

Mount Sinai

Intern Year Medicine

A summation of core seminar topics with associated evidence based medicine

Colin T. Iberti MD

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Hypertension/Hypertensive Urgency/Emergency - attributed to Andy Coyle

- History: CAD, PVD symptoms, medication use, drugs, EtOH, family history
- Exam: AV nicking, cotton wool spots, flame hemorrhages, bruits, pulses, S3, S4
- Normal BP <120/<80, preHTN 120-139/80-89, HTN St 1 140-159/90-99, St 2 >160/>100
- Initial lab work-up: BMP, UA, Lipid Panel, HA1c, EKG
- 1) Do we need to treat? Any possible secondary cause? What's our goal BP?
 - Secondary HTN: renal disease, renovascular disease, hyperaldosteronism, thyroid dysfunction, glucocorticoid excess, OSA, medications (NSAIDS, OCPs, EtOH), coarctation, pheochromocytoma
 - o Goal BPs
 - JNC8: <140/90 if <60yo, <150/90 if >60yo
 - Exceptions: 1) CAD (ACC/AHA recommends <130/80)
 - 2) Non-diabetic CKD with proteinuria <130/80)
- 2) Compelling indication for a certain class of antihypertensive?
 - o JNC8: AA population: CCB or thiazide
 - Non AA population: thiazide, CCB, ACEi, ARB (not BB, AB)
- 3) Any national guidelines to suggest what we should use? 4) Any adherence issues?

Class	Drugs	Indications	Disadvantages	Dosing
Thiazide Diuretics	HCTZ Chlorthalidone	AA	Hypokalemia, urinary frequency, hypercalcemia, hyperuricemia Unlikely to be effective at GFR <30	12.5mg, 25mg 12.5mg, 25mg
ССВ	Amlodipine Nifedipine	AA, Reynaud's	Peripheral Edema	2.5, 5, 10mg 30, 60, 90, 120mg
ACEi	Lisinopril, etc.	DM, CAD, CHF	Hyperkalemia	5-40mg daily
ARB	Losartan, etc.	DM, CAD, CHF	Hyperkalemia	25-100mg daily
BB	Labetalol Metoprolol Carvedilol	CAD, Post MI, cirrhosis	Fatigue, sexual dysfunction, dizziness	100-800 BID to TID 25-100mg BID, XL 3.125 to 25mg BID
Aldosterone antagonists	Spironolactone	Good 3 rd agent, CHF	Gynecomastia, hyperkalemia	25-100mg daily
A2 agonist	Clonidine		Dry mouth, dizziness, rebound HTN	0.1-0.6mg daily
Vasodilator	Hydralazine		Labile BP, Headaches, palpitations	10-50mg QID

- Hypertensive Urgency/Emergency
 - Hypertensive Urgency: lower BP over several days using oral agents
 - Hypertensive Emergency: Goal is for 10-15% reduction immediately, 25% reduction by 24h

Organ	Syndrome	Symptoms	Signs/PE	Labs/Imaging
Neurologic	Ischemic Stroke/ICH	Weakness, aphasia	Focal neuro deficits	CT or MRI brain
	Hypertensive Encephalopathy	Headaches, AMS, N/V	Non focal deficits	
Ophthalmologic	Hypertensive Retinopathy	Rarely vision changes	Flame hemorrhages, exudates, papilledema	N/A

Cardiac	Aortic Dissection Cardiogenic Pulmonary Edema	Chest pain, SOB, HF Dyspnea, SOB,	Levine's sign	CXR, TEE vs. CTA CXR, TTE EKG, trop/CK-MB
	Acute Coronary Syndrome	Chest pain		
Renal	Acute Hypertensive Nephrosclerosis	Hematuria	N/A	UA (hematuria), BMP (rising creatinine)

- Other things to consider:
 - With focal neurological symptoms
 - If tPA candidate: start BP control if >185/110
 - If not, permissive hypertension and start BP control >220/120
 - Aortic Dissection is an exception to the 25% rule: HR of 60, SBP of 100-120 immediately
 - PRES (Posterior Reversible Encephalopathy Syndrome Reversible Posterior Leukoencephalopathy syndrome)
 - Pathophysiology unclear; likely disordered cerebral autoregulation
 - Symptoms similar to hypertensive encephalopathy, often with visual disturbances
 - MRI: symmetrical white matter edema in posterior cerebral hemispheres
 - o Other Hypertensive Emergencies
 - Pheochromocytoma needs alpha blockade, IV phentolamine
 - Scleroderma Renal Crisis IV or PO ACEi at high doses
 - Acute MI with Hypertensive Emergency Labetalol (BB) and or nitroglycerin
 - Acute Hypertensive Nephrosclerosis Consider fenoldopam as no decrease in renal blood flow

Class	Drugs	Mechanism	Advantages	Disadvantages	Dosing
Vasodilator	Nitroprusside Nitroglycerin	Arterial vasodilator Venodilation > arterial dilation	Rapid onset Vasodilation with reduced preload (down pulmonary edema)	Can reduce cerebral/coronary perfusion; cyanide toxicity, reflex tachycardia Less effective, variable, headaches, tachyphylaxis	Can give with sodium thiosulfate, titrate q5m Titrate q5m
ССВ	Nicardipine	Vasodilator	Rapidly effective, fewer side effects, no preload effect	Longer onset and HL limits titration	Titrate q5m
	Clevialpine		immediate onset, HL 1-15m	New, expensive	
Dopamine 1 Agonist	Fenoldopam	Dopamine agonist	Increases renal perfusion	Newer, less studied	
Adrenergic Blocking	Labetalol	Alpha and beta antagonism	Safe in CAD, no HR increase	Avoid asthma/COPD, bradycardia, cocaine	Titrate q10m
	Esmolol	Beta antagonism	HL of 10m, immediate onset	Less BP effect	Titrate q3m

HTN EBM Quick Reference:

HYVET: 5000 >80yo with SBP >160 randomized to thiazide or placebo + ACE if necessary to achieve goal. Reduced stroke and significant decrease in mortality, CV endpoint. (NEJM 2008)

HOPE: 10000 CAD without HF randomized to ramipril or placebo. Ramipril reduced CV death, MI, stroke, mortality, revascularization, MI, HF, DM complications. (NEJM 2000)

ALLHAT: 33000 HTN + CV risk factor randomized to chlorthalidone, amlodipine, or lisinopril. Thiazide diuretics more effective at preventing CV death, less expensive. (JAMA 2000)

ACCOMPLISH: 11,000 HTN randomized to benazepril + amlodipine or HCTZ. Increased CV events, stroke, revascularization in the HCTZ group. (NEJM 2008)

ASTRAL: 800 renovascular disease randomized to revascularization or medical therapy. Increased complications with revascularization without significant benefit. (NEJM 2009)

CATIS: 4000 post stroke, randomized to permissive hypertension vs. 25% reduction within 24 hours. No difference in composite of death and major disability. (JAMA 2014)

SPRINT: 9000 >50yo SBP 130-180 and high CV risk randomized to intensive (SBP 120) or standard BP control. Combined CV endpoint lower in intensive, driven mostly by heart failure. Adverse events: AKI, >30% decline in GFR. (NEJM 2015)

Acute Coronary Syndromes – attributed to Colin Iberti

- Classifying Chest Pain
 - o Diamond Forrester Classification
 - 1 point for sub sternal pressure, provoked by exertion, relieved by rest
 - 1/3 = non-anginal, 2/3 = atypical, 3/3 = typical
 - Pre-test probability of obstructive CAD as depicted below

Age	Non-angina	al Chest Pain	Atypica	I Angina	Typica	l Angina
	Men	Women	Men	Women	Men	Women
30-39	5	1	22	4	70	26
40-49	14	3	46	13	87	55
50-59	21	8	59	32	92	80
60-69	28	18	67	54	94	90

- Unstable angina: Positive EKG with negative biomarkers. Treatment: medical therapy, non-emergent stress test for stratification
- NSTEMI: Positive EKG with positive biomarkers. Treatment: medical therapy, heparin, non-emergent catheterization
- STEMI: +ST elevation in 2+ anatomically contiguous leads with positive biomarkers
 - Sgarbossa criteria for acute MI in pre-existing LBBB
 - ≥1mm concordant STE in any lead (5pts), ≥1mm ST depression in V1, V2, V3 (3pts), ≥5mm discordant STE in any lead (2pts).
 - Score \geq 3 is 90% specific for acute MI
 - Wellens' sign indicates critical LM or proximal LAD stenosis
 - Symmetric deeply inverted precordial T waves or biphasic T waves
 - Treatment: Medical therapy, emergent catheterization
 - Type 1 ACS: mediated by plaque rupture, Type 2 ACS: mediated by supply-demand mismatch
- Risk stratification via TIMI Risk Score: among patients with UA/NSTEMI, patients with TIMI risk score ≥4, represents a higher risk group and benefit from early invasive therapy (IIb/IIIa, catheterization within 24h)
 - 1) Age ≥65, 2) ≥3 risk factors for CAD (HTN, HL, DM< smoking, family history of CAD), 3) prior coronary stenosis ≥50%, 4) ASA use in last 7d, 5) ≥2 angina episodes in last 24h, 6) ST deviation ≥ 0.5mm, 7) Elevated cardiac biomarkers

• Treatment

- o Reperfusion
 - Thrombolysis: beneficial in STEMI, most benefit if given within 3h of symptoms, "old school"
 - Cardiac catheterization: 20% lower rate of cardiac events, 65% lower rate of CVA vs. lysis
 - Emergent indication: for all STEMI patients, cardiogenic shock in the setting of ischemia/infarction
 - Drug eluting stents versus bare metal stents
 - Decreased rate of in-stent restenosis, lower rates of revascularization
 - Increased risk of late stent thrombosis, requiring dual antiplatelet therapy
 - Contraindications for DES: predicted non-compliance, anticipated surgery in 12mos, bleeding risk
 - No consensus on mortality difference
 - Surgical revascularization: preferred for 3 vessel disease, LM disease, 2 vessel disease with proximal LAD stenosis or EF<50%
- Secondary prevention
 - Antiplatelet therapy
 - BMS: ASA indefinitely, clopidogrel at least 1 month

- DES: ASA indefinitely, clopidogrel at least 12 months, longer maybe better (see DAPT)
- Lipids: high dose atorvastatin in acute setting, lipid goal per JNC8
- ACEi/ARBs: indefinitely in STEMI/NSTEMI, especially with EF<40%
- Beta-blockers: indefinitely in post-ACS patients. Titrate carefully in LV dysfunction
- Aldosterone antagonists: generally started out of hospital in post MI with EF <40%, avoid with renal dysfunction and hyperkalemia
- Ranolazine: Decreases reported angina symptoms but no mortality difference
- Early Complications

- Myocardial free wall rupture: 40% occur within 24h, 85% within first week, increased risk with single vessel MI, first MI, thrombolysis, NSAIDS, age >70. Symptoms: cardiac tamponade, cardiogenic shock, electromechanical dissociation. Oliva's triad: pericarditis, repetitive emesis, restlessness
- Interventricular septal rupture: Bimodal at 2h and 3-5 days, increased risks with first MI, single vessel disease (LAD). Symptoms: new harsh holosystolic murmur, hypotension. O2 sat step-up between RA and PA >5, class I indication for IABP.
- Papillary muscle rupture: 2-7 days post MI with abrupt dyspnea, pulmonary edema, hypotension. Treat with aggressive afterload reduction (IABP), emergent surgery.
- Late Complications
 - LV aneurysm occurs in the days to weeks post MI. Increased risks large, anterior MI, uncontrolled HTN, steroids or NSAIDS. Symptoms: diffuse displaced apical impulse, S3 or S4, MR murmur, persistent ST elevations
 - LV thrombus, increased risk in first 3-6 months post MI. Most common in anterior MI, particularly involving LV apex. Treatment anticoagulate for large anterior MI, low EF, large apical aneurysm, dyskinesia
 - Pericarditis, 10% at 2-4d post transmural MI. Dressler's syndrome: late autoimmune pericarditis, rare in reperfusion era
- Stress Testing
 - o Indications: diagnose CAD in patients with intermediate risk of CAD who present with chest pain
 - Indications for imaging are baseline EKG abnormalities (>1mm ST depression at rest, on digoxin, LVH, LBBB, V-paced, WPW)
 - o Exercise Tolerance Test
 - Monitoring for symptoms, EKG changes, METS, change in BP or HR
 - Prognosis worse with degree of symptoms, decreased METS
 - ~70% sensitivity/specificity
 - Adenosine Stress Test
 - Detects ischemia by coronary steal effect via vasodilation by cAMP
 - Can cause wheezing and bradycardia (caution with asthma, COPD, sinus node disease)
 - Imaging generally with echo (~80% sensitivity/specificity)
 - Dobutamine Stress Test
 - Work load induced by positive inotropy and chronotropy via beta-1 agonism
 - May cause tachyarrhythmias (hold BB prior to test)
 - Imaging generally with echo (~80% sensitivity/specificity)

ACS EBM Quick Reference:

HOPE: 9000 vascular disease or DM + CV risk factor randomly assigned to ramipril or placebo. Ramipril significantly reduces death, MI, stroke. (NEJM 2000)

CAPRIE: 19000 randomized to clopidogrel or ASA. Relative risk reduction in combined CV endpoint of 8.7% in favor of clopidogrel, no major safety differences. (Lancet 1996)

CHARISMA: 15000 CAD randomized to ASA + clopidogrel or ASA + placebo. Did not reduce rate of CV events. (NEJM 2006)

PLATO: 18000 ACS randomized to ticagrelor or clopidogrel. Ticagrelor significantly reduced CV related death, stroke without increasing major bleeding. (NEJM 2009).

COGENT: 3800 DAPT randomized to PPI or placebo. Prophylactic use of PPI reduced rate of upper GI bleeding (HR 0.34) with no change in cardiovascular events. (NEJM 2010)

WOEST: 500 randomized to double (OAC + clopidogrel) or triple (OAC + clopidogrel + ASA) therapy. Double therapy with a significant reduction in bleeding, HR 0.36. (Lancet 2013)

DAPT: 9900 post PCI + DES randomized after 12 mos to ASA + placebo or thienopyridine for another 18mos. Reduction of stent thrombosis, CV events, with more bleeds. (NEJM 2014)

PEGASUS TIMI 54: 21000 with MI history randomized to ASA + ticagrelor or placebo. Ticagrelor decreased composite CV events. Major bleeding rates were higher. (NEJM 2015)

4S: 4400 angina, previous MI, HLD randomized to simvastatin or placebo. Simvastatin reduced all-cause mortality, and CAD mortality (RR 0.70). (Lancet 1994)

MIRACL: 3000 UA or ACS randomized to atorvastatin 80mg or placebo. Reduced mortality, non-fatal MI, ACS. (JAMA 2001)

TNT: 10000 CAD randomized to 10 or 80mg of atorvastatin. 80mg reduced CV events. Increased elevated LFTs. (NEJM 2005)

JUPITER: 17000 normal LDL, elevated HS-CRP randomized to rosuvastatin or placebo. Statin reduced CV events. (NEJM 2008)

HOPE-3: 12000 without CAD randomized to rosuvastatin or placebo and candesartan + HCTZ or placebo. CV events were lower in dual treatment group, driven mostly by statin. (NEJM 2016)

FAME: 1000 multivessel CAD pending DES randomized to angiography or fractional flow reserve. FFR reduces CV death, nonfatal MI, repeat vascularization. (NEJM 2009)

FAME-2: 1200 CAD randomized to optimal medical therapy or PCI with fractional flow reserve. FFR + PCI reduced death, nonfatal MI, and urgent revascularization. (NEJM 2012)

COURAGE: 2200 stable CAD randomized to PCI or optimal medical therapy. PCI did not reduce mortality, CV events. (NEJM 2007).

SYNTAX: 1800 3v disease or LM disease to undergo CABG or PCI. Lower rates of CV events with CABG largely due to decreased rate of repeat vascularization. (NEJM 2009)

BARI 2D: 2300 T2DM, stable CAD randomized to CABG/PCI or medical therapy. No difference in mortality. (NEJM 2009)

STICH: 1200 EF <35% and CAD randomized to medical therapy or CABG. No difference in mortality, but reduction in CV death, hospitalizations (HR 0.81). (NEJM 2011)

ORIGIN: 12000 at high risk for CV events + DM randomized to n-3 fatty acids or placebo. Daily supplementation did not reduce the rate of cardiovascular events. (NEJM 2012)

HPS2-THRIVE: 2500 vascular disease randomized to extended release niacin + laropiprant or placebo. No significant reduction in CV events but more adverse events. (NEJM 2014)

HACA: 130 in-hospital cardiac arrests due to Vfib randomized to 32 or 34 degrees. Increased favorable neurologic outcome, decreased mortality, no complications. (NEJM 2002)

TTM: 900 out of hospital cardiac arrest randomized to 33 or 36 degrees. No difference in mortality, neurologic status. (NEJM 2013)

Atrial Fibrillation – attributed to Colin Iberti

- Categorization
 - Chaotic atrial electrical activity resulting in fibrillatory waves at eccentric rate, generally from multiple foci (most commonly in pulmonary veins)
 - Most common sustained arrhythmia, with double mortality rate and 2-7x higher risk of CVA than sinus
 - o Lone: young patients (<60y) with no other cardiopulmonary disease
 - Recurrent: >2 episodes, self-resolving
 - Paroxysmal: self-termination within 7 days
 - Persistent: duration >7 days, requiring chemical or electrical cardioversion
 - Permanent: restoration to sinus is impossible, usually duration >1 year
 - Associated with cardiovascular disease (HTN, CAD, valvular disease), occurs after cardiac surgery, myocarditis, pericarditis
 - o Other predisposing conditions: EtOH, hyperthyroidism, PE, OSA
- Initial Evaluation
 - o 12 lead EKG, CXR, BMP, Mg, TTE, TSH
 - o Consider exercise testing to determine if related to ischemia
- Treatment
 - o Anticoagulation
 - Thromboembolism is the most important complication of AF and AF is the most common factor in stroke in the elderly
 - CHADS₂: CHF, HTN, Age >75, DM, Stroke/TIA 2pts
 - CHA₂DS₂VASc: CHF, HTN, Age>75 2pts, DM, Stroke/TIA 2pts, vascular disease, sex
 - HAS-BLED: HTN (SBP >160), Abnormal Renal function CrCl <50, stroke, bleeding history, labile INR, elderly, drugs (ASA, NSAID, EtOH), Score >3 suggestions caution and follow-up

CHADS ₂ Score	Events per 10	NNT	
	Warfarin	No Warfarin	
0	0.25	0.49	417
1	0.72	1.52	125
2	1.27	2.5	81
3	2.20	5.27	33
4	2.35	6.02	27
5 or 6	4.60	6.88	44

Pharmacologic Agents for Rate Control – Adapted from ACC/AHA/ESC Practice Guidelines					
Drug	Class	IV Dose	PO Dose	Pearls	
Metoprolol	Beta blockers	2.5-5mg q16m	25-100mg q6-q8h	Caution in COPD	
Propranolol		1-3mg q2-5m	10-40mg q6-q8h	Avoid in COPD	
Diltiazem	Non-dihydropyridine calcium-	0.25mg/kg, repeat 0.35mg/kg	30-120mg q6h		
Verapamil	channel blockers	2.5-5mg, up to 20-30mg	30-120mg q6h	More vasodilatory	
Digoxin	Cardiac glycoside	0.25mg q2h up to 1.5mg in 24h	Can load PO (0.0625- 0.375mg daily)	Positive inotrope, useful in low BPs, monitor ECG, check level 12-24h load	
Amiodarone	Class III AAD	150mg over 10m, then 1mg/min x6h followed by 0.5mg/min x18h	Can load PO, 1.2-1.8g/d in 2-3 divided doses	Useful in low BPs, systemic toxicities (pulmonary, hepatic, thyrotoxic)	

- o Cardioversion
 - <48h: safe to cardiovert without anticoagulation, >48h: initiate anticoagulation and perform TEE to evaluate for LV thrombus before cardioversion
 - Indicated for urgent situations where Afib is believed to be causing ischemia, hypotension, HF

Irregular Supraventricular Tachycardias



Figure 1: Link, M. S. (2012). Evaluation and Initial Treatment of Suproventricular Tachycardia. New England Journal of Medicine, 367(15), 1438–1448.

