

there is a normal liver. There could be a gradient *across the liver* from intra-hepatic disease and varices arise regardless of the cause. Finally, there is a *post-hepatic* cause for example from thrombosis of all of the hepatic veins at the same time. Additionally, right heart failure, but that is typically long-standing heart failure.

Esophageal and gastric varices are commonly feared, but small and large *bowel varices* can happen - they are clinically much less significant.

What are the important numbers for *portal hypertension*? A hepatic vein pressure can be obtained by wedging the portal vein. If it is *greater than 12 mmHg, this is a problem*. A value between 5-12 mmHg is abnormal, but does not lead to significant varices. The goal is to *get the pressure less than 12 mmHg*.

Presentation and Medical Management

Clinically there can be massive hematemesis, melena. Large IV access is important. FFP is given liberally for an INR more than 1.5. *Target a hemoglobin of 8-10 [old data] as going above 10 can worsen bleeding*. NEJM early 2013 showed that restrictive blood transfusions [Hb of 7 g/dL] *lowered mortality* in patients with *early cirrhosis* and *active* GI bleeding.

What about NGT placement? *When swallowing, the intra-luminal esophageal pressure can get up to 60-70 mmHg* which is much greater than any NG tube placement; but the sensitivity [*83%*] and specificity [*33%*] of *blood or coffee grounds* on NG tube aspirate for predicting high-grade endoscopic lesions is fairly poor [i.e. 17% of *negative* NG lavages - no grounds, no blood - *had a high risk* bleeding lesion on endoscopy and 67% of *positive* NG aspirates [blood or grounds] *did not have* a high-risk endoscopic lesion] – table 2 RUGBE investigators in [Gastro Endos 2004 page 174]. Further, while a *positive lavage facilitates early endoscopy*, there is no clinically meaningful improvement in outcome when NG lavage is performed in a patient suspected of having an upper GIB; NG lavage is deemed 'antiquated' in modern management of UGIB [Gastro Endos 2011 vol 74 page 981]. *Please stop* performing this procedure on patients suspected of having an UGIB; there is truly no clinical utility.

Erythromycin can be helpful to clear clots – give 125 mg IV or 10 mg IV reglan [though the data for this practice *is poor*]. These patients should be in an ICU certainly for monitoring. *20% are infected at admission, 70% will develop an infection in house*! *Broad spectrum antibiotics for 5-10 days will lower infection rate and mortality rate*. The greatest benefit is in Child's C and pre-EGD. Suggest cefotaxime, levaquin, unasyn.

What about *splanchnic vasoconstrictors* – for example vasopressin. It restricts blood flow via V1a receptors at the celiac and SMA, but also to the peripheral arterioles. *Octreotide* is more specific for the splanchnic beds, mostly over 5 days. Bleeding control was *better with octreotide versus vasopressin with fewer side effects*.

What about octreotide alone? The best is octreotide *plus* endoscopy – no survival improvement, but secondary end-points are better.

Endoscopic Interventions

The risk of bleeding goes by varix size and stigmata. Should banding be done? The tip of the endoscope is placed near the varix, there is suction and then there is banding onto the varix. It may be technically challenging with lots of blood, but can be done. If the varix cannot be seen, injection of sodium morulate can be used. *Banding has reduced infection, reduced ulcers and less strictures as compared to sclerotherapy*. *Banding is therefore preferred when visualization is good*.

10-20% of varices will re-bleed within 5 days [reason octreotide is given for 5 days]. Re-bleed is typically defined as 4 U pRBCs or hypotension

in the first 6 hours. The *risk for re-bleeding is increased with PV thrombus, HVPG more than 20 mmHg, and infection* [probably because of systemic hemodynamics]. Typically, when the risk is high, then GI will go back and take a second look for further therapy. If there is still bleeding, then proceed to TIPS evaluation.

The other option is to break out the Minnesota or Blakemore tube. The difference is the number of lumens [quadruple lumen versus triple lumen, respectively]. The patient must be intubated and sedated. They can be placed orally or nasally, but epistaxis can be caused because of the size. The gastric balloon must be increased in size to 250 cc, it is *air-filled* and it must be pulled up on the GE junction and taped to a football helmet or hockey mask. This may create a hiatal hernia, or a tear. If the gastric balloon is in the esophagus, there can be perforation.

The next step is TIPS which is a Seldinger technique through the IVC, cannulate the right hepatic vein and then, through the liver making a pass into the right portal vein; *there needs to be an US Doppler before TIPS to make sure its patent*. Once in, they can pass a wire through to the portal vein, they then place a mesh stent to prevent the parenchyma from closing down. It is a technically difficult procedure.

What about comparing the modalities for the prevention of variceal *re-bleeding*? TIPS and surgery *out-perform* endoscopy, but endoscopy has a lower rate of encephalopathy. *Mortality is roughly the same between all three*. There are new Teflon stents that have much better one year patency 86 versus 47%, but they are technically more difficult.

What about *out*patient prevention of *rebleeding*? So the patient makes it through the hospital. Patient needs outpatient repeat EGD in 2-3 weeks [repeat banding prn], then q 2-3 weeks. PPI BID to lower esophageal ulcer bleeding [co-morbid] and avoid NSAIDs. Beta blockers decrease re-bleeding too.

The *prevention of recurrent bleeding* from known esophageal varices [board scenario]. Consider a patient with a history of "COPD-asthma" [so the use of beta-blockers is contraindicated]. Thus the correct answer is *repeat esophageal variceal band-ligation* to reduce re-bleeding. There is mention of the use of nitrates as well, but monotherapy tended to worsen outcome in cirrhotics. The use of TIPS is reserved for those en route to an OLT but if the patient is an active alcoholic, OLT is not in the future. Some centers perform splenorenal shunts, there is probably less risk of HE with a distal splenorenal shunt.

In Summation

So with all the therapy when the variceal bleeder comes in, *70% will stop bleeding with medical management*, then get an outpatient EGD. *20% will have early re-bleeding in house that is stopped* with repeat EGD in house. If worsening bleeding or more varices in house, patient should go for Blakemore +/- TIPS [*latter occurs in about 10% of variceal bleeding*].

In summary, variceal bleeding outcome depends upon cirrhosis severity & hemostasis achievement. *Emergent EGD after resuscitation has more than a 90% efficacy [i.e. 10% go on to need TIPS in house]*. Antibiotics improve survival! Octreotide is preferred over vasopressin and if there is early re-bleeding, then EGD should be repeated in house. For uncontrolled bleeding, and selective re-bleeders, balloon tamponade can be done as bridge to TIPS. Secondary prevention is as follows: follow up EGD, BB, PPI and no NSAIDs.

FULMINANT HEPATIC FAILURE

Acute liver failure [ALF] is the onset of sudden coagulopathy with an INR of more than 1.5 and encephalopathy within 8 to 26 weeks in a patient

without prior liver disease – thus cirrhosis, chronic hepatic disease, chronic alcoholic hepatitis, HBV reactivation, sepsis, etc. are exclusions [e.g. cholestasis of sepsis] as these are pre-existing conditions.

Overview

There are only 1-10 cases per 100,000 every year, so less than 3000 cases per year in the US. The leading cause of ALF in the US is Tylenol [APAP] OD, *it is not alcoholic hepatitis*.

Identification of the cause of ALF is therefore paramount because of the varying treatment. Consider sending a drug screen, acute Hep A and Hep B serologies, but these are less common. Rarer causes include autoimmune, pregnancy-related may occur [third trimester], HSV/CMV can do it, but rare. Everyone should get an US Doppler as this may be a result of hepatic venous outflow. *APAP overdose is far and away the most common cause. The second is unknown, the third is drug-toxicity.*

Deterioration can be rapid and unpredictable with the need for a transplant evaluation – *acute liver transplant* has a 75% one year survival. In a patient with ALF, transplant evaluation includes: HIV, CMV, HSV, hepA, IGM, HBsAg, HBcAb, blood cultures, PPD, CXR, Liver US, EKG, TTE.

What is the evidence based management of ALF? *There is benefit for NAC for APAP and non-APAP acute liver failure*, H2 blocker [reduce the risk of GIB, but also PPI likely of benefit] and CVVHD as well as mannitol [for high ICP, but small trials].

There is a low incidence of ALF so this disease is very hard to enlist patients into randomized controlled trials. Survival with APAP, Hep A, ischemic do fairly well. Idiosyncratic drug reaction, indeterminate don't do so well. Remember, *indeterminate*, fulminant hepatic failure or *fulminant hepatitis B* should receive *rapid* evaluation for emergent transplant.

Amanita toxicity treatment is lavage, IV penicillin, and dialysis. Autoimmune ALF can be treated with steroids. Budd-Chiari – treated with AC. Entecavir should be used for acute hep B but outcomes are poor. Fulminant herpes is treated with acyclovir. Pregnancy – C-section, but usually post-partum problems are the main morbidity. Wilson's disease should be treated with rapid copper chelation, but transplant is inevitable.

Tylenol Toxicity

APAP overdose is treated with lavage, charcoal, NAC. *APAP is about 50% of all cases of ALF*. How is the history with APAP? More than 6 grams at once. 4-6 grams over many days. Prolonged fasting [depletes glutathione], nausea, vomiting, chronic ethanol abuse increase the risk.

There is high AST and ALT [in the 1000s] *with normal bilirubins*. For example, if you see a bilirubin of 17, it is less likely APAP toxicity. There is coagulopathy, metabolic acidosis, and renal failure.

The Rumack nomogram is from the early 80s and is only good for a single time point ingestion. Remember that, while uncommon in APAP toxicity, *clinical jaundice will falsely lower APAP levels because it is a colormetric assay*.

NAC enhances glutathione stores, give it until the INR is less than 1.5. Oral dosing is suggested, but acetadote is the IV form. The dosing is 140 mg/kg, then 70 mg/kg every 4 hours to 72 hours or INR less than 1.5. The dosing is different for IV. It is 150 mg per kg for the first dose, 50 mg/kg for 4 hours, and 125 mg/kg over 19 hours. *It is an IV sulfa drug and therefore there are concerns of sulfa allergies*.

Less than 1% die from acute APAP. Half of the worst outcomes cases are therapeutic misadventures. The serum APAP levels tend to be low, having a low level doesn't mean that it wasn't APAP especially if the drug was take over a period of many days. Usually the patients are

taking multiple products with APAP in them, with the majority being OTC. Many are on Vicodin, etc. and then taking OTC medications.

The encephalopathy tends to be worse in non-intentional cases of APAP OD, maybe with delayed presentation or narcotic co-administration from the un-intentional nature. These patients should be in the ICU because of the rapid neurological deterioration. INR is important to follow as is creatinine. ABG, lactates, ammonia are also somewhat helpful. *Blood sugar should be followed closely. Liver biopsy should not be performed as it does not change recovery/mortality*.

Infection is very prevalent as the hepatocytes are being lost [which is the largest source of Kupffer cells]. Some suggest daily surveillance cultures as infection in these patients is usually bacterial in nature – 80% with bacteremia, fungal in about 20%. Cephalosporins and vancomycin should be considered, but *avoid* aminoglycosides.

Fever can worsen HE so cooling is suggested [avoid APAP for temperatures]. Coagulopathy is common and may appear like DIC. *Only about 10% have severe bleeding despite coagulopathy*. FFP and should only be given if there is severe bleeding or a procedure is planned.

Non-Tylenol Related Acute Liver Failure

There is *no benefit for steroids* in non-APAP liver failure, nor enteral decontamination, charcoal hemoperfusion or albumin dialysis. In *acute alcoholic hepatitis* [not ALF], there is improved outcome with steroids for a high discriminant function.

Lee et al Gastroenterology 2009 found that there was *more transplant free survival* in NAC group *especially in those with early stage encephalopathy*, but no improvement in overall 3 week survival with IV NAC versus placebo. There was a trend to improvement in length of stay.

NAC is well-tolerated with an 8% increase in nausea and rash. In kids with ALF, there was not a survival benefit with NAC; transplant can be a consideration. In acute alcoholic hepatitis [again, not ALF] there is suggestion of benefit for NAC [NEJM Nov. 2011].

Cerebral Edema

Cerebral edema is the main cause of mortality in ALF. It typically occurs only in acute cases. In ALF it is the result of ammonia, ischemia, cytokines, toxins; *there is astrocyte swelling and there is loss of cerebral autoregulation*.

The increase in glutamate to glutamine in the astrocytes leads to brain swelling as water is pulled into the brain/astrocytes.

Grade I encephalopathy [EN] is slow mentation with minimal or no change in LOC. The patient should be placed in experienced nursing care in quiet room. *Grade II* there is disorientation, drowsiness, with *asterixis*, inappropriate behavior. *Grade III* are incoherent, typically intubated, usually with renal failure, ICP monitoring should be considered at grade III.

Hemodynamic management of these patients is difficult, CVVHD will most certainly be needed. Levophed is preferred over vasopressin and try to minimize PEEP. An ICP monitor is suggested because CT is insensitive and physical exam is poor in terms of managing the patient's ICP. Neurosurgeons will push back as there is no data to support ICP monitoring, and typically there's a bleeding risk.

In those with ICP monitoring [Liver Transplant 2005] all were intubated, majority were on dialysis, and majority were listed for transplant. *In the ICP group, there was more ICU intervention [more mannitol, more barbs, and more pressors] but no change in outcome*. There was *no* difference in listing rate or transplant rate. Michigan consults neurosurgery for all grade III or IV HE. Does one use rFVIIa to lower bleeding risk

when placing and ICP monitor? There is a 4-6 hour window for this procedure, but no data. Be wary in those with thrombophilia as there may be an increased risk of clotting.

Once the monitor is in, the CPP should be above 50 and ICP not more than 25 for 5 minutes. Hyperventilate to temporize, give mannitol, pentobarb coma but watch out for hypotension and pressors [may reduce cerebral blood flow].

What to do about Grade IV HE? Grade IV is comatose, unresponsive to pain, with decorticate or decerebrate posturing. Liver transplantation [ALT], ABO compatible whole liver usually takes about 2-3 days for critically ill ALT. Again 75% one year survival.

What about hypothermia? There is pilot data with hypothermia to 33 centigrade, often heavy propofol is needed because of shivering. What about worsening coagulopathy, infection risk? Rewarming method? There is no study as yet.

Prognosis

The old *modified King's College Criteria* from the early 2000s, differentiated APAP from non-APAP ALF. *For APAP OD* bad prognosis was lactate more than 3.5 in 4 hours, or lactate more than 3.0 in 12 hours, pH less than 7.3, INR more than 6.5, creatinine more than 3.4, or stage 3 or 4 HE. For *non-APAP*, prognosis was best predicated by INR more than 6.5, *or* 3 of: INR more than 3.5, age more than 40, Bili more than 17.5, Jaundice more than 7 days.

Understand the MELD. It was *initially derived* to predict mortality in patients with *portal hypertension awaiting TIPS*. It is composed of three components 1. INR 2. Creatinine 3. Bilirubin. It is a burdensome calculation but became predictive essentially of all patients with *chronic*, advanced liver disease in terms of survival. In patients with a MELD less than 16, medical treatment is superior to liver transplant. The MELD is now used for allocation of livers. A MELD of 25-29 has a median survival of 200 days, 30-37 is 110 days and more than 37 is about 50 days median survival. MELD is also used to predict survival in *chronic* cirrhosis with various other insults such an infection and variceal bleeding. The use of the MELD score has led to a 15% reduction in mortality in the *chronic* liver failure population because of improved organ allocation. *MELD is not used in patients with acute fulminant hepatic failure awaiting transplant*.

GI BOARD SCENARIOS

Understand caustic ingestion [see also section 9]. A 15 year old swigs a whiskey bottle and it is 25% sodium hydroxide. The next step is admission to the ICU and an emergent endoscopy to evaluate the extent of injury. *Alkaline ingestions tend to be more injurious than acid and tend to injure the esophagus while acid ingestion tends to injure the stomach*. Emesis, drooling and stridor portend a more serious injury to the GI tract. Esophageal necrosis and perforation carries a very high mortality. Deep esophageal ulcer can result in esophageal strictures at 14 days, superficial injury has a good outcome. The patient should have an urgent endoscopy once perforation is ruled out. Stage 3 injury [the worst kind of burn] carries a high mortality, and high risk of stricture. *Some centers perform esophagectomy for stage 3 burns*. The injury to the mucosa is instantaneous so lavage and neutralization is futile. *Emesis and charcoal are contraindicated given the risk of perforation*. The role of antibiotics is controversial, so too are steroids. Perforation is a contra-indication to steroids.

The treatment of *acalculous cholecystitis*. Consider an elderly CVA patient with COPD and CAD who has an aspiration pneumonia but is persistently febrile despite being on broad spectrum antibiotics. His ALP and bilirubin are *slightly* elevated which prompts a RUQ US and this shows a *thickened gall bladder wall* with

sludge with*out* a dilated common duct or cholelithiasis. *The treatment of choice is a percutaneous cholecystostomy because mortality rates in some studies are as high as 50%.* It is thought that acalculous cholecystitis is a form of ischemia reperfusion injury, which occurs in the critically ill. Risk factors for development of this disorder include *biliary stasis secondary to ileus, fasting, dehydration, narcotics, or mechanical obstruction of the biliary tree, mechanical ventilation, total parenteral nutrition, recent surgical intervention, and vasopressor support*. Patients often present with undiagnosed fever or subtle signs of infection without a clear source after careful evaluation. However, fulminant sepsis secondary to acalculous cholecystitis is described.

Recognize and treat *ascending cholangitis*. Note that the patient has Reynold's Pentad which is Charcot's triad *plus altered mental status and hypotension*. Charcot's triad is fever, jaundice and RUQ pain. The RUQ US reveals a dilated common bile duct *without evidence of stone*. *This is still ascending cholangitis* and this patient needs an ERCP which is very effective at treating biliary sepsis.

5. CRITICAL CARE INFECTIOUS DISEASE

PHYSIOLOGY OF SEPTIC SHOCK

Septic shock is about 40% gram negative, 50% gram positive and the rest fungi. Septic shock is the leading cause of death in non-coronary ICUs.

The usual hemodynamics of sepsis is typified by hypotension with increased cardiac output. Nevertheless, there is *impaired myocardial function that lasts for 24-48 hours*.

The nidus of infection such as a pneumonia or abscess allows an organism to proliferate or enter the blood stream. Exotoxins can be released into the blood stream. Endotoxin can be released or a structural component of the bug itself [e.g. teichoic acid, LPS] which cause a cytokine cascade. All organs can be affected.

THE CARDIOVASCULAR RESPONSE

Sepsis causes a 'stunned' myocardium. The EF tends to increase over a period of 10 days. The *survivors of sepsis tended to drop their ejection fractions the most*. The end-diastolic and end-systolic volumes increase during sepsis. Parrillo NEJM 1993 looked at the left ventricle during the acute phase of septic shock and found LVEDV to LVESV values of 225 ml to 150 mL with MAP of 40, CVP of 2, HR of 150 and a cardiac output above 11. The EF was in the low 30s. *During the recovery phase*, LVEDV to LVESV was 150 to 75 mL and EF of 50%, HR of 70 with a cardiac output of 5.3. *Dilation of the left ventricle seems to confer a mortality benefit*, this may be a compensatory response to maintain stroke volume. It is thought to be due to improved LV compliance during sepsis such that LV volume at end-diastole can increase. *But there is also a myocardial depression* seen that is due to TNF and IL-1.

Microvascular endothelial dysfunction is also a problem in severe sepsis.

TREATMENT - ANTIBIOTICS

The treatment of septic shock requires: *early antibiotics*. In mice, *withholding antibiotics* from the onset *of infection* leads to *rapid death* at about *15 to 18 hours*.

In humans*, for every hour* after the onset of hypotension, the incorrect or absence of appropriate antibiotics *increased mortality by 7.6% per hour*.

TREATMENT – VASOACTIVE SUBSTANCES

High dose versus low dose *vasopressin* have differential effects on splanchnic blood flow. Low dose vasopressin [i.e. the doses used in the VASST trial] tends to *increase* splanchnic flow.

Low dose dopamine increases heart rate and contractility and causes some vasodilation while high dose dopamine causes more vasoconstriction. *Norepinephrine* increases heart rate and contractility about the same as dopamine but has a much more pronounced vaso-constriction effect. *Dobutamine* is essentially all HR, contractility and vasodilation. *Isoproterenol* does so to a greater extent [compared to dobutamine]. *Epinephrine* has potent HR, contractility and vasodilatory and vasoconstrictive effects across the board, whereas *vasopressin and neosynephrine* are pure vasoconstrictors [AVP a little more so].

What did the *VASST trial show*? There was no difference between *NE and NE + vasopressin* in severe sepsis and septic shock. There was not an increase in ischemic events with vasopressin as feared. The interesting *subgroup* was those with *low NE requirements* at the onset [less than 15

mcg/min] who had vasopressin added tended to *improve outcome*. This was not what the authors had expected and there was no good explanation for these effects.

What about *the SOAP II trial* [NEJM 2010]? There was no difference between dopamine and norepinephrine in the overall outcome. However, dopamine may *worsen* cardiogenic shock. Overall there was a trend to improved outcome with NE. Dopamine lead to significantly more arrhythmia.

What about the *CATS trial*? This was in Lancet. It compared NE plus dobutamine to epinephrine in severe sepsis and septic shock. There was, in effect, no significant clinical difference between the two arms.

Treatment – Early Goal Directed Therapy

2014 has been a bad year for Dr. Rivers. Both the *PROCESS and ARISE* trials in NEJM have effectively deconstructed the EGDT algorithm, showing that blind application of his initial protocol *to all severely* septic patients does not improve outcome this day in age.

In the *Rivers trial*, [NEJM 2001] in the first 6 hours, the *protocol group received 5 liters* of fluid, compared to nearly 4 liters in the control group. In *both groups about 25% received vasopressors* of some sort. What's interesting is that in the PROCESS trial, the ratio of fluids to pressors seemed to switch in all of the study arms [as compared to the original Rivers study]; that is, *in 2014 there has been a trend to use much less fluid and much more vasoactive substances* when treating septic shock as compared to the original 2001 Rivers trial. Further, as compared to the Rivers trial, the baseline mortality in PROCESS was lower.

The *recent TRISS trial* [NEJM 2014] confirmed what many had believed since 2001, that transfusing to a Hb target of 10 g/dL does not confer benefit in severe sepsis and septic shock.

Treatment – Steroids

'The Annane' study [JAMA] looked at patients with severe sepsis and septic shock. The mortality rate of the control group was 60%. There was an improvement in mortality with the provision of steroids in the setting of *relative adrenal insufficiency* [as determined by a cosyntropin stimulation test]. Then *CORTICUS showed no increase in survival when steroids were given in septic shock*; instead steroids improved time on the ventilator but increased risk of subsequent sepsis.

COMMON INFECTIOUS DISEASE SCENARIOS ON THE BOARDS

HIV

In terms of HIV, the *common* pulmonary disorders are *pneumococcus* [most common & tends to be more severe], haemophilus, PCP, TB and the atypical/viral syndromes.

The *uncommon* pulmonary disorders in HIV are: aspergillus, histo/cocci, staph, toxo, lymphoma and Kaposi.

The rare pulmonary disorders in HIV are CMV, MAC and HSV. CMV can cause pneumonia in transplant patients, it is very, very uncommon to be a pathogen in HIV/AIDS patient.

Other causes of dyspnea in AIDS – CHF, PH, PE, drug toxicity, neoplasms, septic emboli.

PCP is a fungus that is transmitted via respiratory secretions. Therapy with monoclonal antibodies [e.g. adalizumab - for MS] *have been linked to PCP!* CD4 counts are almost always below 200 in patients with PCP [but 10% can have a CD4 above 200]. The risk of PCP increases with lower CD4 counts [54% with a CD4 count less than 50; 35% with a CD4 count between 50-200]. *AIDS patients tend to develop pneumatoceles*. Sometimes there will be an infiltrate in one lung and a PNTX in the other. In general, PCP presents with

bilateral GGO and thin-walled cystic lesions. Pleural effusion and lymphadenopathy are really uncommon in PCP. *PCP in HIV-negative patients typically have a poor prognosis and the presentation typically occurs in the setting of steroid tapering* [patients who have been on more *than 20* mg/day of prednisone for more than *two* months].

What is the diagnostic approach of choice for PCP? *Sputum or BAL stain or immune-fluorescence*. A serum or lavage PCR for PCP is sensitive, *but not specific*. So if it's negative, it's helpful. Induction of sputum can diagnose PCP if the RT is good.

If the patient has a PaO2 less than 70 on air or an Aa gradient more than 35 mmHg, the patient should get steroids, plus 21 days of Bactrim.

Pentamidine can *cause pancreatitis and insulin release leading to low BG*.

Consider a patient with known AIDS, a WBC count of 3,000 with 3% lymphocytes [total of 90 lymphocytes, and maybe half of these are CD4] with cough, fever, infiltrate and recent Central Valley exposure. This patient may have coccidioidomycosis. *The best way to obtain cocci on respiratory secretions is a pap smear* [better than KOH and calcofluor]. Blood and bone marrow cultures for cocci are rarely diagnostic and take days to grow. Similarly, CSF studies are poor. *The gold standard tends to be serologic tests, but even these can be negative in advanced AIDS patients*.

Moving on to *toxoplasmosis*. This is a CNS *mass lesion in a patient with AIDs*. It's almost always either toxoplasmosis or lymphoma. If the CD4 count is high, it is lymphoma. Toxoplasma PCR is quite specific, but only 50% sensitive and becomes negative quickly with therapy.

You need to obtain a CSF for toxoplasma and EBV titre – *the latter making it more likely lymphoma*. If CSF cannot be obtained, two weeks of treatment for toxoplasma and re-imaging should be done. If there is no improvement in the mass lesions, it is most likely lymphoma.

The *treatment for toxoplasmosis is sulfadiazine and pyrimethamine*. Steroids are used if there is edema and anti-convulsants only if the patient seizes. Other causes of brain-lung disease in patients with HIV include: TB, nocardia, rhodococcus.

Anti-retroviral therapy for the intensivist – giving inadequate doses can harm the patient as resistance can occur quickly. *It is better for the patient to be on no HAART, than to give the patient inadequate doses*.

Fever & Rash

This can be a viral exanthema [measles, varicella, mono] or a bacterial exanthema [staph, pneumococcus, meningococcus, leptospira, ehrlichia, rickettsia].

On the boards, '*summer sepsis shouldn't die without doxycycline'* as this could *be Rocky Mountain Spotted Fever* [or Borrelia or Ehrlichia]. The rash can easily be missed and the remaining symptoms are very non-specific. Tick exposure, south or southeast US is more common. But look for low platelets and hyponatremia, liver enzymes might be slightly high. Immuno-fluorescent stain *of a skin biopsy* is the diagnostic test of choice.

Understand the tick-borne zoonoses often present with dermatologic manifestations. Consider a patient with profound ARDS over 10 days that is not improving on fairly broad anti-microbials. You learn that the patient pursues outdoor activities in New England; it is the summertime. Because *all of the following* can cause profound *ARDS – Lyme, Ehrlichia, RMSF*, and *Babesia* and because it is typically *clinically impossible to distinguish between these infections* and because *co-infection* with these zoonoses can occur in up to 16% of patients [the white-footed mouse

which is the mammalian reservoir for these diseases is 40% co-infected] it is prudent to treat for all of them.

The *treatment of Lyme's [Borrelia burgdorferi], Ehrlichia, and RMSF [Ricketsia ricketsii] is tetracycline* or its derivatives. The *treatment of life-threatening babesiosis [B. microtii] is clindamycin and quinine*. The white-tailed deer which is the definitive host for these organisms is increasing in population so these diseases are becoming more common.

Ehrlichia can occur anywhere from New England to the South and South Central US; *it may* present with petechial rash, but this is uncommon.

Rickettsial disease is ubiquitous, despite the name 'Rocky Mountain.' Key to the history were outdoor pursuits, anemia, thrombocytopenia and sometimes hyponatremia with elevated liver enzymes.

