

“The Nifty Fifty” - Gold Service Reading List

Last updated August 23, 2014

Pulmonary/Critical Care

COPD

1. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease.

Anthonisen NR, Manfreda J, Warren CPW, Hershfield ES, Harding KM, Nelson NA. *Ann Intern Med.* 1987;106:196-204. PMID: 3492164

Objective: A randomized controlled trial compared a 10-day course of antibiotics (trimethoprim-sulfamethoxazole, doxycycline, or amoxicillin) to placebo for treatment of COPD exacerbation in the outpatient setting. The outcomes of interest were resolution of symptoms and peak flow.

Conclusions: Patients treated with antibiotics were more likely to have resolution of symptoms by day 21 after onset of a COPD exacerbation (68% vs. 55%) and less likely to have worsening symptoms (10% vs. 19%). The largest benefit was observed for patients with the cardinal symptoms of: 1) increased dyspnea; 2) increased sputum production; and 3) and sputum purulence. Patients treated with antibiotics also had shorter duration of exacerbation (14.1 days vs. 15.5 days) and more rapid increase in peak flow.

Medical care has changed substantially since 1987 including changes in hospital length of stay, antibiotic resistance, and new COPD treatments. Nearly three decades later, however, risk of treatment failure (defined as initiation of mechanical ventilation after hospital day 2, in-hospital mortality, or readmission for COPD within 30 days of discharge) remains lower with at least 2 days of antibiotic treatment than without based on a large retrospective cohort study.¹

2. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group.

Niewoehner DE, Erbland ML, Deupree RH, Collins D, Gross NJ, Light RW, Anderson P, Morgan NA.

N Engl J Med. 1999 Jun 24;340(25):1941-7. PMID: 10379017

Objective: Randomized controlled trial comparing the effect of 8 weeks of systemic corticosteroids, 2 weeks of systemic corticosteroids or placebo on treatment failure (death from any cause, need for intubation/mechanical ventilation, readmission for COPD or intensification of drug therapy).

Summary: The study compared 2 weeks of corticosteroids (3 days of intravenous methylprednisolone [125 mg every 6 hours] followed by a prednisone taper [60 mg daily for 4 days, 40 mg daily for 4 days, and 20 mg daily for 4 days]) with 8 weeks of corticosteroids (same initial treatment as the 2 week course with 20 mg daily for 32 days, 10 mg daily for 7 days, and 5 mg daily for 7 days), and placebo for treatment of hospitalized patients with

¹ Antibiotic Therapy and Treatment Failure in Patients Hospitalized for Acute Exacerbations of Chronic Obstructive Pulmonary Disease. Rothberg MB, Pekow PS, Lahti M, Brody O, Skiest DJ, Lindenauer PK. *JAMA*, May 26, 2010—Vol 303, No. 20. PMID: 20501925

COPD exacerbation. Treatment failure was defined as death from any cause or the need for intubation and mechanical ventilation, readmission to the hospital for COPD exacerbation, or intensification of drug therapy.

Conclusions: Patients treated with corticosteroids were less likely to have treatment failure at 30 days (23% vs. 33% with placebo) and 90 days (37% vs. 48% with placebo), but there was no difference at 6 months. Patients treated with corticosteroids also had shorter duration of hospitalization (8.5 vs. 9.7 days) and modest improvement in FEV₁, but were also more likely to develop hyperglycemia. The 8-week corticosteroid regimen was not superior to the 2-week regimen. The effect of using initial PO rather than IV steroid treatment of patients in the acute exacerbation of COPD (non-ICU) was evaluated in a large retrospective cohort study, which found a trend towards lower treatment failure in patients using initial PO steroid use after multivariable adjustment.²

3. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema.

Fishman A, Martinez F, Naunheim K, Piantadosi S, Wise R, Ries A, Weinmann G, Wood DE; National Emphysema Treatment Trial Research Group.

N Engl J Med. 2003 May 22; 348(21):2059-73. PMID: 12759479

Objective: A randomized trial compared lung-volume-reduction surgery with medical therapy for patients with severe emphysema. The outcomes of interest were all-cause mortality, maximal exercise capacity, pulmonary function, and quality of life. Patients determined to be at high risk for death after surgery were excluded.

Conclusion: There was no difference in all-cause mortality between the 2 groups, except in subgroup analyses, where patients with predominantly upper-lobe emphysema and low baseline exercise capacity were found to have lower mortality (risk ratio = 0.47), and patients with predominantly non-upper-lobe emphysema and high baseline exercise capacity were found to have higher mortality (risk ratio = 2.06). Patients who underwent surgery were more likely to have improved maximal exercise capacity (15% vs. 3% with medical therapy) at 24 months. Changes in pulmonary function and quality of life favored the surgery group.

The cost-effectiveness ratio in the subgroup with the greatest benefit was found to be \$98,000 per quality-adjusted life-year gained at 3 years and \$21,000 at 10 years, which is costly, relative to medical therapy.³

² Association of Corticosteroid Dose and Route of Administration With Risk of Treatment Failure in Acute Exacerbation of Chronic Obstructive Pulmonary Disease. Lindenauer PK, Pekow PS, Lahti MC, Lee Y, Benjamin EM, Rothberg MB. JAMA, June 16, 2010—Vol 303, No. 23. PMID: 20551406

³ Cost Effectiveness of Lung-Volume–Reduction Surgery for Patients with Severe Emphysema Ramsey SD, Berry K, Etzioni R, Kaplan RM, Sullivan SD, Wood DE; National Emphysema Treatment Trial Research Group. N Engl J Med, 2003. 348;21, 2092-2102. PMID: 12759480

Sleep Apnea

4. Sleep apnea.

White DP.

Proc Am Thorac Soc. 2006; 3(1):124-8. Review. PMID: 16493160

Key points:

- Obstructive sleep apnea (OSA) occurs due to reduced size of the pharyngeal airway with resulting repetitive collapse during sleep.
- The most common cause is obesity, although other anatomic factors such as enlarged adenoids and tonsils may also contribute.
- Consequences of OSA include neurocognitive problems such as increased daytime sleepiness due to disruption of sleep and possibly to neural damage from intermittent hypoxia. OSA also contributes to cardiovascular disorders including hypertension, MI, stroke, and CHF.
- Diagnosis of OSA is based on clinical criteria (loud snoring, witnessed episodes of apnea, and neck circumference) with confirmation by an in-laboratory sleep study.
- Therapeutic approaches include behavioral modification (limiting use of sedatives, avoiding supine sleep, and weight loss), nasal CPAP (the mainstay of therapy), oral appliances, and surgery. The 2013 ACP guideline on the management of OSA prioritizes weight loss and CPAP as initial therapy and mandibular advancement devices as the next best alternative therapy. CPAP improved quality of life but was not found to impact other clinical outcomes (blood pressure, A1C, cardiovascular events, stroke, etc). Surgical outcomes compared to CPAP lacked high-quality studies and/or statistical robustness.⁴

DVT/PE

5. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis.

Decousus H, Leizorovicz A, Parent F, Page Y, Tady B, Girard P *et al.*

N Engl J Med 1998; 338(7):409-415. PMID 9459643

Objective: A 2x2 intention-to-treat randomized trial comparing vena caval filter with no filter, and LMWH and UFH in the initial treatment of patients with a proximal DVT felt to be at high risk of pulmonary embolism.