Afib EBM Quick Reference:

ACTIVE W: 6700 Afib randomized to warfarin or clopidogrel + ASA. Stopped early due to superiority of warfarin in CV endpoint, lower rate of vascular events and bleeding. (Lancet 2006)

ACTIVE A: 7500 Afib randomized to clopidogrel + ASA or ASA. At 3.6y clopidogrel reduced the rate of major vascular events, primarily stroke but with increased risk of hemorrhage. (NEJM 2009)

RACE II: 600 Afib randomized to lenient (<110) or strict rate control (<80). Lenient is as effective as strict (less incidence in primary CV endpoint 12.9 to 14.9%) and easier to achieve. (NEJM 2010)

AFFIRM: 4000 Afib randomized to or rate control. Rhythm control increased hospitalizations, adverse drug effects, with a trend towards increased mortality. (NEJM 2002)

BRIDGE: 1884 Afib randomized to perioperative bridging with LMWH or placebo. Placebo was non-inferior in prevention of embolism and with decreased major bleeding in low/medium risk. (NEJM 2015)

ORBIT-AF: Retrospective 10000 Afib. 7000 on OAC. Increased bleeding/hospitalization in patients on oral anticoagulation + ASA. Dual therapy with fewer CV events. (Circ 2013)

RE-LY: 18000 (mean CHADS 2.1) Afib randomized to dabigatran or warfarin. At 2y high dose dabigatran compared to warfarin reduces stroke risk without increasing risk of major bleeding. (NEJM 2009)

ROCKET AF: 14000 (mean CHADS 3.4) Afib randomized to rivaroxaban or warfarin. Rivaroxaban noninferior in preventing stroke, embolism without increasing bleeding rates. (NEJM 2011)

ARISTOTLE: 18000 (mean CHADS 2.1) Afib randomized to apixaban or warfarin. Apixaban was superior to warfarin in preventing stroke, embolism, with less bleeding and lower mortality. (NEJM 2011)

AVERROES: 5500 Afib (mean CHADS 2), unsuitable for warfarin were randomized to apixaban or ASA. Apixaban reduced the risk of stroke, embolism without more major bleeding. (NEJM 2011)

ENGAGE AF-TIMI 48: 21000 Afib (mean CHADS 2.8) randomized to warfarin or edoxaban. Edoxaban noninferior in stroke, embolism with significantly lower rates of bleeding, CV death. (NEJM 2013)

CRYSTAL AF: 440 post ischemic stroke randomized to insertable cardiac monitor or conventional follow-up. ICM was superior in detecting Afib at 12mos (12.4 v 2.0%). (NEJM 2014)

EMBRACE: 572 post ischemic stroke/TIA randomized to 30d event triggered recorder. Recorder significantly improved detection and double rate of anticoagulation treatment. (NEJM 2014)

Supraventricular Tachycardias (excluding Afib) – attributed to Rafael Harari

- Incidence: 35 cases per 100,000 patients
- Prevalence: 2.25 per 1,000 in the general population
- Symptoms: palpitations, chest discomfort, dyspnea, anxiety, lightheadedness, and less commonly, syncope
- Classic SVT is characterized by abrupt onset of symptoms, typically palpitations.
- Triggers include caffeine, alcohol, stress, exercise.
- Three most common types (excluding Afib/flutter): AVNRT (60%), AVRT (30%), Atrial Tachycardia (10%)
- AVNRT (Atrioventricular nodal re-entrant tachycardia)
 - o Most common, more common in women; bimodal distribution with peaks in the 3rd and 6th decades
 - o Re-entrant circuit involves the AV node
 - Two pathways: slow and fast. Slow-fast AVNRT (anterograde via the slow pathway, retrograde via the fast pathway is the most common)
 - o Retrograde p-waves may be seen buried within the QRS complex or immediately after it
- AVRT (Atrioventricular re-entrant tachycardia)
 - More common in men, mean age of onset ~23
 - Re-entrant circuit involves accessory pathway
 - Can have pathways that conduct retrograde or anterograde
 - Orthodromic: antegrade conduction via AV node
 - Antidromic: antegrade conduction via accessory pathway
- Atrial Tachycardia Least common
 - o Tachycardia arises from localized focus in the atria
 - o Incidence increases with age and is more common in patients with structural heart disease
- Valsalva maneuver is generally not very successful at terminating SVT. Reported success rates range from 6-54%, with ~25% success rate being a widely accepted number)
- Modified Valsalva (REVERT trial, Lancet 2015) adding supine repositioning and passive leg raise immediately after Valsalva strain improved response from 17 to 43% achieving sinus rhythm
- Adenosine
 - Efficacy in the conversion of SVT to sinus rhythm 80-100%, with a mean success rate of 93%.
 - Approximately 8.6% of patients revert to SVT after their arrhythmia was initially terminated by adenosine (compared to 3.4% of patients treated with verapamil; difference not statistically significant)
 - Efficacy is comparable to verapamil, without the adverse effects of verapamil (intravenous verapamil is a potent vasodilator that can lead to hypotension)
 - Slows conduction through AV node, producing transient AV block
 - Not useful for terminating arrhythmias that do not involve AV node, such as atrial tachycardia or ventricular arrhythmias
 - Very short half-life (~5 seconds + effects occur 20-30s after administration)
 - o Symptoms include dyspnea, flushing, chest discomfort. Transient, usually resolve in less than 1 minute
 - o Transient bradycardia, complete heart block, and asystole have been reported
- Keys to the administration of Adenosine:
 - Use a 3-way stopcock: Given the extremely short half-life of adenosine, a 3-way stopcock is used to avoid wasting time by connecting a saline flush to the IV line after pushing adenosine. Connect a saline flush to one port, adenosine to another port and the IV line or central line to the third port. Immediately after pushing adenosine, push the saline flush.
 - 2. Attach a defibrillator and pads in case the patient remains bradycardic/asystolic and needs transcutaneous pacing or there is a new arrhythmia that requires defibrillation
 - 3. Attach EKG machine in order to record a strip immediately following adenosine administration.

4. Dosing: start with 6mg IV, and redose 12mg IV 2-3 minutes later if there is no response. Adjust dose to 1-3mg if giving it through a central line.

SVT	Underlying Causes	Regularity	Rate	Onset	P:QRS
Atrial Fib	Cardiac, pulmonary, PE, hyperthyroid	Irregular	100-220	Sudden or gradual	Fibrillatory wave, no relation to QRS
MAT	Pulmonary, theophylline	Irregular	100-150	Gradual	Changing P waves before QRS
Frequent Atrial Contractions	Caffeine, stimulants	Irregular	100-150	Gradual	P before QRS
Sinus tachycardia	Sepsis, hypovolemia, PE, pain, fear, exertion, MI, hyperthyroid, HF	Regular	220 – age	Gradual	P before QRS
Atrial Flutter	Cardiac disease	Regular (irregular)	150	Sudden	Flutter waves, usually 2:1
AVNRT	None	Regular	150-250	Sudden	No apparent activity or R' at end of QRS
AVRT	None	Regular	150-250	Sudden	Narrow: p after QRS Wide: rare p waves Irregular: no p wave
Atrial tachycardia	Cardiac, pulmonary	Regular	150-250	Sudden	P before QRS







Bradycardia - attributed to Andy Coyle

- Causes of bradycardia
 - Intrinsic (cardiac): Ischemic heart disease, hypertensive heart disease, inflammatory (myocarditis, pericarditis, rheumatic fever), "sinus node dysfunction" aka sick sinus
 - Extrinsic (non-cardiac)
 - Medications: Digoxin, clonidine, BB, CCB, amitriptyline, lithium
 - Carotid sinus hypersensitivity
 - Increased vagal tone (coughing, vomiting, cold exposure)
 - Hypothyroidism
 - Hypothermia, hypoxia
 - Electrolytes: especially hypo/hyperkalemia
 - Elevated intracranial pressure (Cushing's triad: HTN, bradycardia, irregular respiration)
- Atropine functions as vagolytic, 0.5-1.0mg IVP, q3-5m for maximum dose of 3mg, HL 2h
- Beta-blocker overdose
 - Atropine as above
 - Glucagon (IVP then IVPB) positive inotropic, chronotropic effects independent of beta-receptor, by stimulating cAMP.
 - Calcium: BBs result in intracellular hypocalcemia, so calcium salts can result in modest improvements in conduction and chronotropy
 - o Sodium bicarbonate: Promote dissociation of TCAs; has been used for wide complexes
 - o IV magnesium, vasopressors, hemodialysis, transcutaneous/transvenous pacing
- Bradycardia post-infarct
 - RCA supplies inferior portion of heart but also supplies SA and AV node.
 - However, the perfusion of the SA/AV nodes is more complex than this and <u>most</u> do not require pacing or have long-term issues with conduction or chronotropy.
- Sick Sinus Syndrome (alternating between rapid AFIB and sinus bradycardia)
 - o Causes
 - Sinus node fibrosis, CAD, infiltrative diseases (amyloidosis, sarcoidosis, hemochromatosis, tumor infiltration), epicardial or pericardial disease, pericarditis, rheumatic fever, Chagas, Lyme disease, hypothyroidism, hypothermia, hypoxia
 - Characteristics:
 - Frequent periods of inappropriate and often severe bradycardia
 - Sinus pauses or arrest with junctional escape rhythms
 - Alternating bradycardia and tachyarrhythmias in up to 50% ("tachy-brady syndrome")
- Permanent Pacemaker

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- ACA/AHA Classes
 - I: permanent pacing is definitely beneficial
 - II: permanent pacing may be indicated, but some conflicting opinions or evidence
 - III: permanent pacing not helpful or may be harmful
- o Sinus Node Dysfunction (Sinus bradycardia, Sick Sinus Syndrome)
 - Class I Indications
 - Sinus bradycardia where symptoms are clearly related to bradycardia
 - Symptomatic chronotropic incompetence
 - Acquired AV Block
 - Class I
 - 3rd-degree AV Block
 - Advanced 2nd-degree AV Block (block of 2 or more consecutive P-waves)
 - Symptomatic 2nd-degree AV Block (Mobitz Type 1 or 2)
 - Mobitz Type 2 2nd-degree AV Block with widened QRS
 - Other Class I Indications:

- Persistent 3rd-degree AV block post-MI
- Significant carotid sinus hypersensitivity (syncope and > 3 seconds of asystole following minimal carotid massage)



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Heart Failure – attributed to Colin Iberti

- Systolic Heart Failure
 - 1 to 2% of the population in developed countries has heart failure, 10% > 70 years old
 - At least half of all CHF patients have a low ejection fraction (<40%)
 - Coronary artery disease is the cause of 2/3 of systolic heart failure, though HTN and DM contribute in many cases
 - Dilated cardiomyopathy may also result from genetic cause, viral infection, alcohol abuse, or chemotherapy
 - Maladaptive changes in surviving myocytes after myocardial injury lead to pathologic remodeling of the left ventricle with dilatation and impaired contractility
 - Untreated, worsens over time secondary to additional insult and activation of the sympathetic and renin-angiotensin-aldosterone system
 - o Diagnosis and evaluation
 - Nonspecific signs/symptoms: dyspnea, fatigue, peripheral edema
 - Specific/sensitive symptoms: orthopnea, PND, JVD, cardiac enlargement, third heart sound have 70-90% specificity, 11-55% sensitivity
 - Routine cardiac investigations: ECG (arrhythmias, QRS duration >120, sinus bradycardia), CXR (pulmonary congestion, primary pulmonary pathology) are insensitive but may offer clinical guidance
 - TTE: confirmation of the diagnosis, with myocardial and valvular structure and function

NYHA F	unctional Classification	ACC-AHA Stages of Heart Failure		
Class I	No limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation, dyspnea	Stage A	At high risk for heart failure; no identified structural or functional abnormality with no signs or symptoms	
Class II	Short limitation of physical activity; comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea	Stage B	Developed structural heart disease that is strongly associated with the development of heart failure but without signs or symptoms	
Class III	Marked limitation of physical activity; comfortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnea	Stage C	Symptomatic heart failure associated with underlying structural heart disease	
Class IV	Unable to carry on any physical activity without discomfort; symptoms present at rest; if any physical activity is undertaken, discomfort is increased	Stage D	Advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy	

Treatment	Indication	Effect	Study	Mortality Benefit
Diuretics	Symptomatic relief	Relief of dyspnea, fluid	DOSE	None
Digoxin	Symptomatic relief	Reduces hospitalizations	DIG	None
ACEI/ARB	1 st line: NYHA I-IV ACEi = ARB	Reduce ventricular size Reduce risk of MI Increase EF	CONSENSUS SOLVD	16-40%
Beta Blocker	1 st line: NYHA I-IV	Reduces symptoms Increase EF (5-10%)	MERIT-HF	34%
Aldosterone Blocker	NYHA II-IV EF<35%	Mechanism of action, not well understood; likely cardiac remodeling	RALES EPHESUS EMPHASIS-HF	30%
Hydralazine/ISDN	African Americans NYHA III-IV	AAs might have less RAAS activity, target non-RAAS	A-HeFT	40%
AICD	NYHA II-III EF<35%	Reduces the risk of sudden death	MADIT-II	30%
CRT	NYHA III-IV EF<35% QRS >120msec	Increasing stroke volume Decrease mitral regurg	CARE-HF MADIT-CRT	34%



Congestion at Rest?



Nohria, A. (2002). Medical Management of Advanced Heart Failure. *JAMA : The Journal of the American Medical Association*, 287(5), 628. http://doi.org/10.1001/jama.287.5.628

- Management
 - Use above neurohormonal agents to prevent disease progression and prolong survival, however decompensations warrant patient evaluation of hemodynamic profile (above).
 - o Profile A: "Warm and Dry"
 - Stable, generally managed outpatient with neurohormonal blockade
 - o Profile B: "Wet and Warm"
 - Focuses on congestive symptoms, with goal to dry patients out through enhanced diuresis (bolus IV lasix, complemented by metolazone)
 - Intravenous vasodilators such as nitroglycerin can relieve congestive symptoms
 - All diuresis and vasodilation needs to be balanced with hypotension and AKI
 - o Profile C: "Cold and Wet"
 - Due to clinical hypoperfusion, may need to withdraw B-blockers and ACEi until stabilization and improve perfusion before correcting congestion/fluid status
 - Often associated with high systemic vascular resistance and may demonstrate improvement with vasodilation alone such as a Nitroprusside drip
 - Usually does not cause hypotension, but concern with cyanide toxicity
 - IV inotropes are associated with increased risk for ischemic events and tachyarrhythmias.
 - Benefits of inotropes may not justify the risk, can be life-saving as bridge to definitive procedures as patients become increasingly hemodynamically unstable
 - Inotropes should be considered as bridge until therapy of transient condition is completed (pneumonia, diuresis, transplantation, death)
 - o Profile L: "Cold and Dry"
 - May be surprisingly stable, with underappreciated congestion
 - Do not generally improve with adjustments to oral medications
 - Inotropic infusions generally lead to tachyphylaxis and dependence
 - Increasing B-blockade can be helpful if tolerated by HR and BP

CHF EBM Quick Reference:

DIG: 7000 with EF <45% randomized to digoxin or placebo. No difference in mortality, fewer HF hospitalizations. (NEJM 1997)

TREAT-AF: 120000 VA HF patients, 23.4% on digoxin. Cumulative mortality rates higher for digoxin patients despite multivariate adjustment. (J of Am Cards 2014)

DOSE: 300 HF exacerbations randomized to furosemide IV by bolus or continuous infusion. No significant difference in symptoms, Cr level. (NEJM 2011)

MERIT-HF: 3900 NYHA II-IV randomized to Toprol XL or placebo. Significant decrease in all-cause mortality. (Lancet 1999)

CIBIS-II: 2600 NYHA III-IV randomized to bisoprolol or placebo. Significant mortality benefit of bisoprolol, HR 0.66. (Lancet 1999)

COPERNICUS: 2200 NYHA III-IV randomized to carvedilol or placebo. Carvedilol reduced the combined risk of CV death or hospitalization by 27%. (Circ 2002)

COMET: 1500 NYHA II-IV randomized to carvedilol or metoprolol tartrate. Carvedilol demonstrated a reduction of all- cause mortality, HR 0.83. (Lancet 2003)

MDPIT: 600 ACS + EF <40% randomized to dilitazem or placebo. Increased rate of CHF exacerbations, larger decrease in EF with diltiazem. (Circ 1990)

RALES: 1600 EF <35% randomized to spironolactone or placebo. Spironolactone decreased all-cause mortality, RR 0.70. Gynecomastia, hyperkalemia increased. (NEJM 1999)

EPHESUS: 7000 ACS complicated by HF randomized to eplerenone or placebo. CV Death, hospitalization was decreased in the eplerenone group RR 0.87. (NEJM 2003)

EMPHASIS-HF: 2700 NYHA II, EF <35% randomized to eplerenone or placebo. Decreased risk of death and hospitalization with eplerenone (HR 0.63). (NEJM 2011)

TOPCAT: 3400 with HFpEF randomized to spironolactone or placebo. Did not reduce CV death, hospitalizations. (NEJM 2014)

A-HeFT: 1050 Black NYHA III-IV randomized to isosorbide dinitrate + hydralazine or placebo. Significantly decreased (43%) mortality and hospitalizations. (NEJM 2004)

MADIT-II: 1200 prior MI, EF <30% randomized to ICD or medical therapy. ICD group reduced mortality, HR 0.69. (NEJM 2002)

SCD-HeFT: 2500 NYHA II-III, EF<35% randomized to placebo, amiodarone, ICD. ICD decreased mortality (23%). (NEJM 2005)

MIRACLE: 360 with EF<35%, QRS>130, NYHA III-IV randomized to CRT + ICD or ICD. CRT improved QoL, exercise. (JAMA 2003)

CARE-HF: 800 NYHA III-IV with cardiac dyssynchrony randomized to standard care or resynchronization. Resynchronization reduced mortality from cardiac causes, HR of 0.63. (NEJM 2005)

MADIT-CRT: 1800 EF<30%, QRS >130msec, NYHA I-II randomized to CRT + ICD or ICD alone. CRT + ICD decreased the HF events 41%, no significant mortality difference. (NEJM 2009)