Recognize *ecthyma gangrenosum* and that the most common cause is *pseudomonas*. Other causes of this foul-looking rash are staph, HSV, candida and mucor but pseudomonas is the most common cause. This rash is typically seen in immunocompromised patients, but also in diabetics, burn patients and the severely malnourished. These lesions are most commonly found in the perineum, but also on the extremities, trunk and face. They typically begin red purpuric macules that then become vesicular, indurated, bullous, *pustular and finally hemorrhagic*. Then within 12-24 hours a gangrenous ulcer begins to form. Biopsy typically reveals bacteria invading the veins. Patients with ANC less than 500 rarely survive. Treatment is with an anti-pseudomonal antibiotic and surgical debridement.

Vibrio vulnificus is a gram negative found in warm marine water. It can cause a primary wound infection if it gets into a cut [large, violaceous plaques and bullae] and also a septicemia in cirrhosis patients who *ingest raw oysters*.

Infectious Diseases with Neurological Symptoms

Pneumococcal meningitis has a high resistance rate, this should be initially treated with *vancomycin and ceftriaxone*. If the patient is *over 50, the patient may have listeria and ampicillin should be added*.

The use of dexamethasone? In children, there is a reduction in neurological complications [mostly in H. influenza meningitis], in adults, it is controversial but *probably should be used in severe disease in pneumococcous or H. influenza* with the first dose or before the first dose of antibiotics.

N. meningitidis. This bug is a gram negative diplococcus that causes meningitis and septicemia in epidemics. Mortality was once 70-90% and it is now 10%. Cefotaxime and ceftriaxone [third gens] are effective therapy for this bug. Adequate treatment of N. meningitidis has been seen with just 3-4 days of antibiotics without failures, though treatment is usually 7 days. *Vancomycin* is usually initially added, but *can be stopped once N. meningitidis is found*. Other treatments have not shown benefit including: activated protein C, heparin in patients with DIC and *dexamethasone* is really only beneficial in patients with *H. influenzae or S. pneumococcus* as above.

Recognize *ciguatera toxin*. This is a type of poisoning that occurs in people who have eaten *fish within 5 hours of symptom onset*. The toxin is heat stabile, so cooking does not inactivate it. It is common in fish from warm areas such as Hawaii and Florida [e.g. red snapper]. The toxin arises from diatoms, but the fish bio-concentrate it. The first symptoms are invariably gastrointestinal and this then progresses to *neurological symptoms that include paresthesia of the lips and extremities and then even paralysis of the respiratory muscles* [the patient ate red snapper and then was intubated about 6 hours later]. Death has been reported, but is rare.

Mackerel and tuna [scromboid fish] can cause *scromboid poisoning* – is a histamine reaction from the spoiled fish that involves characteristic histamine responses in the body including flushing, cramps and diarrhea, headache, mouth burning, nausea and vomiting. *Bronchospasm, and wheezing may occur*, treatment is supportive and death is rare.

Diplopia and dysphagia 2-24 hours following the ingestion of canned foods should prompt an investigation for botulism toxin. There is typically a descending weakness that is bilateral and symmetrical. There is *no fever*. *Botulism is caused by enteric entry of botulism toxin* and is treated by enemas and lavage to remove the toxin. Anti-toxins may also be administered.

The third most common cause of food poisoning in the US [after Salmonella and staphylococcus] is *C. perfringens* food poisoning. It is associated with poorly cooked meats or meat products such as gravy. Diarrhea and cramping abdominal pain 7 to 19 hours after ingestion is typically how this presents. It lasts for a few days. In rare cases, the gut can become necrotic and perforate which leads to a very high mortality. If in the blood, C. perfringens may cause massive hemolysis.

Recognize Tick Paralysis in a young women who recently returned from camping. The distractor is that she ate predominantly from canned food. However, she has *no bulbar symptoms which would make botulism rather unlikely*. Tick paralysis is treated by *removing the Tick* which is usually persistently feeding and releasing a neurotoxin into the patient which causes a bilateral and symmetrical paralysis with preserved sensation. Patients rapidly improve once the Tick is removed.

Recognize West Nile virus infection. Consider a young, transplant patient on multiple immune-suppressives who develops *proximal muscle weakness*, then *bi*lateral lower extremity with *uni*lateral upper extremity *flaccid paralysis* then bilateral upper extremity flaccid paralysis. Both polio and WNV can present exactly like this *also with bulbar and respiratory symptoms*. The kicker is his LP with reveals 10 WBC with a PMN predominance and high protein, this rules out GBS and makes it more likely infectious. Further GBS presents with ascending paralysis and frequent cranial nerve findings, rather than proximal in this patients case. GBS should also reveal markedly slowed or blocked peripheral nerve conduction which is not seen in this patient.

Treat tetanus. The patient sustained a fall and cut 10-14 days prior to presenting with trismus and muscle spasms, neck stiffness and leg stiffness. She should be treated by being *placed into a quiet, dark ICU room and administered benzodiazepines, metronidazole, and tetanus anti-toxin*. The patient should NOT be treated with elective intubation as this is a profound stimulus for muscle spasms. The patients are often given an elective tracheostomy at a later date. In some patients, neuromuscular blockade is required to treat the spams.

C. Difficile

There is a broad range of symptoms, the more severe it is, the more abdominal symptoms and risk of dilatation and perforation of the gut.

C. diff has been associated with every kind of antibiotic [*including metronidazole and vancomycin*] and even anti-neoplastic agents that have anti-microbial activity [*e.g. methotrexate*]. *C. diff causes 25% of all antibiotic associated diarrhea*, but is the most common cause of nosocomial diarrhea. C. diff may present in a whole host of manners from mild diarrhea and unrest, to profound fever, leukocytosis, shock and death. *C. diff of the proximal colon may present without diarrhea [10% of patients]* and this is the kind that can present as mega-colon, perforation and death.

Fever is not characteristic of C. diff; it is present in 10-15% only. Unexplained leukocytosis is common with 50% having more than 15K and 25% with WBC above 30K. C. difficile is NOT most reliably diagnosed by stool culture. Many asymptomatic adults and children have this bug cultured in their stool, but it does not mean disease. Further, 20% of asymptomatic patients in the hospital harbor this bug in their intestine, though the majority of these isolates are non-toxic forming.

The most reliable test to diagnose C. diff is the *tissue culture for cytotoxicity of cytotoxin B*. However, this test is expensive and takes days. Most labs use ELISA from the stool for toxin A and B but *not all labs detect toxin B which will miss patients with C. diff. Additionally, even after three negative ELISAs for A and B, some patients will still be detected by the cytotoxicity assay [this can be 5-10%]* so in patients with a high suspicion with negative stool ELISAs, the cytotoxic assay may be required. Currently, the approach to diagnosis is one stool for PCR, *but no more*. They will have a positive PCR for a long time even after treated.

What is the treatment of choice for severe C. diff in the ICU? *Oral vancomycin plus IV flagyl* [CID 2007].

Fever and Hemolysis

Recognize and treat falciparum malaria. The patient returned from West Africa and has high fevers, anemia, thrombocytopenia, hyponatremia and ARDS. Blood smear reveals intra-cellular parasites. The patient has a parasite load above 11%. Parasite density can help monitor outcome. Greater than 5% is quite bad and in sick patients, should be checked every 4 hours. Bacterial pneumonia can complicate things with falciparum malaria, but *ARDS from micro-vascular unrest is a common event in malaria and may affect the lungs*. A *quinoline* [quinine, quinidine] or artemisinin plus a tetracycline derivative [or doxy or clinda] is the treatment. The *quinoline derivatives are the most effective against falciparum*. IV quinine is no longer available in North America, but IV quinidine is. It carries toxic effects – QT prolongation, arrhythmia, hypotension, and hypoglycemia. It acts by antagonizing heme polymerase which causes *heme to build up and heme is toxic to the parasite*. Artemisinin binds iron and creates free radicals which is also toxic to the parasite. Pentoxyphylline is a phosphodiesterase inhibitor that lowers cytokine levels, and was previously recommended, but *no longer*. Exchange transfusion was once suggested to reduce parasite load, but it did *not* improve mortality either.

Recognize other infectious causes of massive intra-vascular hemolysis. Consider a patient who is profoundly septic after eating old gravy with abdominal symptoms and serum that is blood red. Note that beta-hemolytic strep will cause *hemolysis on an agar plate, but not in vivo*. Massive hemolysis of an infectious variety has a narrow differential including *C. perfringens*, falciparum malaria, babesiosis, and bartonellosis.

Bartonellosis (Oroya fever) is caused by a pleomorphic Gram-negative bacillus and is transmitted by sand flies. It is endemic to mountain valleys in Peru, Columbia, Ecuador and Bolivia.

Babesiosis is a malarial-like illness transmitted by ticks from animals to man; *it can cause massive intra-vascular hemolysis*. Cases have been reported in the United States from Long Island, Nantucket, and Martha's Vineyard. As above, it may present with ARDS and commonly co-occurs with other tick-borne diseases. Rash is not a common feature of Babesiosis.

Noninfectious causes of massive intravascular hemolysis include paroxysmal nocturnal hemoglobinuria, the hemolytic uremic syndrome, which can sometimes follow Escherichia coli and

shigella infections, paroxysmal cold hemoglobinuria, and certain snake venoms.

Weil Syndrome

Recognize and treat leptospirosis. Consider a patient who is a young veterinary technician who likes to camp and hike in the southern US. L. interrogans is a spirochete and a zoonotic infection. Dogs, horses, rodents, cattle and swine may all carry the disease. It is transmitted via contact with animal urine or infected soil and water. It is common in tropical locations such as Hawaii and among those who are exposed to freshwater and to animals. Leptosporosis in pregnancy, especially early pregnancy can be devastating to the fetus. *Conjunctival suffusion* is the classic, specific finding but it is not terribly sensitive. The disease may be mild, or fulminant with the organs most affected being the liver, kidney and spleen. A severe form is *Weil syndrome which is hepatosplenomegaly, jaundice, hyponatremia and renal failure* can be present.

Cases of leptospirosis that require the ICU have a greater than 50% mortality and those with ARDS and or CNS involvement may have a higher mortality. While the disease is usually mild and self-limiting, severe cases should be *treated with doxycycline; ceftriaxone will also work*.

Rocky Mountain spotted fever may also present with *Weil syndrome*, but it will be associated with a tick bite and a rash of the palms and soles. It is caused by Rickettsia Rickettsii – it is typically associated with marked thrombocytopenia.

NOSOCOMIAL INFECTION

Which nosocomial infection has increased over the last 10 years? CRSBIs, VAPs, CAUTIs have all *decreased*; *C. difficile has increased*.

The top 4 healthcare-associated infections are: *coagulase negative staph, staph aureus, enterococcus and candida species*.

The top cause of CRBSIs is coagulase negative staph, for CAUTI its E. coli, for VAP its staph aureus and for skin and soft-tissue infection it's s. aureus as well.

Transmission & Isolation

The most common cause of transmission of nosocomial infections *is by contact*. Large *droplets* travel a few feet and drop with gravity, small droplets [less than 5 microns] stay *airborne* for hours.

Seasonal flu is spread by large droplets. Therefore, the patient must be 3-6 feet away from anyone not in a standard surgical mask.

Standard isolation requires hand hygiene, *droplet precaution* requires hand hygiene, private room if possible and a surgical mask within 3 feet of the patient. *Contact precaution* requires hand hygiene, a private room, gloves and gown. *Airborne precautions* require hand hygiene, private room and an N95. All airborne isolation rooms require negative pressure with no air recirculation unless HEPA-filtered.

Pertussis, mumps, and N. meningitidis are all droplet precautions. There are three common diseases that *require airborne*: measles, chickenpox and TB.

Meningococccus post-exposure prophylaxis. The only people who require PEP are *those who are intimately exposed to the patient with direct fluid contact in an enclosed space for 60 minutes or longer*.

Because C. difficile is a spore-former, it is hardy and only killed by bleach. Nosocomial bacteria that can cause infection via environmental contamination are: C. diff, VRE, MRSA, acinetobacter, pseudomonas, norovirus, HBC, HCV, *aspergillus, mucor and rhizopus* – rhizopus likes to get into the blood stream and cause infarction.

Catheter-Related Blood Stream Infection

*S*hort-term catheters are contaminated via the *s*kin, *l*ong-term catheters via the *l*umen.

The prevention of CRBSI should include the use of a scrub cap. This is because it was a *part of a bundle that was studied and shown to improve CRBSI rate [like blood transfusion in the EGDT trial].* It is hard to know which aspects of the bundle improve outcomes, but it's there.

The use of *coated catheters* may improve CRSBIs *if* the use of bundles does not make the institution CRSBI rate very low. Chlorhexidine patient cleaning can prevent infections as well.

The reduction of *bacterial colonization* of central venous catheters is facilitated by: silver impregnation, antibacterial impregnation, tunneling, heparin coating. *The use of the plastic sheath over the PAC has not been effective at reducing colonization*. Central venous catheters impregnated with sliver and other antimicrobials *have been shown in RCTs to reduce the risk of CRBSI. They only reduce the risk, however, if the institutions baseline CRBSI is above 2%.* Below this risk, they do not improve outcomes. Routine changes of CVCs do not lower the risk of infection and routine changes over a wire *tend to increase the risk of CRBSI*.

Peripheral blood and *catheter tip* growing the same organism *defines catheter infection; or* if the hub is culture positive 2 hours earlier *or* if there is more than 3 x the bacterial load from the catheter culture as compared to the peripheral blood.

The most common pathogens from CRSBIs are coagulase-negative staphylococci [may be over-called], staph aureus, enterococcus, gram negative rods and candida.

What is *the treatment course*? Vancomycin should be, essentially, first line. If the MIC are 1.5 or more, then some suggest using other agents as there could be worse outcome. Daptomycin is one such suggestion. *Gram negative coverage* is also a consideration in some populations. *Candida treatment* is nebulous. Femoral catheters in ill patients should be considered for candida treatment, or sepsis on TPN, heme malignancy, known candida colonization at 'multiple sites.' Candida treatment should include *an echinocandin*. Fluconazole should be considered only if there has been no azole in 3 months *and the likelihood of glabrata or kruseii is considered 'very low*.' [For the board exam, the answer is never fluconazole in this situation].

When deciding to pull a CVC, which is the least likely to indicate an infected catheter? A femoral versus a peripheral catheter should not sway your decision. If the patient has: *positive blood cultures without a focus of infection, hemodynamic instability, erythema at the catheter site or pathogens that are likely to cause CRSBIs*, then strong consideration should be given to removing the catheter.

Long-term catheters requires a higher threshold for removal – e.g. suppurative phlebitis, endocarditis, BSI for more than three days into appropriate antimicrobial coverage, S. aureus, pseudomonas, fungi or mycobacterium.

If it's a short-term catheter, then any of the above should also prompt removal. Less virulent, but difficult to eradicate microbes should also be considered when removing a catheter.

If a patient has bacteremia with a line in, there are various decision points about duration of treatment. *For coagulase negative staph aureus* with an uncomplicated catheter-related BSI, 5-7 days of antibiotics is OK if catheter removed. If there is a desire to keep the catheter, then 10-14 days with an antibiotic lock. *Interestingly, if the catheter is removed and if blood cultures repeated are negative, then no antibiotics are needed*.

For staph aureus, the catheter should be removed and then 4-6 weeks of antibiotics. If the patient is *non-diabetic* [increases the risk of

metastatic seeding], non-immunocompromised, without hardware, a negative TEE, with fever and BSI *resolved within 72 hours*, and the patient is stable without signs of further infection*, then 2 weeks of antibiotics are OK*. If the patient has a positive catheter tip for S. aureus, *but negative peripheral blood cultures*, then 5-7 days is OK with close follow up [*but this is an unusual situation*].

Interestingly, *enterococci and GNBs* are treated for only 7-14 days because these bugs are 'serum susceptible' that is *easily opsonized*.

Candida is also two weeks. There should be eye exams at the end of this 14 days as *3% can have endophthalmitis*. *Duration is determined from the first day with a negative blood culture for all of the above.*

When to perform an echocardiogram? If a shorter course for staph aureus [two weeks] is planned, *then a TEE is recommended*. If there is persistent staph aureus bacteremia. *Wait 5-7 days following diagnosis of BSI* to obtain a TEE to allow the vegetation to ripen. Repeat the TEE earlier if there is persistent fever or BSI 72 hours beyond removal of the catheter.

What not to do? Don't: culture tips unless suspected infection, order qualitative tip cultures [broth], culture the subcutaneous segment of the CVC [unless it's a PA introducer], under-fill blood culture bottles [some labs weigh the culture bottles to see if there is 5-10 cc of blood sampled], start linezolid for suspected CRBSI, use thrombolytics adjunctively, routinely re-culture after stopping therapy [except dialysis catheters].

Ventilator Associated Pneumonia

How to reduce the incidence of VAP? Aseptic technique, ventilator bundles and ETT coatings [silver or chlorhexidine coatings]. Changing the ventilator tubing regularly *does not reduce* the risk of VAP.

Measures to reduce VAP are plenty. Sub-glottic suctioning and oral decontamination have proof, so too do SBTs and elevation of bed, but regular changing of ventilator tubing does not reduce the risk. The CDC guideline for "prevention of VAP and other complications" *includes peptic ulcer disease prophylaxis, and DVT prophylaxis*. Closed versus open tracheal suctioning *does not* alter VAP rates [i.e. a protected tracheal suction catheter].

The diagnosis of VAP is very difficult. In JAMA 2007, there was an article on diagnosis of VAP. *The presence or absence of fever, abnormal WBC or pulmonary secretions do not* alter the probability of VAP. The combination of a *new infiltrate with* at least two of: fever, WBC, or purulent secretions as an LR of 2.8. The lack of an infiltrate lowers the likelihood of VAP with an LR of 0.35. *Less than 50% PMNs on cell count of secretions makes VAP unlikely [LR 0.05 to 0.10].*

How is *VAP treated*? You need to treat both MRSA and pseudomonas. Antimicrobial therapy in the preceding 90 days, in house for *5 or more* days, high frequency of resistance in the community, hospitalization for 48 hours of more in the last 3 months, residence in a nursing home, home infusion therapy, dialysis within one month, home wound care, family member with MDR bacteria are all risks for MDR bacteria. Legionella is a possible pathogen in VAP as is influenza.

There is no evidence that combination therapy improves gram negative pneumonia. In a neutropenic patient with pseudomonas bacteremia, there is evidence that two drugs work for gram negative infection.

Treat for 8 days, unless acinetobacter or pseudomonas, then give two weeks.

Catheter-Associated Urinary Tract Infections

UTIs are caused by a biofilm between the urethra and catheter, and by accessing the drainage port in a non-sterile manner.

Surgical Site Infection

Surgical site infections can be reduced by prophylactic antibiotics within 30-60 minutes of incision and *for no longer than 24 hours*. Razors should not be used as they *increase the risk of infection*. The surgical site should be cleaned with chlorhexidine. Glucose control and normothermia should be attained.

As of October 2008, *medicare stopped paying for* IV catheter infections, mediastinitis post heart surgery and catheter-associated UTIs, decubitus ulcers, fractures or other injuries, objects left in during surgeries, air embolism, blood incompatibility, VTE following orthopedic replacements and poor glycemic control.

A FUNGUS AMONG US

What is the difference between *yeasts and molds?*

Yeast are round, single-celled organisms [e.g. candida, cryptococcus, *and the endemic mycoses*] while molds are filamentous [e.g. aspergillus, fusarium and mucormycoses – the difference between aspergillus and mucor is important because they are treated differently].

In which fungi is a serum beta d-glucan test important? It is very good for *most fungi*, but *NOT* mucor. Blood cultures are probably the best for candidemia. Galactomannan is positive for molds [e.g. aspergillus, fusarium] and *not yeast and NOT mucor*. It can be positive with pip-tazo administration.

Yeasts in the ICU

In terms of *candida*, most are albicans, but there are others. The non-albicans are much less likely to be susceptible to the azoles [e.g. fluconazole]. Glabrata [increasing resistance] and krusei [inherently resistant] are resistant. Parapsillosis are skin flora seen in the NICU.

Mucosal candidiasis of the tongue or esophagus in an AIDS patient *is purely a localized disease* because AIDS patients have maintained mucosal neutrophils. However*, in cancer patients*, or patients on high dose steroids, this can be a source of candidemia. *Candidemia in an AIDS patient is usually from a line*.

Candida albicans is the single most common organism isolated from the urinary tract in patients in the ICU. Risk factors include: advanced age, DM, antibiotics, catheter in place, urinary tract abnormalities. The clinical significance of funguria is uncertain. While most patients with fungemia have antecedent funguria, *the risk of funguria progressing to fungemia was 1.3%.* Both systemic fluconazole and amphotericin B bladder irrigation aide in clearance of funguria, however, recurrence is exceptionally common in both modalities.

Candida in the blood is not a contaminant. In patients with candidemia, the patient needs a retinal exam as treatment is a bit different. Candidemia can result in *target lesions* within the liver, though candida may not be seen in the blood. *Candidemia has a high mortality and seeding is common*.

Skin lesions should be biopsied. Always remove plastic, anywhere. *Candida in a respiratory specimen is never important. Candida pneumonia is essentially non-existent*.

The treatment has been evolving for candida from ampho to fluconazole and now to the echinocandins [the 'fungins']. For candidemia in the ICU, *echinocandin is the therapy of choice initially*, and then fluconazole if susceptible. Echinocandins are very well tolerated as is fluconazole.

Consider a patient on prophylactic fluconazole who then develops candidemia. Recall that the

azoles inhibit cell wall synthesis by reducing ergosterol. By contrast, the echinocandins [like caspofungin] also inhibit cell wall synthesis, but by inhibiting the production of 1,3 BD glucan. Candidemia is becoming increasingly common in the ICU and knowing when to start prophylactic fluconazole can be challenging. *One review* suggests *beginning prophylactic fluconazole* in the presence of *one major* criteria [central line, broad spectrum antibiotics] *and 2 minor criteria* [TPN, pancreatitis, glucocorticoids, renal replacement]. The *administration of fluconazole in this situation seems to reduce the incidence of candida blood stream infection*. *However*, when a blood stream infection with candida does arise, it is typically fluconazole resistant. There can be significant class-resistance effects within candida, so adding another azole is not the right answer. There is *uncommonly mixed resistance* between azoles and echinocandins, so picking caspofungin, anidulafungin or micafungin would be a correct response here in the patient with documented candidemia.

The other *yeast you must know for the ICU is the encapsulated one [Cryptococcus],* pulmonary disease may not need treatment. Meningitis is mostly seen in HIV or other immunosuppressed states.

Cyrptococcal *meningitis* in patients with HIV occurs when the CD4 count is really low [less than 50]. The *CSF should be assayed for CrAg as it is commonly positive* [in the blood too – essentially always positive in the blood]. There is a poor prognosis if there is AMS, high opening pressure [above 25 cm H20], positive blood cultures, low WBC in CSF, high CSF Ag titers. A positive CSF culture at 2 weeks predicts treatment failure. *The first CSF can be totally normal in terms of cell count, etc*. Do not rule out based on a normal initial CSF.

The treatment is *amphotericin plus flucytosine*, then fluconazole. The clinical results are not as good with initial therapy with fluconazole. There should be daily LP. The *opening pressure should be lowered if more than 25 cm H20 to less than 20 cm H20*. This is especially important in patients with symptoms. Do not give steroids, mannitol or acetazolamide.

Molds in the ICU

What are the molds you need to know? *Aspergillus, mucor and fusarium*.

Aspergillus shows, septated, acute-branching hyphae. Cutaneous lesions may be seen. There may be a crescent sign on CT scan. This is a late finding, and it occurs when neutrophils return. There may rarely be CNS disease in aspergillus.

Treatment for aspergillus has moved from ampho to L-ampho to voriconazle now, i.e. *the therapy of choice for invasive aspergillus* is *voriconazole* as it may not be more effective, but it is certainly less toxic.

Mucormycosis or zygomycosis is non-septated [there are many species]. Lung, skin lesions can be seen in neutropenic patients. In diabetics, there can be a rhinonasal form which is horrible. The *treatment is amphotericin and maybe posaconazle* [*NOT voriconazole*].

What about Fusarium? *If there is mold found in the blood, it is fusarium*. The description is branching, hyaline and *septated hyphae*, which sounds similar to Aspergillus. Fortunately, they are treated the same, that is, with voriconazole. There is a skin lesion that is round, elevated with central blackened necrosis and surrounding erythema. *Amphotericin cannot cover* this mold, nor can any of the echinocandins [including caspofungin]. This disease can be seen in neutropenic patients and occurs from inhaling spores. They can be found in hospital water.

ANTIMICROBIALS

Antibacterials and antivirals will be covered here. Remember that there is a mortality benefit in

severe sepsis when patients get appropriate antibiotics early [CCM Kumar study]. In fact, there is a benefit to getting an antimicrobial in *the first 30 minutes compared to the second thirty minutes following the onset of hypotension.*

Bear in mind that different antibiotics have different infusion times and that *some may be effectively given as a rapid bolus*. Daptomycin can be infused *in 2 minutes* and merropenem *within 3-5 minutes,* while pip-tazo requires 20-30 minutes. All other drugs require 30-60 mins. This may also be important in a patient with a limited number of IV ports.

Gram Positive Antimicrobials

For gram positive septic shock, in general, the *best anti-microbials are daptomycin and vancomycin*. There may be poorer results with linezolid for septic shock, but this data is not terribly strong.

The anti-microbial profile between community and healthcare *associated MRSA* is blurred. It is still *quoted that PVL elaboration is* rare in healthcare MRSA, but common in CA-MRSA.

Drugs that are active *against MRSAemia* are: vancomycin, linezolid, daptomycin [should be considered in critically ill patients], tigecycline [considered second-line because of low blood levels], clindamycin, doxycycline and septra [for outpatient treatment]. Know that *nasal carriage* of MRSA [NOT MSSA] is the *greatest risk factor for predicting staphylococcal bacteremia* for unclear reasons. It is a risk above and beyond APACHE score, malignancy, having been administered antibiotics and mechanical ventilation. The risk of MRSA nasal carriage increases with time in hospital, DM, AIDS, ESRD.

Methicillin is nephrotoxic, so it is no longer used. Nafcillin is used [but can cause leukopenia], oxacillin [rarely can cause hepatitis]. A serious staph aureus infection that is MSSA is always treated with oxacillin or *nafcilln as these are preferable to vancomycin*. If the patient is penicillin allergic you should consider desensitization, vancomycin may be used, linezolid and tigecyl are not optimal. Daptomycin might be OK. Combination therapy for MSSA was previously considered useful [with gentamicin] as it *reduces bacteremia by one day*, but there is no difference in outcome and should not be used for more than 3-5 days. Rifampin in combination for MSSA does not increase bactericidal activity, but may be useful with foreign bodies.

Vancomycin is a glycopeptide antibiotic that cannot cross the outer cell membrane of gram negative bugs. Vancomycin is bactericidal against almost all gram positives [including pen resistant strep] except enterococci. *Vancomycin has no activity against gram negatives or anaerobes*. Remember that VRE is common and VRSA is rare [but MICs are increasing since 2000]. The dose of vancomycin is 2 grams per day in normal renal function. If there is CNS coverage needed, maybe 3-4 grams per day are needed. Lung penetration, is poor. No drug is proven superior for MRSA.

Understand 'red man or red neck' syndrome. Patients who receive vancomycin in doses of *more than 500 mg over a time frame of less than 30 minutes* can develop this reaction. The treatment is to infuse the drug over one hour. It is the result of a *non-immunogenic release of histamine* and may be associated with hypotension, especially in a patient with underlying sepsis. In patients who have experienced this reaction before, pre-treatment with an anti-histamine may reduce recurrence rate. *Steroids have not been* shown to reduce red-man syndrome.

Interestingly, vancomycin can be inactivated with large doses of heparin. Other complications of vancomycin include phlebitis, neutropenia and thrombocytopenia.