Summary: The primary outcome was any PE, secondary outcomes of recurrent DVT, death, major bleeding at 12 days and 2 years. The study required 800 patients for adequate power, but was stopped due to slow recruitment at 400 patients. All patients were evaluated if symptomatic PE was suspected within 12 days of study entry, and all remaining patients were evaluated for asymptomatic PE on day 8-12 by V/Q or pulmonary angiogram. After 2 years, patients and PCPs were called yearly and further testing ensued in a symptom-prompted fashion. By day 12, fewer patients with filters vs. no filter were found to have any PE (2 (1.1%) vs. 9 (4.8%), p=0.03). After 2 years, no difference in

⁴ Management of Obstructive Sleep Apnea in Adults: A Clinical Practice Guideline From the American College of Physicians. Qaseem A, Holty JC, Owens DK, Dallas P, Sarkey M, Shekelle P (Clinical Guidelines Committee of the American College of Physicians). *Ann Intern Med*. 2013;159:471-483. PMID: 24061345

symptomatic PE was detected (6 patients with filters vs. 12 patients without , p=0.16). Recurrent DVT was higher in patients with a filter (OR 1.87 (1.10-3.20)). No difference in 12 day or 2 year outcome was detected for LMWH vs. UFH.

Conclusion: Filters appear to reduce early rates of any PE. Rates of PE are difficult to compare between 12 days and 2 years given the different denominators, although symptomatic PE rates appear no different between patients with filters vs. not. The secondary end point of recurrent DVTs was more frequent in patients with filters. Placement of filters has no detectable effect on mortality as expected, potentially related to the low power of the study.

The patients were re-assessed after the initial study with a maximum of eight years of follow-up and a 99% follow-up rate. Pulmonary embolism occurred in 9 patients in the filter group compared with 24 patients (15.1%) in the no-filter group (HR 0.37, 95% CI 0.17-0.79; P=0.008). DVT occurred in 57 patients (35.7%) in the filter group and 41 (27.5%) in the no-filter group (HR 1.52, 95% CI 1.02-2.27; P 0.042). There was no difference in all-cause mortality between the filter and no-filter groups (48.1% and 51.0% respectively) nor worsening post-thrombotic syndrome. The authors conclude that permanent filters should not routinely be used due to lack of clear VTE benefit (increased DVT with decreased PE) and net neutral mortality benefit.⁵

EBM goal: Introduction to power, alpha, and beta; primary vs. secondary outcomes. Perspective on “EBM” - this underpowered study is the only RCT of the effectiveness of filters vs. no filter.

6. Venous thromboembolism prophylaxis in hospitalized medical patients and those with stroke: a background review for an American College of Physicians clinical practice guideline.

Lederle FA, Zylla D, MacDonald R, Wilt TJ.

Ann Intern Med 2011; 155(9):602-615. PMID 22041949

Objective: A meta-analysis assessing the benefits and harms of DVT prophylaxis in hospitalized patients on medical and surgical services from RCTs. The primary outcome was all-cause mortality up to 120 days after randomization. Secondary outcomes included symptomatic DVT, any PE, fatal PE, any bleeding event, major bleeding event (as defined by individual studies), and skin damage for mechanical prophylaxis.

Summary: 4340 initial references were pared down to 40 trials of >52,000 patients, 21 of which were on medical patients, 19 on stroke patients. Heterogeneity was absent using an $I^2 > 50\%$ cutoff. Meta-analysis on multiple comparisons was performed, with noted publication bias for decrease in PE incidence:

- Heparin vs. no heparin (10 medical vs. 8 stroke) - see below.
- LMWH vs. UFH (9 medical vs. 5 stroke) - no differences were found in this group
- Mechanical vs. no mechanical prophylaxis (2 medical vs. 3 stroke) - these patients tended to have skin damage but no other differences in outcome
- 3 stroke studies had unique designs.

⁵ Eight-Year Follow-Up of Patients With Permanent Vena Cava Filters in the Prevention of Pulmonary Embolism. The PREPIC Study Group. *Circulation*. 2005; 112:416-22. PMID: 16009794

Heparin vs. no heparin

- In medical patients, trend towards decreased mortality (OR 0.94 (0.84-1.04)), fewer PE (OR 0.69, (0.52-0.9)), increased major bleeding events (OR 1.34 (1.08-1.66))
- In stroke patients, no effect on mortality (OR 0.91, (0.70-1.18)), trend to decreased PE (OR 0.72 (0.50-1.04)), increased major bleeding (OR 1.66 (1.20-2.28))
- When combined, the total effect led to a trend towards decreased mortality (OR 0.93 (0.86-1.00)), decreased rates of any PE (OR 0.70 (0.56-0.87)), and increased major bleeding risk (OR 1.61 (1.23-2.10))

Conclusions: A well-executed meta-analysis which suggests a trend towards mortality benefit, increased rates of clinically significant bleeding (NNT = 9 in 1000 patients) and lower PE rates (NNT = 3 in 1000 patients). PE rates, however, include fatal, symptomatic and asymptomatic PE and publication bias was found. The ultimate conclusion from this paper is dependent upon the weight given to the trend towards mortality benefit to heparin prophylaxis, although the authors conclude that heparin prophylaxis has little or no net benefit and mechanical prophylaxis leads to harm. NB: mechanical prophylaxis was defined as TED hose (not intermittent compression stockings)

EBM goal: Exposure to meta-analyses as the highest level of evidence and the considerations when evaluating a meta-analysis. Introduction to heterogeneity.

7. Management of venous thromboembolism: a systematic review for a practice guideline.

Segal JB, Streiff MB, Hofmann LV, Thornton K, Bass EB.

Ann Intern Med. 2007 Feb 6; 146(3):211-22. PMID: 17261856

Key points:

- Low molecular weight heparin (LMWH) is superior to unfractionated heparin for treatment of DVT with respect to risk of recurrent DVT, major bleeding, and death. Additional trials are needed to determine the efficacy of LMWH for treatment of PE, but existing studies suggest LMWH is as effective as unfractionated heparin. Use of LMWH is cost-saving or cost-effective compared with use of unfractionated heparin. (A Cochrane meta-analysis including 23 studies (9587 patients) found that thrombotic complications were less frequent in patients treated with LMWH (3.6%) compared with UFH (5.3%) (odds ratio 0.70; 95% CI, 0.59-0.81). LMWH treatment also led to less hemorrhage and a lower mortality rate.)⁶
- Outpatient management of newly diagnosed DVT and PE appears to be safe and effective for carefully selected patients with close follow-up.
- Catheter-directed thrombolysis results in higher rates of long-term patency and lower rates of venous reflux than standard therapy but is associated with relatively high rates of major and minor bleeding. (A meta-analysis performed in 2014 found that systemic thrombolytics were associated with lower all-cause mortality (OR, 0.53;

⁶ Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. Erkens PMG, Prins MH. Cochrane Database of Systematic Reviews 2010, Issue 9. PMID: 20824828.

95% CI, 0.32-0.88) but also higher risk of bleeding. This bleeding risk was attenuated in patients under the age of 65).⁷

- In one randomized trial, IVC filter placement plus anticoagulation compared with anticoagulation alone in patients with proximal DVT reduced the overall risk of PE but not of symptomatic PE. In an observational study, recipients of IVC filters were just as likely to be admitted with PE as patients without filters and were more likely to develop subsequent DVT.⁸
- 3 months of oral anticoagulation with a vitamin K antagonist is likely adequate for definitive treatment of provoked DVT, but extended-duration therapy appears to be optimal for patients with unprovoked DVT or 2nd episode of DVT. Use of LMWH for definitive treatment of DVT is more expensive than oral anticoagulation but may be preferred in cancer patients and in patients for whom the INR is difficult to manage.
- There is limited data regarding use of LMWH and IVC filters in pregnant women.

8. Value of the Ventilation/Perfusion Scan in Acute Pulmonary Embolism: Results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED).

The PIOPED Investigators.

JAMA. 1990; 263(20):2753-2759. PMID 2332918

Objective: A prospective, multicenter study was performed to determine the sensitivity and specificity of ventilation/perfusion (V/Q) scans for acute PE compared with pulmonary angiography.

Conclusions: 755 patients with suspected PE underwent angiography, and 251 (33%) had a confirmed diagnosis of PE. The sensitivity of a high-probability V/Q scan was only 41%, but this increased to 82% with either a high- or intermediate-probability scan. The specificity of a high-probability V/Q scan was 97%. Among those patients with intermediate- and low-probability V/Q scans, 33% and 12% had PE diagnosed by angiography, respectively. The use of V/Q scans to diagnose PE improved when combined with clinical assessment. Among patients with high clinical probability (80-100%) of PE and a high-probability V/Q scan, 96% had confirmed PE. Similarly, among those with low clinical probability (<20%) and a low-probability V/Q scan, only 4% had PE.