PARADIGM-HF: 8400 NYHA II-IV with EF<40% randomized to angiotensin-neprilysin inhibition or enalapril. Reduction in CV death, HR 0.80, reduced hospitalizations. (NEJM 2014)

CARESS-HF: 180 with decompensated HF, renal dysfunction, randomized to standard therapy or ultrafiltration. Standard of care was superior in preservation of renal function, weight loss with a higher rate of adverse events with UF. (NEJM 2012)

RED-HF: 2200 HF and anemia to receive darbepoetin or placebo. Darbepoetin did not improve clinical outcomes. (NEJM 2013)

COPD – attributed to Colin Iberti

- A common, preventable, treatable disease characterized by persistent airflow limitation that is usually progressive and associated with chronic inflammatory response in the airways
- Primary process is an accelerated decline in FEV₁
- Hyperinflation is an additional physiological abnormality that is seen in moderate-severe COPD
 Increase in the functional residual capacity, causing increase work of breathing
- Marked decrease in diffusion capacity, hypoxemia, and alveolar hypoventilation
- Diagnosis & Assessment
 - Symptoms: progressive, persistent dyspnea, chronic cough, chronic sputum production, risk factor (tobacco, smoke, occupational dusts/chemicals)
 - Majority of cases occur in smokers, but others can include α1-antitrypsin deficiency, airway hyperresponsiveness, indoor air pollution.
 - Symptoms may not occur until lung function is substantially reduced so early detection is with spirometry is key.
 - GOLD definition: FEV₁:FVC ratio of less than 0.70
 - Assessment of symptoms using validated surveys including COPD Assessment Test (CAT)
 - Can be risk stratified based on previous exacerbations per year, hospitalization, symptoms
- Management of Stable COPD
 - Smoking cessation
 - Vaccines: influenza and pneumococcal vaccines
 - Influenza vaccines can reduce the risk of serious illness and death in COPD patients
 - o Pulmonary rehabilitation
 - All COPD patients with breathlessness on walking appear to benefit from rehab
 - o Bronchodilators
 - Long-acting, inhaled formulations are preferred due to efficacy and side effects
 - Beta₂ agonists relax airway smooth muscle (formoterol, salmeterol)
 - Short-acting improve FEV₁ and symptoms
 - Long-acting significantly improve FEV₁, lung volumes, dyspnea, exacerbation rate but have no effect on mortality and rate of decline of function
 - Adverse: sinus tachycardia, arrhythmias.
 - Anticholinergic blocks acetylcholine's effect on muscarinic receptors (tio/ipratroprium)
 - Reduces exacerbations and related hospitalizations, improves symptoms
 - Adverse: dry mouth
 - Theophylline modest bronchodilator effect of unknown mechanism
 - Addition of theophylline to salmeterol produced greater improvement of FEV₁
 - Adverse: arrhythmias
 - Combination Therapy combinations of short-acting beta₂-agonists and anticholinergics are superior compared to either medication alone.
 - Corticosteroids
 - Inhaled corticosteroids
 - Regular treatment with inhaled corticosteroids improves symptoms, lung function, quality of life and reduces frequency of exacerbations
 - Long-term treatment with inhaled corticosteroids with long-acting bronchodilators in patients with high risk of exacerbation
 - Regular treatment does not modify the long term decline of FEV₁ nor mortality
 - Withdrawal of inhaled steroids is still under investigation
 - Adverse: oral candidiasis, hoarse voice, increased risk of pneumonia
 - Combination Inhaled Corticosteroid/Bronchodilator

GOLD Stage	FEV ₁ %	3y Mortality
1 Mild	≥80	?
2 Moderate	50-80	11%
3 Severe	30-50	15%
4 Very Severe	<30	24%

- More effective than the individual components in improving lung function and health status, reducing exacerbations. No effect on mortality.
- Oral corticosteroids
 - Long-term side effects including steroid myopathy that contributes to decreased functionality and respiratory failure
- Phosphodiesterase-4 inhibitors
 - Roflumilast reduces moderate and severe exacerbations in patients with chronic bronchitis, severe to very severe COPD
 - Consider in patients with FEV₁<50%, frequent exacerbations to reduce exacerbations
 - Adverse: GI, sleep disturbance, headache (not to be given with theophylline)
- Prophylactic antibiotics no reduction in rate of exacerbations
- o Oxygen therapy
 - Long-term oxygen therapy has shown increased survival in those with SaO2 <88%
- Last options: lung volume reduction surgery, lung transplantation, palliative care
- Management of Exacerbations
 - An exacerbation is an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication
 - o Can be precipitated by several factors, most commonly URI and tracheobronchial infection
 - o Diagnosis relies on acute change of symptoms (baseline dyspnea, cough, sputum production)
 - Short acting inhaled beta₂-agonists with or without short acting anticholinergics are preferred bronchodilators
 - Systemic corticosteroids and antibiotics can shorten recovery time, improve lung function, and reduce the risk of early relapse, treatment failure, and length of hospital stay
 - 40mg of prednisone per day for 5d
 - Moderately or severely ill patients with increase dyspnea, sputum volume, sputum purulence 5-10d, usually empirically with penicillin + clavulanic acid, macrolide, tetracycline
 - COPD exacerbations can often be prevented: smoking cessation, vaccination, inhaler technique, proper long-acting medications, phosphodiesterase-4 inhibitor

COPD EBM Quick Reference:

NOTT: 200 COPD randomized to nocturnal or continuous oxygen. Continuous oxygen was associated with significant reduction in mortality. (Chest 1980)

NETT: 1200 COPD randomized to lung volume reduction surgery or medical therapy. LVRS with improved exercise capacity, but no mortality benefit. (NEJM 2003)

TORCH: 6100 COPD randomized to salmeterol and/or fluticasone or placebo. Slowed FEV₁ decline, improved QoL. Combination reduced exacerbations, hospitalizations, trend towards decreased mortality. (NEJM 2007)

UPLIFT: 6000 COPD randomized to tiotroprium or placebo. Tiotroprium did not slow the decline of FEV₁ but did reduce exacerbations, trend towards increased survival. (NEJM 2008)

REDUCE: 300 COPD exacerbations randomized to 5 or 14d of glucocorticoids. The 5d course non-inferior with no difference in rates of reexacerbation, shorter LOS. (JAMA 2013)

WISDOM: 2500 COPD on triple therapy randomized to continuation or tapering off of the corticosteroid was no increase COPD exacerbation, decrease in FEV₁. (NEJM 2014)

Antibiotics in Exacerbations: Review of 16 studies. Mild-moderate exacerbations, no reduction in treatment failure with antibiotics. In severe, significantly reduced risk of treatment failure with adjunct antibiotics. (Cochrane 2012)

REACT: 2000 COPD randomized to roflumilast or placebo together with corticosteroid + LABA. Rate of exacerbations was 13.2% lower with roflumilast. (Lancet 2015)

Azithro Prophylaxis: 1500 COPD randomized to azithromycin daily or placebo. Decreased exacerbations in azithro group, HR 0.73. Increased risk of hearing loss. (NEJM 2011).

DVT/PE – attributed to Colin Iberti

- Deep Vein Thrombosis
 - o Pathogenesis: Virchow's triad: damage to vessel wall, venous stasis, hypercoagulability
 - Risk factors
 - Inherited: AT deficiency, protein C & S deficiency, Factor V Leiden, G20210A prothrombin gene mutation, dysfibrinogenemia
 - Acquired: major surgery, history of venous thromboembolism, antiphospholipid antibodies, cancer, age, pregnancy, estrogen therapy, SERM therapy, obesity
 - Typically originates in the venous sinuses of the calf muscle but occasionally originates in proximal veins, 25% of untreated calf thrombi extend into proximal veins
 - Proximal vein thrombosis presents a 50% risk of pulmonary embolism
 - o Diagnosis
 - The failure of proximal deep vein to flatten when compressed with ultrasound probe or persistent intraluminal filling defect provides definitive diagnosis
 - Sensitivity and specificity for compression ultrasound is more than 95%, but lower for isolated calf thrombosis
 - o Treatment
 - Old standby: unfractionated heparin to warfarin
 - LMWH are as effective as unfractionated heparin, bridge to warfarin
 - Novel anticoagulants extensively studied and non-inferior as discussed in EBM corner
 - IVC Filters controversial benefit, likely benefit initially especially in patients unable to receive anticoagulation, but long term benefit is more nebulous
 - Duration of anticoagulation

Patient Characteristics	Risk of recurrence in 1 year	Duration of therapy
Major transient risk factor	3	3 mos
Minor risk factor; no thrombophilia	<10 if risk factor avoided	6 mos
	>10 if risk factor persistent	Until factor resolves
Idiopathic event, no thrombophilia	<10	6 mos
Idiopathic event, high-risk thrombophilia	>10	Indefinite
More than one idiopathic event	>10	Indefinite
Cancer, other ongoing risk factor	>10	Indefinite

- Testing for thrombophilia
 - At least one third of patients with idiopathic venous thromboembolism have an identifiable thrombophilia
 - May not represent any change in treatment; no unequivocal indications for testing in either patients or relatives
- o Upper extremities
 - 10% of all DVT cases involve upper extremities, more common due to increased use of central venous catheters, pacemakers, defibrillators
 - Complications are less common in upper extremities than lower extremities (PE 6% v 15-32% in lower extremities, less common recurrence, and post-thrombotic syndrome
 - Catheter removal in most situations in not recommended
 - If massive and not responding to traditional anticoagulation, may consider thrombolysis or surgical procedures
 - Generally, three months of vitamin K antagonist for treatment, novel anticoagulants have not been studied in upper extremity but likely to work as well.
- o Prophylaxis
 - 25% of all cases of venous thromboembolism are associated with hospitalization, 50-75% of cases occur in those on the medical service

- Risk factors: Acute infectious disease, CHF, acute respiratory disease, stroke, rheumatic disease, IBD, previous venous thromboembolism, older age (especially >75 y), recent surgery or trauma, immobility, obesity, central venous catheterization, inherited or acquired thrombophilic states, varicose veins, or estrogen therapy
- Ambulation, exercises, SCDs (50% reduction of VTE in hospitalized post-surgery patients)
- Low doses of heparin reduced the rates of post-op VTE, total PE, fatal PE by 67, 47, and 64%
- Enoxaparin (MEDENOX) 40mg once daily 1102 patients with 5.5% VTE vs 14.9% in placebo

Massive	Submassive	Low Risk
Acute PE with any of the following - Sustained hypotension • Systolic BP <90mm Hg for 15+ mins or requiring inotropic support - Persistent profound bradycardia (<40bpm) - Pulselessness	 Acute PE without systemic hypotension, but with either right ventricular dysfunction or myocardial necrosis Ventricular dysfunction ≥ 1 of: RV dilation defined as apical 4-chamber RV diameter divided by left ventricular diameter > 0.9 or RV systolic dysfunction on Echo RV dilation defined as 4-chamber RV diameter divided by left ventricular diameter > 0.9 on CT BNP > 90 pg/mL EKG changes including new complete or incomplete RBBB, anteroseptal ST elevation or depression, or anteroseptal T-wave inversion or S1Q3T3 sign 	Acute PE without clinical markers of adverse prognosis that define massive or submassive PE
	 Myocardial necrosis: Troponin > 0.4 ng/ml 	





Fig. 1. Estimated mortality for PE, indexed by severity. The presence of shock indicates massive PE. A subgroup of patients with right ventricle (RV) dysfunction are deemed submassive, and can have mortality in excess of 30%. Thus, accurate and timely risk stratification and treatment are important.



Clinical Tools

- Pulmonary Embolism Severity Index (PESI) Class I-V stratified by mortality, based on 11 characteristics associated with adverse outcome or death (1.6% in I, 24.5% in V)
 - Evidence Two trials, 318 hemodynamically stable, 89 with nonmassive PE; higher PESI scores correlated with RV dysfunction, adverse results, and death.²
 - o Application Unlike Wells, Geneva, PERC criteria, meant to risk stratify PE patients
- **Troponin:** 2007 meta-analysis of 1985 PE patients, elevated troponin increases OR of mortality to 5.24, in normotensive patients OR of 5.9, NPV of 92% for survival.
- **BNP:** Elevated BNP with higher short-term risk of death, OR 6.57. Sens/spec to predict death of 93% & 48%. Low BNP had NPV of 99% in excluding adverse outcome.
- **CTA:** 2005 systematic review, a negative CTA has NPV of 99.1% for acute PE. PIOPED II Trial, CTA showed sens/spec of 83% and 96% for acute PE.
 - Application Diagnosis and then risk stratification by demonstrating RV/LV size ratio, clot burden both associated with increased mortality, clinical deterioration.

- ECG: Sinus tachycardia, S1Q3T3, R precordial T wave inversions, RBBB. Findings are not sensitive or specific.
 - Application Adjunctively in risk stratification as supporting evidence.
- Echocardiography: 1000 normotensive patients, RV hypokinesis predicted 30d mortality. Mortality Risk Ratio of RV dysfunction 2.5.
 Only a moderate predictor of death when compared to biomarkers.
 - Application Further risk stratification with severity of RV dilatation, hypokinesis, tricuspid regurgitation, and paradoxical septal movement.

Treatment

- Anticoagulation Anticoagulants extensively studied in low-risk PEs. No studies have examined non-heparin (warfarin, LMWH, novels) anticoagulation in submassive/massive PE.
- **Thrombolysis** Mixed data history; consistently shown to reduce clot burden and improve hemodynamics initially but with substantial risk of intracranial hemorrhage in up to 3%, major bleeding in 20%.
- Alternative options include embolectomy, catheter directed therapy, adjunct IVC filter placement.



Fig. S. Proposed algorithm for treatment of submassive PE. CDT, catheter-directed therapy; IR, interventional radiology; IVC, inferior vena cava.

DVT/PE EBM Quick Reference:

CLOT: 700 cancer patients with DVT, PE or both randomized to dalteparin or warfarin for 6 months. Dalteparin reduced VTE recurrence, no change in bleeds, mortality. (NEJM 2003)

MAGELLAN: 8000 acutely ill randomized to enoxaparin or rivaroxaban. Rivaroxaban reduced the risk of VTE, but was associated with increased risk of bleeding. (NEJM 2013)

PIOPED II: 800 PEs and CT study. Sensitivity of CTA was 83% and specificity was 96%. PPV is high (96%) with concordant clinical assessment. (NEJM 2006)

RE-COVER: 2500 VTE randomized to dabigatran or warfarin. Dabigatran non-inferior in preventing VTE. Mortality, ACS, bleeding was similar in both groups. (NEJM 2009)

EINSTEIN-PE: 4800 with PE randomized to rivaroxaban or enoxaparin followed by warfarin for long term. Rivaroxaban was noninferior for VTE with decreased bleeds. (NEJM 2012)

AMPLIFY: 5300 VTE, randomized to apixaban or LMWH to warfarin. Apixaban was noninferior in recurrence of VTE with significantly less bleeding. (NEJM 2013)

AMPLIFY-EXT: 2400 VTE completed 6-12mos of OAC randomized to apixaban or placebo. Apixaban reduced the risk of recurrent VTE without increased bleeds. (NEJM 2013)

WARFASA: 400 VTE, completed 6-18 months of OAC randomized to ASA or placebo for 2 years. ASA reduced the recurrence with no increase bleedings. (NEJM 2012)

MOPETT: 120 submassive PE randomized to tPA or anticoagulation. tPA reduced pHTN and recurrent PE. (American Journal of Cardiology 2013)

ADJUST-PE: 3300 suspected PE, using age-adjusted d-dimer cutoff 10x age. In combination with pretest probability, more patients could be ruled out safely. (JAMA 2014)

PEITHO: 1000 submassive PE randomized to tPA or anticoagulation. Death, hemodynamic instability was lower in tPA, increased extracranial bleeding and stroke. (NEJM 2014)

PREPIC2: 190 PE randomized to anticoagulation ± IVC filter. Filter did not reduce recurrent symptomatic VTE. (JAMA 2015)

SOME: 850 VTE randomized to limited occult-cancer screening ± CT. Only 3.9% of patients had a new diagnosis occult cancer at 1y. No mortality benefit. (NEJM 2015)

Acute Respiratory Distress Syndrome – attributed to Colin Feuille

- Pathogenesis
 - SIRS -> activation of circulating neutrophils -> neutrophil extravasation and degranulation in the lung parenchyma -> damage to capillaries -> exudate of protein (including fibrin), RBCs, platelets fill distal airspaces -> fibrin accumulates and promotes pulmonary fibrosis
- Common Sources:
 - Pneumonia, sepsis, aspiration, massive transfusion, TRALI, trauma, pancreatitis, drug overdose, burns, fat embolism, inhalation injury, lung transplant, hematopoietic stem cell transplant, cardiopulmonary bypass
- Diagnosis
 - Berlin criteria as below
 - BNP <100 specific for ARDS in the appropriate setting, but low sensitivity
 - Bronchoalveolar lavage
 - Low neutrophil count can exclude ARDS
 - Protein content:
 - Hydrostatic edema: fluid protein / plasma protein < 0.5
 - ARDS: fluid protein / plasma protein > 0.7
 - On pathology: diffuse alveolar damage

Berlin Criteria - Acute Respiratory Distress Syndrome					
Timing		Within 1 week of known clinical insult or new/worsening respiratory symptoms			
Chest imaging		Bilateral opacities – not fully explained by effusions, lung collapse, nodules			
Origin of edema		Respiratory failure not explained by cardiac failure or fluid overload			
		Objective assessment (TTE) to exclude hydrostatic edema if no risk factor present			
Oxygenation	Mild	200 mm Hg < PaO2/FiO2 < 300 mm Hg with PEEP >5 cm H2O			
	Moderate	100 mm Hg < PaO2/FiO2 < 200 mm Hg with PEEP >5 cm H2O			
	Severe	PaO2/FiO2 < 100 mm Hg with PEEP >5 cm H2O			

o Management

- Ventilator goal: prevention of ventilator-induced lung injury
 - Volutrauma: The volume of functional lung tissue in ARDS is much less than in a typical lung, and if high tidal volumes are used, they are delivered only to the unconsolidated functional lung, over-distending it.
 - Barotrauma: pressure-related lung injury, associated with escape of air from the lungs, including pneumothorax.
 - Biotrauma: pro-inflammatory cytokines are released in the lungs and systemic circulation during mechanical ventilation, activating the systemic inflammatory response.
 - Atelectrauma: decrease in lung distensibility results in collapse of small airways at endexpiration. Cyclic opening and closing of these small airways and alveoli during mechanical ventilation creates shear forces that damage the airway epithelium
- Lung protective ventilation strategies
 - Low Tidal Volumes (ARDSNet, NEJM 2000)
 - Goals: TV = 6-8 mL/kg IBW, Ppl ≤ 30 cmH2O, SpO2 = 88-95%, pH = 7.3 7.45, PEEP ≥ 5 cm H2O
 - Permissive Hypercapnia: PaCO2 levels of 60-70 mmHg and arterial pH levels of 7.2-7.25 are safe for most pts and may be allowed to better achieve primary goals of low tidal volume ventilation (low TV and low Ppl).
 - Use PEEP/FiO2 combinations below. If PaO2/FiO2 ≤ 200, use higher PEEP/lower FiO2 strategy (Briel, JAMA 2010).