Recognize vancomycin-related thrombocytopenia in someone concomitantly on ranitidine and

LMWH. Consider a patient in whom the platelet count begins normal, but about one week of vancomycin therapy results in a profound drop in platelets to about 12K. Anti-platelet factor 4 Ab is negative [making HIT rather unlikely]. *Vancomycin associated thrombocytopenia is rare*, but usually results in very, very low platelet counts and bleeding. *This is unlike type II HIT which results in clotting.* This disease is probably Ab-mediated, so giving more platelets usually does not help. *Stopping vancomycin usually results in an increase to normal levels in about one week*, but this can be prolonged in renal failure as vancomycin hangs around. The use of vancomycin and gentamicin in synergy is effective against most staph and enterococci.

What about vancomycin levels? The trough should *be above 10* after the *fourth dose*, if a complicated infection, *troughs should be 15-20*.

What about *linezolid?* Bone marrow suppression can occur, especially thrombocytopenia after about two weeks. With long-term use there can be peripheral neuropathy and optic neuritis – some thought to use with vitamin B6. There is much better *penetration into the lungs and CNS as compared to vancomycin or daptomycin*. Linezolid might be preferable to vancomycin with *MRSA pneumonia, skin and soft tissue infection* and the need for *toxin inhibition* [e.g. like clindamycin].

Daptomycin is inactivated by surfactant and *biologically unavailable within the lungs*. Daptomycin is bactericidal against all gram positive bugs *including VRE*. It should be adjusted for renal failure and there are cases of eosinophilic pneumonia with daptomycin being reported.

How long is staph bacteremia treated for? The answer is whether it's complicated or uncomplicated. Uncomplicated staph aureus means that you have no foreign bodies, no immunosuppression [DM, steroids, etc], with a prompt clinical response and a negative TEE on day 5-7. *Then you can get 14 days*. Otherwise it's at least one month of therapy.

Moving to pneumococcus. Penicillin resistant pneumococci is occurring [MIC above 2]. Clinical failures are rare if penicillin or ceftriaxone used but *with meningitis, there are failures and failures are catastrophic, so vancomycin should be used*.

Gram Negative Antimicrobials

What about difficult gram negative infections? *There is no good data that combination gram negative coverage improves outcomes*. There is some data that doing so harms the kidneys. There are emerging bugs with resistance to carbapenems and quinolones, likely from excessive use of gram negative coverage.

When do you use *cefepime*? It has good activity against gram negatives including pseudomonas [like ceftazidime] but it has the gram positive coverage of ceftriaxone. It has enhanced activity against MSSA, but *not* enterococcus and weak anaerobic coverage.

Carbapenems are frequently used to treat gram negative infections. However, they do have drawbacks. Enterococcus fecium has a fair resistance to the carbapenems. None of the carbapenems cover MRSA, *they cover E. fecalis [but not fecium]*. They all have excellent anaerobic coverage. There is some data that merropenem is less seizurogenic than imipenem, but that data is a bit weak.

What about *quinolones*? *Levaquin and moxifloxacin are considered 'respiratory' quinolones because they have better activity against pneumococcus*. Cipro has some activity against pneumococcus, but not as good. *None have good activity against enterococci*, moxifloxacin has some activity against anaerobes while *Cipro and Levaquin are active against pseudomonas*. They should never be used to cover meningitis. *Quinolones lower seizure*

threshold, which may be additive with carbapenem. Quinolones can all cause delirium. Prolonged QTc can be a problem.

What about *aminoglycosides*? Litigation can be a problem with these drugs. *Once* daily dosing is less nephrotoxic. Peak *killing is concentration, not time above MIC*. They can be used for a short course for bad gram negative infections.

What about *Polymyxins*? They are active against pseudomonas and acinetobacter and other gram negative rods. They are nephrotoxic and neurotoxic, but are a last choice. They are essentially first line therapy in New York City for healthcare-associated pneumonia from certain long-term care facilities.

Tetracyclines and glycylcyclines. Tigecycline has good activity against many organisms including MRSA. *It is not good against proteus, providencia and pseudomonas*. It also has fairly poor blood concentration so should be *last choice* in sepsis or septic shock.

Treatment of Anaerobes

Anaerobes should be treated with either *flagyl* or the *beta-lactam-lactamase inhibitors* or *carbapenems*. Don't be fooled by cefepime, its anaerobic coverage is pretty poor. Moxifloxacin also has mild anaerobic coverage, probably not enough to warrant use in the ICU for this purpose.

Treatment of Viral ICU Infection

The viruses in the ICU are typically limited to *bad influenza*, *CMV* and HSV *encephalitis & trachea-bronchitis*.

Influenza, discussed above, tends to be resistant to amantadine and rimantadine. Zanamivir is given by inhalation, oseltamivir is only oral. Peramivir is IV. *The drugs that end in 'mivir' are the neuraminidase inhibitors.*

Ganciclovir [first-line, but marrow toxic] & foscarnet [second-line, but can cause seizure, renal failure and low mag] are used to treat CMV. In the transplant population [discussed more in section 7], *CMV manifests as pneumonia and colitis*. In AIDS, *CMV manifests as retinitis and colitis, but not pneumonia*.

HSV Encephalitis presents with abnormal behavior, thought and speech because it is *not just the meninges inflamed*. The drug of choice is acyclovir with*out* steroids. It is, essentially, the *only treatable cause of encephalitis once listeria is ruled out*.

The MRI shows temporal lobe enhancement. The CSF PCR is always positive for HSV, *but commercial labs are not so certain*. High dose acyclovir is required with IV fluids [*needle*-shaped crystals in the urine]. *Zoster in the ICU is almost always shingles*, disseminated zoster is rare today; prednisone may reduce post-herpetic neuralgia.

Recognize HSV tracheobronchitis of the critically ill and know its treatment. Consider a patient who has profound wheezing [has a history of COPD] that is not resolving with standard treatment. Additionally, there are *copious amounts of clear secretions* from the ventilator. A bronchoscopy reveals patchy, pearl-white lesions in the trachea and diffuse airway edema. Additionally, there is *a tad-pole shaped cell with odd-appearing intra-nuclear abnormalities. They have the 'triple M' features of being molded, marginated and multinucleated*. The nuclear are many [multinucleated], they stick together [molded] and the material within the nuclei is condensed around the insides of the nucleus [marginated]. After *two weeks of IV acyclovir*, the patient's fever, wheezing, secretions and inability to liberate all vanished. HSV tracheobronchitis has been reported in not only burned, immunocompromised patients with malignancy, but *also the immunocompetent*. HSV is commonly found in the lower respiratory tracts

of patients within critical illness and ARDS [upwards of 80% of patients], however, one RCT did not find that treating these patients improved their course. *Only* patients with overt, *symptomatic HSV* tracheobronchitis *should be treated*.

6. CRITICAL CARE ENDOCRINOLOGY

OVERVIEW OF HYPERGLYCEMIA & LACTIC ACIDODSIS

Physiological Considerations During Hyperglycemia

The body releases glucagon, and adrenergic agents in response to stress. Hyperosmolar states result in altered mental status. There may be hypotension as a consequence of volume depletion and/or infectious trigger. There is a powerful osmotic diuresis in the setting of hyperglycemia. This leads to electrolyte loss. In the pregnant woman there can be normo-glycemic DKA.

The pH may be normal *or* high in the setting of preceding nausea and vomiting. *There must be an increase in anion gap and positive serum ketones to meet the diagnosis of DKA*. There is about *5 liters*, on average, of *isotonic* fluid loss in DKA. *In addition*, there is *free water* loss which can be calculated.

The corrected sodium must be used when calculating the free water deficit. The corrected sodium is 1.6 higher for every 100 the glucose is above 200. *This is essentially what the serum sodium would be if you hypothetically, rapidly corrected the serum glucose to 200*. When this is done, the *calculated sodium is usually higher than 140* and this gives an idea of how much free water has been lost by the patient.

In a patient with improving anion gap, but stable or elevated ketone concentration in the serum, *the important thing is that the gap is being lowered*. Do not fret over a stable level of ketones in the serum. Only beta-hydroxybutyrate and acetoacetate contribute to the anion gap and acidosis. Only acetoacetate and acetone are measured as 'serum ketones' such that the serum ketone level can stay stable as BHB is converted to acetoacetate and then to acetone. When patients initially present, there is a high titer of BHB. So the serum ketone titer, with time, can stay constant as acetone is generated. *The anion gap is the better reflection of the ketoacidosis.*

When calculating the anion gap, *do NOT use the corrected sodium* [unless you also correct the serum chloride and bicarbonate – which no one does].

The boards likes to give patients with both an anion gap metabolic acidosis & superimposed metabolic alkalosis such that the patient's pH is normal, but you must recognize the elevated anion gap and that there is an elevated bicarbonate, usually as a result of chloride loss [vomiting].

Serum osmolarity is calculated by twice the sodium + *glucose over 18* + *BUN over 2.8* + *ethanol over 4.6*. *The effective serum osmolarity* should ignore BUN because BUN moves freely across the membranes.

Treatment of DKA involves giving a roughly 10 unit push of insulin followed by 0.1 U/kg/hour with a target of lowering the blood glucose by at least 50 per hour. In elderly patients, consider using 0.05 U/kg/hour [half the dose for lower muscle mass]. Don't adjust the insulin based on dropping sugar, you give sugar at that point which may require D10 or D50.

The rate of insulin can be lowered when the pH rises to 7.3. Start potassium when the serum potassium is in the normal range. If the potassium is low at onset, start K+ immediately, before insulin [i.e. if K is less than 3.3].

Bicarbonate should *not* be routinely given; it causes a paradoxical lowering of the intracellular pH, there is a leftward shift in the Hb dissociation curve [acidemia might be OK in critical illness because it facilitates oxygen offloading]; sodium bicarbonate will facilitate sodium overload and hypokalemia may worsen.

Phosphorus may be low and that should be replete. The pH and the PvCO2 is very similar to an arterial pH in a patient not in shock.

The hyperosmolar state [HHS]. Glucose tends to be higher in HHS, the osmolarity tends to be higher, the pH is higher, but potassium tends to be lower because of *the diuresis and the presence of some insulin*. The treatment [compared to DKA] is more volume, less [if any] insulin. Sometimes all these patients need is volume.

Lactic Acidosis

Lactic acidosis is often the result of anaerobic glycolysis and this *is type A lactic acidosis*. It is the result of tissue hypoxia and hypoperfusion. Improvement in sepsis-induced lactic acidosis correlates with survival. Is type A lactate bad? It is *not the lactate per se* that is bad, it is the badness underlying the genesis of the lactate that is bad [e.g. asystole].

Type B lactic acidosis is when there is *no tissue hypoxia*. It is seen in hepatic disease, congenital disorders and acute leukemia as well as many type of drugs. Many of the HIV drugs, methanol, cyanide, salicylate, ethanol, beta-agonists, ethylene glycol [as an artifact].

Does giving bicarbonate change pressor requirements? In patients given sodium bicarbonate resuscitation for acidosis, there was *equal* increase in wedge pressure, *equal* increase in cardiac output but a greater increase in pH in those who got bicarbonate [*there was no change in vasopressor requirements*] – Cooper et al. Ann Intern Med 1990; 492-498.

Thyroid Storm

Thyroid storm is hyperthyroidism in the presence of significant cardiac or CNS manifestations. Apathetic affect may also be present, particularly among the elderly.

Thyroid storm is the most extreme form of thyrotoxicosis. *Grave's disease is the most common cause of hyperthyroidism* other causes include: TMN, thyroiditis, pituitary tumors, thyroid cancer, struma ovarii [ovarian tumor making thyroid hormone], drug-induced, HCG-induced.

What is the precipitating factor? This must be asked of all the endocrine emergencies including DKA or HHS. It is typically some physiological stress. Thyroid storm can be triggered by: surgery, pregnancy/childbirth, trauma, or significant acute illness of any kind. As with myxedema, *the diagnosis of thyroid storm is made clinically*, with treatment undertaken in anticipation of confirmatory laboratory tests.

Thyroid storm may appear as psychosis, cardiomyopathy & cardiovascular collapse. Pretibial myexedema is the result of the same substance that causes exophthalmos. In elderly patients, *new onset* afib is the consequence of thyroid storm 3% of the time.

In 99% of ICU patients, *the TSH level will be the most helpful thyroid assay*. The assays for TSH used to be very insensitive, now they are quite good. The tests for thyrotoxicosis can be deceptively normal in the critically ill for multiple mechanisms. There may be reduced TSH production by the pituitary which will lower T4 and T3 levels [with raised rT3 levels]. There can be reduced thyroid binding globulin and therefore lowered T4 levels measured. *The finding of a normal T4* level in a critically ill patient with a *high clinical suspicion of thyrotoxicosis should not* rule out the disease. In this setting, the finding of a *very low thyroid-*

stimulating hormone (TSH) level (less than 0.01 µU/mL) would support the diagnosis of hyperthyroidism, as such *very low levels are not often found in euthyroid patients who have non-thyroidal illness*. Almost all patients with overt hyperthyroidism will have low serum TSH concentrations secondary to appropriate suppression by the high serum thyroid hormone concentrations. A very rare cause of overt hyperthyroidism in which TSH levels are high, is TSH-induced hyperthyroidism, due to either a TSH-secreting pituitary adenoma, or a partial resistance to the usual feedback effect of thyroid hormones on TSH secretion.

Treatment of thyroid storm occurs in *3 steps*: Firstly, propranolol, 60 to 80 mg q4-6h, is administered to block the hyperadrenergic manifestations of thyrotoxicosis. Thyroid hormones are not adrenergic agonists, they increase receptor density. Propranolol should be given because it is non-selective, it crosses the blood-brain barrier, it is old and well-known and it decreases T4 to T3 conversion. [IV esmolol can be used instead of propranolol]. Secondly, thyroid hormone synthesis is inhibited by administering either propylthiouracil, 200 mg q4h, or methimazole, 20 mg q4-6h. The thyroid gland also stores thyroid hormones, so even if synthesis is totally blocked, the gland will continue to release stored hormone over a period of days, weeks and months. Thus, thirdly, iodine, either saturated solution potassium iodide or Lugol solution, is *administered to block thyroid hormone release* from the thyroid gland. Importantly*, iodine must only be administered after thyroid hormone synthesis has been blocked*, in order to avoid exacerbating the problem by enhanced thyroid hormone production. Decreasing conversion of T4 into T3 is accomplished through the administration of propylthiouracil, hydrocortisone, 100 mg q8h, and propranolol. T3 is the biologically active thyroid hormone.

Passive cooling if hyperpyrexia is present is done with APAP as acetylsalicylate increases free thyroid hormone in the serum through displacement on plasma proteins [but this should not preclude ASA in the setting of a thyroid-induced MI].

Thyroidectomy may be required if a patient develops life-threatening agranulocytosis from propylthiouracil or methimazole. Finally, as with myxedema, the patient should be evaluated and treated for the possibility of concomitant hypoadrenalism. Iodine therapy is discontinued and corticosteroids may be tapered once severe symptoms have resolved. Patients with Grave's disease should ultimately undergo thyroid ablation [surgically or with I-131].

An unusual manifestation of thyrotoxicosis is *thyrotoxic periodic paralysis* with hypokalemia. Consider a young Asian man who ate a large meal and then went to sleep. He awoke paralyzed except for his toes and cranial nerves. Interestingly, he had no autonomic symptoms [normal heart rate, blood pressure]. The hypokalemia occurs after the ingestion of a high carbohydrate meal *and in conjunction with thyrotoxicosis* it results in profound hypokalemia and hypophosphatemia. Importantly, the hypokalemia is the result of intra-cellular shift, so replacement needn't be aggressive. *Once the thyrotoxicosis resolves the paralysis never returns.*

Myxedema Coma

Myexedema coma is the severe form of hypothyroidism. The most common cause is auto-immune [burned out thyroiditis] followed by iatrogenic, drug-induced and lastly iodine deficiency.

These patients are very slow with course facial features, periorbital edema and a very delayed response to questions asked. They answer in a course, frog-like voice.

A pericardial effusion may be present, although significant cardiac compromise is uncommon.

Triggers include *narcotics, sedative hypnotics [sometimes only one dose] as well as other physiological stressors* such as myocardial infarction or infection and septic shock [masked by profound hypothyroidism]. Myxedema coma is often the result of prolonged noncompliance with thyroid supplementation in the face of absent thyroid function, such as following I-131 ablation. Drugs that can cause underlying hypothyroidism include amiodarone, propylthiouracil, lithium, and sulfonamides.

When the TSH is very low, patients do not get myxedema coma as the thyroid gland can still secrete small amounts of thyroid hormone. Therefore, *myxedema coma* does not really occur in secondary or tertiary hypothyroidism, *only primary hypothyroidism*. Thus, TSH should be quite high in the patient with myxedema coma.

Myxedema coma patients tend to have a low PaO2, high PaCO2 [from blunted respiratory responses, they are often intubated], hyponatremia, hypoglycemia, elevated CPK, *high TSH with low total and free T4 and low T3*. Also, hyponatremia, a normocytic normochromic anemia, hyperlipidemia. Hyponatremia is due to an *impairment in free water excretion* and can result in seizure activity. Hypoglycemia can occur from hypothyroidism alone or may be due to concomitant adrenal insufficiency.

The treatment of myxedema coma should begin based on clinical suspicion and should not wait for laboratory confirmation. These patients need to be in the ICU *for respiratory support with passive [not active] rewarming to prevent excessive drop in blood pressure*. The patients sometimes require glucose infusions for hypoglycemia, large doses of IV synthroid *and hydrocortisone to avoid Addisonian crisis*.

The treatment of myxedema coma is IV thyroxine - loading dose of 300 mcg of thyroxine then daily administration of doses ranging from 50 to 100 mcg. As unsuspected adrenal insufficiency is frequently also common, *all patients with myxedema coma should be empirically treated for possible adrenal insufficiency* with daily administration of 300 mg of hydrocortisone.

Sick Euthyroid

There may be an *adaptive response during critical illness* whereby the body seeks to conserve energy by *down-regulating TSH* production. Further, metabolism is slowed by *increased conversion of T3 to reverse T3*. T4 levels may also be low, particularly in the setting of protracted critical illness, and the *TSH level can also vary*, being either slightly elevated or decreased. *Free T4* levels are normal, indicating the absence of clinical hypothyroidism. Hence, no thyroid supplementation is required.

The time-course in the critically ill is that free T3 level goes low quickly and rT3 rises. There is *no role for testing T3 in the ICU because it will always be low*. If it is not low in the ICU, then either the test is wrong or the patient should be on the floor. T4 drops later in critical illness. Reverse T3 has no known biological activity.

DKA

Serum glucose level is usually below 800 mg/dL in DKA, whereas in HHS a glucose level in excess of 1,000 mg/dL is not uncommon.

Leukocytosis and altered sensorium are proportionate to the degree of acidemia and can confuse the clinical picture regarding infection, especially CNS infection.

Regular insulin is administered as an IV bolus of 0.10 to 0.15 U/kg/h, followed by a continuous IV infusion at 0.10 U/kg/h. Blood glucose should be lowered by about 50 mg/dL/h and assessed hourly, with downward adjustments made in the insulin drip as blood glucose lowers.

Clinicians should recognize that finger-stick capillary blood glucose measurements can be inaccurate in critically ill patients. *Finger-stick glucose measurements are lower than 'true' glucose measured from venous blood in hypotensive patients* but at other times may be found to be higher than venous blood. Serum electrolytes should be assessed q2-4h in DKA.

Once intravascular volume has been restored and the patient's glucose has lowered to the 200 range, glucose and hypotonic saline solution, in the form of dextrose in 0.45 NaCl, should be administered until the DKA has resolved. This serves to avoid hypoglycemia in the context of ongoing DKA - this permits the continued administration of IV insulin to reverse ketogenesis and replete free water deficit.

Despite initial hyperkalemia, with the administration of insulin, hypokalemia develops and should be treated with IV potassium supplementation*. Usually 20 to 30 mEq/L is added to 0.45 saline solution,* as the addition of potassium to normal saline solution would result in the administration of hypertonic fluids. Hypophosphatemia often develops during treatment of DKA, but it seldom requires supplementation, which should be administered only if clinically significant or severe [less than 1.0 mg/ dL].

After the normalization of the anion gap has occurred, the patient should receive *subcutaneous regular insulin*. The administration of IV dextrose is stopped, and *IV insulin is discontinued 30 min later. These changes are best made once the patient has resumed oral nutrition, otherwise ketogenesis may resume*.

Cerebral edema can occur as a complication of DKA treatment in patients under 20 years of age, but the risk is mitigated if rapid correction of sodium and water deficits are avoided and glucose is added to IV fluids once serum glucose level has dropped to the low 200 range.

Hyperosmolar Non-Ketotic Dehydration Syndrome

The severity of hyperglycemia is often quite significant [>1,000 mg/ dL]. The resultant hyper-osmolality produces depression of the CNS, which, when severe, can cause coma. An anion gap metabolic acidosis from ketogenesis is typically not present.

Serum sodium is often low in HHS due to osmotic shifting of water from the intracellular compartment. As serum glucose levels tend to be higher in HHS than in DKA, this effect can be quite profound. In addition, just as in DKA, plasma volume is contracted at the same time, owing to osmotic diuresis from glucosuria. If, however, the glucosuria effect predominates [especially if PO water is restricted], hypernatremia may be observed. In either circumstance, the serum sodium level is altered by hyperglycemia. A correction factor to determine the estimated serum sodium when the glucose level is 200 is:

Na corrected = Na measured x [0.016 (Glucose in mg/dL - 100)]

The corrected sodium is used to determine free water deficit, which can serve as a guide to the amount of volume resuscitation required. The corrected sodium *should not* be used as the marker for sodium correction *rate*. Rate of correction should still follow the measured serum sodium *as that is the sodium level which determines osmotic water shifts*.

The treatment of HHS involves the same management principles as DKA: vigorous volume replacement and sometimes an IV insulin drip. The amount of normal saline solution required to restore extracellular fluid tends to be greater in HHS than in DKA. Replenishing intra-vascular volume is sometimes all that is needed as it facilitates renal perfusion, glycosuria and diminishes the stress response which maintains hyperglycemia.

Glucose Control in the ICU

Insulin and tight glucose control in surgical patients improved mortality in one trial if BG was kept between 80 and 110. Several additional trials showed worsening mortality in strict glucose control [from hypoglycemia]. This is best shown in the NICE-SUGAR trial. The control group was 150, the intensive group was at 107. There was a worsening outcome in those on strict control; there was an increase in 90-day mortality in patients treated with ''tight glycemic control,'' [80-100 md/dL] compared with a less aggressive approach. Only the subset of patients with trauma or those being treated with corticosteroids demonstrated a trend toward benefit with tight control. However, it should be recognized that the control group in NICE- SUGAR had a mean glucose level around 140 mg/dL. *Thus targeting 150 mg/dL in the ICU seems warranted.*

Hypoglycemia

Hypoglycemia can be caused by drugs, ethanol, sepsis, hepatic failure, renal failure, etc. Hypoglycemia can be a result of the cessation of TPN [for a multitude of reasons]. These patients have insulin on-board and have an abrupt drop in blood glucose. Note that the adrenergic symptoms of hypoglycemia can occur not just based on the absolute value of glucose, but on *the rate of decline*. If a patient does not have an IV for emergent D50, the patient can be given *IM glucagon*. Once treated, the *underlying cause* of the hypoglycemia must be sought or else the low glucose will reappear.

Blood glucose should be monitored hourly. A second ampule may be required within an hour of treatment. Patients should also receive a dextrose drip of either 5% or 10% solution, at a rate appropriate to the clinical circumstances encountered. *Glucagon, hydrocortisone, or octreotide can be administered* if hypoglycemia is profound and refractory to the above measures, but it is seldom required.

Adrenal Crisis

Adrenal insufficiency may be either primary [Addison's *syndrome*], that is, due to insufficient production of glucocorticoids and mineralocorticoids; or secondary, from underproduction of ACTH.

In Addison's day, the most common cause of adrenal insufficiency was TB. Today it is idiopathic, mostly autoimmune. Altogether, the most common cause is the abrupt discontinuation of corticosteroids.

Causes *of primary adrenal insufficiency* include autoimmune, that is, Addison's *disease*; bilateral adrenal hemorrhage; abrupt withdrawal of exogenously administered corticosteroids, TB; septic shock; meningococcemia [Waterhouse–Friderichsen syndrome]; metastatic malignancy; amyloidosis; and drugs such as etomidate and ketoconazole.

Causes of *secondary adrenal insufficiency* include pituitary tumors; craniopharyngioma; as a postoperative complication; postpartum hypopituitarism [Sheehan's syndrome]; infiltrative diseases such as hemochromatosis, sarcoidosis, histiocytosis, or histoplasmosis; TB.

Like thyroid storm, adrenal crisis is often *triggered by physiologic stress* such as trauma, surgery, or acute medical illness.

Abdominal, flank, lower back, or chest pain are common in patients with *bilateral adrenal hemorrhage or infarction*, the main risk factors for which are anticoagulation and postoperative state.

Hyperpigmentation may be seen in patients with primary adrenal insufficiency, but this is uncommon. Patients with secondary adrenal insufficiency lack hyperpigmentation,

dehydration, and hyperkalemia. Hypotension is less prominent, whereas hypoglycemia is more common than in primary adrenal insufficiency.

In summary: in *primary* hypoadrenalism you tend to see the textbook things – hyperpigmentation, hyperkalemia and hypotension whereas in *secondary* hypoadrenalism you tend to see – normal skin tone, normal potassium but more hypoglycemia.

Again, in terms of electrolytes, the common findings in adrenal insufficiency are: *hyponatremia, hyperkalemia*, hypoglycemia, azotemia, hypercalcemia, acidosis, anemia, neutropenia and eosinophilia. By the time these patients are seen in the unit, these findings are uncommon. The urea from adrenal insufficiency is from protein catabolism.

In individuals who are *not stressed, a total* cortisol level of *more than* 15 g/dL is sufficient to *rule out* adrenal insufficiency. A level *less than* 5 mg/dL constitutes absolute adrenal insufficiency with 100% specificity but low sensitivity (36%). A cut-off level of 10 mg/dL is 62% sensitive but only 77% specific.

The appropriate response of the adrenal glands in the setting of critical illness is unknown.

Some authors suggest that a level less than 25 mg/dL may be insufficient in critical illness such as sepsis.

Cortisol is protein bound, *and total cortisol levels bear a variable relationship to free cortisol levels.* Patients who are hypoproteinemic may have a normal free cortisol level despite a seemingly insufficient total cortisol level [remember, it is the free cortisol which is biologically active].

In patients *who are not septic*, a rapid cosyntropin test can be performed. This is a cortisol level 30 and 60 minutes following the cosyntropin. With stimulation, the plasma levels go well above 20 in normal patients. Thus a rise in total cortisol level less than 9 mg/dL or an absolute level less than 20 mg/dL may be indicative of RAI.

In the CORTICUS trial [septic patients], the cosyntropin stimulation test was found to be *unreliable* when correlated with free cortisol levels. In addition a mortality benefit was not observed in the corticosteroid group. Patients receiving corticosteroids were able to be weaned off vasopressor medications 2 days sooner than the placebo group but also *were found to have a threefold risk of subsequent sepsis while in the ICU.*

The standard *dose in sepsis* is hydrocortisone, 50 mg IV q6h for 5 days.

Adrenal crisis is treated with an initial dose of 200 mg of IV hydrocortisone followed by 100 mg q6h. *IV administration of normal saline solution is important to correct volume contraction. Hypotonic fluids should not be administered*, as they can worsen hyponatremia. Mineralocorticoids are not needed when large doses of hydrocortisone are given. When this dose gets to less than 100 mg per day. If a patient is *completely adrenally* insufficient then fludrocortisone should be given when HC doses fall below 100 mg per day.

Pheochromocytoma

A pheochromocytoma is a catecholamine-secreting tumor of chromaffin cells; most common in the adrenal glands, *though it may occur elsewhere in the body.* 10% are malignant, 10% are familial, 10% are bilateral 10% are multiple and 10% are extra-medullary.