Further recommendations for testing for pulmonary embolism came from PIOPED II, including use of an objective clinical assessment tool (e.g. Wells score), D-dimer testing if the clinical assessment tool demonstrated low- or intermediate-risk with further diagnostic testing if abnormal, and initiating empiric anticoagulation and obtaining diagnostic testing without D-dimer measurement in high-risk patients.

⁷ Thrombolysis for Pulmonary Embolism and Risk of All-Cause Mortality, Major Bleeding and Intracranial Hemorrhage. Chatterjee S, Chakraborty A, Weinberg I, Kadukia M, Wilensky R, Sardar P et al. *JAMA*. 2014; 311(23):2414-2421. PMID: 24938564

⁸ White RH, Zhou H, Kim J, Romano PS. A population-based study of the effectiveness of inferior vena cava filter use among patients with venous thromboembolism. *Arch Intern Med*. 2000;160:2033-41. PMID: 10888977

9. Early Palliative Care for Patients with Metastatic Non-Small-Cell Lung Cancer.

Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, et al.
N Engl J Med. 2010; 363(8), 733-42. PMID: 20818875

Objective: Randomized, non-stratified controlled trial comparing the effect of routine oncologic care with routine care plus early introduction of palliative care for ambulatory patients with new diagnosis of metastatic non-small-cell lung cancer.

Summary: 151 patients were enrolled within 8 weeks after diagnosis and had their first monthly palliative care meeting within 3 weeks of enrollment if the patient had a ECOG (Eastern Cooperative Oncology Group) performance status of 2 or lower (symptomatic and in bed < 50% of the day or more active).

The primary outcome was quality of life as measured by the Functional Assessment of Cancer Therapy-Lung (FACT-L). Secondary outcomes included (1) depressive symptoms as measured by the Hospital Anxiety and Depression Scale (HADS) and Patient Health Questionnaire 9 (PHQ-9), (2), initiation of aggressive end-of-life care and (3) mortality.

Early palliative care improved quality of life (5.4+2.4, 95% CI 0.7 to 10.0; P = 0.03), fewer depression symptoms on HADS-D and PHQ-9 (but not HADS-A), less frequent initiation of aggressive care (33% vs. 54%; P=0.05), and significantly longer survival (median 11.6 vs. 8.9 months; P=0.02). Aggressive care was defined as chemotherapy within 14 days of death, no hospice care, or admission to hospice 3 days or less before death.

Conclusion: Early palliative care improved quality of life. Benefit in mortality and reduced depressive symptoms were observed. Less frequent initiation of end-of-life aggressive care was noted although further differentiation of outcomes would allow better interpretation of the data. These findings provide a reasonably compelling argument for the use of early palliative care for this patient population.

Hospital-Acquired Pneumonia

10. Acid-suppressive medication use and the risk for hospital-acquired pneumonia.

Herzig SJ, Howell MD, Ngo LH, Marcantonio ER.
JAMA. 2009; 301(20):2120-2128. PMID 19470989

Objective: A prospective cohort study was performed to examine the association between use of acid-suppressive medication (H2-blocker or PPI) and hospital-acquired pneumonia (HAP).

Conclusions: Among a cohort consisting of 63,878 admissions, 52% received acid-suppressive medication (83% received PPIs, and 23% received H2-blockers). Patients who received acid-suppressive medication were older (median age 62 vs. 40), were more often admitted to a medicine service, and were more likely to have medical comorbidities. Only 23% of patients started on acid-suppressive medication had an underlying diagnosis of peptic ulcer disease/reflux or gastrointestinal bleeding. The risk of HAP was 30% higher in patients treated with acid-suppressive medication. This association was significant for PPIs (odds ratio = 1.3) but not for H2-blockers (odds ratio = 1.2).

Critical Care

11. A Randomized Trial of Protocol-Based Care for Early Septic Shock.

Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F et al.; the ProCESS Investigators.

N Engl J Med. 2014; 370(18):1683-1693. PMID: 24635773

Objective: A multicenter randomized control study to compare early goal-directed therapy (EGDT)⁹, which employs interventions to correct hemodynamic targets measured by a central venous catheter (CVC), with usual care and protocol-based standard therapy (PBST, which used interventions to correct hemodynamic targets without central venous catheterization).

Summary: 1341 patients were enrolled in a 1:1:1 ratio to EGDT, PBST or usual care. For the EGDT care, a protocol was followed within the first 6 hours of care which included CVC placement to monitor central venous pressure and central venous oxygen saturation, which directed the use of IV fluids, vasopressors, and transfusions. The volume and timing of IV fluids, but not the type of fluid, was specified. Thresholds for vasopressor use were detailed but type was not specified. For PBST care, a protocol was also followed within the first 6 hours of care, prompting specific interventions. CVCs were only placed for access purposes, IV fluids/vasopressors were administered to address clinical concerns (hypotension, shock index, fluid status) and blood was administered if hemoglobin levels fell below 7.5g/dl. For usual care, no specific actions were prompted. In all treatment arms, all other care was directed by the bedside physician, including antibiotics.

The primary outcome was all-cause, in-hospital death at 60 days. Secondary outcomes included all-cause death at multiple time points, length of vasopressor use/respiratory failure/acute renal failure, ICU and hospital length of stay, and discharge disposition. Inclusion criteria were (1) > 18 years of age, (2) suspected sepsis by the treating physician, (3) 2+ criteria for systemic inflammatory response syndrome and (4) refractory hypotension or lactate of 4+ mmol/L.

No differences in mortality were observed at 60 days (primary outcome) or at 90 days. Renal failure was more frequent in PBST with a trend towards less vasopressor usage in usual care patients.

Conclusion: EGDT was not found to be superior to PBST or usual care. Routine use of CVC and central hemodynamic monitoring is not warranted. Results from 2 ongoing RCT's may further corroborate these findings.

⁹ Early goal-directed therapy in the treatment of severe sepsis and septic shock. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M; Early Goal-Directed Therapy Collaborative Group. *N Engl J Med.* 2001 Nov 8; 345(19):1368-77. PMID: 11794169

12. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome.

Acute Respiratory Distress Syndrome Network.

N Engl J Med. 2000 May 4; 342(18):1301-8. PMID: 10793162

Objective: A randomized trial compared low tidal volume ventilation (6 mL/kg with plateau pressure \leq 30 cm water) with traditional ventilation (12 mL/kg with plateau pressure \leq 50 cm water) in patients with ARDS. The outcomes of interest were death prior to discharge and breathing without assistance, as well as number of days without ventilator use prior to day 28.

Conclusions: The trial was stopped prematurely because mortality was lower in the low tidal volume ventilation group (31% vs. 39.8%), and patients in the low tidal volume group had more days without ventilator use (12 vs. 10).

13. A Multicenter, randomized, controlled clinical trial of transfusion requirements in critical care.

Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetsir E; Transfusion Requirements in Critical Care Investigators for the Canadian Critical Care Trials Group.

N Engl J Med. 1999;340(6):409-417. PMID: 9971864

Objective: A randomized trial was performed to determine if a restrictive strategy of red-cell transfusion (transfusion for hemoglobin \leq 7) was equivalent to a liberal strategy (transfusion for hemoglobin \leq 10) in ICU patients. The outcomes of interest were death from all causes at 30 days and multiorgan failure.

Conclusions: Overall, 30-day mortality rates were similar between the 2 groups (18.7% for the restricted transfusion group vs. 23.3% for the liberal transfusion group). However, the restricted transfusion group had significantly lower mortality among patients with baseline APACHE II score \leq 20 (8.7% vs. 16.1%) and patients $<$ 55 years of age (5.7% vs. 13%). There was no difference in multiorgan failure between the 2 groups. Cardiac events, primarily pulmonary edema and MI, were more frequent in the liberal transfusion group, and there was no difference in mortality between the 2 groups among patients with pre-existing cardiac disease.