NIH NHLBI ARDS Clinical Network Mechanical Ventilation Protocol Summary

INCLUSION CRITERIA: Acute onset of

- $PaO_2/FiO_2 \le 300$ (corrected for altitude) 1.
- Bilateral (patchy, diffuse, or homogeneous) infiltrates consistent with 2. pulmonary edema
- 3 No clinical evidence of left atrial hypertension

PART I: VENTILATOR SETUP AND ADJUSTMENT

- Calculate predicted body weight (PBW) 1. Males = 50 + 2.3 [height (inches) - 60] Females = 45.5 + 2.3 [height (inches) -60]
- 2. Select any ventilator mode
- 3. Set ventilator settings to achieve initial $V_T = 8 \text{ ml/kg PBW}$
- Reduce V_T by 1 ml/kg at intervals \leq 2 hours until V_T = 6ml/kg PBW. 4.
- Set initial rate to approximate baseline minute ventilation (not > 35 5. bpm).
- 6. Adjust V_T and RR to achieve pH and plateau pressure goals below.

pH GOAL: 7.30-7.45

Acidosis Management: (pH < 7.30)

If pH 7.15-7.30: Increase RR until pH > 7.30 or PaCO₂ < 25 (Maximum set RR = 35).

If pH < 7.15: Increase RR to 35.

- If pH remains < 7.15, V_T may be increased in 1 ml/kg steps until pH > 7.15 (Pplat target of 30 may be exceeded).
- May give NaHCO3

Alkalosis Management: (pH > 7.45) Decrease vent rate if possible.

I: E RATIO GOAL: Recommend that duration of inspiration be < duration of expiration.

PART II: WEANING

Conduct a SPONTANEOUS BREATHING TRIAL daily when:

- $FiO_2 \leq 0.40$ and $PEEP \leq 8$ OR $FiO_2 \leq 0.50$ and $PEEP \leq 5.$ 1.
- 2. PEEP and $FiO_2 \leq$ values of previous day.
- Patient has acceptable spontaneous breathing efforts. (May 3. decrease vent rate by 50% for 5 minutes to detect effort.)
- Systolic BP \geq 90 mmHg without vasopressor support. 4.
- 5 No neuromuscular blocking agents or blockade.

Non-ventilator management 0

- Treat the underlying cause 70% of deaths in ARDS due to multi-organ failure, not respiratory failure 0
- Sedation 0
 - Use a combination of analgesics and sedatives, and attempt to minimize sedation with daily sedation holidays, intermittent rather than continuous sedation or no sedation to decrease time on ventilator.
- 0 Fluids
 - Avoid positive fluid balance to prevent pulmonary fluid accumulation superimposed on the inflammatory exudate of ARDS. No mortality benefit, but conservative fluids do reduce time on ventilator.

OXYGENATION GOAL: PaO₂ 55-80 mmHg or SpO₂ 88-95%

Use a minimum PEEP of 5 cm H₂O. Consider use of incremental FiO₂/PEEP combinations such as shown below (not required) to achieve goal.

Lower PEEP/higher FiO2

FiO ₂	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.
PEEP	5	5	8	8	10	10	10	12
FiO ₂	0.7	0.8	0.9	0.9	0.9	1.0		
PEEP	14	14	14	16	18	18-24		

Higher PEEP/lower FiO2

FiO ₂	0.3	0.3	0.3		0.3		0.3	0.	4	0.4	0.5
PEEP	5	8	10		12		14	14	1	16	16
FiO ₂	0.5	0.5-0	.8	0	.8	0).9	1.0		1.0]
PEEP	18	20		2	2	2	22	22		24]

PLATEAU PRESSURE GOAL: ≤ 30 cm H₂O

Check Pplat (0.5 second inspiratory pause), at least q 4h and after each change in PEEP or V

If Pplat > 30 cm H₂O: decrease V_T by 1ml/kg steps (minimum = 4 ml/kg).

If Pplat < 25 cm H₂O and V_T< 6 ml/kg, increase V_T by 1 ml/kg until Pplat > 25 cm H_2O or $V_T = 6$ ml/kg.

If Pplat < 30 and breath stacking or dys-synchrony occurs: may increase V_T in 1ml/kg increments to 7 or 8 ml/kg if Pplat remains \leq 30 cm H₂O.

B. SPONTANEOUS BREATHING TRIAL (SBT): If all above criteria are met and subject has been in the study for at least 12 hours, initiate a trial of UP TO 120 minutes of spontaneous breathing with FiO2 \leq 0.5 and PEEP \leq 5:

1. Place on T-piece, trach collar, or CPAP \leq 5 cm H₂O with PS \leq 5 2. Assess for tolerance as below for up to two hours.

- $SpO_2 > 90$: and/or $PaO_2 > 60$ mmHq а
 - Spontaneous $V_T \ge 4$ ml/kg PBW b.
 - $RR \le 35/min$ c.
 - d. pH ≥ 7.3
 - No respiratory distress (distress= 2 or more) e.
 - HR > 120% of baseline
 - Marked accessory muscle use
 - Abdominal paradox
 - Diaphoresis
 - Marked dyspnea

3. If tolerated for at least 30 minutes, consider extubation.

If not tolerated resume pre-weaning settings.

Definition of UNASSISTED BREATHING (Different from the spontaneous breathing criteria as PS is not allowed)

- Extubated with face mask, nasal prong oxygen, or 1. room air, OR
- 2. T-tube breathing, OR
- 3. Tracheostomy mask breathing, OR
- CPAP less than or equal to 5 cm H₂0 without 4.
- pressure support or IMV assistance.

- 4.

- o Steroids
 - No consistent survival benefit
 - Consider for early severe ARDS (PaO2/FiO2 ≤ 200 with PEEP 10 cmH2O) and for unresolving ARDS (less than 1-point reduction in lung injury score by 7 days)
 - Early severe ARDS: Reductions in duration of mechanical ventilation, ICU stay, and ICU mortality, but NO reduction in hospital length of stay or survival to hospital discharge
 - Unresolving ARDS: Increased ventilator-free and shock-free days in the first 28 days, but NO
 reduction in 60 or 180-day mortality. Significant *increase* in mortality if started after 14 days of
 unresolving ARDS
- Neuromuscular Blockade
 - Significant reduction in adjusted mortality with paralysis with cisatracurium for 48 hours in patients with ARDS with PaO2/FiO2 ≤ 150
- o Refractory hypoxemia
 - High frequency oscillatory ventilation routine use not recommended.
 - Very small tidal volumes (1-2 mL/kg) by rapid pressure oscillation
 - Can improve arterial oxygenation in pts w/ severe ARDS but no documented survival benefit and may increase mortality
 - Inhaled NO routine use not recommended
 - Temporary improvement in arterial oxygenation, but no survival benefit and may cause renal dysfunction. Epoprostenol (Flolan) is another potential pulmonary vasodilator
 - o Proning
 - May improve gas exchange by improving V/Q matching diverts blood away from consolidated posterior lung towards better-aerated anterior lung.
 - Significant mortality benefit in severe ARDS in a randomized trial, though performed at centers highly experienced with the labor-intensive technique
 - o ECMO
 - Indicated for severe hypoxemic respiratory failure with PaO2/FiO2 ≤ 100 despite optimal ventilator settings when other rescue therapies have failed.
 - Referral to a center experienced with ECMO improved 6-month disability-free survival

ARDS EBM Quick Reference:

ARDSNet: 800 ARDS randomized to low tidal volumes (6 ml/kg IBW) high volume. Mortality benefit with low TV, NNT = 11. More ventilator free days. (JAMA 2000)

FACTT: 1000 ARDS randomized to liberal (CVP 10-14) or conservative (CVP <4). No difference in mortality. More Ventilator free days with conservative fluids. (NEJM 2006)

FACTT/ESCAPE/PAC-MAN: The legacy of the FACTT trial is a decrease in PA catheters. Catheter directed treatment had no survival benefit and twice as many complications. Repeated in heart failure, ICU patients in ESCAPE/PAC-MAN.

Glucocorticoids in Persistent ARDS: 180 ARDS randomized to methylprednisolone or placebo. No difference in mortality. Increased mortality if started after day 14. (NEJM 2007)

Glucocorticoids in Early Severe ARDS: 90 severe ARDS randomized to methylprednisolone or placebo. Quicker extubation, no reduction in hospital mortality. (Chest 2007)

Nitric Oxide: Meta-analysis of 12 trials. No significant effect on mortality or duration of mechanical ventilation. Significant increase in PaO2/FiO2, renal dysfunction. (BMJ 2007)

High v Low PEEP: Meta-analysis of 3 trials. No significant difference in rate of hospital death. In moderate-severe ARDS lower mortality, less vent days with high PEEP. (JAMA 2010)

ACCURASYS: 340 ARDS patients randomized to paralysis or placebo. When adjusted, reduction in mortality, barotrauma, ventilator days, and ICU LOS. However, no difference in unadjusted mortality rates. (NEJM 2010)

OSCILLATE: 540 ARDS randomized to high frequency oscillatory ventilation OR ARDSNet protocol. significant increase in mortality with HFOV. (NEJM 2013)

PROSEVA: 460 ARDS randomized to prone or supine. Mortality benefit with proning: Unscheduled extubation and ETT obstruction more common with proning. (NEJM 2013)

Sepsis – attributed to Andy Coyle, Hooman Poor, Kaitlin Klipper

- Shock Physiologic state characterized by reduction in systemic tissue perfusion, an imbalance between oxygen delivery and consumption
 - o Hypovolemic: decreased preload secondary to intravascular volume loss
 - o Cardiogenic: pump failure (arrhythmias, MI, cardiomyopathy, massive PE, PTX)
 - o Distributive: Sepsis, anaphylaxis, drug or toxin-related, neurogenic shock, sepsis, pancreatitis, burns
 - o SIRS (5% 30d mortality): 2 of:
 - T > 38.0 or < 36.0, HR > 90, R > 20 (PaCO2 < 32)</p>
 - WBC < 4K or > 12K (or > 10% band forms)
 - Sepsis (10-15% mortality): SIRS + suspected infection
 - Severe Sepsis (20-25% mortality) SIRS + organ dysfunction
 - Septic Shock (50% mortality): Severe Sepsis + Fluidresistant hypotension
 - o SEPSIS-3 definitions (JAMA 2016)
 - Sepsis: Suspected or documented infection and an acute increase of ≥2 SOFA points
 - Septic Shock: Sepsis and vasopressor therapy needed to elevate MAP ≥65, and lactate ≥2 despite adequate resuscitation
 - qSOFA: RR>22, altered mental status, SBP <100
 - SOFA: PaO2/FiO2 ratio, GCS, MAP, Vasopressors, Cr/UOP, TBili, Platelets
- Treatment
 - Timely, appropriate antibiotics, source control
 - o Fluids: EGFT patients received 4-5L
 - Crystalloids preferred over colloids (non-inferior, faster/cheaper) >>> starches (increased mortality)
 - Goals: MAP >65 and SBP >90, urine output >0.5 mL/kg/h, CVP > 8-12, mixed venous O2 sat >70%, lactate clearance (decreasing and/or <2)

TYPES OF SHOCK

Type of Shock	Insult	Physiologic Effect	Compensation
Cardiogenic	Heart fails to pump blood out •MI, arrhythmia, aortic stenosis, mitral regurg,	↓CO	BaroRc ↑SVR
Obstructive	Heart pumps well, but the outflow is obstructed *Extracardiac obstructive causes such as PE, tension pneumothorax, tamponade	↓CO	BaroRc ↑SVR
Hypovolemic	Heart pumps well, but not enough blood volume to pump "Hemorrhage "Fluid Loss (Vomiling, Diarrhea, Burns)	↓CO	BaroRc ↑SVR
Distributive	Heart pumps well, but there is peripheral vasodilation "Septic, anaphylactic, and neurogenic shock "Pancreatilis, burns, multi-trauma via activation of the inflammatory response	↓SVR	↑CO

THE SEQUENTIAL ORGAN FAILURE ASSESSMENT (SOFA) SCORE

SYSTEM	0	1	2	э	4
Respiration	≥400	<400	<300	<200 (26.7)	< 100 (13.3)
PaO2/FIO2 mm Hg (kPa)	(53.3)	(53.3)	(40)	with respiratory support	with respiratory support
Coagulation Platelets ×10 ¹ /uL	≥150	+150	<100	<50	<20
Liver Blinubin mg/dt. (umol/L)	<1.2 (20)	1.2·1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70mmHg	MAP <70mmHg	Dopamine <5 or Dobutamine (any dose)	Dopamine 5.1 - 15 or Epinephrine <u><</u> 0.1 or Norepinephrine <u><</u> 0.1	Dopamine >15 or Epinephrine >0.1 or Norepi nephrine >0.1
CNS GCS Score	15	13-14	10-12	6-9	+6
Renal Creatinine, mg/dl (umol/L) Urine Output, ml/d	<1.2 (110)	1.2 -1.9 (110-170)	2.0 - 3.4 (171- 299)	3.5 - 4.9 (300 - 440) <500	> 5.0 (440) <200

echolamine Doses = ug/kg/min for at least 1hr	Sepsis 3 - SOFA Score (JAMA 2016)	

Vasopressor	Receptors Activated	Net Effect	Side Effects
Norepinephrine	Alpha 1, Beta 1	Increased inotropy	Arrhythmias,
		Neutral chronotropy	Hyperglycemia
		Vasoconstriction	Local necrosis
Dopamine	Dopamine receptors	Increased chronotropy	Tachycardia
		Vasoconstriction	Arrhythmias
			Hyperglycemia
Vasopressin	V1 receptors	Vasoconstriction	? Arrhythmia
		Neutral chronotropy	? MI
Epinephrine	Beta 1, Beta 2, Alpha 1	Increased chronotropy	Arrhythmias
		Increased inotropy	Tachycardia, palpitations
		? Vasoconstriction	Hyperglycemia
Phenylephrine	Alpha 1	Vasoconstriction	May decrease SV, HA

• Vasopressors

- Norepinephrine = Phenylephrine (Crit Care 2008) = Epinephrine (Intensive Care Medicine 2008)
 - Norepinephrine > Dopamine (Chest 1993, Critical Care 2012 Meta-analysis)
 - 28-day mortality: 54% in dopamine, 49% in NE, 2x arrhythmias with dopamine
- Early goal directed therapy
 - Manny Rivers paradigm: invasive monitoring using CVP, ScVO2 to guide fluids, pressors, dobutamine infusion as needed. Established basis of current sepsis care, replicated.

- ProCESS, ProMISe trials showed that Rivers protocol increased use of pressors, inotropes and transfusions without mortality benefit.
- Standard of care: timely antibiotics, source control, fluids without invasive monitoring

o Lactate

- Serves as proxy to measure oxygen kinetics and delivery, and tissue hypoperfusion.
- Anaerobic state: glucose to pyruvate via lactate dehydrogenase to generate 2ATP
- 60% cleared by liver, 30% cleared by kidney, remaining cleared by various muscle tissue
- Lactate cleared via Cori cycle going back to pyruvate and back to glucose in gluconeogenesis
- Lactated Ringers uses lactate to buffer solution and does not cause elevation in serum lactate
- Type A: elevated lactate attributed to decreased perfusion or oxygenation
- Type B: elevated lactate due to:
 - Underlying diseases: ketoacidosis, leukemia, lymphoma, AIDS
 - Medication or intoxication: cyanide, beta-agonists, methanol, nitroprusside, EtOH, ARVs
 - Inborn errors of metabolism

Sepsis EBM Quick Reference

RIVERS: 260 sepsis randomized to EGDT with invasive central monitoring of CVP >8-12, MAP >65, UOP >0.5ml/kg/h, ScVO2 >70. Absolute risk reduction of 16% in mortality. (NEJM 2001)

ProCESS: 1300 sepsis randomized to EGDT, non-invasive protocol or usual. More vasopressors, inotropes, blood in EGDT. No difference in mortality or organ support. (NEJM 2014)

ARISE: 1600 sepsis randomized to EGDT or usual care. More fluids, vasopressors, inotropes, blood in EGFT. No difference in mortality, duration of organ support, LOS. (NEJM 2014)

ProMISe: 1200 sepsis randomized to EGDT or usual care. More fluids, vasoactives, blood, CV support, ICU days in EGDT. No difference in mortality, QoL. EGDT increased cost. (NEJM 2015)

COIITS: 500 septic shock randomized to IV/ SQ insulin ± hydrocortisone ± fludrocortisone. No change in mortality with intensive insulin, or oral fludrocortisones. (JAMA 2013)

VISEP: 500 sepsis randomized to intensive or conventional insulin + starch or LR. Starch increased severe hypoglycemia, serious adverse events, acute renal failure and RRT. (NEJM 2008)

SEPSISPAM: 770 septic shock patients randomized to MAP of 80-85 or MAP of 65-70. No difference in mortality between the groups at 28 or 90d. (NEJM 2014)

CATS: 330 septic shock randomized to dobutamine + epi or norepi to MAP >70. No differences in efficacy or safety. (Lancet 2007)

SOAPII: 1600 shock randomized to dopamine or norepinephrine. No difference in mortality, increased arrhythmic events in patients treated with dopamine. (NEJM 2010)

VASST: 770 septic shock receiving norepinephrine randomized to either low dose vasopressin or more norepinephrine. Low dose vasopressin did not reduce mortality rates. (NEJM 2008)

SIRS Criteria: 1.1 million with infection categorized to SIRS positive or SIRS negative. Two or more SIRS criteria excluded one in eight similar patients and failed to define a transition point in the risk of death. (NEJM 2015)

TRICC > TRISS: 1000 septic shock randomized to Hgb of 9 or 7. Mortality and ischemic events were similar among groups, but lower goal used 50% fewer units of blood. (NEJM 2014)

Annane: 300 septic shock randomized to hydrocortisone + fludrocortisone or placebo. In patients with confirmed adrenal insufficiency, decrease in mortality. (JAMA 2002)

CORTICUS: 500 septic shock randomized to hydrocortisone or placebo. Hydrocortisone conferred a more rapid reversal of shock in all subgroups, but no mortality benefit. (NEJM 2008)

ACCESS: 1900 severe sepsis randomized to eritoran (lipid A antagonist) or placebo. No reduction in mortality with no significant difference in adverse events. (JAMA 2013)

Antithrombin III: 2300 septic shock patients randomized to antithrombin III or placebo. No effect on mortality. ATIII + heparin increased hemorrhage. (JAMA 2001)

OPTIMIST: 1700 severe sepsis randomized to tifacogin (recombinant tissue factor pathway inhibitor) or placebo. No mortality benefit, increased hemorrhage. (JAMA 2003)

PROWESS > PROWESS-SHOCK: PROWESS (2001) survival benefit of activated protein C in severe sepsis. PROWESS-SHOCK (2008) 1600 randomized to APC. No effect on mortality. (NEJM 2012)