The classic triad of *episodic headache, sweating, and tachycardia* is *seldom present*. Episodes don't last more than a few hours at time [usually 20 minutes or so].

Mimics of pheochromocytoma in the ICU are many, including autonomic dysfunction [e.g.

spinal injury or Guillain-Barre syndrome]; the use of sympathomimetic drugs such as cocaine, phencyclidine, or amphetamines; and the ingestion of tyramine-containing foods in patients taking monoamine oxidase inhibitors.

Diagnosis is made via *plasma levels* of metanephrine and normetanephrine or *24-h urine levels* of metanephrines and catecholamines *when the patient is stable and not critically ill, as the stress of critical illness can produce misleading values* that may be false positives*. Plasma normetanephrine* has the *best distinguishing characteristics*. The administration of tricyclic antidepressants can also result in falsely elevated results.

Subsequent to a chemical diagnosis, imaging such as CT scan or Iodine 123-metaiodobenzyl guanidine scan localize the tumor. MRI can light up chromaffin tissue quite well.

Patients with known pheochromocytoma for elective surgery should receive preoperative management with an alpha-agent, such as phenoxybenzamine.

BB administration is contraindicated unless prior alpha- blockade has been accomplished. The CCB nicardipine can be a useful adjunct. Metyrosine, an inhibitor of catecholamine synthesis, may also be used.

As with the other endocrinopathies, stress can precipitate a hypertensive crisis in pheo patients. *Undiagnosed pheochromocytoma patients presenting with post-operative hypertensive crisis have a high mortality – these patients are treated with phentolamine* intravenously 2 to 5 mg every 5 min until the target BP is achieved.

Diabetes Insipidus

When water adsorption by the collecting tubules of the kidney is impaired, either from a *1.* lack of the antidiuretic hormone [ADH] also known as arginine *vasopressin* [AVP] [ddAVP or *desmopressin is the synthetic analogue*] or due to *2.* the lack of responsiveness of the collecting tubules. *1. & 2.* are central and nephrogenic DI, respectively.

Patients with complete central DI will have a very dilute urine and a low urine osmolality. Patients in the ambulatory setting *do not have hypernatremia because they drink a lot*, they are always drinking water! Once in the hospital, this intake can be impaired. These patients will have large amounts of dilute urine. *Urine osmolality should be less than the plasma osmolality.*

Clinically, this does not distinguish nephrogenic from neurogenic DI. The use of a V2 [selective] agonist [ddAVP – desmopressin] can be done to distinguish central from nephrogenic DI; further, V2-selectivity does not cause vasoconstriction [as AVP or vasopressin does].

Administration of *1 mcg* desmopressin SQ is done. If the urine osmolality increases by *10-50%*, then DI is partial central, if it increases *more than 50%*, then its complete central DI. If there is *no change*, then this is nephrogenic DI.

One unusual form of "central" DI is *gestational diabetes insipidus*. Consider a patient who presents in her third trimester with acute cholecystitis and over a 24 hour period urinates large amounts of free water and the serum sodium shoots up 20 points. The onset of gestational diabetes insipidus can occur in *the third trimester and is typically mild and self-limited*. The placenta elaborates vasopressinase an enzyme that degrades vasopressin, but normally maternal vasopressin levels increase in response. In this patient, she was made NPO for surgery and was unable to regulate her serum sodium. Importantly, the use of *vasopressin is typically less effective because of the innate vasopressinase elaborated by the uterus*. The synthetic desmopressin, however, is resistant to vasopressinase and therefore is the correct response in addition to giving free water. Thus

this disease will behave in a manner similar to central DI.

Nephrogenic DI can be caused by several drugs, including lithium, demeclocycline, amphotericin B, and antiretroviral drugs such as tenofovir and indinavir. Hence, *ADH levels are elevated in nephrogenic DI* but are diminished or absent in central DI.

Treatment *of central DI* entails *correcting the free water deficit* as well as *prevention of ongoing polyuria* through the administration of desmopressin 1 or 2 mcg subcutaneously q12h. Without this, there can be 20-25 liters of water lost in 24 hours. This can very, very rapidly result in hypernatremia and shock.

Patients who are *hypotensive due to hypovolemia* should receive *normal saline* until intravascular volume has been replenished. Otherwise, hypotonic fluids may be administered.

Management *of nephrogenic DI* – desmopressin is not administered. The discontinuation of any nephrogenic DI drugs is an important. A thiazide diuretic leads to mild extracellular fluid volume depletion, and increased water reabsorption at the PCT. There is less water delivered to the DCT and less urine is produced.

Summary - key points with endocrine emergencies: the TSH is the best test of thyroid function in the ICU, the cosyntropin stim test is the best test of adrenal function, isotonic fluids are always given for hypovolemia, closely titrate IV fluids in DI and use phentolamine to right high blood pressure in pheochromocytoma.

NUTRITION IN THE ICU

Altered metabolism that results from a disease process is the most common cause of malnutrition in the ICU. What is the difference between *starvation and stress hyper-metabolism*?

STARVATION

Starvation occurs when nutrient supply cannot meet nutrient demand. The body responds to preserve lean body mass and this response is usually carried out by *decreasing energy expenditure*, use of alternative fuel sources and *reduced protein* wasting. Glycogen is gone in about 24 hours, glucose creation goes on for a few more days by breaking down protein from amino acids. Then *fatty acids, ketones and glycerol* become the primary fuel sources in all but obligate glucose-utilizing tissues [brain and RBCs]. In the fully adapted starved state there *is decreased protein catabolism and ureagensis* [as compared to the fed state]. The starved animal must preserve muscle mass so as to obtain a meal in the near future.

CRITICAL ILLNESS HYPER-METABOLISM

This is different from stressed *hyper-metabolism* – this occurs *at the expense of the lean body mass*. It is a general response where energy and substrate are mobilized to support inflammation and the immune system. It is often associated with poor tissue perfusion. It is seen with high lactate, high urinary nitrogen excretion. *The RQ is increased compared to the starved state [see below]*. There is a decrease in insulin-mediated glucose uptake and increased gluconeogenesis [stress-hyperglycemia]. There is more glucose oxidation [increased non-insulin mediated glucose uptake]. There is increased Cori cycle to convert lactate to glucose.

There is increased total protein *anabolism and catabolism* [net *increase in catabolism*] with *increased muscle release of amino acids*. There is a rapid drop in lean body mass with less albumin synthesized and increased urinary nitrogen losses with increased ureagenesis. The amino acids that are released are used as fuel and for immune system function at wound sites. They serve and gluconeogenic substrates and are used in the liver to create acute phase reactant proteins. *In*

other words, the skeletal muscle is degraded to become the substrate for processes of inflammation and tissue repair.

Insulin is very important not only for glycogen storage but also fat and protein synthesis and storage. Cortisol, glucagon and catecholamines are all important for breaking down these biomolecules. Injured tissue hormones are often the cause of the stress-hyper-metabolic response aforementioned [e.g.TNF, IL-1, IL-2, etc.].

Starvation Versus Hyper-Metabolism

The key differences between starvation and hyper-metabolism are the following: *energy* use is *increased* in the stress response and *decreased* in the starvation response. The *respiratory quotient*, similarly is *low and high, respectively* while the *primary fuel* is *fat* and *mixed* respectively.

Hyper-metabolism results in much more synthesis of glucose and a large breakdown of protein [though there is some protein synthesis – more than starvation]. Ureagensis is high in hyper-metabolism. By contrast, ketone formation and response to feeding in starvation is very high. *If you feed a starved patient, the starvation response will go away*. This is *not true* in hyper-metabolism, where the response will resolve *when the underlying problem is treated*.

Route and Timing of Nutrition in the ICU

Nutritional support is important for malnourished patients and in those in whom it is likely to occur [e.g. severe injuries]. Start nutrition support as soon as need is recognized, *but always within 7 days*. Early TPN, however, is bad.

It is important to *minimize starvation effects*, prevent specific deficiencies, and treat the underlying disease.

Randomized trials have not shown a benefit from approaches that try to counteract the natural catabolic state that occurs in the acute phase of critical illness and some experts suspect catabolism during acute critical illness is in fact adaptive, or at least not harmful in and of itself.

Providing enteral nutrition early to people with critical illness *may reduce* their infection risk, as compared to delaying enteral nutrition or not providing any. *Enteral nutrition should be provided within 48 hours to people with critical illness who are not at high risk for bowel ischemia*. This conclusion comes from a meta-analysis of 15 randomized trials showing an approximately 50% reduced risk for infection among those receiving early enteral nutrition. Another meta-analysis suggested early enteral nutrition reduced mortality risk by 50% as well, but fell just short of statistical significance. However, these data are fairly old and from heterogeneous trial designs; some have argued these findings might be due to publication bias or other biases. Also, most of the included patients in these randomized trials were surgical [burns, trauma, etc.] and not medical patients [who have mainly been studied in observational trials].

As stated above, caloric goals are theoretical and controversial, and were developed without outcomes-based evidence. In patients who were *previously adequately nourished*, providing minimal calories [trophic feedings] enterally for up to 7 days led to equivalent outcomes as compared with more aggressive feeding, in mechanically ventilated critically ill patients. A 2011 randomized trial suggested feeding critically ill patients *below caloric goals* might improve survival.

Many critically ill patients have reduced gut motility and fail to tolerate enteral feedings in the amounts calculated to meet their theoretical caloric needs. *For these patients, there appears to be no benefit to starting total parenteral nutrition in the first week* after impaired gut motility occurs, and doing so may increase the risk for nosocomial infection. Providing no nutritional support or dextrose infusions are as good as, or

better than, early TPN for critically ill. That being said, *early total parenteral nutrition has never been shown to increase mortality from critical illness – it increases the nosocomial infection risk by 4-5%*.

What are the other early risks of TPN? Arrhythmia, hemolysis, rhabdomyolysis are all acute complications of TPN. Metastatic calcification *is not* an acute complication. The reason for many of these risks is re-feeding or the rapid uptake of intra-cellular electrolytes such as potassium, phosphate and magnesium. The provision of glucose leads to profound uptake of these electrolytes with depletion in serum levels. Acute depletion of the serum levels is known as the re-feeding syndrome. These drops result in the rhabdomyolysis, etc.

During recovery from critical illness, the body rebuilds muscle and fat (anabolism) and replenishes other energy stores (fat and glycogen). Nutritional supplementation should often continue after acute critical illness to support this process.

Dose and Content of Nutrition in the ICU

How *many calories to provide*? The Harris-Benedict formula can be used to calculate BEE with a stress factor of at least 1.2 [just to be a person], severe illness is a factor of 2.0 [and everything in between].

Excess calories can cause hyperglycemia, excess CO2, and lipogenesis. The basic rule of thumb is 25-30 kcal/kg/day total [5 gram/kg/day] *total*. How much of this is *glucose*? It should be about *60-70%* of the calories to be given or *20 kcal*/kg/day. What about *fat*? It should be about 15-40% of calories. Limit fat to 1 gram/kg/day. *Protein catabolism is not suppressed by the provision of adequate calories, protein or amino acids*. Therefore to attain nitrogen balance, there should be provision of protein synthesis with *1.2-2 gram/kg/day* [which is higher than normal daily protein requirements]. A negative nitrogen balance is common in critical illness despite what you give. Rule of thumb for *fat-protein-carbohydrate is 1-2-3*. That is 1g/kg/day of fat, 2 g/kg/day protein and 3g/kg/day of carbohydrates in the critically ill patient.

There is not a lot of evidence in terms of vitamins and minerals in the ICU. There is some data that increased zinc and vitamin C may help wound healing. When you give TPN, *vitamin K is not* a part of the bag. It needs to be given vitamin K once per week in this situation as it is not light stable.

The types of enteral formulae are many. *Intact* formulae contain intact protein with*out* gluten; they are lactose free. They are isosmotic with low residue and fiber. The *hydrolyzed* formulae provide protein as peptides or amino acids, they are low in fat. *Elemental* formulae provide protein as crystalline amino acids and carbohydrates as mono or disaccharides. This classification is based on protein form.

Another means of breaking down formulae is based on their clinical use. There are *standard* formulae – for starved patients who cannot eat. *High protein* formulae are for the hyper-metabolic, critically ill patients and they contain 45-60 grams of protein per 1000 kcal. *Calorie dense* formulae contain 2 kcal per mL and they are for fluid restricted patients and are relatively low in protein.

There are also organ *specific formulae and immunity enhancing formulae* which are designed to alter immune function and reduce the inflammatory response. The organ specific formulae include those for *pulmonary failure* which are used for acute on chronic respiratory failure. There is *50% less fat* for less carbon dioxide production. Probably avoiding over-feeding is more important. *Hepatic failure* formulae contain high levels of branched chain and low aromatic amino acids in an effort to

reduce encephalopathy, but probably don't work all that well. *Renal failure* formulae are developed for patients *who are not being dialyzed*. Once on dialysis, they should be on a standard high protein diet. Renal failure formulae are low in protein, potassium and phosphorus. *None are of proven benefit*.

When a patient is being weaned from mechanical ventilation who has a high RQ, and high daily calories should first have his total calories reduced, before modifying the content of the feeds. Protein and carbohydrate swapping will *not* significantly change CO2 load to the lungs.

What about the immunity enhancing enteral formulae? *Arginine* is a nonessential amino acid that is a nitric oxide precursor and a non-specific immune stimulant with enhanced wound healing. *Glutamine* is conditionally essential and is fuel for enterocytes, lymphocytes and macrophages & reportedly improves gut barrier. Glutamine has been looked at in a meta-analysis in 2002 that showed decreased infectious complications and mortality in patients receiving TPN [surgical patients]. Then a follow up RCT showed that *glutamine supplementation is harmful and should not be done*.

Omega-3 PUFAs are metabolized to 'less inflammatory' leukotrienes than the omega-6 PUFAs. These formulae have been tried to alter the inflammatory responses of critical illness. There was a meta-analysis of 22 randomized trials of 2500 patients and there was no difference in mortality but there was a reduction in infectious complications. Then 4 years later there was an RCT of 600 ICU patients and found no difference in anything. Oxepa was studied in ARDS patients in 1999 and found to significantly improve outcomes and then this was repeated again in 2006 and shown to improve outcomes, but in 2009 the largest trial [an ARDSnet trial] OMEGA trial casted doubt.

Calorimetry & Summary

Indirect calorimetry is not often used, but may be on the boards. An *RQ of 0.6-0.7* means that fat is the fuel source and occurs *during starvation*. *0.8-0.95 means that the fuel source is mixed* and this is the *normal condition*. An *RQ of 1.0* means that the fuel source is *carbohydrate* and this occurs when excessive carbs are used and when the RQ is *more than 1.0*, the fuel source is fat synthesis and this *occurs in over-feeding*. Critically ill patients should have an RQ of 0.8 to 0.95 based off of a mixed fuel source.

In summary, stress-hypermetabolism from starvation is an important physiological distinction. Critically ill patients require more energy but are *less able to tolerate* glucose and require fat to meet energy requirements. Critically ill patients require more protein to achieve nitrogen balance. Enteral nutrition is preferred.

7. CRITICAL CARE HEMATOLOGY

STEM CELL TRANSPLANT

Autologous & Allogeneic Stem Cell Transplants

The general approach to an *autologous* stem cell transplant is – cytoreduce the malignancy, wipe out marrow, restore marrow by peripheral blood stem cells or cryopreserved stem cells. *Autologous* transplants are *first line* therapy for multiple myeloma as it prolongs progression free survival [PFS] and survival and is *second line* for relapsed NHL and Hodgkin's disease.

Mortality rates are less than 5% now. Why they die post auto-transplant – mostly relapse of disease, very little procedural complication – [total body radiation, infection & organ toxicity].

Allogeneic transplants, by contrast, procure stem cells from *a donor*, or allogeneic *cord blood*. Allogeneic transplant gives the patient a *whole new immune system* and this is the basis of the graft-versus-tumor and graft-versus-leukemia effects. The patient is cytoreduced and hematopoietic function is returned from *the donor*. Allogeneic transplants are conventionally via myeloablative [MA] conditioning i.e. eradication of malignant cells first. Now there are *non-myeloablative [NMA]* or mini-transplants based on the concept that graft-versus-leukemia may be all that is needed to destroy the residual malignancy. NMA transplants are designed for patients over 55; reducing conditioning regimen via mini-transplants could decrease the toxicity of treatment *and potentially* cure them. MA is still more frequent, but NMA is increased [~ 20%].

The preference is to use conventional MA stem cell transplant [SCT], unless the patient is old or has medical co-morbidities – *there may be a higher risk of recurrence in reduced-intensity [NMA] transplants*. In the late 80s-90s very few *over the age of 50* got transplants, now many more are, even 10% or so are above the age of 60. Of all patients going through allogeneic transplant about 25% will have an HLA identical donor [sibling]. Now with the increase in unrelated donor registry there is *about a 50% chance of finding an HLA identical unrelated donor*. Up to 60% of Caucasians will have a fully HLA matched unrelated donor as Caucasians are less HLA diverse.

The risk of *graft versus host* disease is much higher using *matched unrelated donors*, but this has decreased given the use of high resolution HLA typing, to levels similar to matched siblings.

Unrelated Cord Blood Stem Cell Transplants

What about the 25-30% who don't have matches? These patients could be suitable for unrelated cord-blood transplantation.

Cord-blood is a rich source of hematopoietic progenitor cells. They can be frozen for later use. The cord-blood cells are very naïve, so *they can be mismatched for 1/6 or 2/6 HLA loci with less GVHD MHC mismatching*. The rates of GVHD are comparable to *identical siblings* and chronic GVHD may be less likely!

Matched unrelated donors versus cord blood *have superior outcome for survival at 24 months by about 5-10%* [still total survival around 50% for leukemia]. Cord blood has significant morbidity and mortality during transplant for *two* big reasons, the *first is that engraftment is delayed about 25 – 30 days* of PMN recovery [normally about 10 days] so opportunistic infections are really common in the first 30 days with cord blood transplants; secondly, *cellular immunity in these patients does not exist in 100 days*. So if CMV reactivates, it may take 3-4 months to have an adaptive immune response, CMV

pneumonitis, colitis, adenovirus reactivation, if EBV reactivates there can be lympho-proliferative disorders; all together there is a *44% mortality in the first 100 days and about 60% in the first 180 days.* There is a lot of work being done now to develop transplants – dual cord transplants – to shorten the neutropenia phase, with the addition of viral reactive T cells to restore cellular immunity.

Allogeneic SCT Outcomes

There were 30,000 allogeneic transplants performed historically and outcome over two decades comparing 90s to 2000s - there was a significant reduction in all infections, less liver toxicity, less veno-occlusive disease, there is a reduction in GVHD, reduction in 200 day transplant-related mortality – about a 40% reduction in mortality. Relapse is much less common in allogeneic transplants, but *GVHD is a big cause of death following allogeneic transplant*. Infection is another big cause of death.

SCT Drug Toxicities & Infectious Overview

What kinds of toxicities can occur in terms of drugs used? Calcineurin inhibitors are used for GVHD prevention and they cause renal insufficiency, HTN, hypomagnesemia, gingival hyperplasia, PRES with seizures. PCP PPx – everyone is on Bactrim, but it can cause marrow suppression and hyperkalemia. For CMV reactivation – gancyclovir and valgancyclovir can cause neutropenia especially after one week – patient can then go to foscarnet, but this causes renal insufficiency. CMV pneumonitis – which drug to use? If bone marrow is suppressed– use foscarnet, if kidneys are injured, use gancyclovir.

GVHD treatment – steroids, cyclosporine [CSA], sirolimus, monoclonal Abs all of which can cause opportunistic infections.

Infectious complications – conventional peripheral SCT – *neutropenia* for about 10 days, in bone marrow transplant about 18 days, cord blood 25-30 days maybe longer. This is when fungal and bacterial infections occur.

Following neutrophil recovery, the problem is compromised *cellular immunity* – usually a consequence of CSA, which is kept on for *at least 6 months* and then tapered. About 2 of 3 patients will have their CSAs completely tapered off as the new immune system takes hold and recognizes the host after about 1 year.

RSV is bad December to early April. RSV is a big problem in transplant – RSV PNA has a 60-70% mortality rate, *there is no effective therapy* other than taper immune suppression. *PCP* incidence is common 6 months to one year. *Chronic GVHD* can occur 100 days to 2 years. Risk factors for *invasive fungal infections* is problems with PMNs – delayed engraftment [e.g. cord blood], acute and chronic GVHD [e.g. on steroids], secondary neutropenia post-transplant [e.g. drug toxicity like gancyclovir]. However, death from invasive fungal infections from acute GVHD has dropped with new anti-fungal drugs.

CMV

CMV reactivation occurs in 30-50% of SCT patients – defined as detection of CMV in blood by PCR or antigenemia without evidence of CMV disease. While *CMV* reactivation can occur, if there is no reactivation by 100 days, CMV is unlikely to reactivate; usually these patients are screened with serum CMV PCRs and treated pre-emptively.

However*, CMV disease* is an organ-specific disease – most commonly affecting the lung with a very high mortality rate [*50%*], CMV also causes hepatitis and colitis. From *reactivation to disease is 2-3 weeks*, unless cord-blood, it's probably shorter as there is no immunity as the T cells from the cord are totally naïve.

Those at risk for CMV reactivation – the *patient* or [less likely] the donor are CMV seropositive

pre-transplant. About 20% of the adult population are CMV sero-negative.

Those *not* at risk for CMV are when *the patient and donor are both seronegative* for CMV pre-transplant. *CMV disease is almost always reactivation of CMV virus dormant in recipient cells* – *not* de novo infection. Thus, *if the patient is seronegative pre-transplant, reactivation is highly unlikely*.

If the donor has T cells that can recognize CMV, they are more likely to prevent reactivation in the *seropositive* recipient. *If the recipient is seropositive, and the donor is CMV sero-negative*, there is *more likely to be reactivation* and chronic CMV as the new immune system is CMV naïve.

CMV reactivation comes 14-100 days post-transplant. Those getting T depleted transplants, in patients getting suppressed from drugs for acute GVHD, or in patients who received a *CMV negative donor* transplant the risk for reactivation is higher.

The *highest* risk of CMV reactivation comes when the *patient is positive, but donor negative*, then patient and donor positive. *If patient is negative & donor positive the risk is very low* and if both are negative, *the risk is, essentially, zero*.

Consider a patient with aplastic anemia who received an allogeneic peripheral blood stem cell transplant – patient was CMV positive, donor negative. On day 24 the patient is with RLL infiltrate with BAL growing stentotrophomonas. The patient gets Bactrim but becomes neutropenic and after 7 days of GMCSF the ANC goes from 100 to 200. CMV routine shows 2500 copies [*more than 250 copies warrants treatment*] and the patient has low grade fevers. The correct answer is to give foscarnet – because the patient is neutropenic. *Gancyclovir will worsen the Bactrim-associated neutropenia*, this is could lead to graft failure. Foscarnet can cause renal failure.

Cidofovir is a salvage treatment for both foscarnet and gancyclovir, the response rate is only 30% with cidofovir. *IVIg is not a treatment for CMV reactivation, only CMV pneumonitis*.

What about non-infectious complications of SCT? *Veno-occlusive disease* or sinusoidal-obstructive syndrome occurs in *the first week-3 weeks*. *Engraftment syndrome* within 96 hours of PMN recovery. *Idiopathic PNA syndrome* first 120 days. *Acute GVHD* up to 100 days, *chronic GVHD* 100 days to 2 years and disease relapse up to 2 years, past 5 years essentially cured.

Sinusoidal Obstructive Syndrome

Veno-occlusive disease aka sinusoidal obstruction syndrome [VOD or SOS], is now less than 5%. High dose alkalator therapies did this. It is a clinical syndrome typified by painful hepatomegaly, elevated bilirubin, ascites and edema. Sinusoidal obstruction syndrome [SOS] is rarely the cause. It occurs within 3 weeks of conditioning and presents just like Budd Chiari – high dose alkalator therapy injures venous endothelial cells with progressive hepatic venous occlusion. *It is a clinical diagnosis*. A PAI-1 test is 100% sensitive but very poor specificity, it's *like a d-dimer for PE*. It also takes a while to get the blood test back. Treatment is supportive and complications are common. Hepatorenal syndrome requiring CVVHD is common in SOS. Anticoagulation and tPA have been investigated and indeterminate. Difibrotide is a single-stranded oligonucleotide with AT and fibrinolytic effects on the microvascular endothelium; it does not improve outcome. Other treatments include TIPS, or liver transplant.

Consider a 43 year old male with CLL who undergoes NMA allogeneic transplant using cyclophosphamide and fludarabine from HLA identical sibling. Both are CMV neg. Nausea and vomiting ensue with TPN for 2 weeks. Day 8 the patient gets gram negatives in the blood. PMNs come back day 13. Day *14 bili is 3.4* with ALP

133, CSA [cyclosporine] is therapeutic. No ascites, *PAI is very high*. Why is the bilirubin high? The patient is on TPN, NPO, sepsis, CSA; it *is not* because of SOS.

Pulmonary Complications of SCT

Bone marrow transplant has had a generally positive effect on outcomes in adult acute leukemia and multiple myeloma and may be curative in lymphoma. However, *pulmonary complications occur in more than half of transplant patients, resulting in admission to the ICU in 25 to 50% of patients during the course of illness*.

Autologous bone marrow transplantation and peripheral stem cell transplantation (AHSCT) are used with increasing frequency. In this procedure patients are infused with their own hematopoietic stem cells after high-dose chemotherapy. AHSCT has virtually eliminated graft-vs-host disease, and infection with cytomegalovirus (CMV) and Toxoplasma gondii are very rare compared to allogeneic bone marrow transplantation. Although overlap is common, *respiratory complications can usually be grouped temporally*.

Most *pulmonary* problems occurring in the *first month* [prior to engraftment] are *not infectious* and include reactions to chemotherapy, diffuse alveolar hemorrhage [DAH], and ARDS. From the *second month on*, even after resolution of neutropenia, *infectious complications become more common*.

While *CMV* infection still occurs in bone marrow transplant patients, it is *unusual in AHSCT* (< 2%) and usually occurs after 2 months. The *lower incidence of chronic graft-vs-host disease may be an important factor in the reduction of late CMV infection*. CMV pneumonia may present with a patient who has *DAH on bronchoscopy and bilateral diffuse infiltrates with severe hypoxemia*. The trans-bronchial biopsy reveals enlarged lung epithelial cells with large intra-nuclear inclusions [owls' eyes] characteristic of CMV. PCR of the BAL will reveal high CMV DNA copies. CMV is known to cause DAH secondary to DAD. The mortality is extremely high – reaching 60-95%! It is treated with ganciclovir or foscarnet for recalcitrant cases. Valgancyclovir does not treat CMV pneumonia but may be used as prophylaxis for 3 months post-transplant. EBV does not classically cause bad pneumonia, nor DAH. It typically causes a lymphoproliferative disorder in the post-transplant setting.

Pneumocystis pneumonia is uncommon in patients who have received adequate prophylaxis. *Aspergillus pneumonia* occurs in the *early post -transplant* period, but is associated with profound neutropenia and nodular or cavitating infiltrates on chest radiograph. It would be unusual to develop Aspergillus pneumonia after the neutrophil count has normalized. *Bronchiolitis obliterans* would be an unusual late complication in AHSCT as it is associated with chronic graft-vs-host disease. The radiograph is either normal or shows hyperinflation. Pulmonary function testing usually demonstrates an obstructive pattern. *BOOP or COP* is also an immune sequelae, though sometimes infectious.

Differentiating organizing pneumonia [*bronchiolitis obliterans with organizing pneumonia*] from *brochiolitis obliterans*. In *BOOP*, the CT scan shows peripherally based, *patchy opacities* with GGO and biopsy reveals *granulation plugs within the airspaces* with preservation of normal lung architecture. BAL is with lymphocytosis and *a low CD4/CD 8 ratio*.

Biopsy in *BO* [on constrictive bronchiolitis] demonstrates peribrochiolar fibrosis that can progress to complete scarring of the lumen. There is an obstructive pattern on PFTs.