14. Transfusion Strategies for Acute Upper Gastrointestinal Bleeding.

Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, et al.

N Engl J Med. 2013;368(1):11-21. PMID: 23281973

Objective: To measure the effect of restrictive versus liberal transfusion strategy in patients admitted with severe upper gastrointestinal bleeding on mortality.

Summary: 921 patients underwent emergency gastroscopy within the first 6 hours with a subsequent standardized treatment plan based upon the source of bleeding (directed endoscopic therapy to bleeding sites; continuous intravenous PPI for peptic ulcer disease; continuous intravenous somatostatin and antibiotics for portal hypertension). Patients were randomized to a restrictive (threshold of 7g/deciliter or lower) versus a liberal (threshold of 9g/deciliter or lower) strategy. Only single units of blood were transfused and the hemoglobin level was measured after each transfusion to see if the threshold for

transfusion was met. Hemoglobin levels were measured after admission and again every 8 hours during the first 2 days and every day thereafter.

The primary outcome was all-cause mortality within 45 days of the index bleed, stratified according to the presence/absence of cirrhosis. Survival was higher for all patients that received the restrictive (5%) versus liberal-transfusion (9%) strategy (HR 0.55, 95% CI 0.33-0.92, $P=0.02$), particularly for patients with cirrhosis with Child-Pugh class A or B (HR 0.30; 95% CI 0.11-0.85, $P=0.02$). More patients avoided a transfusion in the restrictive group (51% vs. 14%), the overall rate of further bleeding was lower (10% vs. 16%, $P=0.01$), fewer patients died from uncontrolled bleeding (0.7% vs. 3.1%, $P=0.01$), and fewer adverse events were noted (40% vs. 48%, $P=0.02$).

Conclusion: A restrictive strategy towards transfusions for patients from an acute upper gastrointestinal bleeding leads to lower mortality and reduced morbidity.

Cardiology

Acute Coronary Syndrome

15. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial.

Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R, Collins R, Liu LS; COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. *Lancet*. 2005; 366(9497):1607-21. PMID 16271642

Objective: A randomized controlled trial compared the combination of aspirin and clopidogrel (continued until hospital discharge or for the first 4 weeks of hospitalization) with aspirin alone in patients presenting with STEMI. The outcomes of interest were (1) the composite of death, reinfarction, or stroke and (2) death from any cause during the treatment period.

Conclusions: 45,852 patients were enrolled (patients scheduled to undergo primary PCI were excluded). Patients assigned to the clopidogrel group had a lower rate of the composite endpoint (9.2% vs. 10.1% in the placebo group). Specifically, the rate of reinfarction was 2.1% in the clopidogrel group and 2.4% in the placebo group ($p = 0.02$), and the rate of stroke was 0.9% in the clopidogrel group and 1.1% in the placebo group ($p = 0.11$). The rate of death from any cause in the clopidogrel group was 7.5% vs. 8.1% in the placebo group ($p = 0.03$). 54% of patients received thrombolytic therapy, and 75% received anticoagulation, primarily with heparin. There was no difference in bleeding events between the 2 groups, including among older patients and patients who received thrombolytic therapy.

16. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation.

Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators.
N Engl J Med. 2001 Aug 16; 345(7):494-502. PMID: 11519503

Objective: A randomized controlled trial compared the combination of aspirin and clopidogrel (given for 3-12 months) with aspirin alone in patients with NSTEMI. The primary outcomes were (1) the composite of death from cardiovascular causes, nonfatal MI, or stroke and (2) the composite of the first primary outcome or refractory ischemia (recurrent chest pain with EKG changes leading to additional intervention). Secondary outcomes were severe ischemia (similar to refractory ischemia with no intervention performed), heart failure, and need for revascularization.

Conclusions: 12,562 patients were randomized (patients with a history of coronary revascularization within the past 3 months or receipt of a glycoprotein IIb/IIIa inhibitor within the past 3 days were excluded). The first primary outcome occurred less often in the clopidogrel group (9.3% vs. 11.4%, $p < 0.001$). The second primary outcome occurred in 16.5% of the clopidogrel group and 18.8% of the placebo group ($p < 0.001$). Rates of severe ischemia (2.8% vs. 3.8%), heart failure (3.7% vs. 4.4%), and need for revascularization were lower in the clopidogrel group (36% vs. 36.9%). Only a small percentage of patients in this study received thrombolytic therapy, but most received heparin (72.3% in the clopidogrel group and 73.1% in the placebo group), and some received glycoprotein IIb/IIIa inhibitors after randomization (5.9% and 7.2%, respectively). The rate of major bleeding events was higher in the clopidogrel group (3.7% vs. 2.7%, $p = 0.001$).

17. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction.

Cannon CP, Gibson CM, Lambrew CT, Shoultz DA, Levy D, French WJ, Gore JM, Weaver WD, Rogers WJ, Tiefenbrunn AJ.
JAMA. 2000 Jun 14; 283(22):2941-7. PMID: 10865271

Objective: A prospective multicenter observational study was performed to determine the impact of symptom-onset-to-balloon time and door-to-balloon time on outcome in patients presenting with acute MI with ST-elevation or LBBB. The outcome of interest was in-hospital mortality.

Conclusions: A total of 27,080 patients presenting with acute MI treated with primary angioplasty were evaluated. The median time from symptom onset to angioplasty was 3.9 hours. The adjusted odds of in-hospital mortality did not increase significantly with increasing delay. The median door-to-balloon time was 1 hour and 56 minutes. The adjusted odds of mortality were significantly increased for patients with door-to-balloon times > 2 hours (for 121-150 minutes, OR = 1.41; for 151-180 minutes, OR = 1.62); and for > 180 minutes, OR = 1.61). The overall mortality rate was 6.1%, ranging from 4.2% in patients with door-to-balloon time < 60 minutes to 8.5% for patients with door-to-balloon time 151-180 minutes.

18. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock.

Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, Buller CE, Jacobs AK, Slater JN, Col J, McKinlay SM, LeJemtel TH.

N Engl J Med. 1999 Aug 26; 341(9):625-34. PMID: 10460813

Objective: A randomized trial was performed to determine if early revascularization (angioplasty or bypass surgery within 6 hours of randomization) resulted in lower 30-day mortality for patients presenting with acute MI complicated by cardiogenic shock, compared with initial medical stabilization.

Conclusions: Almost all patients received inotropes/vasopressors, intraaortic balloon counterpulsation, and pulmonary-artery catheterization. 49.3% of patients in the early revascularization group received thrombolytics, compared with 63.3% in the medical therapy group. 86.8% of patients in the early revascularization group underwent angioplasty or bypass surgery, compared with 25.3% in the medical therapy group. The median time from randomization to revascularization was 1.4 hours in the early revascularization group and 102.8 hours in the medical therapy group. There was no significant difference in mortality at 30 days (46.7% in the early revascularization group vs. 56% in the medical therapy group), but 6-month mortality was lower in the early revascularization group (50.3% vs. 63.1%).

Preventive Care

19. Mortality and morbidity in patients receiving encainide, flecainide or placebo (the Cardiac Arrhythmia Suppression Trial).

Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, Arensberg D, Baaker A, Friedman L, Greene HL, Huther ML, Richardson DW; the CAST investigators.

N Engl J Med 1991; 324(12):781-88. PMID: 1900101

Objective: An intention-to-treat multicenter randomized trial was performed to establish an expected mortality and morbidity benefit for the use of class I anti-arrhythmic therapy compared to placebo for post-myocardial arrhythmia. The primary outcome was death or cardiac arrest with resuscitation, attributable to arrhythmia (specific criteria included in the paper).