Acute Pancreatitis - attributed to Andy Coyle

- History
 - o Pain: maximal intensity within 10-20m in gallstone; in EtOH more gradual and less localized
 - Radiates to back in ~50% in most case series
 - o 90% will have nausea/vomiting
 - Dyspnea can be an early warning sign: pain causing atelectasis, diaphragmatic inflammation causing atelectasis, pleural effusions, ARDS
- Etiology
 - #1 Gallstones (35-40%) > #2 EtOH (30%)
 - Other: trauma, post-ERCP, hypercalcemia, hypertriglyceridemia, medications, viral infections, pregnancy
 - Rare: Bacterial infections (mycoplasma, legionella), vascular disease (SLE, PAN), autoimmune pancreatitis, celiac disease
- Physical Exam
 - o Epigastric tenderness, distention, hypoactive bowel sounds, scleral icterus
 - Ecchymotic discolorations > Hemorrhagic pancreatitis
 - Cullen's: Periumbilical, Grey Turner Sign: Flank, Fox Sign: Inguinal area
 - Hepatomegaly in alcoholics, xanthomas in those with severe hyperlipidemia, parotid swelling in those with mumps
- Diagnosis Need 2/3 of typical symptoms, amylase/lipase >3x ULN, or imaging findings
 - Lipase highly specific at 3x ULN
 - In patients with typical symptoms, elevated lipase imaging is not required unless patient is deteriorating or not improving at 72h
 - Amylase >3x ULN sens 67-83% and spec 85-98%
 - DDx: pancreatic disease, acute cholecystitis, intestinal obstruction, parotitis, malignancy, ovarian/fallopian tube disease
 - Lipase >3x ULN specificity >95%
 - DDx: pancreatic disease, acute cholecystitis, intestinal obstruction, celiac disease, CKD, Renal failure, HIV
- Prognosis
 - General prognostic factors age, EtOH use, obesity, organ failure
 - Poor prognosis factors hemoconcentration, elevated CRP, elevated BUN/Cr
 - Scoring systems
 - Ranson: 11 variables, measured at admission and 48h. No one uses.
 - APACHE II: Score <8 predicts <4% mortality, >8 indicate higher risk
 - BISAP (Gut 2008): Score of 0 had mortality <1%, Score of 5 had mortality of 22%
 - One point for BUN >25, impaired mental status, SIRS, Age >60, pleural effusion
 - CT Severity Score (Balthazar): Based on CT findings
- Treatment:
 - o IV fluids with some evidence that lactated ringers is better than NS
 - Aggressive fluid resuscitation in first 12h can improve results, 5mg/kg/h (250-500mL/h)
 - o Should start refeeding early if hungry and rapidly advance diet
 - o If unable to tolerate diet at 72h, place NG tube and start enteric feeds

Pancreatitis EBM Quick Reference:

BISAP: Retrospective 390 cases, BISAP score predicted mortality. BISAP score ≥3 increased risk of organ failure pancreatic necrosis. (Gastro 2009)

LR vs. NS: 40 acute pancreatitis randomized to LR vs NS. Reduced SIRS criteria and CRP with LR. (Clin Gastro & Hep 2011)

Initial Fluid Rate: Retrospective. Early resuscitation (>33% of total fluids in first 24h) had 0% mortality, 18% later. (Panc 2010)

Nutrition in Severe Acute Pancreatitis:

- **TIMING:** 208 acute pancreatitis randomized to 24h or 72h (if not tolerating oral diet), no difference in infections, LOS, mortality. 69% of patients in 72h group tolerated oral diet. (NEJM 2014)
- ROUTE:
 - 78 patients with severe acute pancreatitis randomized to NG or NJ tube. Statistically more infections in NJ group, noninferiority in pain, LOS, intestinal permeability, endotoxemia (Panc Journal 2012)
 - Cochrane Review: Enteral nutrition v. parenteral nutrition in acute pancreatitis. Enteral nutrition significantly reduced mortality, multiple organ failure, systemic infections, operative interventions, with a trend towards lower LOS. (Cochrane 2010)

GI Bleed – attributed to Colin Iberti

- Acute upper gastrointestinal bleeding
 - Bleeding above the ligament of Treitz (duodenojejunal junction), >500,000 hospital admissions annually
 - Risk factors: NSAIDS, ASA, SSRIs, corticosteroids, *H. pylori* infection, alcohol, tobacco
 - Causes: Peptic ulcer (mostly duodenal, gastric) 62%, mucosal erosion 14%, esophageal varices 6%, Malory-Weiss, esophageal ulcer, malignancy, Dieulafoy lesion
 - o History
 - Mallory Weiss tear preceded by retching, vomiting, seizure
 - Peptic ulcer disease nighttime pain, pain reduction on eating
 - Malignancy abdominal pain and weight loss
 - AVM older (>70yo) with painless bleeding
 - Esophagitis or esophageal ulcer heartburn, indigestion, dysphagia

Finding	Sensitivity %	Specificity %	Positive Likelihood Ratio
History of GI bleed	22	96	6.2
History of melena	77-95	81-87	5.1-5.9
Melena on exam	49	98	25
NG lavage with blood or coffee groups	44	95	9.6
BUN/Cr >30	51	93	7.5

- o Management
 - 2x PIV, T&S, PPI, Fluid resuscitation, Blood for Hgb goal >7
 - Pre-endoscopic risk assessment scale
 - Rockall Age, Shock, Comorbidity then endoscopic findings to predict mortality
 - Blatchford BUN, Hgb, SBP, HR, Melena, Syncope, Hepatic disease, Heart Failure to predict the need for acute intervention
 - EGD within 24h if possible, 12h if high risk clinical features
 - PPI reduces stigmata of recent hemorrhage but does not reduce mortality or rebleeding
 - Intermittent PPI as effective as continuous PPI therapy in reduction of rebleeding in patients
- Acute lower gastrointestinal bleeding
 - o Bleeding below the ligament of Treitz (duodenojejunal junction), 25% of patients presented with GIB
 - o Risk factors: NSAIDS, ASA, alcohol, tobacco
 - o Causes
 - Diverticular bleeding is MCC, hemorrhoids, anal fissure, inflammatory bowel disease, ischemic colitis, neoplasia (consider metastatic non GI-cancer), angiodysplasia, AVM, infectious colitis, Osler-Weber-Rendu syndrome
 - o Management
 - 2x PIV, T&S, PPI, Fluid resuscitation, Blood for Hgb goal >7, bowel prep, colonoscop

Finding	Sensitivity %	Specificity %	Positive Likelihood Ratio
History of lower GI bleed	6	64	0.17
Clots in stool	15	99.2	0.05

GIB EBM Quick Reference:

PPI: Cochrane review of 2200 GIB. No differences in mortality, rebleeding, or surgery between PPI and control. PPIs did reduce stigmata of recent hemorrhage. (Cochrane 2012)

Intermittent v Continuous PPI: Meta-analysis for intermittent vs. continuous PPI therapy. Intermittent no increase in rebleeding, mortality, blood transfusions, or LOS. (JAMA Intern Med 2014)

Risk of restarting warfarin post GI Bleed: Retrospective 440 with warfarin associated index GIB. Resuming warfarin had decreased thrombosis, death, without more GIB. (Arch Intern Medicine 2012)

PPI v H2: Meta-analysis of 35000 patients demonstrated that GI hemorrhage, *c.difficile* infections, PNA less likely in H2 group. (JAMA Intern Med 2014)

TRICC: 830 ICU without GIB randomized to restrictive (>7) or liberal (>10) transfusion strategy. Restrictive had decreased mortality. (NEJM 1999)

Restrictive v Liberal Transfusion Strategies: 900 UGIB, randomized to restrictive (>7), or liberal (>9). Restrictive had 45% RRR in mortality, shorter LOS. Also fewer rebleeding events in EVB patients. No benefit in Child-Pugh class C patients. (NEJM 2013)

Acute Hepatic Failure / Alcoholic Hepatitis – attributed to Colin Iberti

- Definitions
 - Clinical manifestation of sudden and sever hepatic injury from a myriad of causes, leading to encephalopathy, coagulopathy, and progressive multiorgan failure
 - o Rare, 1-6 cases per million every year in the developed world
- Causes
 - Viral infections

- Developing world: infection with hepatitis A, B, and E viruses account for most cases
- In the USA, viral infection is an uncommon cause with drug induced injury predominates
- Hepatitis A fecal-oral contact, closely associated with poor hygiene and sanitation
 - Greatly declined due to hepatitis A vaccination, <1% of patients develop failure
 - Hepatitis E fecal-oral contact endemic in tropical/subtropical countries
 - Most common cause of acute liver failure in India, China
 - Infection is common in pregnant women, in the third trimester, with a high mortality rate
- Hepatitis B transmitted vertically or horizontally by exposure to blood or other body fluids
 - Fewer than 4% of acute cases will develop failure, but mortality higher than A or E
 - Vaccination has led to large decreases in hepatitis B incidence, failure, mortality
 - Failure can also occur in chronic infection when viral status changes with replication surge, reactivation, superinfection with hepatitis D
- Uncommon: HSV1, HSV2, HHV6, VZV, EBV, CMV, Parvo B19, Hepatitis C
- Drug-induce injury
 - Predominates as main cause of liver failure in much of the developed world.
 - Acetaminophen by far most common cause
- Evaluation
 - Viral hepatitis panel (other viruses including CMV, EBV, HSV), serum drug screen (tylenol), ceruloplasmin, AIH serologies (ANA/ASMA/LKM-1), abdominal US
- Clinical Management
 - o Obviously requires intensive care management with an eye towards liver transplant in advanced disease
 - Within 24h of acetaminophen ingestion, N-acetylcysteine can prevent or reduce liver damage
 - Initial loading dose 150 mg/kg per hour over one hour followed by 12.5 mg/kg per hour for four hours, then continuous infusions of 6.25 mg/kg per hour x 16 hours
 - Pathogenesis of hepatic encephalopathy in acute liver failure is poorly understood, raised concentrations of neurotoxins, especially ammonia
 - Patients with grade III encephalopathy (confusion and somnolence, incoherent speech, but responsive to painful stimuli) or grade IV encephalopathy (comatose, unresponsive to noxious stimuli) should be considered for intracranial pressure monitoring with goal 20-25mmHg.
 - Can use mannitol, hyperventilation, barbiturates, and hypothermia to reduce intracranial pressure.
 - Ultimate therapy is liver transplant
- Alcoholic Hepatitis
 - o The risk of cirrhosis increases proportionally with consumption of more than 30g of alcohol per day
 - o Clinical presentation
 - Jaundice, liver failure that occurs after decades of heavy alcohol use (>100g per day)
 - Fever, ascites, proximal muscle loss, encephalopathy
 - Female sex is an independent risk factor, but more men drink to excess
 - Laboratory studies reveal AST >2x ULN (rarely >300) and lower ALT, serum bilirubin >5
 - Assessing the severity of alcoholic hepatitis

- Maddrey's discriminant function 4.6 × (patient's prothrombin time control prothrombin time, in seconds)] + serum bilirubin. >32 indicates severe and initiating corticosteroids
- The Glasgow score identify the patients at greatest risk of death without treatment
- MELD score MELD score designed to predict risk of death while waiting for liver transplant, but has been shown to predict short term mortality in alcoholic hepatitis
- Lille score used to decide whether to stop corticosteroids after 1 week
- o Therapy for Alcoholic Hepatitis
 - Abstinence from alcohol
 - Corticosteroids controversial due to divergent study findings, meta-analysis pointed to mortality benefit in patients with Maddrey's discriminant function >32 with NNT of 5
 - Prednisolone (already active form, not requiring liver activity) 40mg daily x28d
 - Pentoxifylline A phosphoesterase inhibitor, demonstrated reduced short term mortality in small randomized study with discriminant function >32.
 - Anti-TNFα Therapy Infliximab stopped early due to increase in significant severe infections and nonsignificant death. Etanercept showed a worse 6mo survival rate than placebo.
 - Liver Transplantation considered an absolute contraindication to liver transplantation. Now mostly allowed after 6mo of abstinence.

Acute Hepatic Failure EBM Quick Reference:

Prednisolone: 60 severe alcoholic hepatitis with DF >32. Increased survival with prednisolone 88% vs 45% with a NNT of 3. (NEJM 1992)

Pentoxifylline: 100 severe alcoholic hepatitis randomized to pentoxifylline or placebo. 22% absolute reduction in mortality, mostly due to decreased hepatorenal syndrome. (Gastroenterology 2000)

COPE: 70 patients with severe alcoholic hepatitis (DF >32) randomized to prednisolone + pentoxifylline or prednisolone. No difference in survival. (Dig Dis Sci 2012)

Early Liver Transplant: 25 severe alcoholic hepatitis at high risk of death placed on liver transplant with 13d after non-response to medical therapy. 6mo survival higher with early transplant. Three resumed alcohol consumption post-transplant. (NEJM 2011)

STOPAH: 1100 severe alcoholic hepatitis randomized to placebo, prednisolone, pentoxifylline, both. Prednisolone non-significant reduction in 28d mortality and no improvements at 90d, 1y. Pentoxifylline did not improve survival. (NEJM 2015)

End Stage Liver Disease – attributed to Andrew Zimmerman, Calley Levine

- 12th most common cause of death in the US, with up to 40% asymptomatic and only diagnosed when patients present with decompensation and the complications of portal hypertension
 - o Most commonly due to chronic Hepatitis B (30%), Hepatitis C (27%), EtOH (20%)
- Cirrhosis is the development of scar tissue and fibrosis that replaces normal parenchyma after repeated cellular injury. The scar tissue blocks the portal flow of blood through the organ disturbing synthetic and metabolic function.
- Hepatic Encephalopathy
 - Precipitants: non-compliance with tx, GIB, TIPS, constipation, infections (ex. SBP), narcotics or benzodiazepine use, electrolytes abnormalities (ex. hypokalemia), alkalosis, diuretic use, dehydration, HCC, worsening liver function
 - o Diagnosis: AMS, asterixis, hypo/hyperreflexia
 - Ammonia levels have poor specificity and should not be used for diagnosis or monitoring
 - o Treatment
 - Identify and treat precipitants particularly infection (UA, paracentesis, CXR, cultures)
 - Lactulose 30g/3-4x per day with goal of 3-5 BMs daily
 - In severely altered patients can give lactulose q1-2h until mental status improves
 - Rifaximin 550mg PO BID
- Spontaneous Bacterial Peritonitis
 - o Diagnosis
 - PMNS >250 in ascitic fluid
 - Patient may be asymptomatic, and all patients therefore should be considered for dx paracentesis at admission to rule out SBP.
 - Can include abdominal pain, fever/chills, jaundice, hepatic encephalopathy
 - o **Treatment**
 - Cefotaxime 2g q8h
 - IV albumin 1.5g/kg on day 1 and 1g/kg on day 3 to prevent renal dysfunction
 - All patients should be discharged on SBP prophylaxis
- Variceal Bleeding
 - o Diagnosis
 - Suspect variceal bleeding patient with known cirrhosis who presents with GI bleeding
 - Endoscopy should be performed to confirm diagnosis and treat variceal bleed
 - Patients with cirrhosis should under diagnostic endoscopy to document presence and determine risk for variceal hemorrhage
 - o **Prophylaxis**
 - Small varices with red wale signs, Child B-C, or medium varices should be on prophylactic treatment with non-selective beta-blocker
 - In medium varices, chose between non-selective beta blocker and esophageal variceal ligation.
 In large varices, EVL is preferred.
 - Titrate to decrease hepatic venous pressure gradient by 10% or HR 55-60 bpm
 - In decompensated cirrhosis may need to stop beta blocker for refractory ascites, hepatic encephalopathy, or SBP
 - o **Treatment**
 - 2 Large bore IVs/IVF, pRBC, overtransfusion can exacerbate variceal bleeding
 - Endoscopy within 12h of admission with band ligation
 - Octreotide 50mcg IV bolus followed by continuous infusion 50mcg/h (3-5d)
 - Cipro 400mg BID IV or 500mg BID PO or ceftriaxone 1g/day (5-7d) for SBP ppx
 - PPI (IV bolus and then infusion) if unclear etiology of bleeding and to prevent post intervention rebleeding

- Hepatocellular Carcinoma
 - o Diagnosis
 - Usually asymptomatic until late in the course when RUQ pain, weight loss, decompensated liver disease may be present.
 - Generally, found by MRI or triple phase CT in patients with known cirrhosis
 - Serum AFP greater than 500 in a high risk patient is diagnostic of HCC
 - o **Treatment**
 - Definitive treatment is liver transplant
 - The Milan criteria identify patients with HCC and cirrhosis who are expected to benefit from liver transplant
 - Local regional therapy with transarterial chemoembolization (TACE) or radiofrequency ablation (RFA)
 - Sorafenib, a tyrosine kinase inhibitor, has mortality benefit in advanced HCC
- Hepatorenal Syndrome
 - o Diagnosis
 - It is a diagnosis of exclusion based on the presence of a reduced GFR in the absence of other cause of renal failure in patients with chronic liver disease
 - Two types based on the rapidity of decline in kidney function
 - Type 1: 2x increase in serum creatinine to >2.5 in <2 weeks
 - Type 2: Moderate and stable reduction in GFR over a longer period of time, patients typically have diuretic-resistant ascites
 - Assess for precipitants infection, nephrotoxic drugs, hepatic failure, hypovolemia, intrinsic renal disease, and bleeding
 - Urine electrolytes: Urine Na <10, FeNa <1
 - o Treatment
 - Initial fluid challenge/albumin x48h if little response; suspect HRS
 - Once HRS suspected: combination of midodrine, octreotide, albumin
- Hepatopulmonary Syndrome
 - o Diagnosis
 - Triad of hypoxia, liver disease, intrapulmonary vascular dilatations
 - Platypnea: SOB with upright posture; improved with recumbency
 - Orthodexia: Fall in arterial blood oxygen with upright posture
 - Though to occur due to higher concentration of intrapulmonary shunts at the lung bases, sitting upright results in preferential perfusion of the shunts
 - Alveolar-arterial gradient >15 or a PaO2 <80 on room air
 - Contrast enhanced echo to assess for intrapulmonary shunt
 - o Treatment
 - Supportive care, liver transplant
 - Hepatic Hydrothorax
 - o Diagnosis
 - Pleural effusion, usually greater than 500mL, in patients with cirrhosis and without primary cardiac, pulmonary, or pleural disease (rule out with thoracentesis and CT chest)
 - The most likely cause of pleural effusions in patients with cirrhosis is the passage of a large amount of ascites from the peritoneal to the pleural cavity through diaphragmatic defects
 - Typically, the defects are smaller than 1 cm and tend to occur on the right side. This right-sided predominance likely occurs due to the close anatomical relationship of bare areas of the liver with the diaphragm as well as the fact that the left side of the diaphragm is thicker and more muscular than the right.