Pulmonary engraftment syndrome [*PES*] – occurs within 96 hours of *PMN recovery*; it is essentially an ARDS like picture as PMNs come back online.

Fever, rash, dyspnea, hypoxemia. It is a diagnosis of exclusion, not fluid overload, *not DAH*. Patients need BAL to rule these things out. *Patient then needs steroids*, these patients go from ICU to room air with treatment. This diagnosis is missed because the PMN count can rise very rapidly.

IPS or idiopathic pneumonia is non-infectious pulmonary injury after conditioning regimen *up to 120 days* or so. IPS is a diagnosis of exclusion, probably immune in origin. 12-15% in all patients with high historical mortality. IPS is thought to be a consequence of: TNF-alpha, transplanted donor T-cells, cytokines release into the lungs. *Treatment high dose steroids*, and there is data that etanercept might help. The median survival was 14 days historically, now 140 days.

DAH is idiopathic pulmonary hemorrhage usually in the *first three months*. They present with hypoxemia with bilateral pulmonary alveolar infiltrates, and rising LDH, often with hemoptysis. There is a 50% mortality. All infectious etiologies are ruled out. *Hemosiderin-laden macrophages is a buzz word.* High dose steroids, 2-10 mg/kg once per day tapered over 2-4 weeks. rVIIa has been used recently, but unknown why, but used in conjunction. More than one DAH episode gives a mortality rate of about 90%.

Consider a patient who is CMV seropositive, and gets *allogeneic* peripheral blood SCT from HLA identical sibling [CMV negative]. There is full donor engraftment on transplant day 14. 60 days post-transplant with the patient is with DOE, desaturations. There are BL infiltrates, rising LDH. The patient is on PPx mediations, CMV serum is negative. *PCP PCR on BAL is positive*, *silver stain negative*, also *macrophages are full of hemosiderin.* Positive PCP PCR is commonly positive, with negative immune-staining. Bilateral infiltrates, BAL with blood, elevated LDH. The answer is DAH despite the patient having a positive [false positive] PCP PCR from the BAL.

There is no CMV is blood or lung making reactivation of CMV much less likely.

Graft-Versus-Host Disease

GVHD occurs up to 100 days post-transplant – affecting the skin [sunburn], GI tract [upper and lower more commonly lower with large diarrhea], and liver [obstruction or hepatitis both common].

Chronic GVHD occurs over 100 days – skin, GI, lung, liver, SICCA, fasciitis syndrome. Chronic skin GVHD looks like a sunburn [diagnose via biopsy]. GI tract GVHD - T cells *from donor* attack the recipient's lower or upper GI epithelium. The differential is very broad – many drugs can do it, such as CSA, magnesium, reglan, etc. Also CMV colitis, C. Diff or even Beaver Fever. CMV does not usually cause *large volume* diarrhea. GVHD grade depends on volume of diarrhea. Grade I is less than 500 cc per day, grade III more than 1 litre per day. There is a 30-50% mortality rate with high grade GVHD of the gut. The diagnosis of GI tract GVHD depends upon clinical criteria: there *must be* an engrafted donor immune system, there *must be* clinical symptoms, there *must be no other cause* [and biopsy is preferred]. There can be false negative biopsies as the disease can be patchy. The GI tract may look totally normal, don't get thrown off*, the histology can be totally wonky [GVHD] despite a grossly normal appearance.* Acute GVHD requires very prompt treatment with high dose steroids. The GI tract can go from normal to totally denuded in one week. *Consider restarting CSA*.

Survival depends on grade of disease, grade I is 100% survival, *Grade IV 45-60% survival*. Once C. diff is negative, start steroids in the setting of *bigtime diarrhea* in the transplant patient. Steroid refractory GVHD affects 10-15% with a historical mortality > 85%.

Consider a patient who gets NMA PBSC transplant [cyclophosphamide and fludarabine] from *unrelated donor*, T-replete allograft. The

patient gets 3 L of diarrhea with abdominal pain on day 19 post-transplant. T-cell chimerism shows *100% donor engraftment*. CMV PCR low positive [negative one week prior]. No flex sig until Monday [patient presents Friday night]. Very few things give you 3 liters of diarrhea. The key is get a C. Diff sample and, when negative, give steroids early to treat acute GVHD of the gut; histology can *persist for 5 days despite steroids*, so don't fret about biopsy yield with steroids.

DISORDERS OF COAGULATION

Coagulation requires three things: a blood vessel wall, functioning platelets and adequate coagulation cascade. 30-40% of all patients in the ICU will have some sort of bleeding disorder.

Consider the reason why the patient is in the ICU [e.g. sepsis – think DIC]. Also consider where the bleeding is located, is it mucosal [e.g. petechial think of platelet problems] or visceral [consider coagulation defects] is it immediate [platelet defect] or delayed [coagulation defect]. This is because platelets act first [primary hemostasis] and the coagulation cascade acts second [secondary hemostasis]. Pre-morbid medical conditions and drugs are very important when considering the differential.

Primary hemostasis - consider looking at a peripheral smear. There may be platelet clumping or a decreased number of platelets. Bleeding time is an assessment of platelet function, bleeding time will increase when platelet counts are less than 100K.

Consider a patient who is given a GPIIbIIIa inhibitor and has a sudden, profound drop in platelet count. In patients receiving these drugs there is about *a 3% risk of true, severe thrombocytopenia and a 1% risk of pseudo-thrombocytopenia*. The gold standard of diagnosis is to look at the peripheral smear for clumping. If there is clumping, it is a pseudo-thrombocytopenia and is the result of EDTA. Repeat in a citrate tube can prevent clumping, but that technique is not fool proof

Secondary hemostasis – consider the PTT and PT, there may be thrombin inhibitors [e.g. heparin].

Approach to Thrombocytopenia

Are platelets being destroyed? Are they not being produced? Are they being sequestered?

Drugs are common problems that decrease platelet production [e.g. ethanol, chemo] or there may be infiltrate of the bone marrow.

Platelet destruction can be immune or non-immune in nature. The treatment is always the underlying cause, and giving platelets rationally.

Platelets are scarce, and they only last one week in the blood bank. There are two flavors: random donor and pharesis [single donor] units. There is an order of magnitude *more* platelets in the latter type. In *TTP* and *HIT*, *platelets are relatively contra-indicated*.

The dosing of platelets is 1 unit of random donor platelets per 10 kg of patient, or 1 unit of single donor platelets per 90kg of patient. *The majority of ICU patients will not change their platelet count when transfused platelets*.

Immune-Mediated Thrombocytopenia

This is typified by large platelets in the periphery. You may see only one large platelet per HPF which corresponds to a peripheral count of about 10K. When immune-mediated, there is often a very rapid and profound drop in platelets.

The treatment of ITP is steroids, IVIg [a transient response] if there is an immediate need for an invasive procedure. Anti-Rh[D] can be used, but the patient must be Rh + and have a spleen. If steroids fail, rituxan is the next step. There are tPO agonist for refractory ITP.

Vancomycin-mediated thrombocytopenia is immune mediated. It's an Ab only active in the

presence of vancomycin. Bleeding can occur in these patients [about 30%] – see section 5.

Thrombotic Thrombocytopenic Purpura

This is a favorite on the boards. It is a *deficiency* of the vWF-cleaving protease ADAMTS 13. Absence of ADAMTS 13 prevents cleavage of wWF and the large multimers stick to platelets and cause diffuse thrombosis. It presents classically with fever, anemia, thrombocytopenia, renal failure and neurological symptoms. This pentad is usually not present. The *only things* required for diagnosis are *low platelets* and *MAHA*. Fever and renal dysfunction are present in about 40%, CNS dysfunction in about 75%.

The treatment of choice is pharesis, the provision of FFP *or both*. The pharesis removes the inhibitor of ADAMTS 13 and FFP replenishes this enzyme [pharesis + FFP = plasma exchange]. Steroids are given to lower the Ab production [which may be the cause of the low ADAMTS 13]. Platelets are relatively contraindicated.

Heparin Induced Thrombocytopenia

Type I HIT is *non-immunogenic* and may be direct heparin binding to platelets. It is common and may occur in *up to 30%* of patients receiving heparin; it occurs in the first two days of heparin administration. The platelet count rarely falls below 100K and clotting does not occur. Platelet counts normalize with continued administration of heparin.

In *0.3 to 3%* of patients treated with UFH, the more serious, *immunogenic* form of HIT can occur. This is an *IgG* mediated response against heparin-PF4 [*type II HIT*], which can occur with administration of both UFH, and LMWH [the shorter the polysaccharide chain, the lower the incidence of HIT – so less common with LMWH]. The platelets usually fall *days 5-10 of administration*, but will occur earlier in patients who have already received heparin. The treatment is stopping all heparins – do so when platelets *drop by more than 50% OR` to less than 50k*, if there is bleeding or if there is thrombosis [clotting occurs in 20-50% where venous is more common than arterial].

HIT risk factors – greatest in *CV patients and orthopedic patients* who may have higher PF4 circulating, also ICU more than floor patients, women more than men, UFH more than LMWH, therapeutic more than prophylactic doses and the appropriate clinical scenario.

The diagnosis is based on clinical judgment; the *ELISA* test can be helpful which *is an anti-PF4 antibody assay*. This test *is quite sensitive*, but not specific. It is positive in *more than 50%* of cardiac and vascular surgery patients [*less than one third of these positive patients will have HIT*].

The *functional assay* is platelet aggregation – a *h*eparin-*i*nduced *p*latelet *a*ctivation study or a serotonin release assay which both have high specificities but low sensitivities.

How about those who have thrombosis? 40% will have a platelet decrease *before* a thrombotic event, 30% will drop their platelets the *day of* the clot and 30% of patients will have their platelets drop *following* the thrombotic event. Further, *thrombosis can occur after heparin is stopped [for up to weeks!].*

The treatment of HIT is argatroban & lepirudin. The latter is renally cleared and should be avoided in renal insufficiency; the former is hepatically cleared. Bivalirudin is used in PCI, fondaparinux is not approved for HIT, it is renally excreted with a long half-life and *there are case reports of fondaparinux HIT*.

Some have suggested *that anyone with HIT* [clots or not] *should be anticoagulated for weeks*, but this is not generally held. *Warfarin cannot be started until the platelet count is normalized*.

Disseminated Intravascular Coagulation

DIC is a clotting disorder, intra-vascular clotting – fibrin deposition in the vessels which leads to vascular thrombosis and organ failure.

There is depletion of platelets and coagulation factors. *The diagnosis of DIC is clinical* – the right clinical condition, with an elevated PT/PTT, low platelets, low d-dimer also with low fibrinogen, high thrombin time, high FDP and *low anti-thrombin*. Treat the underlying condition, transfusion only for bleeding or invasive procedures, *do not treat numbers*.

Fresh Frozen Plasma

FFP is *frozen*, so it takes some time to thaw [it requires 20 mins to thaw] unless at a large trauma center. A random donor *unit* has 200 to 250 mL. A pharesis *unit* is 2 units of FFP. Indications are a documented coagulopathy, massive transfusion, reversal of warfarin defect and TTP or HUS. The *initial dose is usually about 2 U of FFP or 1 pharesis unit*. Note that *5-6 units of platelets* contain *about 1 U of FFP* [no V or VIII]. If the INR is less than 2 there will not be much change with FFP [normal INR of FFP is about 1.7].

Cryoprecipitate

Cryoprecipitate is a *source of fibrinogen*. It is no longer used to treat von willebrand disease [vWD], now *use factor VIII for vWD*. DDAVP only works in about 30%. Cryoprecipitate is a second line choice. Use cryoprecipitate for low fibrinogen [less than 100].

Massive Transfusion and Coagulopathy

What about the coagulopathy of trauma and massive transfusion? The etiology is multifactorial. It is secondary to hemodilution, acidosis, hypothermia and DIC. This can be seen with massive GI bleeders as well. The goal is to maintain perfusion and oxygen delivery.

What is the blood product ratio? On the surgical boards, it is typically more FFP to pRBC. There is poor data in the MICU. Is it 1:1, 1:2, 2:5? Recent data suggests giving near whole blood during MTP – see section 9.

There is no clinical scenario where factor VII improves outcome. When should it be used? The patient should be salvageable, there should be initial interventions such as surgery and factor replacements, the acidosis should be corrected and *patients with thromboembolic* conditions should *not* receive factor VII.

Hemophilia

If a patient has hemophilia and is bleeding – call a hematologist. Type A is VIII deficiency, there are factor VIII concentrates; these patients have very high requirements when they bleed, it should be an emergent consult to hematology. Type B is a IX deficiency. *PCC can be used*. Prothrombin complex concentrate [PCC or KCentra] contains *factors II, VII, IX, and X*, as well as the antithrombotic *proteins C and S.* aPCC [or FEBIA] is very similar, however FEIBA contains *activated* components of X, IX, VII and II.

Pharmacological Misadventures

For the treatment of *warfarin* overdose, FFP, PCC [KCentra], or aPCC [FEIBA] can be used. There are reports of clotting with some of these. *PCC does not have high levels of VII*. Vitamin K takes 24 hours for full effect.

LMWH bleeding is tough – protamine will not be very effective, can give FFP.

Reversal of fondaparinux is with FEIBA. Reversal of the new anti-thrombin inhibitors should begin with FEIBA if life-threatening. Dabigatran can be dialyzed, but there can be rebound with cessation of dialysis.

What about *anti-platelets*? Plavix is tricky – consider platelet transfusion, there are retrospective studies that suggest some clinical improvement with platelets, but the data is sparse.

ERYTHROCYTES IN THE ICU

Understand erythrocytosis. Consider a patient with pulmonary atresia and a hematocrit of 76% from chronic hypoxemia. The patient's blood pressure *will be higher* because of hyperviscosity. There is no data to support the use of routine phlebotomy in adult patients with cyanotic heart disease to prevent stroke. The data for that practice comes from patients with PCRV who are older with thrombocytosis. In adult patients with congenital heart disease, phlebotomy should only be done when *there are symptoms of hyperviscosity*. These patients have a spuriously high PT and PTT because with the erythrocytosis, there is *less plasma per volume*. Thus when their blood is put in tubes, there is less plasma relative to anticoagulant. Special tubes are required for hematocrits above 55%. While chronic hypoxemia is the major culprit for stimulation of red cell mass, the renin angiotensin axis is also implicated. In fact, in some patients, the use of ACEI can lower red cell mass!

Understand the immune-modulatory effects of pRBCs. The transfusion of red cells is associated with multiple, significant immune-modulatory effects that *are NOT related to the red cells per se*. Instead, they are most likely related to trans-fused lymphocytes and leukocytes within the blood. These transfused white cells have been shown to *circulate within the recipient for years and even cause graft-versus host disease*. This has been *implicated in immunosuppression* and even *tumor growth in some cancers!* Cytokines, plasticizers, viruses and proteins within the transfused blood are also implicated.

The administration of EPO to critically ill patients has been shown to reduce the need for transfusion by 0.4 units per patient on average, though in *ICUs that use a restrictive blood use policy [7 g/dL transfusion trigger] to begin with*, this probably does not make a difference. There is no change in mortality, and there may be an increase in thrombosis risk in critically ill patients. There is certainly no difference in time on the ventilator.

Understand blood conservation in the ICU. *Routine* use of *parenteral iron* has *not* been shown to *decrease the need for red cell transfusion in the intensive care unit*. The use of a lower transfusion threshold has, so too has been the use of aprotinin the cardiac surgery, so too has been the use of recombinant epo and autologous blood cell transfusion from patients undergoing elective surgery. Cell savers have been shown to improve hemoglobin, but it is unclear if they reduce transfusion. *When matched for organ dysfunction, patients who receive blood transfusion have a higher mortality than those who don't* [Vincent J, Baron J, Reinhart K, et al. Anemia and blood transfusion in critically ill patients. JAMA 2002; 288:1499-1507].

8. CRITICAL CARE NEUROLOGY

SEDATION & ANALGESIA

The dictum is less is more – e.g. daily sedation interruption with a spontaneous breathing trial. Enacting the aforementioned increases ventilator free days; decreases ICU and hospital LOS.

Strom in 2010 showed only analgesia [no sedation] seemed to do even better. A post-hoc analysis of the Strom study showed that *in the no sedation group there was less fluid administered, increased urine output; and more renal dysfunction in the sedated group*. There was no difference in delirium or VAP.

DEXMEDETOMIDINE

Dexmedetomidine *does not decrease the rate or depth of breathing*. It is a centrally-acting alpha 2 agonist. It has analgesic properties and it can be used in extubated patients. Never bolus the patient, just start a continuous infusion.

There is less time on the ventilator and less delirium *compared* to *valium*. There is bradycardia with a loading dose and decrease in the length of stay in the ICU. If you need the patient to participate in their care [e.g. neurological examination] dexmeditomidine is a good drug. Extubations were about two days earlier, there were fewer infections on dexmedetomidine. Dexmedetomidine may have a benefit in septic patients for unclear reasons. Dexmedetomidine is a cost-effective treatment [Dasta JF CCM 2010 497-503].

Dexmedetomidine resulted in less delirium and fewer ventilator-days than midazolam [SEDCOM]or lorazepam, but *did not reduce length of stay* in the ICU or hospital, in 3 randomized trials [JAMA 2009, 2007, 2012].

Propofol appeared equivalent to Precedex in sedation efficacy, length of stay and ventilator-days in the 2012 JAMA trial.

A *2013 meta-analysis* of 6 trials [including some of the above] suggested non-benzodiazepines *[dexmedetomidine or propofol] reduced ICU length of stay by ~1.5 days, ventilator days by ~2*, but had *no impact on delirium* or *short-term mortality* rates, as compared to benzodiazepines [midazolam or lorazepam].

OPIOIDS

Opioids are great analgesics, but there are side-effects [nausea and vomiting, constipation, pruritis, sedation, tolerance, dependence, respiratory depression].

What are the side-effects of mu opioids? There is blockade of the propulsive peristalsis by increased smooth-muscle tone and inhibition of the coordinated peristalsis required for propulsion – leading to nausea, vomiting and unrelenting constipation.

Methylnaltrexone cannot cross the blood-brain barrier, *it does prevent nausea and vomiting*. Methylnaltrexone [NEJM 2008; 2332] given to treat constipation resulted in a *45% laxation* response in 4 hours compared to *15% in placebo*. So there is a roughly 50% laxation failure with methylnaltrexone.

There are other causes of constipation including immobility, decreased oral intake, low fiber intake, metabolic imbalances, advanced age, other drugs. Constipation in the ICU is very common 5-83% and is associated with increased LOS, increased time on the ventilator. In patients in the ICU who were constipated, if no BM by day three, lactulose versus PEG versus placebo.

Making bowel movements got patients out of the ICU earlier.

Remifentanil is not superior to fentanyl in terms of pain and sedation in the ICU. There may be negative immunomodulatory effects of opioids. Morphine and remifentanyl has been shown impair the immune response.

Propofol

Propofol compared to benzodiazepines has been shown to decrease length of stay and potentially mortality as well [Wunsch CCM 2009; 3031].

Propofol-related infusion syndrome [PRIS] can cause rhabdomyolysis, renal failure, hyperkalemia, and cardiac abnormalities. PRIS was found in 1.1% in a large study, it could be present after small amounts of propofol and for a short period of time. This data has been shown in neuro-intensive ICUs where high doses are given for short periods of time and this may be a risk for cardiac arrest. The *ECG finding of PRIS is the RBBB that is convex* and curved ST segment in the right precordial leads. It is suggested that trigs be monitored after two days of use.

Ativan

Like propofol, it activates the GABA receptor and is good for the production of amnesia. Most benzodiazepines are cleared by the liver. Ativan is associated with metabolic acidosis at high levels [propylene glycol] and it is an independent risk factor for delirium.

DELIRIUM

What is the epidemiology of delirium? About *50% in non-vent and 70% in ventilated patients*. This is acute brain injury = organ dysfunction. *The vast majority of delirium is a quiet delirium = hypoactive delirium*. Hyperactive delirium is 5% or less.

The cardinal feature of delirium is inattention! So the little old lady with her head down unable to pay attention = inattentive. To test this, you can ask a patient to squeeze your head every time you hear a letter. 10 letters, 1 per second. If they are right 8 of 10, they are attentive. 75% of delirium is missed.

Delirium – Dementia Link?

Delirium raises the risk of death by 10% per day! Delirium increases the risk of critical care associated brain injury. There is a 50-70% risk of neuropsychological cognitive impairment like a dementia. *There is evidence to suggest that the increase in dementia risk in the country on the whole is being made by ICU experiences*. As compared to those never hospitalized, those who were hospitalized and those in the ICU had a graded increase in dementia. Most of the ICU type dementias were *non-Alzheimer*. Sepsis seems to be a big risk as well. ARDS too.

Part of the problem might be the underlying leaky blood-brain barrier, inflammatory mess that occurs in ICU patients.

Sedation: Less-is-More

In the mid-90s, Ely studied *spontaneous breathing trials* [NEJM] and found that 2 days were shaved off of mechanical ventilation.

Then Kress studied *spontaneous awakening* in 2000 in NEJM and also found 2 days shaved off of the MV.

Then in 2008 in Lancet they paired them. *SBT and SAT showed benzo use cut in half, narcotic use cut in half*. They didn't stop narcotics when the patient was in pain. Narcotics were stopped, only if the pain was controlled. In modern ICUs, there were 4 days off ICU stay and *reduced mortality with an ARR of 14%*.

Benzodiazepines and Delirium

What about the type of drugs used? GABA-ergics have been the most widely used sedative in the last 20 years worldwide, though propofol is used

much more in the US. What is analgo-sedation? *It means using a narcotic as a single agent* = sedation and pain relief. Strom in Lancet 2010 called this 'no-sedation'. Another is to use dexmedetomidine. Another way is to use an anti-psychotic.

The use of large doses of narcotics in burn ICUs tend to *protect against delirium* even in the setting of pain as deliriogenic. GABA drugs affect a portion of the brain that will render a patient unconscious, but the patient is not getting sleep, repeat, *they are not getting slow-wave sleep*.

The locus ceruleus is lower down and is where the dexmedetomidine hits. As above, Dex versus midaz – SEDCOM trial – After 24 hours there was much less delirium in the dex group [less brain dysfunction], there was also less time on MV.

Assessment

Assessing for consciousness = *arousal* [RASS, etc] plus *content* [CAM-ICU]. When using the RASS, it separates verbal from physical stimuli. So you begin the scale by talking to someone, if they don't respond with eye contact, then they are at least -3 and this is moderate sedation. If tactile stimulation is required, this is deep sedation and is a -4. Responding to neither physical nor verbal stimulation is unarousable and is -5. The difference between -1 and -2 is duration of eye contact for 10 seconds. If longer than 10 seconds, then the patient is -1, if less than 10 seconds then -2. This was described in 2002, it is kind of an expanded 'eye' response from the GCS. How does the GCS work? 4 points for eyes and 6 limbs. The most points for verbal is 5.

BRAIN DEATH

Irreversible cessation of circulatory and respiratory functions is death, *OR* irreversible cessation of all functions of the entire brain including the brain stem. 2010 Wijdicks.

In order to begin brain death testing, the patient must have a mechanism of brain injury that would result in brain death. Irreversible loss of the clinical function of the brain, including the brainstem, and there must be a mechanism that must be compatible with this. Otherwise think about metabolic issues.

Mitigating Factors & Brain Death

Mitigating factors include *drug intoxication*, *cervical spine injury* [motor exam, apnea test do not work so you *need an ancillary test*], the recent use of neuromuscular blockade. Vecuronium with renal failure can lead to a prolonged effect of NMJ blockade, as can cisatracurium.

Remember that the *NMBs act upon nicotinic* receptors, the muscarinic receptors [*pupils*] still work. Nevertheless, post arrest may result in large pupils following adrenergic or anti-muscarinic drugs, so check reflexes then. If there are reflexes, then there is no NMB. Look for train of 4, if there are any twitches, there is no prolonged NMB. Recall that if there are *4* twitches 0-74% of nicotinic receptors are blocked, if there are *3* twitches then 75% block is present, *2* twitches = 80% block, *1* twitch = 90% block and no twitches = 100% block.

The *body temperature* must be *more than 36* degrees celsius. Now the systolic must be more than 100 mmHg previous guidelines were 90.

Determination of Brain Death

So the WHOLE brain needs to be dead, both hemispheres and brainstem.

Thus the following really must be present: pupils dilated and unresponsive, usually mid-line [CN III], the *oculocephalic reflex [Dolls' Eyes]* requires III, IV, VI – not performed if there is concern for spinal cord injury so instead do the cold-caloric vestibule-ocular response. *A 'normal' or 'present'*

VOR is slow towards cold ear and fast away, this is NOT seen if the patient is BRAIN DEAD.

The corneal response tests V afferent and VII efferent as does facial pain application. IX and X is gag response. There should be absent cough with tracheal suction.

Note that posturing [decerebrate or decorticate] *requires brainstem function*, so if present, there is brainstem function and the patient is not brain dead. Further, *the following DO indicate* brain activity: seizure & facial grimacing.

Importantly, upwards of 50% of brain-dead patients can display peripheral reflexes in response to manipulation of the head, and stimulation of the extremities. Thus, the triple flexion response *does not* require *brain stem* function, *nor do deep tendon reflexes* as these are both spinal reflexes. The triple flexion response is: *ankle, knee and hip flex with pain applied to the toe or inner thigh* – it is a spinal reflex, so it may be present with brain death. *Finger jerks, undulating toe signs* can occur with brain death. If there is any concern get an ancillary test!

Apnea testing in patients with preexisting conditions, such as *severe COPD or sleep apnea, may be inaccurate* because these patients may have an abnormal hypercapnic reflex. The *apnea test* occurs when you pre-oxygenate the patient, normalize PCO2, unless a chronic retainer. Apply intra-tracheal oxygen at 6 L per minute. The patient must be *undressed and evaluated for movement*. Check an ABG 8 minutes and every few minutes thereafter to see if the PaCO2 is above 60. If the patient becomes unstable, get an ABG and reconnect. What does stopping the apnea test requires? If they are breathing, if the saturation falls below 90 for organ donors or 85 for non-organ donors. If there are cardiac arrhythmias, hypotension despite bolus and pressors [that is an SBP less than 100] or if the PaCO2 gets above 60 or 20 above baseline. *The time of death is the time the PaCO2 reached the target level* or when the *ancillary test is officially reported*.

EEG is commonly cited as a means to confirm brain death but it is subject to *false positive* brain death assessments [patient on barbiturates, heavy sedatives, or undetectable subcortical neuronal activity] *and false negative* brain death assessments [agonal EEG activity or ICU artifacts]. Transcranial Doppler *should not* be used as 10-15% of the time no blood flow will be reported, but this is likely technical in nature. Cerebral angiography is the gold standard, followed by nuclear imaging followed by MRI and CT angiograms.

Nuclear blood flow is the classic confirmatory study, but sometimes there is a tiny bit of flow, and there must be a delay and repeat study 12-24 hours. You can do an angiogram, but it is more time-consuming and requires a dye load. *An EEG is not required unless it's a child*. They are difficult to perform.

SUMMARY

So brain death is: no cough or gag, no extensor posturing, no oculocephalic response or Doll's eyes, but there can be triple flexion.

10 states require 2 MDs [CA and NY two of them], some hospitals still require 2 MDs. *Except for organ support for donors, all therapeutic modalities must be discontinued and DO NOT require consent*.

STATUS EPILEPTICUS

Status epilepticus is which of the following? Easily terminated, seizures more than 2-3 minutes, non-detrimental if non-convulsive, can sometimes only be detected by EEG and is most commonly caused by trauma?

The answer is *that it can sometimes only be detected by EEG* [e.g. in the comatose patient]. *After 7-9 minutes*, the probability of a seizure

stopping *spontaneously is* essentially *zero*. In animal models *neuronal damage* begins to occur *at about 30 minutes*. Thus, the classical definition *is* 30 minutes of continuous seizure while *operationally it is probably 7-10 minutes of continuous seizure*. Quick termination decreases the chance of continued seizure activity. Treat quickly if the seizure is more than 5 minutes.