Summary: 857 patients were enrolled in the trial 6 days to 2 years after their index myocardial infarction if (1) they had 6 or more PVCs per hour for more than 18 hours, (2) no frank sustained ventricular tachycardia, (3) a sub-normal EF and (4) PVCs and non-sustained ventricular tachycardia were suppressed by anti-arrhythmic medications (established in a preceding pilot test). Patients would preferentially receive encainide with an EF < 30% and flecainide if >30%. This trial was ended early – 63 patients receiving therapy experienced the composite outcome (relative risk 2.64, 95% CI: 1.60 to 4.36, p = 0.0001) compared to 26 patients who received placebo 2 years into the trial. Death from any cause was also higher in the therapy group. Non-fatal cardiac secondary outcomes were equivalent in treatment and placebo arms.

Conclusions: This study fundamentally changed the paradigm of post-myocardial infarction anti-arrhythmic therapy. The window for interventional electrophysiology was opened further by this study.

EBM goal: This study highlights the importance of using clinically relevant outcomes (mortality) compared to surrogate markers (suppression of arrhythmia).

20. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction.

Moss AJ, Zareba W, Hall J, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML; Multicenter Automatic Defibrillator Implantation Trial II Investigators.

N Engl J Med. 2002; 346(12):877-883. PMID: 11907286.

Objective: A multicenter, intention-to-treat non-blinded randomized trial was performed to evaluate the benefit of prophylactic implantation of a defibrillator in patients with reduced EF from myocardial infarction of <30%. The primary outcome was death from any cause.

Summary: 1232 patients with evidence of prior ischemic event (via Q wave on EKG, clinical diagnosis, or echo/stress test/coronary catheterization) and EF < 30% were enrolled over four years and followed for an average of 20 months in a 3:2 grouping (defibrillator: control). Power was set at 95% to detect a RR of 38% based on a 19% mortality rate in the conventional group. Despite the crossover of 54 patients, death occurred in the defibrillator group less frequently than the control (14.2% vs. 19.8%, hazard ratio of 0.69 (95%CI: 0.51 to 0.93, p=0.016).

Conclusions: Prior studies that had demonstrated benefit of ICD placement in patients with ischemic cardiomyopathy, but those patients received invasive electrophysiology to “prove” that patients had suppressible ventricular tachycardia prior to placement of ICD. This study demonstrates benefit of ICD with a simple surrogate marker of reduced EF in patients with MI without the need of provocative EP testing. This trial with the CAST trial results uncoupled the need to demonstrate suppressible ventricular tachycardia from benefit of anti-arrhythmic therapy.

Appropriate medical therapy for post-myocardial reduced EF includes spironolactone and beta blockers. The 2009 ACCF/AHA guidelines¹⁰ have further details about the benefits of related to ICD placement in ischemic and non-ischemic cardiomyopathy, for primary and secondary prevention of ventricular arrhythmias.

¹⁰ Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009;119:1977-2016. PMID: 19324967

21. Optimal medical therapy with or without PCI for stable coronary disease.

Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS; COURAGE Trial Research Group.

N Engl J Med. 2007 Apr 12; 356(15):1503-16. PMID: 17387127

Objective: A randomized trial was performed to determine if PCI with optimal medical therapy (intensive pharmacologic therapy and lifestyle intervention) was superior to optimal medical therapy alone for patients with stable coronary disease. The primary outcome was death from any cause and non-fatal MI during the study period.

Conclusions: 2,287 patients were randomized and followed for 2.5 to 7 years (median, 4.6) after study enrollment. There were 211 primary events in the PCI group and 202 in the medical therapy group. Cumulative primary event rates at 4.6 years were 19% in the PCI group and 18.5% in the medical therapy group. There were no significant differences in the composite of death, MI, and stroke (20% vs. 19.5%), hospitalization for ACS (12.4% vs. 11.8%), or MI (13.2% vs. 12.3%).

In contradistinction, patients with acute STEMI undergoing percutaneous coronary intervention (PCI) upon culprit arteries received significant benefit with intervention upon additional vessels with incidentally discovered major stenoses. Benefit was seen in death from cardiac causes, nonfatal MI and refractory angina as well as the combined outcome of these endpoints.¹¹

22. Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events.

Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Brennan DM, Fabry-Ribaud L, Booth J, Topol EJ; CHARISMA Investigators.

N Engl J Med. 2006; 354(16):1706-17. PMID 16531616

Objective: A randomized controlled trial compared low-dose aspirin plus clopidogrel with low-dose aspirin plus placebo for patients with clinically evident atherothrombosis or multiple risk factors. The primary outcome was a composite of MI, stroke, or death from cardiovascular causes.

Conclusions: 15,603 patients were randomized and followed for a median of 28 months. There was no difference in the primary outcome between the 2 groups (6.8% in the clopidogrel group vs. 7.3% in the placebo group). However, patients in the clopidogrel group did have a lower rate of hospitalization (16.7% vs. 17.9%). The rate of the primary outcome among patients with multiple risk factors was not different between the 2 groups, but patients in the clopidogrel group had a higher rate of death from cardiovascular causes (3.9% vs. 2.2%). On the other hand, patients with clinically evident atherothrombosis who received clopidogrel had a lower rate of death from cardiovascular causes (6.9% vs. 7.9%). The rate of severe bleeding was slightly higher in the clopidogrel group (1.7% vs. 1.3%), but this was not statistically significant.

¹¹ Randomized Trial of Preventive Angioplasty in Myocardial Infarction. Wald DS, Morris JK, Wald NJ, Chase AJ, Edwards RJ, Hughes LO, et al. *N Engl J Med.* 2013. 369(12):1115-1123. PMID: 23991625

23. Coronary-artery revascularization before elective major vascular surgery.

McFalls EO, Ward HB, Moritz TE, Goldman S, Krupski WC, Littooy F, Pierpont G, Santilli S, Rapp J, Hattler B, Shunk K, Jaenicke C, Thottapurathu L, Ellis N, Reda DJ, Henderson WG.

N Engl J Med. 2004 Dec 30; 351(27):2795-804. PMID: 15625331

Objective: A randomized trial compared coronary-artery revascularization (PCI or bypass surgery) with no revascularization prior to vascular surgery (for expanding AAA or severe symptoms of arterial occlusive disease involving the legs). Patients were enrolled only if they had at least 70% stenosis of one or more coronary arteries on angiography. The primary outcome was long-term mortality.

Conclusions: Of 5,859 patients undergoing vascular surgery, 510 (9%) were eligible and enrolled in the study. 33% of patients underwent surgery for expanding AAA, and 67% underwent surgery for arterial occlusive disease of the legs. Among the patients randomized to coronary-artery revascularization prior to vascular surgery, 59% underwent PCI, and 41% underwent bypass surgery. Surgery was significantly delayed in the revascularization group compared with the norevascularization group (54 vs. 18 days). At 2.7 years, there was no difference in mortality between the 2 groups (22% vs. 23%), and there was no difference in postoperative MI within 30 days (12% vs. 14%).

EBM goal: The differences in outcomes may be related to the consequent effect of the intervention. In this patient population, the delay associated with scheduling and the anticoagulation window for cardiac catheterization for patients with significant AAA lead to as many deaths as proceeding with surgery and perioperative death.

24. Extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial.

POISE study group.

Lancet 2008; 371:1839-1847. PMID: 18479744

Objective: An intention-to-treat, randomized controlled study performed to determine the effect of perioperative beta-blockade on a composite outcome of cardiovascular death, non-fatal myocardial infarction and non-fatal cardiac arrest at 30 days post-surgery, for non-cardiac surgery patients.