- o Treatment
 - Refer for liver transplant
 - Mild & severe: sodium restriction, diuretics, thoracentesis
 - If refractory, consider TIPS while awaiting transplant
- Transjugular Intrahepatic Portosystemic Shunting (TIPS)
 - o Introduction
 - Creation of a low-resistance channel between the hepatic and portal veins
 - o Indications
 - Recurrent variceal bleeding despite adequate endoscopic therapy
 - Refractory ascites and bleeding gastric fundus varices
 - Limited data for Budd-Chiari, venoocclusive, hepatic hydrothorax, portal hypertensive gastropathy
 - o Contraindications
 - Absolute: CHF, severe TR, severe pHTN, multiple hepatic cysts, sepsis, biliary obstruction
 - Relative: Obstruction of all hepatic veins, severe coagulopathy, portal vein thrombosis, thrombocytopenia <20k, moderate pHTN, hepatic encephalopathy
 - Side effects
 - Portosystemic encephalopathy (PSE): 30-35% of patients with TIPS
 - Cardiovascular complications: Increased venous return to heart, unmask/worsen cardiomyopathy
 - Complications
 Hemol
 - Hemolytic anemia from shear stress and mechanical trauma of red cells, severe hyperbilirubinemia, infection and vegetations of stent, liver decompensation

Cirrhosis EBM Quick Reference:

IV albumin: 12 SBP, cirrhosis treated with 2g ceftriaxone, 1.5g/kg of albumin day 1, 1g/kg of albumin day 3. Demonstrated significant improvement in circulatory function (increase in MAP, fall in HWR, suppression of plasma renin activity, decrease in Cr levels). (Hepatology 2004)

Restrictive v Liberal Transfusion Strategies: 900 UGIB, randomized to restrictive (>7), or liberal (>9). Restrictive had 45% RRR in mortality, shorter LOS. Also fewer rebleeding events in EVB patients. No benefit in Child-Pugh class C patients. (NEJM 2013)

Primary prophylaxis for SBP: 60 cirrhosis and low protein randomized to norfloxacin v placebo. Reduced development of SBP (7 v 61%) and hepatorenal syndrome, and improved survival (60 v 48%). (Gastro 2007)

Norfloxacin v Ceftriaxone in GI hemorrhage with cirrhosis: 110 cirrhosis and GIB randomized to oral norfloxacin or intravenous ceftriaxone. Intravenous ceftriaxone decreased bacterial infections (33 v 11%), and SBP (12 v 2%). (Gastro 2006)

Rifaximin + Lactulose: 120 overt hepatic encephalopathy randomized to lactulose ± rifaximin. Decreased mortality with dual treatment, mostly due to lower rate of sepsis. No differences in GIB, HRS. Shorter LOS in lactulose + rifaximin group. (Am J of Gastro 2013)

Sorafenib in advanced HCC: 600 randomized to Sorafenib or placebo. Stopped early due to high deaths, but median survival and time of radiologic progression were 3mos longer with Sorafenib. No complete response. Diarrhea, weight loss, head-foot reaction more common with treatment. (NEJM 2008)

Beta Blockers in Decompensated Cirrhosis: Observational study with 150 cirrhotics with refractory ascites. Propranolol reduced median survival to 10 months versus 20 months, 41% versus 19% 1 year survival. (Hepatology 2010)

Terlipressin: Cochrane review of 1600 EVB of terlipressin. Significant decrease in mortality (RR 0.66) with no increased adverse events. (Cochrane 2003)

SBP Broad Spectrum: 30 nosocomial SBP randomized to meropenem + daptomycin or ceftazidime. Broad spectrum was more effective (86.7 vs 25%) with no difference in transplant free mortality. (Hepatology 2016)

Pneumonia – attributed to Colin Iberti

- Definitions
 - o Community Acquired Pneumonia obtained from community without healthcare acquired risk factors
 - Healthcare-Associated Pneumonia risk factors:
 - IV therapy, wound care, or chemotherapy within 30d
 - Residence in nursing home or long-term care facility
 - Hospitalization in acute care hospital for 2 or more days within previous 90d
 - Attendance at hospital or HD clinic within 30d
 - Hospital-Acquired pneumonia: pneumonia that occurs 48h or more after admissions that did not appear to be incubating at time of admission.
- Bacteriology
 - o Streptococcus pneumoniae caused 95% of pneumonia pre-antibiotics
 - Pneumococcus remains the most commonly identified pathogen, but only makes up 10-15% of inpatient cases
 - Decline largely due to widespread use of pneumococcal polysaccharide vaccine in adults, pneumococcal conjugate in children, and decreased rates of cigarette smoking
 - Other CAP bacteria include: *Haemophilus influenzae, Staphylococcus aureus, Moraxella catarrhalis, pseudomonas aeruginosa*, other gram negative bacilli.
 - Atypical bacterial causes of CAP: Mycoplasma pneumoniae, Chlamydophila pneumoniae
 - Viral causes: influenza, respiratory syncytial virus, parainfluenza virus, human metapneumovirus, adenovirus, coronavirus, rhinovirus
- Diagnosis
 - Typical: new lung infiltrate to with fever, cough, sputum production, shortness of breath, leukocytosis
 - However especially elderly people will not have cough, produce sputum, or have leukocytosis and 30% are afebrile at admission. New lung infiltrates can be difficult to identify in patients with chronic lung disease, obesity, or where only portable CXR is available.
 - Make a conscientious effort to determine the organism: better for antibiotic stewardship, decreased cost, and complications such as *C. diff* associated with broad spectrum antibiotics.
 - Gram stain and culture of sputum
 - Positive in 80% of pneumococcal pneumonia with good quality sample
 - Diminishes 6-12h after initiation of antibiotics
 - o Blood cultures
 - Positive in about 20-25% of pneumococcal pneumonia
 - In Staphylococcus aureus, blood cultures are nearly always positive
 - Urinary legionella/pneumococcal testing, multiplex PCR for atypicals and respiratory viruses.
 - Legionella is positive in 74% of patients with serotype 1
- Treatment
 - o Scoring systems to predict severity of disease
 - Pneumonia Severity Index, CURB-65, IDSA/ATS Guidelines, SMART-COP
 - o Empiric treatment
 - Outpatients are generally treated empirically, generally a macrolide (IDSA/ATS guidelines)
 - Admitted patients treated empirically with beta-lactam + macrolide, or quinolone (IDSA/ATS guidelines) and produce a cure in about 90% of patients with CAP of mild/moderate severity
 - ICU admission patients treated with beta-lactam + macrolide, or quinolone (IDSA/ATS guideline)
 - Influenza season: consider oseltamivir even if 48h have elapsed, also consider ceftriaxone and vancomycin or linezolid for MRSA in setting of superinfection
 - Patients with high risk for MRSA (glucocorticoids, influenza, repeated hospitalizations) vancomycin or linezolid should be added. Maybe ceftaroline in the future.
 - Pseudomonas aeruginosa in patients with structural lung disease (COPD, bronchiectasis) upgrade to antipseduomonal beta-lactam.

- Duration of therapy
 - Meta-analysis of 7d or less v 8d or more showed no differences in outcomes
 - Prospective studies have shown that 5d of therapy are as effective as 10d and 3d as effective of 8d
 - Generally agreed upon 5-7d of treatment
 - Hematogenous Staph aureus pneumonia mandates longer 2-4w.

Pneumonia EBM Quick Reference:

PSI: A derived prediction rule that stratifies patients by mortality risk. Based on age, coexisting disease, abnormal physical findings, abnormal laboratory findings. <2% risk of death in class I, II, III validated in multiple cohorts. (NEJM 1997)

CURB-65: 1000 PNA using a six-point score for confusion, urea >19, respiratory rate >30, low systolic/diastolic BP, age >65. Score 0-2 low risk <3% mortality, score 3 or above with escalating mortality 17%, 41.5%, 57%. (Thorax 2002)

SMART-COP: 880 PNA scoring system to predict intensive respiratory or vasopressor support. Low systolic BP, multilobar findings, low albumin, high respiratory rate, tachycardia, confusion, poor oxygenation, low arterial pH. A score of >3 identified 92% who received intensive respiratory or vasopressor support. (Clinical Infectious Diseases 2008)

Single Beta-Lactam: 3300 PNA randomized to beta-lactam ± macrolide or fluoroquinolone. In 90d mortality, mono beta-lactam was non-inferior to beta-lactam + macrolide, or fluoroquinolone. (NEJM 2015)

PCV13: 85000 65 or older received PVC13.Vaccine was effective in preventing vaccine type pneumococcal CAP, but not in preventing CAP of any cause. (NEJM 2015)

Pathogens: 2400 CAP population based study with pathogen detected 38%. Viral 23%, bacteria 11%. Most common pathogens human rhinovirus, influenza virus, streptococcus pneumoniae. (NEJM 2015)

Procalcitonin: Cochrane review of 4200 PNA to examine procalcitonin in initiating/duration of antibiotics. No increase in mortality, treatment failure. Antibiotic use was significantly reduced, less antibiotic associated adverse events. (Cochrane 2012)

Steroids in CAP #1: 780 CAP randomized to 50mg prednisone x7d or placebo. No difference in mortality, shortened time to clinical stability without increased complications. Increased hyperglycemia. (Lancet 2015)

Steroids in CAP #2: 120 Severe CAP, CRP >150mg/L randomized to 0.5 mg/kg IV methylprednisolone q12h or placebo x5d. No difference in mortality, decreased treatment failure. Increased hyperglycemia. (JAMA 2015)

Steroids in CAP #3: Meta-analysis reviewing 12 studies suggested systemic corticosteroid therapy may reduce mortality 3%, mechanical ventilation 5%, LOS by 1 day. Suggestion steroids more effective in severe CAP. (Ann Intern Med 2015)

DM: Inpatient Management and DKA - attributed to David Lam, Colin Iberti

- Inpatient Management
 - o New on insulin
 - Weight x 0.4-0.6 units/kg (0.4 if CKD, 0.6 in younger, healthier patients)
 - Alternatively; can use what patient has received on sliding scale over last 24h
 - Take total daily dose and divide by two to get basal dose (glargine)
 - Divide basal dose by three to get prandial dose (lispro)
 - o Basal heavy regimen
 - Reduce the heavy basal regimen by 20% to account for PO intake differences
 - Divide new dose by two to get new basal dose (glargine)
 - Divide basal dose by three to get prandial dose (lispro)
 - Switching from 70/30 to basal/bolus
 - Add up total of 70/30 insulin taken at home and reduce by 20%
 - Divide total units by two for basal dose (glargine)
 - Divide basal dose by three to get prandial dose (lispro)
- DKA
 - o Hyperglycemia, ketosis, and metabolic acidosis
 - Causes of DKA: insulin deficiency, infection, ischemia, pregnancy
 - o Metabolic work-up: BMP, Mg, Phos, serum/urinary ketones, ABG
 - Precipitant work-up CBC, infection (CXR, BCx, UA), ischemia (EKG), B-HCG
 - Follow-up: Blood glucose hourly, chemistry q4-6h, pH q4-6h (ABG or VBG)

	Mild DKA	Moderate DKA	Severe DKA
Arterial pH	7.25-7.30	7.00-7.24	<7.00
Serum HCO3	15-18	10-15	<10
Serum Ketone	+	+	+
Anion Gap	>10	>12	>12

- Goals of DKA treatment:
 - Correct metabolic disturbance, correct hyperglycemia, treat underlying precipitant, transition the patient to a standing insulin regimen and prepare for discharge
- o Treatment of DKA
 - IV Fluids goal is to correct fluid deficit in 24h
 - 1st hour: 0.9% NSS 1-1.5L
 - Maintenance: 0.45% NS or D5 ½NS 250-500 (initiated when sugar is below 200)
 - Frequent reassessment of cardiopulmonary status and is tailored to patient
 - Target blood sugar = 150-200, target decrease rate 50-75 mg/dL/h
 - Initial insulin therapy 0.1 units/kg IV bolus followed by 0.1 units/kg/h infusion
 - 0.14 units/kg/h without the bolus
 - Check blood sugars q1h while on insulin therapy
 - Blood sugar <70: hypoglycemia protocol
 - Blood sugar 70-150:
 - If drip >3U/h, decrease to 1h
 - If <3U/h decrease to 0.5U/h
 - o Blood sugar 150-200
 - At goal! Change rate to weight x0.02
 - Blood sugar >200
 - Rate >75, decrease rate by ½
 - Rate 50-75, no change in rate
 - Rate <50, double rate

- Potassium
 - Check potassium every 4-6h
 - Severe hypokalemia on presentation should be corrected before insulin given

Serum K	K to add to IV fluids
<3.5	40 mEq/L
3.5-4.5	20 mEq/L
4.5-5.5	10 mEq/L
>5.5	No potassium

- Magnesium give 1g Magnesium sulfate when Mg <1.5
- Bicarbonate give if pH less than 6.9
 - Give 100mmol NaHCO3 in 400 mL H20 with 20 mEq KCl over 2h
 - Phosphate give 20-30 mEq/L KPO4 when PO4 <1.0
- The transition to a SQ insulin regimen
 - When?
 - Blood glucose <200, venous pH > 7.3, HCO3 > 15, anion gap <12
 - Overlap first SQ administration by 1-2 hours with IV insulin
 - Use glargine for basal
 - Can go back to home regimen
 - 0.5- U/kg/day of insulin as total dose (½ as basal, ½ as prandial)

DM EBM Quick Reference:

UKPDS 33: 3800 T2DM randomized to intensive or conventional control. Intensive group had lower A1c, mildly reduced risk for microvascular endpoints, but no difference in macrovascular endpoints with increased rates of hypoglycemia. (Lancet 1998)

UKPDS 34: 4000 T2DM randomized to metformin vs conventional control. Metformin reduced 32% for all endpoints, 42% diabetes-related death, 36% all-cause mortality. Also associated with less weight gain and fewer hypoglycemic events. (Lancet 1998)

RENAAL: 1500 T2DM related nephropathy, randomized to losartan v placebo. Losartan reduced doubling of serum creatinine, progression to ESRD. Reductions in CHF hospitalizations, no difference in mortality. (Arch Intern Med 2003)

ADVANCE: 11000 T2DM randomized to standard or intensive control (HA1c <6.5). Intensive improved microvascular outcomes (principally nephropathy), no change in mortality, macrovascular events. Increased rate of severe hypoglycemia, hospitalizations. (NEJM 2008)

ACCORD: 10000 T2DM randomized to standard or intensive (HA1c <6.0). Intensive increased mortality, no change in CV events. (NEJM 2008)

NICE-SUGAR: 6100 ICU patients randomized to intensive glucose control (81-108) or conventional (<180). Intensive increased mortality, likely due to increased moderate-severe hypoglycemia especially in patients with distributive shock. (NEJM 2009)

VADT: 1700 with suboptimal response to T2DM therapy were randomized to intensive or standard glucose control. No differences in micro or macrovascular complications. (NEJM 2009)

ACCORD BP: 4700 T2DM randomized to intensive BP therapy (<120) or standard (<140). No reduction in CV events. (NEJM 2010)

VA-NEPHRON D: 1400 T2DM and nephropathy randomized to losartan + lisinopril or placebo. Trial was stopped due to increased hyperkalemia, AKI without benefit to reduction of GFR, ESRD or death. (NEJM 2013)

EMPA-REG OUTCOME: 7000 T2DM, high CV risk randomized to empagliflozin or placebo. SGLT-2 inhibitors decrease CV and overall mortality with marked reduction in HF, no impact on stroke. (NEJM 2015)

Oncologic Emergencies - attributed to Colin Iberti

- Tumor lysis syndrome
 - Primary TLS is a set of metabolic derangements from death of malignant cells and release of intracellular contents.
 - o Secondary TLS develops a short time after beginning treatment
 - Laboratory TLS: 2 or more abnormal values of uric acid, potassium, phosphorus, calcium at presentation of 25% change from pretreatment
 - Clinical TLS: Laboratory TLS + renal dysfunction, seizures, arrhythmia, sudden death
 - o Risk and severity is influenced by many factors
 - Tumor burden, potential for rapid cell lysis, pre-existing nephropathy, LDH
 - High risk cancers: non-Hodgkin lymphomas, acute lymphocytic leukemia
 - Low and intermediate:
 - Multiple myeloma, acute myeloid, chronic lymphocytic leukemia
 - Solid tumors with high turnover rates or rapid response to cytotoxic therapy (testicular,
 - small-cell lung cancer, neuroblastoma, breast cancer). Otherwise uncommon in solids.
 - o Treatment & Prevention
 - Maintain a high urine output of 80-100cc/h, maintenance IVF x2 generally
 - Hyperkalemia: treat using the usual cocktail of drugs (avoid calcium as below)
 - Hyperphosphatemia: dietary phosphate restriction, oral binders
 - Hypocalcemia: avoid repleting calcium due to ability to increase calcium-phosphate product and crystallization in kidney tubules
 - Hyperuricemia: Most uric acid is renally excreted but with poor solubility



- Allopurinol blocks the conversion of xanthine and hypoxanthine to uric acid by inhibiting xanthine
 - oxidase, but does not decrease uric acid levels already present and takes 1-3 days to reduce levels.
- Rasburicase, recombinant urate oxidase, reduces the level of uric acid by promoting catabolism of uric acid to allantoin, which is more soluble.
 - Used in non-responders to allopurinol, uric acid >9.
 - Must test G6PD deficiency before use as hydrogen peroxide is a byproduct of rasburicase and cannot be broken down leading to hemolysis or methemoglobinemia.
- Urinary alkinization no longer recommended, uric acid solubility increased but increased precipitation of xanthine and calcium phosphate
- Dialysis if above unable to maintain metabolic homeostasis
- Neutropenic fever From IDSA guidelines
 - o Prophylactic fluoroquinolones reduce all-cause mortality and infection related mortality
 - Initial antibiotics should be directed at covering Pseudomonas, GNB because of higher morbidity, but with central venous catheters more than 50% of bacteremias are GPB
 - Single agent beta lactam: cefepime, carbapenem, zosyn
 - Vancomycin added initially in cases of soft-tissue, suspected catheter related infections, known colonization, hemodynamically unstable patients, blood culture positive for GP, mucositis, radiographic pneumonia
 - American Society of Clinical Oncology Practice Guideline
 - Only use prophylaxis if expected to remain neutropenic >7d, or other risk factor
 - Oral fluoroquinolone is preferred treatment, oral triazole for antifungal

- Various contact precautions lack required evidence for recommendation
- MASCC score see below
- Fluoroquinolone plus Augmentin recommended for initial therapy
- Malignancy Associated Hypercalcemia (MAH)
 - Mechanisms: 1) PTH-related protein induced humoral hypercalcemia (80%) 2) local osteolysis from bone metastasis 3) lymphoma associated calcitriol production (seen almost exclusively in Hodgkin, non-Hodgkin) 4) ectopic PTH secretion
 - o Symptoms: Lethargy, confusion, constipation, hypovolemia, and cardiac dysrhythmias
 - EKG: prolonged PR, widened QRS, shortened QT
 - o Restore adequate intravascular volume, consider lasix, dialysis if extremely deranged
 - Bisphosphonates: pamidronate, zoledronate act as pyrophosphate analogues that inhibit bone crystal dissolution and osteoclastic resorption (decrease 2-4d after admin)
 - o Calcitonin has negligible toxicity and rapid onset of action but potential for tachyphylaxis
- Hyperleukocytosis
 - o Differentiate between hyperleukocytosis and symptomatology of leukostasis
 - o Leukostasis is intravascular accumulation of blasts preventing normal flow
 - CNS (brain, eyes), lungs, kidneys, heart, penis can be effected
 - No randomized trial of leukopheresis in patients. Historical use of brain radiation, recent dexamethasone has also not been shown to be effective.

Table 1. WBC counts (×	10%L) as	indication for	leukapheresis in
hyperleukocytosis			

	Symptomatic	Asymptomatic
AML	> 50 000	> 100 000
ALL	> 150 000	> 300 000
CML	> 150 000	No
CLL	> 500 000	No
APL	No	No

In the presence of unequivocal retinal findings, leukapheresis may be performed for even lower WBC counts.

CML indicates chronic myeloid leukemia; and CLL, chronic lymphocytic leukemia.