Status may be convulsive [easy to see], non-convulsive [twilight], or partial with continuous focal neurological abnormalities such as motor [including the cranial nerves] or sensory *without impairment in consciousness*.

The most *common causes of SE are*: an epileptic off of his or her meds or after a change in medication or dose, ethanol, then much less likely: infection, trauma, tumor, stroke, anoxia, metabolic.

Status epilepticus occurs as the first seizure episode in the majority of patients. The overall mortality of status is estimated as less than 30% in adults.

Pathophysiology

The pathophysiology of status is excito-toxicity; there is also a reduction in the sensitivity of the GABA receptors in the brain with prolonged seizures, such that GABAergic medicines can become less effective with time. This is particularly important in the hippocampus.

Early on in status [first 30 minutes], there is significant motor activity and adrenergic tone leading to low pH, high glucose, high lactate, high heart rate, etc. but as a seizure continues, there begins to be 'electromechanical dissociation' as the brain 'burns out' there is a transition from convulsive to non-convulsive status and vital signs tend to normalize as well as metabolic derangements. Brain damage is much more likely and rises exponentially with time. *Non-convulsive status still causes brain damage*, *but at a slower rate* as oxygen is being depleted less profoundly.

Treatment

The benzodiazepine receptors become more refractory with seizure time. Diazepam is very lipophilic, it works quickly but *comes off quickly*. You want Ativan *because it stays in the blood longer*. Coming off propofol can result in re-emergent seizures.

The treatment requires escalation, initially with benzodiazepines such as *Ativan* 0.04-0.08 mg/kg, then with *phenytoin* 15-20 mg/kg [higher doses may provoke seizure activity and more than 50 mg/min administration can have cardiac toxicity with Qt issues], and then with *phenobarbital* at 20 mg/kg; is *very long acting*.

For persistent convulsive seizures, reach for pentobarbital. Refractory status is bad, with very high mortality rate.

Could consider ketamine [NMDA receptor antagonist] use a general induction dose of 1-5 mg/kg with infusion of 1-5 mg/kg/hour.

Valproate has been shown to be very helpful in status epilepticus. There is no respiratory depression. Follow ammonia levels.

Levetiracetam, does not go through P450s, but it is renally metabolized. It *should be* adjusted in renal failure in terms of its dose, but no need to follow levels. Lacosamide has emerging literature to suggest that it does *not* work. Topiramate can be used.

What about *hypothermia*? Status has been treated with this and seizures have been shown to stop, but seizures tend to recur as the patient is rewarmed. If a patient has a para-neoplastic, or non-neoplastic limbic encephalitis [e.g. autoimmune] *consider steroids*. The mortality of SE is dependent upon age, seizure duration. The *best prognosis is in those with known epilepsy, the worst in ethanol withdrawal*. Unless, the

patient has a known devastating CNS condition, there can be prolonged seizures that can be treated. Anecdotally there have been patients *with a 3 month-long seizure* - who walked out of the hospital.

INTRACEREBRAL HEMORRHAGE

Primary injury is the area of maximal neuronal damage, the penumbra is the area of less injured and potentially recoverable neuronal tissue.

Secondary injury follows primary injury and causes further neuronal damage. There are multiple causes of secondary injury – *hypoperfusion* is one such cause and why the systolic must be kept more than 90 mmHg. In the trauma literature, a single systolic less than 90 increases morbidity and doubles mortality. Similarly, *hypoxemia* is a great cause of secondary damage with a PaO2 of less than 60 mmHg this increases poor outcomes from 28% to 71% and increases mortality as well. So perfuse the patient and improve oxygen.

Hemorrhagic stroke can be seen in the putamen, thalamus, cerebellum, pons, caudate and are often related to hypertension, amyloidosis, etc.

Basic Pathophysiology

The Monroe-Kellie doctrine – there are 3 compartments – *brain, blood, CSF*. An increase in one must be compensated by a decrease in the others *or the ICP will increase*. The pressure is related to volume by compliance. The compliance curve *works against the young*.

Cerebral auto-regulation is also important. As the CPP goes up, the vessels reflexively constrict such that flow remains the same. The curve is shifted rightwards with chronic hypertension.

In the area of ischemia, the auto-regulation is lost, such that blood flow is just *pressure dependent* – there is a straight line from ischemia to edema. Remember that in addition to MAP, the PaO2 and PaCO2 also have effects on cerebral blood flow. *The PaCO2 curve* to blood flow approximates a sigmoid curve, while the *PaO2-cerebral blood flow* graph makes nearly a 90 degree angle such that at low oxygen tensions, there is a very sudden and abrupt vasodilation, and increase in cerebral blood flow which will increase ICP quite a bit.

Neuromonitoring

The CPP is MAP less the ICP. Normal CPP ranges from 70-100 mmHg, adequate is 50-60 mmHg. The normal ICP is about 5 mmHg. *The arterial line should be zeroed at the tragus*! When treating neurological insults, the ICP should be less than 20 mmHg and CPP of 50-70 mmHg. EVDs are commonly used as the ICP monitoring device. Be careful if you don't have a bolt to monitor the ICP. Why? *An increase in BP may be a sign of increased ICP.* If you reflexively treat the BP, you will drastically drop the CPP.

Faced with this situation, a consideration is to *give a bolus of 3% saline*. If the MAP then drops, it suggests that the ICP was the primary problem [because the 3% would treat the elevated ICP and break the stimulus for MAP elevation]. If the BP continues to climb in response to a 3% bolus, then ICP might not be the primary problem. Pain and agitation should always be sought and treated first.

Jugular venous oximetry is sometimes used to assess cerebral perfusion. One trial pushed up CPP in response to jugular venous oximetry and this fluid overloaded patients *without a change in outcome*. Pbto2 is available; this is a direct measure of tissue oxygen utilization. Goal-directed therapy was used to push up PbtO2 to more than 25 mmHg. Initially there was a mortality benefit, and then there was no change, and then there was slightly higher mortality. Sometimes the PbtO2 is an early marker of worsening systemic oxygenation.

Management

How does one approach an ICP more than 20 mmHg? First, *HOB up* which drains the veins. If there is pain, treat with opioids as well as sedation. What about the second tier therapy?

Firstly, *hyperventilation has a peak effect in 30 minutes*. A PaCO2 of 25-30 can cause significant vasoconstriction and diminished blood flow. Patients randomized to hypocapnia had a *worsened outcome*. If the patients remain at a low PaCO2, there will be a change in bicarbonate to compensate and there will be *rebound vasodilation*. Also air-trapping [as a consequence of hyperventilation] can increase ICP.

Osmotic rescue should be done. Mannitol is 1 gram per kilogram. It acts within 20-30 minutes. Filtered needles must be used. It causes an osmotic gradient from everywhere. It will pull fluid into the vascular space, improves blood cell rheology, and maybe a free radial scavenger. What is the mannitol end-point? Serum osmolality of *less than 320 but preferred is the osmolal gap of more than 10*. Watch for osmotic diuresis and maintain euvolemia. Mannitol can aggravate vasogenic edema in the area of injury if given in multiple large doses. Only use it when you need to.

Hypertonic saline is picking up steam. 3% comes in 250 cc bolus. Run it in as fast as possible, just like Mannitol. Remember that a rule of thumb is that 1 mL/kg of 3% saline will increase the patient's serum sodium by roughly 1 mEq/L. 7% saline bolus or 23.4% [30 cc bolus over 10 minutes] can also be used. NMDA receptors can be activated by hypertonic saline which can result in excitotoxicity, though a small trial showed no difference between mannitol and HTS.

Shivering is bad; it increases cerebral metabolic rate. Cooling is not indicated, but fever should be treated. Each increase in 1 degree Celsius increases cerebral metabolic rate by 7%.

Hyperthermia does have a lot of known metabolic derangements.

In patients with GCS of 3-7, *hypothermia was unhelpful* in multiple trials and a large meta-analysis; it may decrease ICP in some refractory ICP patients. Pentobarbital coma may result in unreactive large pupils, it makes them hypothermic and an isoelectric EEG, such that blood flow and blood volume drop in the brain. Loading dose is 10-20 mg/kg. The toxicity of pentobarbital is sepsis-like. They are vasodilated, but cold, hypotensive, there is ileus edema and immunosuppression in addition to unreactive large pupils.

What BP meds to use to maintain the CPP? Consider levophed over dopamine if the patient is hypotensive. *However, these patients are rarely hypotensive, especially at the outset*. As hemorrhagic strokes are partially caused by high blood pressure, and blood pressure goes up after intracerebral hemorrhage often to shocking levels - does this acute hypertension represent an adaptive response by the body, pushing blood up into the brain where it's needed? Or does high blood pressure during an intracerebral hemorrhage make everything worse?

American Heart Association's guidelines' target *mean arterial pressure of < 110 mm Hg* or BP < 160/90, absent evidence of decreased cerebral perfusion pressures [*MAP < 130 if increased intracranial pressure or decreased cerebral perfusion pressure are present*].

The *INTERACT trial* showed rapidly lowering blood pressure reduced hematoma growth over 72 hours in patients with intracerebral hemorrhage, without apparently hurting anyone [n=404 patients].

The *ATACH trial* rapidly reduced or normalized blood pressures, and found it wasn't harmful [n=60 patients].

NEJM 2013 - *INTERACT2* trial was published 2,839 patients who had just had an intracerebral hemorrhage [<6 hours].

Rapid blood pressure reduction [sBP less than 140 mmHg] did *no worse* and appeared to do better, with 52% experiencing death or severe disability, compared to 56% in the standard care group. Mortality was identical between groups at 12%. *Interestingly, the possible benefit seen in the first INTERACT — reduced growth of hematoma — was not found in INTERACT 2.*

In summary, the blood pressure should be treated to reduce extension of the size of the blood. Never use nitrates in neurological patients as they can increase ICP; nicardipine or labetolol are great choices.

Surgical evacuation is generally unhelpful in ICH, *so don't call the neurosurgeons unless it's a cerebellar stroke*. These can be evacuated, the clot should be removed by the surgeon. When else to call the neurosurgeon? When the GCS is 8 or less with elevated CPP, get an EVD, when there is hydrocephalus or need for hemicraniectomy or a cerebellar bleed more than 3 cm in diameter.

Other things, seizure prophylaxis for one week with phenytoin, corneal protection, early enteral nutrition, GI & VTE prophylaxis.

SEVERE STROKE AND SUBARACHNOID HEMORRHAGE

65 year old woman with severe PNA, at noon, the patient is normal, at 215, the patient is aphasic with hemiplegia. What is the correct therapeutic step?

Give IV tPA if the non-contrast head CT is negative. The treatment of ischemic stroke is to evaluate for thrombolysis. The non-contrast head CT is the fastest. If there has been a long-standing stroke, there will be edema, and effacement. DWI or diffusion weighted imaging and PWI perfusion weighted imaging is the use of gadolinium MRI to look for a mismatch in the brain – to target patients who may benefit from intra-arterial [IA] therapy. Also, a very large stroke with a large perfusion defect will not do well and these patients will be observed in the ICU.

Management of Ischemic Stroke

3 hours is the reperfusion window for IV tPA. Too late will result in a leaky BB barrier. The faster the better the outcome. The initial trial gave tPA at 0.9 mg/kg in patients with an NIHSS score between 4 and 22. Up to 4.5 hours is OK, *unless* over 80, on oral AC regardless of INR, with a large NIHSS [more than 25] or in those with a history of stroke *and* diabetes.

Thus, acute focal neurological change requires the time of onset determination! The patient must be assessed for contra-indications to tPA. Also, check glucose – if it is very high or very low they can have a stroke mimic.

What *about IA therapy*? The window is *6 hours* due to an occlusion of the MCA. But start the IV tPA while the lab gets set up. In a patient who has recently had surgery, there are systems that retrieve clots. With clot extraction, there is a stroke and death rate of about 10%. Further, here is a very high risk in posterior circulation, or in patients with blood glucose above 200.

After a thrombotic-ischemic stroke what is a reasonable treatment choice to prevent future stroke? The answer is anti-platelets. Do not give *until 24 hours after finishing tPA*. The combination of *ASA and Plavix* for stroke is *NOT* indicated [for stroke prevention alone]. Options are: ASA, ASA + dipyridamole, or Plavix. Either ASA + dipyridamole *or* Plavix are favored over ASA alone, but the data is far from robust.

What about *heparin*? There is no role in acute ischemic stroke. However, heparin should be used in *cerebral venous thrombosis* even with cerebral hemorrhage! Also, if the patient has a

hyper-coagulable state, if there are extra-cranial carotid or vertebral dissections [unknown efficacy], but especially for cardioembolic strokes. *The risk of bleeding with clopidogrel plus ASA is about the same as warfarin alone for cardio-embolic events*.

What about *hypertension treatment*? Start within 24-48 hours with oral medications. How about blood pressure control? There is a U-shaped curve for mortality. If they are not a tPA candidate, if over 220/120, lower by 15% in the first 24 hours. If tPA is in the works, then get SBP *less than 185*. If tPA given, must be *less than 180 mmHg*.

NPO, swallow evaluation, bed rest, *no* heparin, warfarin or *ASA for 24 hours*. Statins for all patients unless LDL less than 70.

The guidelines for glucose are 140-185 in the first 24 hours. Hyperthermia should be treated as well, with Tylenol [APAP], but it is unknown if this helps patients. What about steroids? They are not effective in cytotoxic edema related to infarct or bleed. Steroids might help with *neo-vascularization* seen in tumors, abscesses, etc.

Is there *a role for surgery*? In young patients with severe, diffuse non-penetrating TBI, [or rarely *large ischemic MCA strokes*] *hemicraniectomy patients* had fewer ventilator days and shorter ICU stay, but there was no difference in LOS. The hemicraniectomy patients spent less time with an ICP of less than 20 mmHg [DECRA trial]. *BUT*, the primary outcome or outcome score was worse with surgery [*made more chronically debilitated patients*]. DESTINY II trial – NEJM 2014 concluded: "Hemicraniectomy increased survival without severe disability among patients 61 years of age or older with a malignant middle-cerebral-artery infarction. The majority of survivors required assistance with most bodily needs." Who should get a hemicraniectomy? It may be a life-saving procedure, *but they may have life-long disability*. The size of the craniectomy is important, there needs to be at least 13 cm. The zygoma needs to be removed.

PRES

What about PRES? Hypertensive, leukoencephalopathy, both grey and white matter affected. There is visual blurriness. It is not a PCA stroke. It is a blood-brain barrier leak usually in the setting of high blood pressure. Immunosuppressive drugs can also do it. So PRES is not in a vascular distribution.

Sub-Arachnoid Hemorrhage

Worst HA of life, nausea, vomiting. LP should be done and 1st and 4th spun for xanthrochromia.

Get a non-contrast scan. Look for early hydrocephalus. The patient needs *angiography to look for an aneurysm*.

They need an *urgent neurosurgical evaluation*. Early surgery is recommended in the *first 72 hours* – aneurysm clipping. Coils can be used beyond that – especially in older patients. *Unsecured aneurysms have a 4% re-bleed risk on day zero*, then *1.5% per day* for the *next 13 days* or about *25%* in *the first two weeks*. If the patient cannot be seen by a surgeon, consider anti-fibrinolytic therapy.

Blood pressure control: systolic *less than 140 mmHg* with labetolol or nicardipine to prevent re-bleeding and nimodipine 60 mg po every 4 hours to prevent vasospasm. Vasospasm is *the SAH issue*. The leading cause of death and disability following subarachnoid hemorrhage is vasospasm. Clinically evident vasospasm occurs in 20-30% of patients with SAH and is thought to occur in response to spasmogenic substances released by subarachnoid clot lysis. Vasospasm is *very uncommon* in the first 3 days following rupture. Its incidence tends to peak *between day 3 and day 7 or so*. Angiographic vasospasm is quite common, but only clinically symptomatic vasospasm portends a poor prognosis.

Vasospasm can present with focal neuro deficits days following a definitive procedure. The benefit of nimodipine in SAH is that it will improve the odds of a 'good outcome.' Nimodipine must be given orally [60mg q4h PO or NG], IV nimodipine has been associated with significant hemodynamic compromise. The treatment of choice of ruptured aneurysm is the placement of a clip at the neck of the aneurysm by an experienced surgeon. Endovascular repairs may be beneficial in select patient groups.

Further management of *vasospasm* requires *triple-H therapy* [hypertension, hypervolemia and hemodilution]; however, some have questioned the benefit of this therapy. It is probably best to keep the pressure head up, and consider angioplasty, or intra-arterial nicardipine.

What about the approach *hyponatremia* in the SAH patient? Volume status is key as those with SIADH are euvolemic and those with *cerebral salt wasting are hypovolemic*. Consider treating with 3% saline with 250cc boluses. *Do not fluid restrict SAH patients* as they tend to vasospasm more.

Lastly, the heart can get stressed out in patients with SAH, contraction band necrosis which causes subendocardial problems from symphathetic discharge. This can cause cerebral T waves, also heart failure being takotsubo cardiomyopathy.

Seizures are not prophylaxed with SAH.

Prognosis in SAH

Sudden death in about 20%, 58% regained premorbid level. Hunt and Hess grading 1 is mild headache with a mortality of 11%, Hunt and Hess of 5 is coma and this is a 71% mortality – this is for SAH and refers to the *symptoms at onset of the lesion*.

SPINAL CORD INJURY

SCI is 10-20% fatal at the scene. Breathing and coughing require the thoracic intercostal muscles and this can result from C7 injuries. These patients can't cough and have impaired respiratory status; for example, a C7 spinal cord injury [acute] with acute dyspnea and a normal CXR is likely caused by *parasternal muscle weakness* [board question].

Vital capacity can help gauge the prognosis and follow deterioration. Normal the VC is 45 to 65 mL per kg. Once *below 30*, there is *poor cough* and an inability to clear secretions, once below 25 cc/kg sigh is lost, there is excessive atelectasis and shunting and once in the 5-10 cc/kg range there will be hypoventilation and hypercapnia. If intubation is required, RSI with in-line spinal immobility is the preferred choice, a fiber-optic approach could be used if time is not a concern. *About one third of cervical spinal cord injuries require intubation in the first 24 hours*.

Recognize and treat autonomic dysreflexia. Consider a patient with a *T5 spinal cord injury* from 6 months ago who presents with severe sweating, flushing, confusion, and a BP more than 200/130. He has a fully distended abdomen from a large bladder [in retention]. It is treated with urinary catheterization.

Autonomic dysreflexia [AD] is exceptionally common [*20-70% of chronic SCI patients* and 5-6% of acute patients] and typically only occurs *when lesions are above the T6 level*. A noxious stimulus causes the insult. When a cord *lesion* is *below T6*, the *splanchnic circulation* remains with *normal autonomic control*. Dilation of this vascular bed, offsets the sympathetic charge from noxious stimuli so AD is much less common in lower lesions. Untreated AD results in pulmonary edema, seizure and death. Other triggers of AD include fecal impaction, medical procedures, sexual stimulation, childbirth, abdominal distension/gas, and somatic pain. Once corrected, the hypertension usually resolves, if not, then anti-hypertensives may be tried.

Understand the treatment of acute *spinal cord injury with perfusion goals and steroids*. Consider a patient with a bad C5/6 transection.

Primary injury involves trauma, shear force and contusion. Rarely is the entire spinal cord transected, even when the vertebrae are totally sheared. *Secondary injury* involves the evil humors thereafter; it is thought that steroids may mitigate this risk and been shown to improve neurological outcome. Further, while there is little data to support spinal perfusion goals, it is suggested *keeping MAPs above 85 to 90 mmHg* to prevent secondary ischemic injury.

The NACIS II trial [NACIS I was controversial] treated patients with a bolus of methylpred [MP] *within 8 hours of injury* followed by a 23 hour MP infusion and there was slight neurological improvement. If steroids are given beyond 8 hours of injury, there may be benefit to extending the MP infusion dose for 48 hours. A Cochrane review in 2012 calls for more RCTs on this topic.

Spinal cord injury patients carry a very high risk of *DVT/PE 72 hours to 14 days post injury* [*50-100% of all untreated*], so prophylaxis is paramount. The level and severity of the spinal injury does not alter the clot risk. If there is a contra-indication for anticoagulation, then an IVC filter should be strongly considered. The use of either *compression stocking or unfractionated heparin [low dose] is considered inadequate* monotherapy compared to LMWH. The use of *both* UFH and compression stocking *may be* equivalent to LMWH for prophylaxis.

NEUROGENIC RESPIRATORY FAILURE

Intubation Considerations

In a patient with multiple sclerosis, elevated ICP and with a ruptured globe secondary to MVA, which medication is optimal for RSI?

The answer *is IV lidocaine* [not IV succinylcholine, IV etomidate, IT lidocaine or IV Demerol].

Patients can herniate with intubation. Comparing IV lidocaine to IT lidocaine has shown that the *ICP rise can be completely blunted by IV lidocaine.*

Definitely avoid depolarizing NMBs in patients with neurological disorders *such as MS* as they express fetal Ach receptor subunits that result in an excessive depolarization with potassium efflux and hyperkalemia.

Etomidate can result in myoclonus which can cause *a ruptured globe to extrude*. The patient had a ruptured globe, so don't use.

Abnormal Respiratory Patterns

What about respiratory patterns in neurological insults? The respiratory pattern – *first Cheyne Stokes* occurs in bi-hemispheric lesions, central *neurogenic hyperventilation* is typically mid brain, below that is *apneustic breathing* [inspiration, long pause, expiration] from a pontine lesion, *cluster breathing* is below that in the medulla which resembles Biots, and *ataxic breathing* is the lowest lesion and is totally random.

GBS

Guillain-Barre is the most commonly encountered neurology exam scenario. GBS *or AIDP* is cross-reacting antibodies to the peripheral nerves causing demyelination. *Immunosuppression is not helpful as the antibodies have already been elaborated*. Classically, reflexes are absent in GBS.

Plasma exchanges decreases the time on MV and improves ambulation *by about 50%*. Usually do *5 exchanges* over 10 days. The earlier the better. *4 treatments are better than 2*, but *6 not better than 4* in bedbound patients. If GBS is mild, patient still ambulatory, these patients should still get plasma exchange. IVIg is an alternative, but there is insufficient evidence to suggest one over the other [IVIg versus exchange]. It should

be started within *2-4 weeks of symptom onset*. But IV Ig likely has more side-effects, e.g. hyper-viscosity.

Sequential treatment doubles the cost, but there is not much clinical improvement. Sequential treatment is pharesis *followed by* IVIg [for obvious reasons] though not recommended.

AIDP can be complicated by autonomic dysfunction such as sinus tachycardia some can get severe pacer-dependent bradycardia. There can be wide variation in blood pressure.

Differentiate CIDP from AIDP. Chronic inflammatory demyelinating polyneuropathy presents with symmetrical extremity weakness *over a period of months*. Typically there is a slow, compensated respiratory acidosis such that the bicarbonate is high. There is no clear association between infection or immunization and the development of CIDP. Numbness, pain and autonomic dysfunction can occur *though motor symptoms dominate*.

The LP will reveal, like AIDP, *an elevated protein*. These patients commonly do poorly with 60% having a progressive course, 40% have a response to corticosteroids.

Plasmapharesis and IVIg are both beneficial in this disease, but they are required chronically as opposed to AIDP.

Critical Illness Polyneuropathy

Critical illness polyneuropathy [CIPN] is the most commonly acquired NM condition in the ICU in up to *50%-70% with sepsis and MODS*. There is *flaccid limbs* and respiratory weakness; reflexes are present in up to 33% [making GBS less likely on clinical grounds]. There is axonal degeneration of *motor and sensory* fibers. CPK is normal, and muscle biopsy reveals axonal degeneration of both *motor and sensory fibers*. CIPN but it doesn't manifest until 7-14 days in the ICU.

Importantly, in severe disease, the phrenic nerve may be involved, which means that diaphragmatic injury can occur.

While initial reports stated *that CIPN was mixed motor and sensory, follow up study reveals that sensation CAN BE NORMAL*.

Delayed offset of neuromuscular blockade and frank myopathies [with elevated CPK] are the key differentials in the ICU.

Considering patients who fail to wean from the ventilator secondary to a neuromuscular etiology *the most common cause is CIPN*, followed by a failure of central drive followed by phrenic nerve palsy and primary myopathies.

Greater than *50% of those who survive CIPN* have a *full recovery*.

Myasthenia Gravis

A *significant proportion* of people with myasthenia gravis experience *myasthenic crisis* accompanied by sudden respiratory failure requiring mechanical ventilation. With immune treatment [below], most recover and are liberated from the ventilator. The steady decline seen in other neuromuscular diseases causing chronic respiratory failure *does not* occur.

MGC is defined as myasthenia gravis complicated by respiratory failure necessitating ventilatory support - this happens in 20% of patients, typically within the first two years of diagnosis. Any physiological stress can trigger an MGC - notably infection [most often], but also aspiration, surgery, trauma, childbirth, reduced MG medications, or reduction in other immunosuppressive medication, botox injections, and certain medications [especially fluoroquinolones, aminoglycosides, beta blockers and CCBs].

Consider a scenario with a patient who is an elderly, 'sleepy-appearing' man with 18 months of dysphagia which prompts an EGD. *Shortly*

after the EGD he develops respiratory distress that is marked by profound hypoxemia and an inability to ventilate. Multiple extubation attempts are made and each time he fails with midline vocal cords noted. He undergoes nerve stimulation with repetitive fatigue noted, his edrophonium test was positive and he had high levels of anti-cholinesterase antibodies.

Consider a middle aged woman who had upper respiratory symptoms followed by prominent bulbar symptoms, weakness with exertion and combined hypoxemic and hypercapneic [uncompensated] respiratory failure. Hypothyroidism should be considered in the differential diagnosis, however, with a PaCO2 of over 100, there should be more prominent cardiovascular and autonomic symptoms at such an advanced stage of hypothyroidism. With a pH of 7.29 and PaO2 of 45 mmHg, the most appropriate management step would be initiation of non-invasive mechanical ventilation. If succinylcholine is an option it *should not* be given as this can cause fatal hyperkalemia in MGC.

Daily FVCs can help monitor respiratory function. A normal FVC should be above 65 mL/kg, the patient's was 0.99L or 16 m/kg. *Vital capacity < 15-20 mL/kg or MIP that is less negative than -30 cmH2O have been proposed as cutoff values* for mechanical ventilation.

Ach receptor antibodies are about 90% sensitive for the diagnosis of MG, but may be only 70% sensitive in those *with only ocular symptoms*. In the latter patients, there are usually other auto-antibodies that are positive to muscles specific kinase [MuSK], to sodium and potassium channels and to titin, etc.

Plasma exchange or IVIg may be used, with the former usually providing a more rapid improvement though trials have failed to find that one therapy is superior to the other. Chronic treatment includes steroids and immunosuppressive therapy, though steroids [alone] are *NOT typically used in the acute* management of MGC as steroids make MG transiently worse.

MG may be paraneoplastic [thymoma] in 10-15% of cases – [surgical resection is the treatment here] once the patient is stable & out of the ICU.

Botulsim

What about botulinum toxin? It causes an irreversible inhibition of acetylcholine release at the synapse. There can be food-borne, enteric, wound, inhalation and iatrogenic. Unlike other toxins, *botulinum toxin causes the same disease after inhalation, oral ingestion or injection*. There is *no natural* inhalation of botulism.

Difficulty swallowing begins with *symmetrical cranial nerve dysfunction*. There can be GI dysfunction. There is no fever. Inhalational botulism is very hard to detect. Miller-Fisher variant of GBS can present very similarly to botulinum inhalation *as there are cranial nerve defects*. It is very similar to MGC, Tick paralysis [no bulbar symptoms] and paralytic fish poisoning.

Recognize wound botulism in a skin-popper. C. botulinum infection of a wound can lead to profound bulbar weakness and xerostomia. There is typically hyporeflexia often most prominent *where the infection begins*. Symptoms begin 4-14 days after the infection. Patients should be intubated when their FVC reaches 30% predicted. Diagnosis requires culturing the organism or isolating the toxin.