Summary: 8351 patients with risk factors approximating those found in the Revised Cardiac Risk Index score of 1 or greater were randomized to 100mg of metoprolol ER vs. placebo, 2-4 hours prior to surgery. The patient was administered the first post-operative dose within the first 6 hours of after surgery and then a 200mg dose 12 hours after the first dose. SBP and HR measurements delayed but did not preclude administration of the medication. EKG and troponin/CKMB were measured routinely after surgery and at 30 days. Power was set at 92% for relative risk reduction of 25% with 10,000 patients. The primary endpoint was lower in the metoprolol group (OR 0.84 (0.70-0.99, p=0.0399)), driven by fewer MI (OR 0.73 (0.60-0.89, p=0.0017)) and fewer non-fatal MI (0.70 (0.57-0.86, p=0.0008)). More patients receiving metoprolol had a stroke (OR 2.17 (1.26-3.74, p=0.0053)) and died (OR 1.33 (1.03-1.74, p=0.0317)). Subgroup analysis suggests that sepsis was the leading cause of death that was disproportionately higher in the intervention group.

Conclusions: The aggressive administration of metoprolol in a protocolized fashion in the immediate perioperative and post-operative time period leads to stroke and death and should not be utilized.

EBM goal: This study highlights the importance of understanding the methods in the study. The results for POISE are remarkable but metoprolol was administered in a fashion inconsistent with routine practice in the United States - and yet, this led to an early update of the ACC perioperative guidelines, limiting the role of beta-blockers in the perioperative period.

Atrial Fibrillation

25. Selecting Patients With Atrial Fibrillation for Anticoagulation: Stroke Risk Stratification in Patients Taking Aspirin.

Gage BF, van Walraven C, Pearce L, Hart RG, Koudstaal PJ, Boode BSP, Petersen P. *Circulation* 2004;110:2287-2292. PMID 15477396

Objective: A prospective cohort study was performed to determine the accuracy of 5 previously published stroke risk stratification schemes for patients with atrial fibrillation taking aspirin for stroke prevention.

Conclusions: The study pooled data for 2,580 participants from 6 randomized trials, most of which involved prescription of aspirin alone (only 1 included patients who had contraindications to warfarin). The overall incidence of ischemic stroke was 207 per 4,887 patient-years of aspirin therapy. All of the risk stratification schemes predicted the risk of stroke better than chance, but results were variable. The CHADS2 scheme (Congestive heart failure, Hypertension, Age >75, Diabetes, and prior Stroke or TIA) predicted the risk of stroke most successfully, with incidences of 0.8 strokes/100 patient-years for low-risk patients, 2.7 strokes/100 person-years for moderate-risk patients, and 5.3 strokes/100 person-years for high-risk patients. Based on the CHADS2 scheme, the number needed to treat with warfarin instead of aspirin for 1 year to prevent 1 stroke would be 30.

26. Rhythm Control versus Rate Control for Atrial Fibrillation and Heart Failure.

Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, et al. (Atrial Fibrillation and Congestive Heart Failure Investigators). *N Engl J Med* 2008; 358(25):2667-2677. PMID: 18565859

Objective: To determine whether rhythm control had cardiovascular mortality benefit compared with rate control in patients with significant heart failure and atrial fibrillation.

Summary: 1376 patients with EF < 35% documented 6 months before enrollment, a history of heart failure (symptoms or admission for heart failure within 6 months of enrollment or EF < 25%), and a history of atrial fibrillation (episode lasting 6 hours or cardioversion within 6 months or previous cardioversion with an episode > 10 minutes within 6 months) were included.

The primary outcome was death from cardiovascular cause. Secondary causes included hospitalization frequency, overall survival, stroke, worsening heart failure and a composite outcome of cardiovascular death, stroke, worsening heart failure. No differences were

observed in any of these outcomes. Additional secondary outcomes showed increased hospitalization for any cause (64% vs. 59%, $P=0.06$), increased hospitalization for atrial fibrillation (14% vs. 9%, $P=0.001$) and increased electrical cardioversion (59% vs. 9%, $P<0.001$) for patients undergoing rhythm control.

Conclusion: Rhythm control for atrial fibrillation in patients with significant heart failure demonstrated no mortality benefit and may result in increased resource utilization and/or morbidity compared with rate control.

27. The net clinical benefit of warfarin anticoagulation in atrial fibrillation.

Singer DE, Chang Y, Fang MC, Borowsky LH, Pomernacki NK, Udaltsova N, Go AS. *Ann Intern Med.* 2009; 151(5):297-305. PMID 19721017

Objective: A mixed retrospective and prospective cohort study was performed to determine the net clinical benefit of anticoagulation with warfarin in patients with atrial fibrillation. Net clinical benefit was defined as the annual rate of ischemic strokes and systemic emboli prevented by warfarin minus the impact of intracranial hemorrhages (ICH) attributed to warfarin.

Conclusions: Data from 13,559 patients were reviewed. The incidence of thromboembolism for patients not receiving warfarin was 2.29/100 person-years compared with 1.25/100 person-years for patients receiving warfarin. The incidence of ICH was 0.33/100 person-years without warfarin and 0.57/100 person-years with warfarin. The overall net clinical benefit of warfarin was 0.68% per year. The net clinical benefit was highest for patients with a history of stroke (2.48% per year) and patients ≥ 85 years of age (2.34% per year). The net clinical benefit was essentially 0 for patients considered low-risk by the CHADS2 scheme but increased to 2.22% per year for high-risk patients.

For patients that were felt to have a contraindication to Coumadin therapy, Plavix in addition to aspirin resulted in a lower risk of major vascular events (primarily driven by a lower rate of stroke) at the cost of increased major bleeding events compared with aspirin alone.¹²

28. Dabigatran versus warfarin in patients with atrial fibrillation. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators.

N Engl J Med. 2009; 361(12):1139-51. PMID 19717844.

Objective: A randomized trial compared adjusted-dose warfarin with fixed-dose dabigatran (either 110 mg or 150 mg) for prevention of stroke or thromboembolism in patients with atrial fibrillation.

Conclusions: 18,113 patients were enrolled and followed for a median of 2 years. Dabigatran was noninferior to warfarin with rates of stroke or thromboembolism of 1.69% per year in the warfarin group, 1.53% per year in the 110 mg dabigatran group, and 1.11% per year in the 150 mg dabigatran group. Rates of major bleeding were 3.36% per year in

¹² Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation. Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, Chrolavicius S (The ACTIVE Investigators). *N Engl J Med.* 2009. 360;20:2066-2078. PMID: 19336502.

the warfarin group compared with 2.71% in the 110 mg dabigatran group ($p = 0.003$) and 3.11% per year in the 150 mg dabigatran group ($p = 0.31$). Rates of intracranial hemorrhage were significantly lower in both dabigatran groups (0.12% per year and 0.1% per year, respectively), compared with the warfarin group (0.38% per year). There was a trend toward lower mortality in both dabigatran groups (3.75% per year and 3.64% per year, respectively) compared with the warfarin group (4.13% per year).

Heart Failure

29. The effect of spironolactone on morbidity and mortality in patients with severe heart failure.

Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J; Randomized Aldactone Evaluation Study (RALES) Investigators. *N Engl J Med.* 1999; 341(10):709-17. PMID 10471456

Objective: A randomized controlled trial compared spironolactone with placebo in patients with severe left heart failure (EF <35%) who were on standard medical therapy. The primary outcome was death from all causes.

Conclusions: The trial was discontinued early, after a median follow-up of 24 months, due to significantly lower mortality in the spironolactone group (35%) compared with the placebo group (46%). The rate of death from cardiac causes or hospitalization for cardiac causes was 32% lower in the spironolactone group. 41% of patients in the spironolactone group had symptomatic improvement based on NYHA class compared with 33% in the placebo group. The only significant adverse effect of spironolactone was gynecomastia or breast pain, which was reported by 10% of men in the spironolactone group compared with 1% in the placebo group.