Oncology EBM Quick Reference:

2010 Guideline for Neutropenic Patients: High risk patients: monotherapy with pseudomonal B-lactam, carbapenem, or zosyn. Vancomycin not recommended empirically. Fluoroquinolone prophylaxis should be given to high-risk patients with expected durations of prolonged neutropenia. Consider antifungal therapy in setting of persistent/intermittent fevers after 4-7d. (IDSA 2011)

CLOT: 770 cancer related DVT, PE or both randomized to LMWH (dalteparin) for 5-7d + Coumadin or dalteparin for 6mo. Dalteparin reduced VTE recurrence without increasing the risk of bleeding or mortality in cancer patients. (NEJM 2003)

Levofloxacin in neutropenia: 760 chemotherapy induced neutropenic patients randomized to levofloxacin daily or placebo until resolution of neutropenia. Lower rate of fevers, infections, bacteremias. Mortality and tolerability were same. (NEJM 2005)

Zoledronic Acid v Pamidronate: 280 hypercalcemia of malignancy randomized to zoledronic acid or pamidronate. Complete response rates were higher (88.4 to 69.7%) with zoledronic acid. (J of Clin Onc 2001)

MASCC: A score to be used at development of neutropenic fever using 7 factors (burden of symptoms, hypotension, COPD, no previous fungal, no dehydration, outpatient status, age <60), score <21 high risk, score >21 low risk, up to 95% sensitivity and specificity. (Support Care Cancer 2004)

Anemia - attributed to Andy Coyle

Kinetic Approach

- Decreased RBC production Low reticulocyte count
 - o Substrate deficiency folate, B12, iron
 - Bone marrow disorders aplastic, Fanconi, pure RBC aplasia, marrow infiltration, myelophtisis
 - Bone marrow suppression drugs, chemo, irradiation, malignancy
 - o Hormonal decreased EPO, hypothyroidism, hypogonadism
 - o Anemia of Chronic Disease reduced availability of iron
 - Ineffective erythropoiesis megaloblastic anemia, thalassemia, MDS, sideroblastic anemia
- Increased RBC destruction High reticulocyte count
 - Intrinsic (intracorpuscular) hereditary spherocytosis, elliptocytosis, abetalipoproteinemia, pyruvate kinase deficiency, G6PD deficiency, hemoglobinopathies, PNH
 - Extrinsic (extracorpuscular) autoimmune (warm, cold, Rh, transfusion reactions), microangiopathic hemolytic anemias (TTP, HUS, DIC), infections (malaria, babesiosis), valvular heart disease, hemodialysis, hypersplenism, sepsis
- Blood loss High reticulocyte count

Morphologic Approach

- Microcytic (MCV<80): Iron deficiency > Thalassemia > ACD
 - o Iron deficiency
 - Each 325mg tab of contains 66mg of iron, 1-2% absorbed. Vitamin C does not seem to help absorption.
 - Absorption impaired by antacids, antibiotics, fiber
 - Side effects include nausea, mild abdominal pain, constipation
 - PO iron takes weeks to result in increased Hgb levels
 - Continue iron 3-6 mos to replete stores once anemia resolved
 - Ferritin: <15 specific for deficiency, 15-100 non-specific, >100 excludes (acute phase reactant)
 - o Anemia of chronic disease
 - Patients with inflammatory anemia typically have normal or low serum iron levels, a low total iron-binding capacity and elevated serum ferritin level, and normal findings or microcytic hypochromic erythrocytes on the peripheral blood smear.
 - Inflammatory anemia typically results in mild to moderate anemia, with a hemoglobin level usually greater than 8 g/dL
 - The reticulocyte count is typically low in inflammatory anemia. Inflammatory anemia is the
 result of elevated hepcidin levels that develop in response to inflammatory cytokines,
 including interleukin-1, interleukin-6, and interferon. Hepcidin decreases iron absorption
 from the gut and the release of iron from macrophages by causing internalization and
 proteolysis of the membrane iron pore, ferroportin
 - o Thalassemias
 - Other causes make up less than 1% of microcytic anemias: lead poisoning, sideroblastic anemia, porphyrias

• Macrocytic (MCV>100)

- B12 deficiency
 - Macrocytic anemia, thrombocytopenia, mild neutropenia, and an inappropriately low reticulocyte count are the hallmark hematologic findings in vitamin B₁₂ deficiency
 - MCV > 115 almost always drug-related or folate/B12 deficiency. Can see false values that are very high in cold agglutinin disease
 - Found in animal products; large stores so deficiency from decreased intake develops over many years
 - Deficiency is almost always from malabsorption (antibody mediated, age-related changes and achlorhydria, celiac disease, pancreatic insufficiency, or bacterial overgrowth).



- Absolute Reticulocyte Count: Corrects for degree of anemia = % reticulocytes x (Patient's Hct / 45)
- Reticulocyte Index: Corrects for degree of anemia AND for reticulocyte maturation time: > 2% indicates adequate response, < 2% indicates hypoproliferation



B12 deficiency: hypersegmented neutrophils, macrocytosis

- Metformin is weakly associated with B12 deficiency.
- B12 level < 200 is diagnostic and > 400 excludes diagnosis. 200-400 is borderline and serum methylmalonic acid and homocysteine can help:
 - See elevated methylmalonic acid and homocysteine in B12 deficiency
 - See elevated homocysteine alone in folate deficiency
- Antibody Testing: Anti-parietal cell Abs in 90% with pernicious anemia (but also in 5% of normal population). Anti-IF Abs in 70%.
- Treatment: Oral = Parenteral for most. 1000-2000ug/day PO or 1000ug/month IM.
- Cochrane Review: 2000mcg oral daily equivalent to IM
- Folate deficiency
 - Found in green leafy vegetables and some fruits; grains in US are fortified
 - Limited stores in body, deficiency can develop over weeks to months
 - Can be seen as a consequence of hemolytic anemia or desquamating skin disorders (psoriasis)
 - Measuring Folate levels has limited utility even one folate-rich meal can artificially elevate blood levels. Serum homocysteine is > 90% sensitive; however, most effective means of diagnosis is therapeutic trial
- Other causes include: Drugs (Zidovudine, hydroxyurea), reticulocytosis, MDS, acute leukemia, 0 large granular leukocyte leukemia, EtOH, liver disease, hypothyroidism
- Normocytic (MCV 80-100)
 - Acute blood loss, early iron deficiency
 - 0 Anemia of chronic disease
 - 0 Bone marrow suppression, invasion, aplasia
 - Aplastic crisis: generally, in people with underlying chronic hemolytic anemia, infected by parvovirus B19. Confirm with IgM antibodies or PCR.
 - 0 Hemolysis
 - Intracorpuscular vs. extracorpuscular, hereditary vs. acquired, or intravascular vs. extravascular.
 - Intracorpuscular are nearly all hereditary (except PNH, acquired alpha thalassemia)
 - Defects in membrane production (spherocytosis, elliptocytosis)
 - Defects in hemoglobin production (thalassemia, sickle cell)
 - Defects in red cell metabolism (G6PD deficiency, pyruvate kinase deficiency)
 - Acquired hemolytic episode after exposure to oxidant drug like TMP-SMX, bite cells 0 on peripheral smear
 - Extracorpuscular are acquired
 - Cold agglutinin disease
 - Infections including malaria, babesiosis, clostridium sepsis (massive intravascular hemolysis)
 - Autoimmune hemolytic anemia
 - Warm autoimmune hemolytic anemia: insidious symptoms of anemia, jaundice, splenomegaly, spherocytes and direct Coombs (antiglobin) positive for Igg, negative/weakly positive for complement
 - Microangiopathic hemolytic anemias (DIC, HUS, TTP)
 - Mechanical trauma (valvular disease, LVADs)
 - PNH, Wilson's disease, hypersplenism, lead poisoning, transfusion reactions
 - Other causes include: Early iron deficiency, CKD, hypothyroidism, hypopituitarism, 0 hypogonadism, factitious bleeding, surgical blood loss, trauma







Bite cells and Heinz bodies traditional of G6PD deficience

CKD - attributed to Andy Coyle

- Electrolytes in CKD
 - o Hyperkalemia
 - Antagonizing membrane effects of K: calcium gluconate, works in minutes, short lived (30-60m)
 - Driving K intracellularly: Albuterol (peak at 90m) Insulin + glucose (10m, peak at 30-60m), sodium bicarbonate
 - Removing excess K (kayexalate, furosemide), new: sodium zirconium cyclosilicate, patiromer
 - o Metabolic Acidosis
 - Chronic metabolic acidosis increased bone resorption and osteopenia, increased catabolism, worsening of secondary hyperparathyroidism, increased resistance to insulin and growth hormone, systemic inflammation
 - Observational studies have demonstrated worsening metabolic acidosis associated with higher mortality and more rapid progression of CKD to ESRD
 - Hesitancy to treat with NAHCO3 due to concerns that increased Na load -> HTN and fluid retention
 - NaHCO3 therapy associated with increased albumin, lean body mass. Slows CKD progression, goal HCO3 >23.
 - Erythropoiesis-Stimulating Agents (ESAs)
 - 90% of HD patients are on ESAs as US Renal Data System database showed improved survival in those with Hgb > 11
 - KDIGO: Consider initiation at Hgb <10, goal of 10.5-11.5, never target >13
 - Multiple studies as detailed below: trend toward increased mortality in normal hematocrit group, increased risk of graft/fistula thrombosis, significantly increased risk of hospitalization, no difference in MI or stroke
 - Iron Deficiency in CKD
 - o Patients with increased risk of GI bleeding (mainly via AVMs)
 - Absolute iron deficiency present if transferrin sat (iron/TIBC x100) <20% and ferritin <100 in pre-HD and <200 in HD
 - Functional iron deficiency present if ferritin >200 but transferrin sat <20%
 - Role for intravenous supplementation of iron in HD dependent patients.
 - Mineral and Bone Disease
 - Pathogenesis: Interrelated increases in phosphorus and PTH with decreased in vitamin D and calcium levels.
 - Decreased GFR -> decreased excretion of PO4 and decreased production of active vitamin D
 - Decreased vitamin D and increased PO4 -> decreased calcium
 - Decreased calcium, decreased vitamin D -> increased PTH
 - o Clinical forms:
 - Osteopenia/osteoporosis
 - Osteitis Fibrosa Cystica: bone pain, increased risk for fractures
 - Rapid osteoclastic activation and peritrabecular fibrosis -> Brown "tumors"
 - Secondary to increased PTH
 - Adynamic Bone Disease: low bone turnover, osteoid (collagen) accumulation. Secondary to low PTH
 - o Phosphate Binders: Goal 3.5-5.5 in HD
 - Calcium Salts (calcium acetate): tend to cause hypercalcemia and suppress PTH, so avoid in hypercalcemic patients or those with PTH <150
 - Ergocalciferol (D2), Cholecalciferol (D3)
 - Will increase vitamin D levels, but no evidence of improved calcium or phosphate balance in HD patients
 - No evidence they improve clinical outcomes in HD patients

• Meds in HD patients

- Calcitriol (vitamin D hormonally active form)
 - Suppresses PTH levels, increase phosphorus levels so use with phosphate binders
 - Use when PTH >300, serum calcium <9.5, serum phos < 5.5
- Paracalcitol (Zemplar = 19-nor1a-25-OH vitamin D)
 - Suppress PTH levels, less effect on Ca/PO4
 - Clinical trials have not demonstrated clinically relevant difference.
- Calcimimetics: Increase sensitivity of calcium sensing receptor in parathyroid
 - Cinacalcet; only approved in HD patients
 - Decreases PTH without increase in calcium/PO4
 - Side effects: hypocalcemia, GI distress
- Step 1) Fix calcium, phosphorus 2) Assess vitamin D status 3) Assess PTH level
 - Non-HD Patient
 - Step 1: Manage Ca / PO4: Ca goal normal, PO4 2.7-4.6. Can attempt dietary restriction first.
 - If Ca < 9.5, start calcium salts
 - If Ca > 9.5, start sevelamer
 - Step 2: Assess Vitamin D status
 - $\circ~$ If < 25-OH vitamin D < 30, start vitamin D2. Stop if calcium > 10.2
 - Step 3: Assess PTH status once vitamin D repleted. If elevated, consider transition to vitamin D analog such as calcitriol. **DON'T GIVE IF PHOSPHATE NOT CONTROLLED**. Can consider off-label cinacalcet use if PTH refractory to vitamin D treatment
- ACEI have been proven to reduce progression as compared to alternate anti-hypertensives
 - Significant benefits in preventing progression of renal disease compared to placebo and CCB
 - o ARB/ACEi in combination increase progression to ESRD without reducing mortality
 - The highest dose groups had the greatest reduction in proteinuria, suggesting dose effect.
- Numerous trials have shown that intensive diabetic control (i.e. HBa1c 7% or lower) reduces risk of microvascular outcomes including nephropathy
 - o Data on macrovascular outcomes less clear
- Dialysis Indications
 - Acute: AEIOU (acidosis, electrolytes, ingestion, overload, uremia)
 - Chronic Kidney Disease:
 - Absolute: Uremic pericarditis or pleuritis, uremic encephalopathy
 - Common: declining nutritional status, difficult to control fluid overload, fatigue/malaise, mild cognitive impairment, refractory acidosis/hyperkalemia/hyperphosphatemia
 - Old paradigm: 30-20-10 rule (initiate discussions about HD at GFR 30, HD access at GFR 20, initiate HD at GFR 10)
 - o General consensus: Refer when GFR hits 30, if not before.
 - Late referral associated with increased need for urgent HD, worsened acidosis, more significant anemia, and worsened electrolyte abnormalities (hypocalcemia, hyperphosphatemia)
 - Later referral associated with greater likelihood of prolonged hospitalizations and associated with increased cost
 - Late referral makes first HD less likely to occur through AV fistulas
 - Late referral may be associated with higher mortality, 2007 meta-analysis; RR 1.99
 - VA Study (Arch Intern Med 2008): Retrospective Cohort of patients with CKD stage III or IV
 - More visits to a nephrologist were associated with lower mortality. The more visits, the more benefit.

CKD EBM Quick Reference:

NaHCO3 Therapy: 130 CKD with HCO3 16-20 randomized to supplementation or standard care, goal HCO3 >23. Rapid progression significantly decreased (9 v 45%), ESRD decreased (6.5 v 33%). Improved nutritional status. (Am Soc Nephrology 2009)

CHOIR: 1400 CKD randomized to epoetin alfa to Hgb 13.5 or 11.3. High goal increased mortality, MI, stroke, hospitalization. (NEJM 2006)

CREATE: 60 CKD randomized to epoetin beta to Hgb 13.5 or 11.5. Trend to increased primary CV events high goal group. (NEJM 2006)

TREAT: 4000 CKD, T2DM randomized to darbepoetin alfa to Hgb 13 or 9. Increased rate of stroke (HR 1.92) in high goal group. No difference in death, nonfatal MI, HF. (NEJM 2009)

DRIVE: 130 CKD randomized IV ferric gluconate 125mg x8 or placebo. Significant increased Hgb in iron group. Transferrin sat >30%, ferritin >500 did not have meaningful response to iron. (Am Soc Nephrology 2007)

EVOLVE: 3800 HD patients randomized to cinacalcet. No difference in death, CV events, kidney transplant or parathyroidectomy. (NEJM 2012)

REIN-1 -> **REIN-2**: REIN-1 reduced progression of CKD with ACEi. Benefit seen in those with >3g/day of proteinuria, smaller benefit in those with 1.0-2.9g/day, no benefit seen in those with < 1g/day. REIN-2 no significant difference in ramapril + CCB vs. Ramapril alone. (Lancet 1998, 2005)

Benazepril in CKD: 420 randomized based on serum creatinine, group 1: Cr 1.5-3.0; group 2: Cr 3.1-5.0. Benazepril demonstrated a 43% reduction in doubling creatinine, ESRD, death, 52% reduction in proteinuria, 23% reduction in rate of GFR decline. (NEJM 2006)

COOPERATE -> ONTARGET: COOPERATE demonstrated significant reduction in progression of CKD in patients treated with ACEi + ARB; later redacted for data fabrication. ONTARGET 24000 randomized to ARB/ACE/Both demonstrated equivalence between ACE and ARB. The combination was associated with more adverse events including hypotension, renal dysfunction. (Lancet 2003), (NEJM 2008)

RENAAL: 1500 CKD, T2DM randomized to losartan or placebo. Losartan demonstrated 28% RR of ESRD, 25% RR of a doubling of creatinine, 35% decrease in the risk of elevated serum creatinine. (NEJM 2001)

IDNT: 1700 CKD, HTN, T2DM randomized to irbesartan, amlodipine, placebo. Irbesartan was associated with a 23% reduction of doubling of creatinine, ESRD, death compared to amlodipine/placebo. (NEJM 2001)

SMART: Compared candesartan at various doses, including supra-maximal. Patients in the highest dose group had the greatest reduction in proteinuria at 30w compared to those who received the lowest dose. (Am Soc Nephrology 2009)

IDEAL: 800 CKD randomized to start dialysis early (GFR 10-14) v late (GFR 5-7). No differences between the two groups. (NEJM 2010)

EARLY vs. LATE REFERRAL: 2011 meta-analysis of 27 longitudinal cohort studies; comparative hospitalizations and mortality higher in patients referred later. Better uptake of peritoneal dialysis, earlier AV fistula placement and utilization at first dialysis. (Am J Med 2011)

Acid-Base Disorders – attributed to Samira Farouk

- Acid-Base in 5 Steps
 - pH > Labs > Anion gap > Compensation > Other processes
- pH
 - The normal range for arterial blood pH is 7.35 7.45.
 - Looking at the pH will help identify the primary acid/base disturbance
 - (< 7.35 = acidemia, >7.45 = alkalemia).
 - Several studies have shown that venous blood pH can estimate arterial pH by adding approximately 0.04 to the venous pH (normal range for venous pH is approximately 7.31 7.41.
 - Note: this estimation does not hold if the patient is in shock.
- Labs
 - pCO2 & HCO3 Looking at both the pCO2 and HCO3 will identify the primary process that led to the pH change.
 - Arterial pCO2 can be estimated by subtracting 4 mm Hg from the venous pCO2
 - For an acidemia: If the pCO2 is elevated pCO2 (>45), the primary process is a respiratory acidosis. If the HCO3 is low (<22), the primary process is a metabolic acidosis.
 - For an alkalemia: If the pCO2 is decreased pCO2 (<35), the primary process is a respiratory alkalosis. If the HCO3 is high (>32), the primary process is a metabolic alkalosis.
- Anion gap
 - Use the bicarbonate from the chemistry panel to calculate the AG, or unmeasured cations
 - (Na Cl HCO3).
 - To identify an elevated anion gap, estimate the patient's expected anion gap by using the serum albumin.
 - Lower albumin levels lead to a lower normal anion gap, as albumin is an anion
 - Albumin x 2.5 = patient's expected AG
- Compensation
 - Once the primary process has been identified, use the formulas below to see if the patient is compensating.
 - o If compensation is inadequate, then there may be another process going on
 - The body will never overcompensate for a primary process, and even with compensation the pH may not return to normal.
 - Respiratory compensation is almost immediate while metabolic (renal) compensation may take several days.
 - o Metabolic acidosis
 - Compensated pCO2 (within 2 mm Hg) = 1.5 (HCO3) + 8 (Winter's formula)
 - Metabolic alkalosis
 - For every 1 mEq/L increase in HCO3, pCO2 should increase by 0.7 mm Hg
 - o Respiratory acidosis
 - Acute for every 10 mmHg increase in the pCO2, there should be a 1 mEq/L increase in HCO3
 - Chronic for every 10 mmHg increase in the pCO2, there should be a 4 mEq/L increase HCO3
 - Respiratory alkalosis
 - Acute for every 10 mmHg decrease in the pCO2, there should be a 2 mEq/L decrease HCO3
 - Chronic for every 10 mmHg decrease in the pCO2, there should be a 4 mEq/L decrease HCO3
- Other processes
 - Can have up to 3 acid-base disorders an anion gap metabolic acidosis may coexist with a metabolic alkalosis OR non-gap metabolic acidosis AND 1 respiratory disorder.
 - To uncover this process, use the delta/delta which will tell you if the change in the HCO3 is fully accounted for by the change in the anion gap.
 - If it isn't, then another process is driving the HCO3 up (metabolic alkalosis) or down (metabolic acidosis).