The treatment is the *anti-toxin*. *Ingestion or inhalation* is *not treated* with antibiotics, but maybe useful for wound botulism but that also need debridement. GI lavage may be used.

Myopathies

What about myopathies? Thick filament myopathy will result in *a small increase in CPK*

and this is associated with steroids and NMJ blockers [steroid-based]. On muscle biopsy there is an absence of thick myosin filaments. This is different from acute nectrotizing myopathy where the CPK is markedly elevated, there is myoglobinuria, severe quadriparesis and the muscle biopsy shows widespread muscle necrosis. Cachectic myopathy or disuse atrophy reveals a type 2 fiber atrophy on biopsy.

There are the three entities of critical illness myopathy. The clinical features are *flaccid weakness, myoglobinuria and ophthalmoplegia.*

ICU Weakness: Summary

So how are the causes of generalized weakness in the ICU differentiated? MGC is *proximal*, GBS is distal in terms of limb weakness. In CIPN the weakness is distal, *rarely is there cranial nerve* involvement [unlike GBS]. *Reflexes are commonly absent in GBS and usually [2/3rds] in CIPN and botulism, in MG reflexes are normal* as is sensation. CIPN and AIDP have sensory deficits so CIPN is very similar to AIDP with the only clinical difference being cranial nerve involvement. Acute quadriplegic myopathy is differentiated in that the *sensory defects are rare in myopathy*.

GBS typically has an ascending pattern, but less-commonly can present in a descending manner with bulbar involvement. *The LP in AIDP will reveal high protein*, but not so in botulism. MG can present like this, but should improve with edrophonium testing.

Neurogenic Pulmonary Edema

Neurogenic pulmonary edema is last – classically within minutes to hours after neurological injury. To be diagnosed, these patients should not have received tons of fluids. NPE can be seen in catasthrophic neurological injuries. It is clinically like congestive heart failure. Sympathetic innervation causes increased pulmonary venous pressure with a transient increase in pulmonary capillary pressure. Treatment is supportive in nature with oxygen, PPV, diuretics, alpha-adrenergic blockers, and dobutamine.

9. CRITICAL CARE OBSTETRICS & ENVIRONMENTAL MISADVENTURES

OBSTETRICS

In general, drugs to avoid in OB ICU patients are: ACEI, barbiturates, warfarin, fluoroquinolones; also void drugs that lower placental blood flow.

Physiological Changes During Pregnancy

The physiological changes of the *cardiovascular system* include an *increase* in: *blood volume* [plasma > red cells], *cardiac output* [SV and heart rate], *oxygen delivery* relative to consumption [but also an increase in consumption] and a *decrease* in: *blood pressure* [lowest in second trimester] and *systemic vascular resistance*. Filling pressures tend to remain stable.

Respiratory changes include *an increase* in: *Mve* [by 20-40%, mostly tidal volume with a chronic respiratory alkalosis], *airway edema* and a *decrease* in: *functional residual capacity* and *chest wall compliance*. There is no change in the A-a gradient *or vital capacity* in the sitting position. *Reflux is worse*, so aspiration may be more likely, especially if supine [i.e. Mendelson syndrome].

The *AST and ALT* levels *tends to drop*, such that an increase is significant. The WBC may be elevated in pregnancy and pregnancy is a thrombotic state as all clotting factors are increased.

Hypertensive Disorders of Pregnancy

The hypertensive disorders are a common cause of maternal death and ICU admission. In the ICU *pre-eclampsia* is seen. *HTN after 20 weeks* gestation [BP more than 140/90] *with proteinuria* is the definition of pre-eclampsia – note that there is no need to have edema to meet the definition.

Severe pre-eclampsia occurs with *systemic symptoms* and *a higher blood pressure*. There is often renal dysfunction, pulmonary edema, blurred vision, AMS, hepatic dysfunction and low platelets. *Eclampsia* occurs when *seizures are present* and this can occur up to 2 weeks post-partum.

Severe pre-eclampsia should be admitted and delivery should be considered if the fetus is more than 34 weeks. Otherwise it depends on the status of the fetus. The two keys aspects of management are *seizure* control *and blood pressure control*.

These patients should *not get diuretics*! Magnesium has a mortality benefit; it should be given IV to prevent seizures. A *diastolic blood pressure above 100-115* is an indication for magnesium. Severe hypertension *plus* organ dysfunction, also *indicates magnesium administration*. Anti-hypertensives are indicated; it's a hypertensive emergency. A diastolic pressure goal is 90 mmHg. The medication of choice is labetolol, though hydralazine is equivalent. Nifedipine and nicardipene are safe. AVOID nitroprusside, *diuretics* and ACEI.

Placental blood flow *does not* have auto-regulation, so if maternal blood pressure drops, so too does the fetal BP and flow.

In overlap with severe pre-eclampsia is the *HELLP syndrome*; it is perhaps, more dire. There is hemolysis, elevated liver enzymes and low platelets [less than 100-150K]. The lower the platelets, the worse the outcome. There is *less hypertension* and high BP can be *absent* in about 20%. This syndrome is associated with roughly 10% of patients with pre-eclampsia and

eclampsia. *However, HELLP may also occur post-partum*. HELLP is also typified by malaise, non-dependent edema and RUQ pain. The pathophysiology of HELLP is not totally known, but it is thought that vasoconstriction leads to RBC and platelet destruction. The liver tends to be most affected and hepatic hematomas can form. An acute abdomen, shock, or severe RUQ pain should prompt a search for a *ruptured sub-capsular hematoma*. This is not the same as acute fatty liver of pregnancy which can present as acute, fulminant hepatic failure *without hemolysis* [see below]. As well, HELLP can present with ICH and stroke.

The treatment is *urgent delivery and magnesium sulfate*, BP control as needed. If there is TTP, plasmapharesis can be done. Dexamethasone has been tried, but an RCT did not show benefit.

TTP of Pregnancy

TTP in pregnancy can occur and has some 'overlap' with HELLP. There should be *normal liver enzymes*, there is more mental status change in TTP; *DIC is NOT present in TTP and TTP will not resolve following delivery*. TTP is treated with pharesis.

AFLP

Acute fatty liver of pregnancy is a fulminant, uncommon disease in pregnancy. *It is not* cholestasis or pregnancy *or* the high liver enzymes of HELLP. There is low albumin, high ammonia, low glucose, and *very high liver enzymes*. The treatment is termination of the pregnancy.

Cardiomyopathy

Peripartum cardiomyopathy can occur in the final month of pregnancy to *5 months postpartum.* The LVEF is *less than 45%* for diagnosis and there must be no other cause. The management is similar to systolic heart failure. The majority of these cases occur following delivery, so ACEI can be given. Strong consideration should be given to *anticoagulation* because there is a high incidence of thrombosis with peripartum cardiomyopathy.

The patient should not get pregnant again because it can recur and *if LVEF does not* spontaneously improve, *mortality can be quite high*.

Hemorrhage & Trauma in Pregnancy

World-wide the most common cause of maternal death is hemorrhagic shock. *Painless* bleeding may be a hint at *placenta previa*, these patients need transfusion and operative delivery. *Placental abruption* can present with painful bleeding and *is associated with DIC*. There may *be no* overt bleeding. Ectopic pregnancy can occur early in pregnancy. Uterine rupture, atony and retained placenta may also cause profound hemorrhage. The source of bleeding needs to be controlled, and this may involve delivery and hysterectomy.

Trauma in pregnancy should begin with being placed in the left-lateral decubitus position to improve venous return. A pregnant woman can *lose 2 liters of blood and still have normal vital signs*. The fetus will show abnormal vital signs much earlier than the mother. Elevating the right hip can also move the placenta off of the vena cava to improve venous return. Rh –ve blood can be given for blood loss.

ACLS in a pregnant woman should also begin with elevating the right hip, and displacement of the left breast for the defibrillation pad. Perimortem c-section can be done if the fetal age is more than 24 weeks.

Hemodynamics in the traumatic pregnancy patient can be difficult. Recall that there is an increase in cardiac output [increase in heart rate and stroke volume] and a decrease in systemic vascular resistance which tends to improve oxygen delivery. Plasma volume increases more than RBC volume, so there is *a relative anemia*.

The *uterine artery is normally maximally dilated during pregnancy*. Fetal oxygen delivery is a function of 1. *Maternal oxygen content* and 2. *Uterine artery blood flow*.

The normal umbilical vein oxygen tension is in the high 30s, but this results in an oxygen saturation of 80-90% because of the marked left shift of the fetal hemoglobin dissociation curve. Because under normal conditions, the uterine artery is maximally dilated, acidemia does not facilitate uterine blood flow, but acidemia may *improve* fetal oxygen transfer by *right-shifting the maternal Hb curve*. Maternal and fetal circulations interact via a CONcurrent exchange mechanism which *is less efficient* than a countercurrent exchange mechanism. To compensate, the fetal hemoglobin curve is normally left-shifted relative to the mothers such that it is highly saturated in a lower oxygen tension state. Fetal hemoglobin is also much less sensitive to maternal pH change.

There will be *reduced uterine blood* flow during states of *maternal alkalemia*, profound *hypotension* and *catecholamine release*. Maternal alkalemia also left shifts the maternal hemoglobin-dissociation curve which reduces oxygen delivery to fetal hemoglobin.

The *most important* aspect of maintaining fetal oxygen saturation and content is *maternal oxygen content* [i.e. via hemoglobin and cardiac output] much more than maternal PaO2.

Mechanical Ventilation & Respiratory Considerations in Pregnancy

Mechanical ventilation should begin with a smaller endotracheal tube [7.0]. Maintain a saturation above 94% and a PaCO2 in the low 30s to replicate the *normal compensated* alkalosis of pregnancy, i.e. the pH should *be kept normal*. Permissive hypercapnia effects on the fetus are unknown.

Higher airway pressures are OK because of the decreased chest wall compliance. Note that situations that reduce maternal minute ventilation can lead to significant hypoxemia in the mother. Maternal FRC is reduced as a function of reduced ERV and RV [*vital capacity is not reduced*]. There is an increase in oxygen consumption and respiratory work. The *increase in oxygen consumption* and *reduced FRC* lower's the mother's *oxygen reserve* such that in the face of hypoventilation or apnea, hypoxemia may develop rapidly. Remember, that in pregnancy there is an *increased tidal volume and minute ventilation* [stimulated by the increased carbon dioxide and progesterone] which leads to a normal physiological *compensated* respiratory alkalosis in pregnancy.

Considering other respiratory issues in pregnancy, *tocolytic associated pulmonary edema* should be considered. This can occur in response to beta-agonists such as terbutaline. The mechanism is not completely known. The treatment is diuretic and cessation of the tocolytic. Mechanical ventilation is not typically needed to treat this disorder.

Asthma is most likely to get worse during second trimester. Inhaled agents are preferred, systemic steroids are safe.

What about *amniotic fluid embolism [AFE]*? The *presence of DIC* should really prompt this diagnosis. It can present in a very similar fashion to venous air embolism in terms of sudden cardiovascular collapse, but AFE presents with DIC, so bleeding can occur. Tumultuous labor, precipitous deliveries may be the basis for AFE.

Venous air embolism may present with a mill wheel murmur. The patient should be placed in left lateral decubitus to 'trap' air in the right atrium, but this is a time-honored tradition and not based on much evidence. 100% FiO2 should be administered and consideration for hyperbaric therapy.

DVT/PE can occur as pregnancy is a pro-thrombotic state. They usually occur post-partum. D-dimer levels are totally unhelpful in pregnancy. The first step is usually LE ultrasound. V/Q scans can be done, usually just a Q scan is done and if normal, the patient is low risk. CT angiograms exposed the engorged breasts to a high radiation dose and should be avoided. If a pregnant patient is diagnosed with a DVT or PE, the treatment with *LMWH is at a higher dose*. There is a higher volume distribution in pregnant woman. *Coumadin is contra-indicated*. Treatment should be continued for 6 weeks post-partum or 3 months total. Thrombolysis has been done in pregnant women [pregnancy is a relative contra-indication to tPA].

TOXICOLOGY

Approaching the overdosed patient requires the ABCDs. Remember the 'coma cocktail' with naloxone 0.4 to 2 mg, thiamine 100 mg, 25-50 grams of glucose – remember that fingersticks can be unreliable.

The timing of medication ingestion is important as well as *if the drug formulation is regular or sustained released* and if the drug is used acutely or chronically.

The important findings on examination are vital signs and neurological examination. Things that *speed up the vital signs include*: amphetamine derivatives, anti-cholinergics while things that *slow down the vital signs* include the sedatives, narcotics and pro-cholinergics or anti-adrenergics.

Gastrointestinal Catharsis

Induced vomiting and cathartics are *no longer* used. *Gastric lavage* is falling out of favor for most drug overdoses. It can be considered if a lethal substance is ingested *within one hour*. Very large tubes are required for lavage and there are complications of their use.

Whole bowel irrigation [intensive application of Go-Lytely] is suggested but there is probably poor clearance and it is probably unhelpful. It is 1-2 liters of PEG and it requires NG tube as no one will drink that much.

Activated charcoal [AC] also has a 1 hour time limit because beyond that the drug is passed the pylorus and absorbed. The dose of AC is one gram per kilogram and should be used within 1-2 hour of ingestion. It *does not* absorb iron or lithium.

If someone is *critically ill* with a life-threatening ingestion, give charcoal and *consider* lavage. If moderately ill, charcoal is given [if early ingestion]. If a benign ingestion, just monitor.

Other Means of Elimination

Other means of elimination – don't use forced diuresis. *Alkaline diuresis* is used for salicylates and barbiturates. Hemodialysis and hemoperfusion may be seen in the ICU. There is most experience with iHD and it gets toxins out quickly as compared to CVVH.

Hemoperfusion is a technique whereby blood is run across an absorbent substance such as charcoal to remove toxins that are highly lipid or protein bound and therefore difficult to dialyze.

If drugs can be removed by dialysis, it is preferred because of the high incidence of complications with hemoperfusion including: leukopenia, thrombocytopenia, hypoglycemia, hypocalcemia, and hypotension. For this reason, hemoperfusion is generally reserved for the treatment of severe intoxications not amenable to other therapies. Drug intoxications that are amenable to treatment with hemoperfusion include: paraquat, tricyclic antidepressants, barbiturates, theophylline, methaqualone, and glutethimide.

Tylenol Overdose

Tylenol [APAP] should always be considered as a co-ingestion. 40% of acute hepatic failure may be

due to APAP and many of these patients were unaware of the amount of APAP that they were taking. These patients will have high liver enzymes, high APAP level [above 10] and sometimes fulminant failure.

Assess the APAP level 4 hours after the ingestion, before 4 hours, *do not draw a level*. The nomogram is only valid for *single, acute* ingestion.

Oral or IV NAC can be given and it is most effective in the first 8 hours. The short course of IV NAC may not be sufficient. The critical, critical factor is to *start the NAC within 8 hours* because hepatic failure is low if NAC started early. If it is a chronic, multiple or late ingestion, still give NAC. Charcoal can be given for APAP OD.

Toxic Alcohols

All alcohols are degraded by alcohol dehydrogenase to various acids or other compounds [e.g. isopropyl alcohol goes to acetone]. Once the alcohol is metabolized, the *osmolal gap will shrink* and the anion gap will rise if the byproduct is an anion [e.g. isopropyl alcohol metabolism does not raise the anion gap because acetone is not an anion].

Once the osmolal gap has normalized, there is little or no benefit to giving fomepizole or IV ethanol to block alcohol dehydrogenase because the anionic horse is out of the dehydrogenase barn. If the patient is still quite ill, the patient needs hemodialysis at this juncture.

The situations where you might see an elevated osmolal gap *without* an anion gap would be an *early presentation* of ethylene glycol or methanol ingestion [which is clinically uncommon], if there is co-ingestion of a toxic alcohol *with ethanol* as the ethanol will be metabolized first such that the toxic alcohol will hang around longer and contribute to the osmolal gap, or if the ingestion *is isopropyl alcohol* for reasons already discussed. A common board scenario is a toxic alcohol ingestion that provides and osmolal gap with negative anion gap but *positive ketones*. The answer is isopropyl alcohol ingestion.

Oxalate crystals are present in less than one third of ethylene glycol ingestions and methanol presents with visual disturbances. These toxic alcohols are treated with inhibition of alcohol metabolism and then hemodialysis to remove alcohol metabolites and the alcohols themselves. *HD is required when there are very high levels of the alcohol [more than 25 mg/dL], metabolic acidosis, renal failure or visual symptoms*. There is a high mortality rate, otherwise.

Ultimately, most of these patients require a vigorous dialysis. Folinic acid can be helpful with methanol toxicity. The patient should also get thiamine, folate and glucose.

What about *propylene glycol toxicity*? This is seen in the patient with high dose of Ativan infusion in the ICU – typically more than 3 days and there is more agitation with an evolving anion gap and osmolal gap. The patients lactate will rise and there may be seizures, arrhythmias and hemolysis. The patient may be thought of as 'getting septic.' Midazolam *does not have* prophylene glycol. Propylene glycol is a commonly used diluent in many ICU medications including *IV:* Ativan, valium, phenobarb, pentobarb, phenytoin, etomidate, esmolol, nitroglycerin and IV Bactrim as well! Build-up of propylene glycol causes water to shift from the intra-cellular space and this causes a hypertonic hyponatremia ['dilutional']. Propylene glycol is acted upon by alcohol and aldehyde dehydrogenase respectively to produce lactate – which causes the lactic acidosis. Interestingly, commercially available propylene glycol is both D and L such *that d-lactate is produced* by propylene glycol and will accumulate – potentially the cause of the mental status change. Dialysis is typically not needed to treat propylene glycol.

Narcotic Misadventures

Narcotic overdose is getting very common. Oxycodone and hydrocodone are common causes of death. The antidote is naloxone 0.4-10 mg [per dose]! It can be given endotracheally and also *injected* sublingually! Fentanyl is *not* detected on drug screens. Overdose with narcotic patches often require a *naloxone infusion* because the patch creates a small depot-like effect in the skin; there will be hours of narcotic release.

Morphine and Demerol clearance. Demerol [meperidine] is metabolized to *normeperidine which is 2-3 times as neurotoxic as meperidine*. It can accumulate in renal failure and cause seizures. Morphine is metabolized to morphine 6 glucuronide which *also accumulates in renal failure* and is much longer acting and a potent *CNS depressant.*

Comparing fentanyl with morphine – more likely to see *chest wall rigidity with fentanyl* [and alfentanyl and sufentanyl] than morphine. The mechanism is not known. Morphine has more cardiovascular effects that fentanyl including histamine release, veno and vasodilation, and sino-atrial node blocking properties [? stimulation of the vagus nerve]. *Both morphine and fentanyl* are metabolized by the liver and then cleared by the kidney. Morphine has metabolites that are opioid and therefore build in renal failure [*not fentanyl*]. Both fentanyl and morphine will be cleared less effectively in the elderly. Chest wall rigidity seems to occur at fairly high doses of fentanyl.

Hydromorphone, is the least affected by renal failure as it does not have active metabolites and does not accumulate. *Elderly patients and those with liver disease may have a more pronounced effect from dilaudid*.

Benzodiazepines

Moving to *benzodiazepines*. *Alprazolam* is the most common and most toxic in overdose. These patients are treated with intubation and support. Have an exceptionally *high* threshold for giving flumazenil [especially in chronic benzo use] because it will result in unremitting seizure activity. *Midazolam* is metabolized in the liver by 3A4 to alpha-hydroxymidazolam which is a *potent sedative* and is renal-cleared – will therefore become prolonged in the kidney injured chap.

Zolpidem is an imidazopyridine compound with relative selectivity for the type–I GABAA–benzodiazepine receptor. It has no pharmacologically active metabolites and is eliminated primarily by renal excretion. *Overdoses usually result in an altered sensorium*.

Sympatholysis

When patients present with bradycardia don't just think *BB and CCB*. There may be digoxin, clonidine, or *pro-cholinergic* drugs as the cause as well.

The treatment of BB and CCB overdose is a 2-5 mg bolus of glucagon [an inotrope] plus an infusion, calcium chloride one gram, ventricular pacing. IV catecholamines may or may not be helpful. Milrinone may work better as it *by-passes the beta-receptor*. Insulin [also an inotrope], eugycemia can be tried with an insulin infusion and glucose infusion. Lipid emulsion [intra-lipid] is being used to counteract *anti-arrhythmic* overdose as well.

Pesticides & Herbicides

Pesticide intoxication [organophosphates] present with cholinergic syndromes. Sarin is a nerve gas that causes a cholinergic syndrome. It is the 'hyper-secretory' syndrome that includes urination, lacrimation, salivation, defecation, etc. *The treatment is atropine* [*first*], because these patients can die from secretions in the airway. *Pralidoxime* is given *next* to overcome the other side-effects; pralidoxime breaks the bond

between the organophosphate and the enzyme anti-cholinesterase; this allows the enzyme to return to inactivating acetylcholine at the synapse.

Paraquat is an herbicide that causes multi-organ badness including pulmonary edema, pulmonary hemorrhage and pulmonary fibrosis [perhaps mediated by oxygen toxicity]. It is treated with hemoperfusion.

Sympathomimetics

Cocaine toxicity is multi-faceted. It is a sympathomimetic with a transient surge of blood pressure. Acute coronary syndromes can occur and the temporal relationship to the time of cocaine use can be variable [e.g. days to *weeks* after use].

The treatment of *cocaine chest pain* is ASA, nitroglycerine, benzodiazepines, phentolamine, BB, and potentially, reperfusion. Beta-blockers are probably OK in cocaine chest pain. Beta-blockers, retrospectively, may improve outcome in cocaine users [Arch Intern Med. 2010; 170 (10):874-9].

Intra-cranial bleeds can occur with cocaine use. Stroke can occur with complete occlusion of a cerebral vessel. Cocaine augments vasoconstriction and platelet aggregation.

Pulmonary edema can occur with cocaine, it is less common now because the purity is better and there is less pulmonary edema. Sometimes the cocaine is cut with levamisole and this can *cause leukopenia*.

Other problems are hyperthermia, renal failure, bowel infarction and rhabdomyolysis.

Amphetamines and methamphetamines have a similar toxic profile, but they are *longer* acting so there can be chronic cardiomyopathies and *pulmonary hypertension*. Charcoal and gastric lavage have a limited role. Mostly treatment is benzodiazepines.

Ephedra was banned in 2004, so its toxicity is less commonly seen. But new supplements have *synephrine* in them [aka bitter orange] and there are reports of vascular deaths here. Caffeine and energy drinks have been associated with cardiac arrest and hypercoagulability. It is a common cause of atrial fibrillation in the ED. Hospital acquired overdose can occur.

Inhalation of Tolulene

Recognize the electrolyte panel of a patient who is sniffing glue. Tolulene is metabolized to benzoic acid and then hippuric acid. Each molecule of hippuric acid is buffered by a bicarbonate such that bicarb levels can be very low. The hippurate is renally excreted and pulls potassium with it such that potassium levels can also be very low. *Quite often with glue sniffing, there is a mixed anion gap non-anion gap metabolic acidosis* [e.g. anion gap is 22, but the venous bicarb is 10]. Recall, assuming a normal AG of 12, the excess of 10 anions would cause a predicted venous bicarbonate of 15 [25 – 10]. However, a measured bicarbonate of 10 means that there is bicarbonate wasting. With respect to glue-sniffing, this reflects a tolulene-induced distal [type I] RTA [inability to acidify the urine]. *In general, the hippurate effect is greater than the RTA effect*.

Psychiatric Medications

SSRIs cause CNS depression, seizures, arrhythmia, tremor, *hyperreflexia*. Remember that *linezolid and tramadol are MAOIs* that if used with cocaine can cause the serotonin syndrome.

The treatment is removing the precipitating agent, cooling, sedation with benzodiazepines, NMB [rarely], and serotonin antagonists [consider cycloheptadine].

Tricyclic anti-depressants can cause a wide-complex arrhythmia. SSRIs and atypicals can do this as well, but less common. The treatment is *sodium bicarbonate*. If early, charcoal can be

given, lavage can be considered. *Hypertonic saline in refractory cases*. The TCAs *block sodium channels on the myocardium*, so giving *high sodium* can overcome this toxicity [probably why bicarbonate works and why hypertonic saline can also be tried]. If you use a vasopressor, choose *an alpha agonist*.

Valproic acid toxicity [VPA] can present with coma, hypotension, hyperammonemia that is due to mitochondrial dysfunction. Check a VPA level and may need serial levels if it is a sustained release form. There can be severe hemodynamic instability. There are case reports of treatment with L-carnitine and hemodialysis. L-carnitine has a bad smell. Sometimes VPA takes days to wear off.

Gabapentin toxicity is becoming very common especially in the setting of renal failure. It presents with AMS and coma.

Lithium has a narrow therapeutic index and toxicity can occur with acute usage, acute on chronic, or with chronic usage. Typical symptoms with acute poisoning include gastrointestinal complaints initially, followed by central nervous system symptoms. Although adequate urine output should be maintained, *forced diuresis is not effective and diuretics worsen lithium toxicity by causing salt and water depletion and increased lithium resorption*. Dialysis is effective for lithium overdoses, but it should be kept in mind that redistribution between intracellular and extracellular departments can result in a rebound elevation in lithium levels 6 to 8 hours later.

Recognize *neuroleptic malignant syndrome*. This may be presented as a patient who is post-operative and receiving Haldol for agitation. He develops a *fever to 105* with *profound rigidity* [not hyperreflexia] and *hypertension with AMS*. You will likely be told that the CPK is mildly elevated. NMS is a 'central' hyperthermic syndrome. NMS may also present with *rhabdomyolysis* and autonomic dysfunction; while the classic trigger is Haldol, all typical and atypical antipsychotics can be at fault. Depot forms of Haldol can result in NMS for a long time. NMS is idiosyncratic and typically in response to dopamine blockade [or the removal of dopamine agonsits such as Parkinson medications]. It tends to affect younger males. Re-challenge *does not* reliably reproduce symptoms. Untreated NMS has a mortality upwards of 30% as it can go on to produce multi-organ system failure including hepatic necrosis, DIC, rhabdo, cardiac dysfunction with arrhythmia. *While this syndrome is not a disorder of a calcium channel*, *dantrolene* can be effective in *mitigating the symptoms* of NMS by preventing calcium entry into the muscular cytoplasm. The rigidity is thought to be the primary mechanism of injury, though CNS autonomic dysfunction also plays a role. Treatment has also consisted of administration of *dopamine agonists* [e.g. bromocriptine, amantadine and levodopa/carbidopa are used in that order]. Death is usually from aspiration.

Malignant hyperthermia is fairly similar in clinical presentation to NMS, but it is rarer and occurs within 30 minutes of exposure to an inhalational anesthetic or depolarizing muscle relaxant [*nitrous oxide is not a culprit in MH*]. It is a genetic defect in calcium transport in skeletal muscle. There is variable inheritance patterns, but MH is typified by *hyperthermia*, *muscle contraction*, and *cardiovascular instability*. Increased PaCO2, hypertension, skin mottling, and *masseter spasm* with muscle rigidity all signal MH – especially a rapidly increasing PaCO2. Hypothalamic regulation is intact in MH. MH is like a rapidly progressing rhabdo with profound rigidity and rapid cardiovascular collapse. The treatment is giving dantrolene *and stopping the inhaled anesthetics* – start propofol. If dantrolene has been administered, *do not use calcium channel blockers* as they can interact to produce *fatal hyperkalemia and cardiovascular collapse*.

ASA

Salicylate intoxication may be seen on the board exam. It is known as *'pseudo-sepsis'* syndrome. Chronically, it presents with AMS, *fever*, *acidosis*, pulmonary edema. Its clue on the boards is the *metabolic acidosis with an exaggerated respiratory alkalosis*. The treatment is urinary alkalanization and potentially dialysis.