Patients with preserved EF (> 45%) but symptomatic heart failure that achieved similar dosing levels of spironolactone with this trial did not experience any difference in a composite primary outcome of cardiovascular death, aborted cardiac arrest or hospitalization for heart failure compared with placebo.¹³

Endocrinology

30. Systematic review: intensive insulin therapy in hospitalized patients.

Kansagara D, Fu R, Freeman M, Wolf F, Helfand M. *Ann Intern Med.* 2011;154: 268-282. PMID: 21320942

Objective: A meta-analysis performed to (1) clarify the discrepancy between early RCTs that suggested mortality benefit for intensive insulin therapy (IIT) in surgical patients and subsequent RCTs that showed non-benefit/harm to medical ICU patients (2) provide recommendations for insulin therapy for SICU, MICU and non-ICU patients. The primary outcome was 28 day mortality. Secondary outcomes included 90 and 180 day mortality, hypoglycemia, infection, and length of stay.

¹³ Spironolactone for Heart Failure with Preserved Ejection Fraction. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B et al. (TOPCAT investigators). *N Engl J Med.* 2014. 370;15:1383-1392. PMID: 24716680

Summary: 21 studies including 14768 inpatients were included, 13 of which included 90 and 180 day mortality. No difference in 28, 90 or 180 day mortality was detected with 0% heterogeneity. Subgroups in the MICU, SICU, mixed ICU, perioperative cardiac surgery and with acute MI had no net benefit to ITT. No benefits for secondary outcomes were detected for ITT except reduced rates of sepsis (RR 0.79 [CI 0.62-1.00]) although heterogeneity was significant ($I^2=53.1\%$). 10 trials found that ITT was associated with hypoglycemia in all settings (RR 6.00 [CI 4.06-8.87]) although heterogeneity was detected ($I^2=57.9\%$; $p < 0.001$). Risk of hypoglycemia was equal regardless of target serum glucose.

Conclusions: While ITT may reduce the frequency of sepsis, it is not associated with mortality benefit and is associated with a significant increased risk of hypoglycemia. If a target glucose level is used, 140-200mg/dL is felt to be safer than $< 120\text{mg/dL}$.

EBM goal: exposure to meta-analyses as the highest level of evidence.

A prescient prospective cohort study¹⁴ was performed in 1997 to determine predictors of hyperglycemia and hypoglycemia in hospitalized diabetic patients with a focus on the effectiveness of sliding scale insulin regimens - 23% of patients experienced hypoglycemic episodes, and 40% experienced hyperglycemic episodes. 76% of patients were placed on sliding-scale insulin regimens. When used alone (without longer-acting insulin), sliding-scale insulin regimens were associated with a 3-fold higher risk of hyperglycemic episodes compared with no pharmacologic therapy.

Gastroenterology/Hepatology

31. Management of adult patients with ascites due to cirrhosis: an update.

Runyon BA; AASLD Practice Guidelines Committee.

Hepatology. 2009; 49(6):2087-2107. PMID: 19475696

Key points:

- Cirrhosis is the most common cause of ascites in the U.S., and ascites is the most common complication of chronic liver disease, occurring in 50% of patients within 10 years of diagnosis. Ascites in the setting of cirrhosis is a poor prognostic sign, with only 50% of patients surviving for 2 years.
- Paracentesis should be performed in all patients presenting with new-onset ascites, as this procedure can help to identify the cause of ascites using the serum-ascites albumin gradient. Furthermore, 20% of patients with ascites due to cirrhosis will have ascitic fluid infection on hospital admission. Coagulopathy does not preclude paracentesis. Cell count and culture (inoculated into blood culture bottles) should be sent routinely.
- Restriction of dietary sodium and use of oral diuretics are the primary treatments for ascites. Sodium balance can be approximated by comparing intake with urinary sodium excretion, which can help with adjustment of sodium intake and dosing of diuretics. The oral diuretic combination of spironolactone and furosemide is recommended.

¹⁴ 33. Glycemic control and sliding scale insulin use in medical inpatients with diabetes mellitus. Queale WS, Seidler AJ, Brancati FL. *Arch Intern Med*. 1997 Mar 10; 157(5):545-52. PMID 9066459

- Refractory ascites can be managed with periodic large-volume paracentesis. There is conflicting data about the use of plasma volume-expanders such as albumin and dextran after large-volume paracentesis. Other treatments for refractory ascites include TIPS and liver transplantation.

32. Methylprednisolone therapy in patients with severe alcoholic hepatitis. A randomized multicenter trial.

Carithers RL Jr, Herlong HF, Diehl AM, Shaw EW, Combes B, Fallon HJ, Maddrey WC. *Ann Intern Med.* 1989 May 1; 110(9):685-90. PMID 2648927

Objective: A randomized controlled trial compared methylprednisolone (32 mg daily for 28 days followed by taper) with placebo for management of severe alcoholic hepatitis (hepatic encephalopathy or discriminate function >32). The primary outcome was 28-day mortality.

Conclusions: Patients in the methylprednisolone group had lower 28-day mortality (6%) compared with the placebo group (35%). In patients with hepatic encephalopathy, the 28-day mortality rate was 7% in the methylprednisolone group and 47% in the placebo group. Patients in the methylprednisolone group also had more rapid decline in INR and AST. Factors associated with mortality included encephalopathy and age. Methylprednisolone was discontinued early in 3/35 patients due to psychosis, pancreatitis, and gram-negative sepsis. Refer to Louvet et al. 2007¹⁵ for the Lille model (compared with the discriminant function) for initiation of steroids for alcoholic hepatitis. Also refer to Akriviadis et al., 2000¹⁶ for the use of pentoxifylline instead of steroids for treatment of alcoholic hepatitis).

33. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis.

Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L, Castells L, Vargas V, Soriano G, Guevara M, Gines P, Rodes J. *N Engl J Med* 1999; 341(6):403-9. PMID: 10432325.

Objective: A randomized control trial evaluating the benefit of IV albumin for patients admitted with spontaneous bacterial peritonitis (SBP). The development of renal impairment was the primary outcome used to calculate the size of the study, although the authors also list mortality as a primary outcome measurement. Renal impairment was defined as the irreversible development of a BUN or Cr > 50% of index measurements upon enrollment.

Summary: 126 patients with cirrhosis from any cause who were admitted with uncomplicated SBP, defined as diagnostic paracentesis fluid with a PMN count > 250/mL. Patients with fluid shifts (e.g. GI bleeding or dehydration) or with baseline Cr > 3 were excluded from the study. Therapeutic paracentesis and diuresis were against protocol until resolution of the infection (signs of infection have resolved and PMN count < 250/mL), although 7 patients violated protocol and received paracentesis. Intervention was 1.5g of

¹⁵ Louvet A, Naveau S, Abdelnour M, et al. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. *Hepatology* 2007;45:1348-54. PMID: 17518367

¹⁶ Akriviadis E, Botla R, Briggs W, Han S, Reynolds T, Shakil O. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000;119:1637-48. PMID: 11113085

albumin per patient weight in kg on day 1 and 1.0g albumin/kg on day 3. All patients received a second-generation cephalosporin.

Infection resolved in most patients. Renal impairment occurred in 6 (10%) patients receiving albumin and in 21 (33%) patients in the control group ($p=0.002$). 6 (10%) patients died prior to discharge in the albumin group compared with 18 (29%) in the control group ($p=0.01$). At three months, 14 (22%) of patients had passed in the albumin group while 26 (41%) had died in the control group ($p=0.03$). Higher renin levels are associated with the control, implying a pathophysiologic mechanism of death associated with hepatorenal syndrome.

Conclusions: Albumin reduces the incidence of hepatorenal syndrome associated with SBP and thus reduces the incidence of death associated with SBP.

Infectious Diseases

34. Dexamethasone in adults with bacterial meningitis.

de Gans J, van de Beek D; European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators.

N Engl J Med. 2002 Nov 14; 347(20):1549-56. PMID: 12432041

Objective: A randomized controlled trial comparing dexamethasone (10 mg given 15-20 minutes prior to first dose of antibiotic, then q6h for 4 days) with placebo for adult patients with bacterial meningitis. The primary outcome was an unfavorable Glasgow Outcome Scale score, and a subgroup analysis based on causative organism was performed.