- Delta/delta = (Anion gap expected anion gap) / (Pt's HCO3 Normal HCO3)
 - If D/D > 2, then there is a concomitant non-gap metabolic acidosis
 - If D/D < 1, then there is a concomitant metabolic alkalosis.
- Side note: check a "urine anion gap" (Na + K Cl) if you suspect a non-gap metabolic acidosis to differentiate between GI and renal losses of HCO3. If the number is negative (think neGUTive), HCO3 is being lost from the GI tract (diarrhea/fistula). If it's positive, HCO3 is being lost renally.



Electrolyte Balance - attributed to Andy Coyle

- Hypernatremia
 - Unreplaced Water Loss: Loss of fluid with a Na + K concentration < plasma
 - Skin/insensible losses
 - GI losses: vomiting, osmotic diarrheas
 - Urinary losses
 - Central or Nephrogenic Diabetes Insipidus: Decreased ADH release or resistance to its effect
 - Osmotic Diuresis: Glucose, mannitol, urea
 - Sodium Overload

- Salt poisoning
 - latrogenic salt loading
 - Uncontrolled DM in which osmotic diuresis from glycosuria is replaced with isotonic
 - Recovery from severe azotemia in which urea diuresis is replaced with isotonic
 - NG tube suction
 - Edematous, critically ill patients s/p IVF, then given Lasix
- Evaluation often clinically diagnosed
 - Check Uosm
 - <300: Central or Nephrogenic DI
 - 300-600: DI or osmotic diuresis. Can confirm by checking 24h solutes.
 - >600: Unreplaced GI, renal, or skin losses (or rarely sodium overload). Next check urine sodium:
 - UNa < 25: Water loss and volume depletion, FeNa <<1%
 - UNa elevated: suggests salt overload
- o Treatment
 - Free Water Deficit = Current TBW x [(Serum Na / 140) 1]
 - 60% of body weight in younger, 40-50% in older adults
 - Goal is to correct at rate of 0.5 mEq/L per hour
- Hyponatremia
 - Hypovolemic Gastrointestinal losses, renal losses
 - o Euvolemic Glucocorticoid deficiency, hypothyroidism, pain, psychiatric disorders, drugs, SIADH
 - Hypervolemic Nephrotic syndrome, CHF, cirrhosis, renal failure
- Evaluation of hyponatremia
 - o Plasma osmolarity
 - Low: Majority of patients with hypoosmolar hyponatremia
 - Normal: Pseudohyponatremia (hyperglycemia, paraproteinemia, hyperlipidemia), severe renal failure, ingestion of excess alcohol, post TURB/TURP
 - High: Rare, most commonly from extra solute that cannot enter cells (ie: mannitol)
 - o Assess volume status with exam, urine sodium
 - Exam findings are neither sensitive nor specific for differentiating between euvolemic, hypovolemic.
 - Spot UNa of <30 is 80% sensitive, 100% specific for saline responsiveness
 - Serum uric acid <4mg/dL 75% sensitive, 89% specific for SIADH
 - o Urine osmolarity
 - Hyponatremia should suppress ADH secretion excrete urine with Uosm <100
 - <100 could also primary polydipsia, beer potomania, tea & toast</p>
- Treatment of hyponatremia
 - Severe symptomatic
 - Intravenous 3% until improvement of symptoms, then correction at 6-8 mEq/L in 24h
 - o Asymptomatic, mildly symptomatic

- Hypovolemic: NS to restore intravascular volume, ½ NS if worried about rapid correction
- Euvolemic: SIADH (high Uosm >100, high UNa >30), fluid restriction
- Hypervolemic: Fluid restriction, loop diuretics, ACEi



• Hyperkalemia

Therapy	Strategy	Dosing	Duration/Peak Effect
Calcium Gluconate	Antagonize membrane effects	1g IV given over 2-3m	30-60m
Insulin + Glucose	Intracellular shift	D50, 10U regular insulin	Peak at 1h, effect 4-6h
Beta-2 agonists	Intracellular shift	Albuterol 10mg neb	Peak effect at 90m, effect 4h
Sodium bicarbonate	?Intracellular shift?		
Kayexalate	Remove excess potassium	15-30g q4-6h	Hours to days
Furosemide	Remove excess potassium	40-160mg IVP	Hours to days
Zirconium cyclosilicate (ZS-9)	Remove excess potassium	*pending FDA approval	Works within 4h, daily dosing
Patiromer	Remove excess potassium	*pending FDA approval	Daily dosing

- Hypokalemia
 - Decreased potassium intake rare
 - o Increased entry into cells
 - Increased insulin, beta-adrenergic activity, elevated extracellular pH, hypokalemic periodic paralysis, hypothermia
 - o Increased blood cell production: B12/folate repletion, G-CSF
 - o Increased GI loss
 - Upper GI Loss: Low K+ content in upper sections, so mostly caused by alkalosis
 - Lower GI Loss: High K+, especially seen in Ogilvie's syndrome (acute colonic pseudo obstruction with secretory diarrhea characterized by high potassium content)
 - o Increased sweat loss
 - o Increased urinary loss
 - Increased mineralocorticoid activity
 - Bartter's syndrome (similar to loop diuretics), Gitelman's syndrome (like thiazide diuretics), Liddle's syndrome
 - Other: Diuretics, RTAs, amphotericin, hypomagnesemia

Electrolyte EBM Quick Reference:

SALT 1 & 2: 450 hyponatremic randomized to tolvaptan or placebo. Sodium increased in the treatment group. Concerns remain with hepatotoxicity, lack of mortality benefit, cost. (NEJM 2006)

HARMONIZE, Patiromir: Sodium Zirconium Cyclosilicate: Reduced serum potassium to normal within 48h, at 28d compared to placebo lowered potassium levels and had higher proportion of normal potassium levels. Patiromer: 78% reached normal potassium level, only 15% of people in patiromer group recurred to hyperkalemia, constipation in 11%. (JAMA 2014)

Nephrolithiasis - attributed to Andy Coyle

- Pathogenesis: Stone formation occurs when normally soluble material (like calcium, oxalate) supersaturates
- Risk factors: Dehydration, male gender, age (30s-40s), family history, comorbid conditions
 - o Urine specific risk factors: Hypercalciuria, hyperoxaluria, cystinuria, hypocitraturia, UTIs
- Differential Diagnosis: Nephrolithiasis, renal cell carcinoma, pyelonephritis, diverticulitis, appendicitis, aortic aneurysm, dissection, zoster. Female: dysmenorrhea, ovarian cyst rupture/torsion, ectopic pregnancy)
- Hematuria in urolithiasis
 - o Gross, microscopic hematuria in majority of patients (J. Urology 2003: 95% on day 1, 65% on day 3)
- Diagnosis
 - KUB: poor sensitivity and specificity; can detect large radiopaque stones (calcium, struvite, cysteine), will miss radiolucent (uric acid) stones and may also miss small stones overlying bony structures
 - o Ultrasound: Appropriate for pregnant woman, and may be just as good as CT (NEJM 2014)
 - o Intravenous pyelogram: contrast injected with serial x-rays, outdated.
 - CT without contrast: sensitivity 95%, specificity 98-100%
 - Exception: HIV protease inhibitor (atazanavir) related stones may need intravenous contrast
- Management
 - Small stones and passage: 98% of stones <5mm pass spontaneously
 - o Indications for urologic consultation
 - Urosepsis, acute renal failure, anuria, unremitting pain/nausea/vomiting, stones unlikely to pass spontaneously (>10mm for sure, recommended consideration >5mm)
 - Large stones unlikely to pass: consider shock-wave lithotripsy, ureteroscopy, percutaneous nephrostolithtomy (>20mm stones)
 - o IV hydration: May help, but no studies demonstrating improvement with high volumes/rates
 - o Pain control
 - NSAIDS: no concerns for abuse v nephrotoxicity and slow onset
 - Opioids: rapid onset v does not address underlying pain mechanism, abuse potential
 - Smooth muscle relaxers: Alpha blocker preferred over CCB, although new data questions utility
- SmoStone Types
 - Calcium oxalate (75-80%), calcium phosphate (15% in alkaline urine), uric acid (5%), struvite stones
 - Is further work-up indicated?
 - Step 1: Determine risk (large stone, severe symptoms, family history)
 - Step 2: Determine if management would change with stone information
 - BMP, serum calcium, PTH, 24h urine, UA (>7 suggests calcium phosphate, struvite)
- Lifestyle modifications
 - Increase fluid intake, low sodium diet, normal calcium diet, low oxalate diet
 - Medical Therapy to prevent recurrent calcium stone formation: Moderate evidence for thiazide diuretics, potassium citrate

Nephrolithiasis EBM Quick Reference:

US vs CT: 2700 randomized to POC US, radiographic US, or CT. Demonstrated no difference in serious adverse events, return emergency department visits, hospitalizations, or diagnostic accuracy. (NEJM 2014)

Small Stones: A meta-analysis of 300 studies found that 98% of smaller stones (<5 mm) passed spontaneously. Distal ureteral stones passed more frequently than proximal ureteral stones. (AUA 1997)

IVF: 50 patients randomized to bolus vs minimal hydration; no change in pain scores, medication needed, passage rate/time (Endourology 2006)

Cochrane Review vs SUSPEND: Review of 32 studies showing alpha blockers improved stone expulsion rate, speed, reduced analgesics, reduced hospitalization. SUSPEND randomized 1100 patients to placebo/tamsulosin/nifedipine with no difference. (Cochrane 2014), (Lancet 2015)

Stroke – attributed to Colin Iberti

- Acute ischemic stroke
 - o Second after ischemic heart disease in lost disability-adjusted life-years and death worldwide
 - o 80% of strokes are caused by focal cerebral ischemia and 20% are caused by hemorrhages
 - o 30d mortality rates for stroke in Western societies range from 10-17%
- Initial assessment
 - Deficits include: dysphagia, dysarthria, hemianopia, weakness, ataxia, sensory loss, neglect. Generally unilateral with intact or only slightly impaired consciousness.
 - Generally straightforward diagnosis, but if unusual features consider alternative diagnoses including: migraine, postictal paresis, hypoglycemia, conversion disorder, subdural hematoma, brain tumors
 - Ptosis, miosis contralateral to deficit (carotid artery dissection)
 - Fever and cardiac murmur (infective endocarditis)
 - Headache and elevated ESR (giant cell arteritis)
 - Lab testing: glucose, CBC, coagulation, ECG
 - Non-contrast CT more widely available, faster, less susceptible to motion artifacts, less expensive
 - Both CT and MIR have high sensitivity for intracranial hemorrhage, MIR has much high sensitivity for ischemic changes, particularly in posterior fossa and the first hours post stroke
 - CT angiography or MRA may be useful to identify the site of arterial occlusion for advanced procedure
 - TTE for possible cardiac sources of embolism other than atrial fibrillation
- Intravenous thrombolysis
 - Must be initiated within 3h of last known normal, improves rate of favorable neurologic outcome at the expense of risk of intracranial hemorrhage
 - Contraindications: >3h before start, hemorrhage on CT/MRI, head trauma or stroke within 3mos, MI within 3mos, GI/GU hemorrhage within 21d, major surgery in previous 14d, history of intracranial hemorrhage, SBP >185 or DBP >110, active bleeding, oral anticoagulants or INR >1.7, heparin in previous 48h, platelet count <100k, blood glucose <50, seizures
- Post-stroke management
 - Patients who have had a previous ischemic stroke or TIA are at high risk for recurrent stroke, MI, or death from vascular causes
 - Aggressive risk-factor management and lifestyle advice are essential for all patients.
 - 10 risk factors accounted for 90% of stroke risk: hypertension, current smoking, a high waist-to-hip ratio, a high dietary risk score, lack of regular physical activity, diabetes mellitus, excess alcohol consumption, psychosocial stress or depression, cardiac causes (e.g., previous myocardial infarction or atrial fibrillation), and a high ratio of apolipoprotein B to apolipoprotein A1.
- Blood pressure lowering
 - Most important modifiable risk factor in both primary and secondary prevention
 - Data is lacking regarding goals, but benefits linked to reductions of 10/5 mmHg.
 - Be mindful that there are risks to lowered BP in the setting of acute stroke
 - Benefits of blood pressure lowering do not seem to depend on particular class of antihypertensive drugs although this is still controversial
- Cholesterol lowering with statins
 - Cholesterol lowering with statin drugs, effective in primary stroke prevention is also effective in secondary prevention (up to 20-25% risk reduction)
- Antiplatelet therapy
 - Unless anticoagulation is indicated, patients should receive antiplatelet therapy for secondary stroke prevention (up to 13% risk reduction with ASA)
 - Clopidogrel & ASA + Pyridamole shown to be superior to aspirin but with only small absolute benefits
 - Excess hemorrhage in patients treated with dual antiplatelet therapy
 - Short term combination clopidogrel and ASA after TIA/stroke
- Carotid endarterectomy and carotid artery stenting

- Endarterectomy is indicated for the treatment of patients with a history of TIA or nondisabling stroke who have high grade (70-99%) carotid stenosis with risk reduction in stroke over next 18mos
- o Early intervention, within 2 weeks is recommended to enhance the benefits of the surgery
- Stenting has limited long-term data regarding outcomes, but generally the benefit risk profile favors endarterectomy in patients >70y, whereas stenting may be equivalent in <70yo.
- Atrial fibrillation and anticoagulation
 - Atrial fibrillation causes at least 15% of ischemic stroke, perhaps more found now with loop recorders
 - Warfarin has been mainstay of therapy with risk reduction from 40-60% of recurrent stoke
 - More effective than aspirin, or combination of aspirin + clopidogrel

Stroke EBM Quick Reference:

NINDS: 290 strokes randomized to tPA or placebo. No benefit at 24h, but significant NIHSS benefit at 3mos if given within 3h of ischemic stroke onset. Did not confer survival rate and had elevated intracerebral hemorrhage rates. (NEJM 1995)

MR RESCUE: 110 acute strokes randomized to mechanical embolectomy or standard care. Ischemic penumbral pattern did not predict successful embolectomy, embolectomy was not superior to standard of care in mortality, hemorrhage, Rankin scale. (NEJM 2013)

MR CLEAN: 500 large proximal anterior strokes randomized to intra-arterial therapy or standard of care. Improved rates of functional independence without increase in ICH or mortality. (NEJM 2015)

SBS3-BP: 3000 recent lacunar stroke randomized to SBP 130-149 or <130. Lower target did not reduce induced stroke, CV events, but non-significant trend towards mortality benefit. (Lancet 2013)

PROGRESS: 600 stroke or TIA randomized to ACEi or placebo. Relative risk reduction 28% of stroke, and other major vascular events. (Lancet 2001)

SCAST: 2,000 strokes, randomized to ARB or placebo. No difference in CV events, with increased risk of hypotension, renal failure. (Lancet 2011)

SPARCL: 4000 previous stroke or TIA, LDL 100-190 randomized to 80mg atorvastatin or placebo. Atorvastatin absolute reduction of risk of 2.2% stroke, 3.5% CV events. Mortality and adverse events were similar in both groups. (NEJM 2006)

ATTC: Meta-analysis of ASA v placebo 135000 for primary prohylaxis. Aspirin had a relative risk reduction of 13.0 with a NNT of 100 when looking at an end point of nonfatal stroke, nonfatal MI, death from vascular causes (BMJ 2002)

CAPRIE: 19000 prior stroke or MI randomized to clopidogrel or ASA. Relative risk reduction of 8.7% in favor of clopidogrel. (Lancet 1996)

ESPS2: 6600 previous stroke or TIA randomized to ASA, dipyridamole, or ASA + dipyridamole with stroke. Stroke risk reduced by 18% for ASA alone, 16% dipyridamole, and 37% with combination therapy. No mortality effect. ASA increased GI bleeding. (J of Neuro Sci 1996)

CHANCE: 5000 24h after minor ischemic stroke or TIA to combination therapy with clopidogrel and ASA for 90d. Combination was superior to reducing the risk of stroke in the first 90d and does not increase the risk of hemorrhage. (NEJM 2013)

CHARISMA: 15000 CV disease or multiple risk factors randomized to ASA ± clopidrogrel. Clopidogrel + ASA did not significantly reduce rate of primary CV endpoint. (NEJM 2006)

MATCH: 7600 with recent ischemic stroke or TIA on clopidogrel randomized to ASA or placebo. Absolute risk reduction of ASA 1% but with 1.3% increase in life-threatening bleeds. (Lancet 2004)

NASCET: 11000 moderate (50-69%) carotid stenosis and TIA or nondisabling stroke on ipsilateral side were randomized to CEA or medical care. Reduced risk of ipsilateral stroke with a NNT of 15 patients. Severe stenosis patients >70% had durable benefit from CEA. (NEJM 1998)

CREST: 2500 randomly assigned to CEA or stenting. No significant difference in the CV endpoint between the stenting and endarterectomy groups. Higher risk of stroke during the periprocedural period with stenting and higher rate of MI with CEA. (NEJM 2010)

CSTC: Meta-analysis of 4700 randomized to CEA or carotid artery stenting. CEA was clearly superior to stenting in patients 70y and older, completely attributable to the increased periprocedural stroke risk. (Lancet 2016)

EAFT: 1000 Afib, past TIA, minor ischemic stroke randomized to warfarin, ASA, or placebo. 66% relative risk reduction with warfarin. 2.8% risk of major bleeding on warfarin. (Lancet 1993)

CLOSURE I: 900 randomized to closure or medical therapy alone after cryptogenic stroke or TIA with PFO. Closure did not affect recurrent stroke/TIA, mortality, death. (NEJM 2012)

RESPECT: 980 ryptogenic stroke randomized to medical therapy or closure of patent foramen ovale. PFO closure did not reduce nonfatal ischemic stroke, stroke mortality, or all cause mortality when compared to medical therapy. (NEJM 2013)

CRYSTAL AF: 440 post ischemic stroke randomized to insertable cardiac monitor or conventional follow-up. ICM was superior in detecting Afib at 12mos (12.4 v 2.0%). (NEJM 2014)

EMBRACE: 572 post ischemic stroke/TIA randomized to 30d event triggered recorder. Recorder significantly improved detection and double rate of anticoagulation treatment. (NEJM 2014)