Hypoglycemia in the Diabetic

Oral hypoglycemic agents are common board testing overdoses. Glucagon or octreotide should be given. Octreotide is a somatostatin analogue that blocks insulin release. It is given 50-100 mcg q 8 hours SQ. It shortens the hypoglycemic interval.

Chemotherapies

Recognize ATRA syndrome. Consider a young APML patient who received ATRA and then developed pulmonary edema and effusions. A high percentage of patients develop ATRA within the *first three weeks* of therapy with the drug and the symptoms include unexplained fever, weight gain, respiratory distress, interstitial pulmonary infiltrates, *and pleural or pericardial effusions*.

In the past, the ATRA has been fatal in up to 50% of untreated cases. *High dose corticosteroid* therapy [10 mg IV dexamethasone b.i.d. for 3 or more days] is effective in reversing the syndrome in a high percentage of cases. In a recent study, 45 of 172 (26%) patients developed the syndrome. *Of 44 treated with dexamethasone, only 2 died*. Prednisone prophylaxis during treatment with ATRA will reduce the incidence of pulmonary toxicity.

Cyclosporine side-effects include nephrotoxicity hepatotoxicity, hypertension, hypertrichosis, gingival hyperplasia, hypomagnesemia hyperkalemia, photosensitivity, skin lesions and neurological manifestations [the latter range from hand tremors to *seizures*, coma and death].

Ketoconazole markedly inhibits 3A4 such that the degradation of cyclosporine is inhibited and can lead to profound increases in cyclosporine levels. *Be aware of the transplant patient started on ketoconazole for thrush - a seizure may result*.

Recognize calcineurin-inhibitor [cyclosporine] induced TTP/HUS. Consider a patient post lung transplant two months prior and is on TMP-SMX as well as cyclosporine. She presents with fever, new anemia, thrombocytopenia, renal failure and confusion. TTP-HUS has multiple causative agents including infection from E. Coli 0H157, drugs [quinine, Plavix, OCPS, mitomycin], malignancy, *pregnancy*, HIV and bone marrow transplantation. Some drugs are known to interfere with ADAMSTS13 which then results in an accumulation of vWF multimers and platelet aggregation. *Both calcineurin-inhibitors [tacrolimus and cyclosporine]* are well known to cause TTP-HUS. It is OK to substitute one calcineurin inhibitor for another in this situation. Treatment also includes *plasma-exchange* which does multiple things: replaces normal ADAMSTS13, removes bad wWF and removes bad antibodies against ADAMSTS13 if present.

Snake Bites

There are 20 species of venomous snakes in the U.S. with the majority of human envenomations occurring at the fangs of croatalidae [pit vipers] which include rattlers, cottonmouths and copperheads. Croatilids produce venom that is a mixture of enzymes and toxic proteins that cause serious badness including - DIC, myocardial toxicity, vasodilatation, myoglobinuria and AKI - as well as significant local tissue destruction.

The degree of envenomation can be judged by the progression of local site erythema, and - more importantly - *the severity of systemic signs and symptoms* [tachycardia, blood pressure]. CBC and coags should be obtained frequently.

Local excision to the fascia of a bite has been advocated, though only very early after the bite; the presence of systemic signs suggests that tissue dissection is too late. *Antivenom [AV] should be administered as quickly as possible, but* only if there is systemic toxicity from the venom; AV binds to and neutralizes venom already present - they do not reverse damage already done. Benadryl can be administered to those with minor reaction to the antivenom itself.

A specific antivenom is always preferable to the polyvalent antivenom as it will be lower volume of administration and there will be less chance of serum sickness. Calling ahead to the hospital is critical as these antivenoms are hard to get. *Never pretest for antivenom allergy as it will delay treatment*, and potentially precipitate anaphylaxis, sensitize the patient and fails to predict anaphylaxis. While the package insert of the anti-venom suggests performing a skin test to assess for an allergic reaction prior to administering the full dose, this test is poorly sensitive and specific for identifying reaction and the venom should be given regardless. Nevertheless, in patients with a positive skin test, corticosteroids, anti-histamine and IV fluids should be given. There is no good data to support the use of tourniquets, surgical exploration, antibiotics, warfarin or heparin in these patients.

DIC is actually uncommon with croatilid envenomation, so empiric treatment with factors is not recommended. There are probably over 2.5 million venomous snakebites in the world every year and 125,000 deaths.

TRAUMA

Basic Hemodynamics

Class I shock in trauma is *less than 750 mL* of blood loss or 15% of blood volume, *class II* is a loss of 750 cc to 1.5 L of blood loss [15-30%], *class III* shock is 1.5-2L of blood loss [or 30-40%] and *class IV* shock is more than 2 L of blood loss or more than 40% of TBV.

There is an *increase in heart rate from class II shock and above*. Blood pressure tends to be normal until class III and IV. Urine output trends heart rate, that is tends to drop with class II and above. In other words*, in class I shock, heart rate, BP and UOP are all unchanged*. Note that a *normal urine output can be due to ethanol, DI, hyperglycemic, hypothermia in the trauma patient*. A 70kg man has about 5 L of intravascular volume.

The SVR is mathematically coupled to the MAP, CVP and cardiac output. The SVR is MAP – CVP over the cardiac output multiplied by 80. The *normal oxygen delivery is 600* and the *normal oxygen utilization of 150* which is an O2 ER of about 25%. When oxygen delivery is poor, as in hypovolemia, the extraction ratio increases. The adrenergic response increases the mathematically-coupled SVR calculation.

ATLS

The approach to the trauma patient is to secure the airway with intubation, RSI, and neck immobilization. The patients need to be oxygenated above 90%, the hemorrhage must be stopped.

In the last 10 years [Iraq and Afghanistan conflicts], tourniquets should be used – they can be life-saving, quick-clot [kaolinite based products]. You can lose half of your circulating blood volume into an unstable pelvis.

Interventional radiology can stop bleeding! Appropriate access is important in trauma, large bore IVs, intra-osseous approach, cordis-introducers. If you put *in two 9 French cordis introducers, in two minutes, 5 liters of crystalloid can be infused! In 2.5 minutes, you can give 5 units of blood*. Intra-osseous infusers can give large flow as well. Warmed infusion is very

important when giving these fluids, but there is controversy about *warm fluids* and *head injury*.

In 1994, hypovolemic resuscitation was tested. 600 patients were randomized. The *difference* in treatment was *the pre-hospital and ER setting* where one group received about 900 cc of fluid and the intervention group got about 100 [in the ER 1.6L versus 300 cc additional fluids, respectively]. Then in the OR, the patients were given fluids *equally* [about 7 additional liters]. The group that received less field and ED fluid had *diminished hospital stay and improved mortality*. The moral of the story is to give less fluids *until bleeding has stopped*.

There is also controversy between LR and NS. *NS is only preferred in head trauma and head trauma only*. Albumin stays around in the body for about 20 days, *it stays almost entirely intra-vascular for many hours*. It accounts for 80% of plasma colloid pressure. Overall the difference between colloids and crystalloids is small in nearly all trauma patients. There is *no* difference between colloid and crystalloid in terms *of pulmonary edema, length of stay, mortality, & pneumonia*.

Anemia in Traumatic Shock

The decreased viscosity *improves* cardiac output and stroke volume. There is an increase in oxygen extraction. In JWs there were no deaths at Hb above 5 and there is no effect of transfusion on mortality in patients with hip fracture. *Anemia may not be a bad thing* in trauma. Our transfusion triggers should be lower than we probably think. Certainly in the stable patient [TRICC trial], a Hb of 7 is OK [even in the *actively bleeding GI patients* [NEJM January 2013]].

The risk of blood-borne infection is low [one in 500,000 for a fatal hemolytic reaction, HIV], [one in 100,000 for HCV or HBV], [one in 5,000 for ALI]. *Blood is also an immunosuppressant* and was given prior to early renal transplants to reduce the immune response.

Blood can be auto-transfused [cell-saver] if large amounts are lost [e.g. in a massive hemothorax] but is not used when there is risk of contamination [e.g. bowel perforation].

Early in the massive transfusion protocol it was argued for 1:1:1 transfusion [whole blood], this then dropped to 2:1:1 and 4:1:1 in terms of blood units to plasma to platelets. The pendulum is swinging back now to whole blood.

CHEST TRAUMA

Commotio cordis is when a non-penetrating trauma to the thorax induces ventricular fibrillation.

Only about 15% of thoracic injuries require a definitive operation. 85% require an intervention to improve circulation, oxygenation, etc.

The main *causes of hypoxemia* in chest trauma patients are: hypovolemia, perfusion of an unventilated lung, ventilation of an un-perfused lung and abnormal pleural and airway relationships.

Pulmonary Contusion

Blunt chest injury results in pulmonary contusion often. There is loss of alveolar-capillary membrane integrity and this results in focal pulmonary edema with an interstitial infiltrate. But it is *not blood in the alveolar space nor is it blood in the pleural space*. There is a crush and recoil tearing/shearing effect of the lung. The secondary shearing effect tends to cause the most problems.

The treatment of contusion is to give oxygen, intubate, *conservative* fluids and analgesia because of rib fractures.

Rib Fractures

Where the rib fractures are can tell you about the injury. The *higher ribs* [1-3] usually represent a *high kinetic energy* mechanism – there may be *great vessel injury* here. If the *ribs 4-8* are injured then there may be pulmonary injury – bone spicules can puncture the lung and injure intercostal muscles. If *9-12 are injured*, think splenic and hepatic injury.

Pain can lead to splinting, atelectasis, impaired secretion clearance and pneumonia. Early mobilization is important as is *spinal anesthesia with opiates*. NSIADs can also be helpful. In fact, in patients with thoracic trauma and rib fractures, the use of epidural analgesia *reduces days on mechanical ventilation and the risk of pneumonia*. Mortality in elderly patients with rib fractures is double that of young patients with rib fractures.

Flail chest results in paradoxical respirations such that spontaneous inspiration sucks the segment inwards, and exhalation pushes the flail portion outwards. This leads to impaired V/Q matching of the respiratory pump.

Pneumothorax & Hemothorax

Pneumothorax is often the result of a rib fracture. When the collapse becomes too big, the treatment is with a chest tube. Traumatic pneumothoraces *should not be treated with needles or small catheters because* this will not evacuate blood; there should be suction when treating traumatic pneumothorax. Nitrogen can be absorbed from air by *giving high FiO2*. Air [nitrogen] anywhere in the body where it shouldn't be is treated with 100% oxygen. Tension pneumothorax is an emergency, if the patient is blue you are in trouble because at that point it's nearly too late to sustain life.

A persistent pneumothorax should prompt consideration for a ruptured bronchus. Even if there are broken ribs and flail chest, persistent pneumothorax with chest tube in place can certainly be a consequence of ruptured airways. If unrecognized, the patient may require resection though they can usually be repaired.

Hemothorax looks like a white out of the lung, it will be lung and without breath sounds. If 2 L of blood is in the chest, this is a massive hemothorax. This should prompt a look for a vascular injury. Auto-transfusion [cell saver] can be important.

All of the blood must be removed to prevent a fibrothorax.

Injury of the Heart and Great Vessels

Myocardial contusion can also occur. It is a focal region of *myocardial bruising* and the *right* ventricle is most commonly affected. It may present with atrial arrhythmias. The diagnosis is difficult. Many cardiac contusions are admitted and monitored, but there *is generally little complication*.

IF the patient has pump failure, there is some sort of infarction going on and these patients can get sick quickly.

Traumatic aortic rupture is highly mortal. It is the most common cause of death in a fall from great height or very rapid deceleration; it occurs at the ligamentum arteriosum. With this mechanism, a wide mediastinum on CXR can be diagnostic of aortic rupture. Contrast CT scan is the diagnostic procedure of choice. Many of these patients are being treated with endovascular grafts now.

Injury of the Mediastinum, Diaphragm & Abdomen

Tracheobronchial injuries are diagnosed by bronchoscopy. Esophageal rupture can be diagnosed with endoscopy, barium, thoracostomy.

Recognize *torsion of the lung*. Consider a patient who had been shot in the chest and had a portion of his left lower lobe removed in the OR. Then there is excessive blood in the chest tube and the entire left lung is opacified with some shift of the

mediastinum away. It is possible that this is hemothorax or effusion, but also torsion of the lung; this occurs when the lung *twists around its vascular pedicle*. This, as you can imagine, can be a catastrophe with profound hemodynamic and gas-exchange abnormalities. Usually de-torsion results in *ischemia reperfusion* injury of the lung with *showering of emboli to the left atrium* and systemic circulation. Patients may have a spontaneous de-torsion of the lung, but this may lead to multiple embolic events to the brain.

Diaphragmatic injuries may result in the stomach entering the thorax. Positive pressure ventilation can sometimes reduce this injury and thus with *extubation the injury can be made worse*.

Abdominal trauma can also complicate chest trauma as well as pelvic injury. Grey Turners sign suggests RP bleeding, this could be an aortic injury or pancreatic injury. Decompress the stomach with an NG tube, but do not do so with head injury. The NG tube can get into the brain, which is problematic.

Liver injuries are complex because of its dual blood supply and its outflow. The liver can be totally avulsed which is usually fatal, but transplants have been done. Pelvic injuries can bleed heavily, there can be damage of the GI and GU tract from pelvic injury.

BURN INJURY

In burn injury, there is *smoke inhalation* which is the *leading cause of death in burn injury* and predicts death better than patient age, or extent of burn.

SMOKE INHALATION

The mortality rate of smoke injury [isolated] is about 10%. Smoke inhalation carries with it the *thermal injury*, *asphyxiation* and *toxic/carbonaceous injury of the airways*.

The thermal injury tends to be minimal because the nasopharynx mitigates temperature change quite well in both cold and hot situations. The injury from purely thermal sources tends to be restricted to the naso and oropharynx [imagine swallowing scolding hot soup]. The exception to this is steam which a great capacity to carry heat. Upper airway obstruction from thermal injury is about 20-30% in prevalence. Such patients are usually tripoding and drooling.

The *asphyxiants* from smoke *inhibit cellular respiration*. For example carbon monoxide [CO] toxicity. Weakness, seizures and coma can be a symptoms of CO. Standard pulse oximetry cannot make the diagnosis of carbon monoxide poisoning. Co-oximetry must be used, because the *CO level can be toxic despite a normal saturation on the pulse oximeter*. A normal CO-Hb is less than 5% but can be less than 10% in smokers and truckers.

Carbon monoxide level at the time of a fire is difficult to predict, but is important. The *half-life of carbon monoxide on air is about 4 hours* [250 minutes], on *FiO2 of 1.0, this half-life drops to one hour*. If the CO level is 5%, 3 hours following a fire while on FiO2 of 1.0, the initial exposure may have been very high [i.e. 40%].

There is no dose-response curve between CO level and outcome. Less than 5 minutes of exposure can get CO levels very high [above 20%].

Hyperbaric oxygen is suggested, but difficult to perform. *At 2 atms, the half-life of CO-Hb is 27 minutes*. But when bringing a patient from 2 atmospheres back to sea level, gas will expand and there can be barotrauma. Hyperbaric oxygen is *typically reserved only for pure CO poisoning* or if there are profound symptoms, high CO levels above 20% and cardiovascular instability despite 4-6 hours of normobaric oxygen. What is the outcome with hyperbaric therapy? There is *no mortality benefit but at 6-8 weeks, it improves cognitive outcomes*.

What about *cyanide poisoning*? There are many toxic compounds in smoke. They come from burned plastics, PVC [produces cyanide gas]. CN poisons the electron transport chain which shuts down the Kreb's cycle secondarily. This results in anaerobic metabolism and the shunting of pyruvate to lactate. Cyanide is an asphyxiant *despite high levels of PaO2 and oxygen delivery*.

There are no good tests for cyanide poisoning. You can get a venous blood gas to look for a high PvO2 because oxygen won't be consumed [or 'off loaded'] in the tissues. Look for *the trifecta* of: *metabolic acidosis, carbon monoxide poisoning and a high venous oxygen tension*. These together should highly suggest cyanide poisoning.

The treatment for CN toxicity has evolved over the last 100 years. Initially the 'Lilly Kit' induced met-hemoglobinemia because *Met-Hb will preferentially bind CN and be degraded in the liver*, but this is inducing another toxic hemoglobin moiety [in addition to any carbon monoxide poisoning that may be involved] such that the patient may have 20% Met-Hb, 20% carboxy-Hb and therefore only 60% normal Hb. And the pulse oximeter may read in the mid-80s throughout.

The most recent kit is the *cyanokit* which causes a brilliant red discoloration of the skin and urine and this discoloration can interfere with common lab tests. The hydroxycobalamin *directly binds* to the cyanide.

Lastly, smoke inhalation is mediated by *carbonaceous debris* that is not directly related to toxins or thermal injury within the lung. There is about *48 hours of honeymoon before the endothelial cells of the airways become denuded* and the airways fill with cellular debris. *Bronchoscopy is the best* method to diagnose smoke inhalation injury. There can be cobblestoning of the airway. *Soot in the sputum, singed nasal hairs and facial burns* are not as reliable as a bronchoscopy. A bronchoscopy is positive only if there are positive findings and will identify *twice* as many patients than solely physical signs and symptoms. The *absence of positive findings on a bronchoscopy does not mean that there was not smoke inhalation*.

Treatment involves aggressive chest physiotherapy and airway clearance techniques. IPPV and the VDR4 ventilators may facilitate aboral secretion movement. Intermittent bronchoscopy may also be needed.

Burn Resuscitation

What about burn resuscitation? There is a *reduction in cardiac performance* in burn patients despite fluid resuscitation. It is a reaction to profound cytokine release as in sepsis. It tends not to improve despite fluid resuscitation.

The classic formula is the *Parkland formula*. It uses *4 mL per kilogram per % TBSA*. Then *one half of this* is given at the time of injury [in the *first 8 hours*] and the *other half* during the *following 16 hours*. Usually Parkland is invoked when *TBSA is more than 20% because that is the level of burn at which capillary leak becomes pronounced*. The Parkland formula *does not* factor in maintenance fluids for the first 24 hours [see below].

What are the *zones of burn*? Necrosis [dead], stasis [needs perfusion] and hyperemia [high flow]. Burn resuscitation is to *improve oxygen delivery to the zone of stasis*. *Over resuscitation* will increase interstitial edema and increase the distance between the capillary and the tissue mass [i.e. *increase the distance for oxygen diffusion*].

What is the preferred fluid in burn resuscitation? *The answer is LR*. This will prevent hyperchloremic metabolic acidosis. *Hypotonic fluid* is particularly bad given capillary leak syndrome. What is the maintenance fluid for a burn patient *following resuscitation*? You have to take into consideration the evaporative losses of patients

with large burns. *Daily ins and outs in these patients are totally meaningless*.

Basic maintenance fluid [for everyone] is *1.5L x m [squared]* [body surface area], then you must add to that *[25+ %TBSA] x m [squared] x 24* which is the evaporative losses. So if an average person requires maintenance of 125 mL/hour, if that person has a 60% burn, there will be an *additional* 165 mL/hour of evaporative losses from the burn. Note there are also 800-1200 mL loss per day being on a ventilator *and inhalation injury increases these losses*.

Electrical Burns

In these patients, *if* there is a *normal ECG*, *no LOC* and *no other indication* for admission, they can be *discharged from the ED*.

What is the most common cardiac dysrhythmia following electrical injury? The answer *is atrial fibrillation*. Following a cardiac contusion the most common dysrhythmia is sinus tachycardia. In electrical injury, the cardiac events will occur early, so admission does not typically need to be prolonged. Note that both low *and* high voltage current can result in Vfib.

Electrical injury burns patients from the *inside out*. *Bone* results *in very high thermal injury* because of its high resistance. Muscle tissue is often damaged severely in electrical injury such that *myoglobin and potassium are released in large amounts*. Therefore, in electrical burns, the treatment is quite similar to rhabdomyolysis. The pKa of myoglobin is in the 4 range, *so the urine only needs to be mildly alkaline*.

If such a patient requires intubation, succinylcholine should *not* be used. In a burn injury, there is a dramatic increase in cholinergic receptors, but this occurs months later so succinylcholine is *probably OK very early on*, but it is still discouraged. Regardless, these patients *often have acute hyperkalemia* which is a contra-indication to succinylcholine.

Chemical Burns

Acids cause coagulative necrosis while bases give a liquefactive necrosis. Coagulative necrosis creates a barrier such that the acid cannot penetrate deeply. Liquefactive necrosis, by contrast, creates a milieu whereby *the base can continue to erode and destroy tissue deeply*.

Hydrofluoric acid produces a profound hypocalcemia. It is a calcium chelator. Calcium gluconate can be *applied topically* to stem the extent of the burn injury, but *not in the hand*; HF injury to the hand requires intra-arterial calcium infusion!

The hypocalcemia produced by hydrofluoric acid can prolong the Qt interval, so ECG monitoring is important as well as serial calcium and magnesium levels.

HYPO AND HYPERTHERMIA

The anterior hypothalamus is the temperature regulation center of the brain. It responds to heat by increasing sweating, vasodilation and decreasing muscle tone. To warm up, you vasoconstrict, shiver and increase muscle tone.

Manifestations of Hypothermia

There are 700 deaths per year in the US. They are the urban destitute, but also the wilderness and sports enthusiasts. Hypothermia can also happen in Texas. Hypothermia is a core temperature *less than 35 degrees celsius*. 28-32 is moderate, and *severe* is *less than 28 degrees* [less than 82 farenheit]. These classifications are a bit different in trauma.

Adrenal insufficiency, pan hypopituitarism and hypothyroidism all *predispose* to hypothermia. Various diseases *and* drugs can cause dysregulation of temperature [e.g. Parkinson's disease].

Patients who are *profoundly hypothermic* are also *profoundly hypovolemic*. Shivering is exhausted

by 32 degrees celsius because the patient has used up glycogen. By 28 degrees there is muscle rigidity and shock, by 24 degrees there is the appearance of death, with minimal cardiac activity and by 20 degrees there is an isoelectric EEG and asystole.

Bradycardia, hypotension, increased SVR as well as fibrillation of the atria and ventricles can occur. *J waves are classically seen* [aka Osborne wave], and this is a small positive deflection immediately following the QRS. It is not pathognomonic for hypothermia, but it should raise suspicion. It may *only be in some* leads.

All organ systems are affected by hypothermia. The *respiratory manifestations* are that of decreased Mve [both RR and Vt]. There is also a *cold diuresis* which comes from shifting blood volume to the central organs, so the kidneys may sense hypervolemia and cause a diuresis. There is also confusion, lethargy*, ileus and hepatic dysfunction*. There may be an increased hematocrit, *low platelets* [from sequestration], *coagulopathy, but with a normal PT or PTT because the lab warms the blood*. Platelet function is slowed by low temperature.

Electrolytes can be variable. Glucose levels tend to rise unless it's an alcoholic. There is acidemia with no need to correct the ABG for temperature [remember an ABG is put on ICE].

Management of Hypothermia

If intubation is needed, try not to nasotracheally intubate these patients because of bleeding. The neuromuscular blockers *tend not* to work as well in hypothermia. Pulse checks during ACLS should be longer than 10 seconds. Bradycardia is not treated, Vfib should be treated with *one defibrillation* and if unsuccessful, the patient should *be rewarmed* to more than 30 degrees and then re-attempted. Similarly, ACLS drugs will be minimally effective below 30 degrees celsius. *Chest compressions and re-warming are the focus*.

How does one re-warm? There are no rigid protocols, but it depends on the clinical situation. *Passive external* rewarming is essentially insulation, but it is the least invasive. It is a warm environment with protective clothing. The *patient must be able to generate heat*. It is good for mild hypothermia [32-35 C]. *Active rewarming is the application of external heat* such as lamps, immersion, bare-hugger, etc. These are better for moderate hypothermia [28-32 C] and can raise the temperature *1.5-2.5 degrees celsius per hour*. Slower re-warming may be preferred, don't feel a need to rapidly rewarm the patient.

Core re-warming is the application of heat to the core of the body from non-invasive to very invasive methods. Heated, humidified oxygen, heated IV fluids, gastric, bladder, rectal massage, peritoneal lavage, pleural lavage and endovascular rewarming [case reports] are all such means. Clinical pearl: you can microwave a bag of NS for one minute and shake the bag. The tubing should be short to minimize heat loss. Lavaging the stomach can *increase the risk of aspiration*. Pleural lavage is probably the fastest means. Extracorporeal techniques can be done such as CVVH with warm water as the counter current in the filter. These techniques are reserved for severe hypothermia.

Complications of rewarming are pulmonary edema, coagulopathy, rhabdomyolysis, compartment syndrome, ATN. There are no good predictors of death. *Continue resuscitation until 32 degrees celsius*. Individualize termination of resuscitation. *There are case reports of 13.7 degree celsius patients with 4 hour resuscitations still surviving*!

Near Drowning

There is no one factor or combination of factors that portend good or bad outcome in drowning cases, thus a prognostic scoring system is unavailable. '*Dry drowning*' *is uncommon*. At the outset of drowning, laryngospasm occurs and prevents water from entering the lungs, but this reflex abates in over 85% of people and large volumes of water are aspirated into the lungs. Early reports of near drowning commented upon differences in fluid and electrolyte shifts based on fresh water versus salt water drowning, but later reports have not confirmed this.

Know that *aeromonas species are commonly inhaled during near drowning in fresh water, but also in salt water near drowning*. 70% of patients with aeromonas inhalation go on to suffer *bacteremia* and there is a high mortality rate. Aeromonas is susceptible to *third* generation cephalosporins and beyond.

Francisella philomiragia has been rarely reported during salt water near drowning [never freshwater]; interestingly, *klebsiella pneumoniae is commonly a cause of pneumonia following sea water inhalation*.

Pseduoallescheria bodyii is a ubiquitous fungus that is found in most dirty, stagnant water beds and should be considered in any patient with pneuomonia following drowning with consequent neurological abnormalities such as brain abscess. *Intra-ventricular miconazole is the treatment for P bodyii in the CNS*!

The cardiac rhythm of drowning is bradycardia and electromechanical dissociation. Vfib is rare unless it's cold out.

Manifestations of Hyperthermia

Classic heat stroke is typically the elderly with chronic illness, it develops *over days* with dehydration. There may be more drowsiness, altered mental status and then collapse.

Exertional heat stroke occurs sporadically in athletes and military recruits. There is *milder dehydration*, but this type of heat stroke occurs very quickly. This does *not* occur in professional athletes because they are well taken care of.

Medication and environmental heat can interact. When humidity is high, the sweat does not evaporate so the body cannot lose heat. *Sweat that drips* is *not* doing its job. Patients on *anti-cholinergic* agents such as anti-histamines, anti-psychotics, etc. or those with cardiovascular disease and the *inability to vasodilate* can all be at risk for hyperthermia.

Generally, the patient's hospital temperature on presentation does not match the exposure temperature. The *hallmark is CNS dysfunction* such as AMS, seizures, cerebellar abnormalities. Patients are tachycardic, hypotensive and tachypneic.

Hyperthermia results in electrolyte abnormalities *similar to rhabdomyolysis* with renal insufficiency, respiratory alkalosis, and lactic acidosis. There is also *coagulopathy*, hepatic dysfunction and variable electrolytes.

Management of Hyperthermia

Evaporative cooling can *reverse* vasodilatation and *hypotension* seen in many patients, so *aggressive* fluid resuscitation is not generally needed [especially in older, heart failure patients]. Do not flood the patients, *cooling will increase blood pressure*!

Conductive cooling is achieved by placing ice packs in the groin, axilla, and neck [near great vessels]; further, cold IV fluids can be helpful [4 degrees celsius NS]. But the production of shivering can make things worse in this situation.

Evaporative cooling *is warm water mist* with fans. A fan with spray bottles over a naked patient can rapidly resolve body temperatures even above 108 degrees.

The patient should *be cooled to 102 degrees*. The absolute temperature does not predict outcome but *rather the exposure and duration* of hyperthermia. The elderly with lactic acidosis, renal failure and coma [i.e. *classic heat stroke*] typically have the worst outcome.