Conclusions: Treatment with dexamethasone was associated with reduced risk of unfavorable outcome (15% vs. 25%, RR = 0.59) as well as reduced 8-week mortality (7% vs. 15%, RR = 0.48). Predictors of unfavorable outcome included coma on admission, pneumococcal meningitis, and hypotension. Among patients with pneumococcal meningitis, dexamethasone was associated with reduced risk of unfavorable outcome (26% vs. 52%, RR = 0.5). However, there was no benefit in patients with meningitis due to *Neisseria meningitidis*. Adjuvant treatment with dexamethasone did not have an effect on neurologic sequelae, including hearing loss. Treatment with dexamethasone did not result in increased risk of adverse events.

35. Clostridium difficile – more difficult than ever.

Kelly CP, LaMont JT.

N Engl J Med 2008 Oct 30; 359(18): 1932-40. PMID: 18971494

Since its initial discovery, *C. difficile* infection has been recognized as an increasing source of morbidity and mortality in immunocompetent and immunocompromised patients¹⁷. The rise of recurrent *C. difficile* infections and increasing virulence have driven the exploration of additional treatment options such as tapering treatment, new antibiotics and formal studies of fecal transplant.¹⁸

¹⁷ Current Status of Clostridium difficile Infection Epidemiology. Lessa FC, Gould CV, McDonald LC. Clin Infect Dis. (2012) 55 (suppl 2): S65-S70.

¹⁸ Current State of Clostridium difficile Treatment Options. Venugopal AA, Johnson S. Clin Infect Dis. (2012) 55 (suppl 2): S71-S76.

36. Fever of unexplained origin: report on 100 cases.

Petersdorf RG, Beeson PB.

Medicine. 1961; 40:1-30. PMID 13734791

Objective: A prospective analysis of 100 cases of FOU was performed to determine etiologies. The following criteria were used for FOU: illness of >3 weeks duration, temperature >101°F on several occasions, and diagnosis uncertain after 1 week of evaluation in the hospital.

Conclusions: A reasonably certain diagnosis was made in all but 7 cases. Infectious etiologies were most common, accounting for 36 cases. The most frequently diagnosed infectious diseases were TB (11), liver or biliary tract infection (7), bacterial endocarditis (5), and abdominal abscess (4). Neoplastic disease was the second most common cause of FOU, accounting for 19 cases. In this category, lymphoma/leukemia (8) and disseminated carcinoma (7) were identified most often. Collagen vascular disease accounted for 13 cases of FOU, primarily due to rheumatic fever (6) and SLE (5). Other etiologies of fever included periodic fever syndromes (5), factitious fever (3), hypersensitivity states (3), pericarditis (2), sarcoidosis (2), temporal arteritis (2), post-MI (1), thrombophlebitis (1), and miscellaneous (5).

Update: The etiology of FOU changed significantly since the publication of this paper both due to changing epidemiology of disease as well as technological advances. More recent review articles can be found by Mourad et al., 2003,¹⁹ or by Kaul et al., 2006.²⁰

37. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service.

Durack DT, Lukes AS, Bright DK, and The Duke Endocarditis Service.

Am J Med. 1994; 96(3):200-9. PMID 8154507[r18]

Objective: 421 consecutive cases of suspected endocarditis were reviewed to validate new (Duke) clinical criteria for the diagnosis of endocarditis. The new clinical criteria include 2 “major criteria” (typical blood culture and positive echocardiogram) and 6 “minor criteria” (predisposition, fever, vascular phenomena, immunologic phenomena, suggestive echocardiogram, and suggestive microbiologic findings). Patients were grouped into 3 diagnostic categories: (1) “definite” based on pathologic or clinical criteria, (2) “possible,” and (3) “rejected.”

Conclusions: 55/69 (80%) of pathologically confirmed cases of endocarditis were classified as clinically definite endocarditis using the new criteria, compared with only 35/69 (51%) using older clinical criteria. No cases of pathologically confirmed endocarditis were rejected by the new criteria, compared with 12/69 (17%) for older criteria. Among those cases of suspected endocarditis that were not pathologically confirmed, the new criteria identified more patients as having definite or probable endocarditis.

¹⁹ Mourad O, Palda V, Detsky AS. A comprehensive evidence-based approach to fever of unknown origin. *Arch Intern Med* 2003;163:545-51. PMID: 12622601

²⁰ Kaul DR, Flanders SA, Beck JM, Saint S. Brief report: incidence, etiology, risk factors, and outcome of hospital-acquired fever: a systematic, evidence-based review. *J Gen Intern Med* 2006;21:1184-7. PMID: 17026728

38. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America.

Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Bolger AF, Levison ME, Ferrieri P, Gerber MA, Tani LY, Gewitz MH, Tong DC, Steckelberg JM, Baltimore RS, Shulman ST, Burns JC, Falace DA, Newburger JW, Pallasch TJ, Takahashi M, Taubert KA; Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease; Council on Cardiovascular Disease in the Young; Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia; American Heart Association; Infectious Diseases Society of America. *Circulation*. 2005;111:3167-3184. PMID: 15956145

Key points:

- TEE is the imaging study of choice for diagnosis of endocarditis.
- Antibiotic therapy of endocarditis depends on the causative organism and whether a native or prosthetic valve is involved. Addition of an aminoglycoside is typically required for enterococcal endocarditis and for prosthetic valve staphylococcal endocarditis. Duration of therapy typically ranges from 2-6 weeks.
- Empiric therapy for culture-negative endocarditis should be based on potential etiologies identified by epidemiologic clues.
- Complications of endocarditis include CHF, embolic events, perivalvular extension, splenic abscess/infarction, and mycotic aneurysms.
- Due to potential drug toxicity and the risk of recurrent endocarditis, close clinical monitoring is required during and after treatment.

39. Toxic-shock syndrome associated with phage-group-I Staphylococci.

Todd J, Fishaut M, Kapral F, Welch T.

Lancet. 1978 Nov 25; 2(8100):1116-8. PMID: 82681

Objective: A case series of 7 children presenting with staphylococcal toxic shock syndrome was described.

Conclusions: Patients presented with high fever, headache, confusion, conjunctival hyperemia, scarlatiniform rash, subcutaneous edema, vomiting, and watery diarrhea. All patients had profound, refractory hypotension and acute kidney injury. All patients were treated with penicillinase-resistant penicillin as well as intravenous fluids. One patient died, and all of the survivors developed desquamation of the hands and feet. Two patients had *S. aureus* isolated from foci of infection (buttock abscess, empyema), and 3 had *S. aureus* isolated from mucosal swabs. None had positive blood cultures. All of the *S. aureus* isolates produced a novel epidermal toxin.

Hematology/Oncology

40. Clinical presentation of infection in granulocytopenic patients.

Sickles EA, Greene WH, Wiernik PH.

Arch Intern Med. 1975 May; 135(5):715-9. PMID: 1052668

Objective: Clinical manifestations of 344 infections occurring in patients being treated for malignancy were compiled. The impact of absolute neutrophil count (ANC) on clinical manifestations was determined (neutropenia = ANC <1,000).

Conclusions: The infections identified were pneumonia (42%), UTIs (24%), skin infections (17%), pharyngitis (11%), and anorectal infections (6%). 49% of patients presenting with infection had leukemia, 26% had lymphoma, 15% had solid tumors, and 11% had brain tumors. Among those patients with pharyngitis, patients with neutropenia were more likely to have fever and less likely to have exudates. For skin infections, patients with neutropenia were more likely to have fever but were less likely to have typical clinical manifestations such as swelling and fluctuance. Neutropenic patients with anorectal infection were also less likely to have typical symptoms such as fissure, fluctuance, or exudate. Neutropenic patients with UTI had dysuria, frequency, and pyuria less often but were more often bacteremic than patients with ANC >1,000. Similarly, neutropenic patients with pneumonia were less likely to have cough and sputum production but were more likely to become bacteremic.

Update: please refer to the 2010 IDSA guidelines for the current bacterial epidemiology and management of neutropenic patients.²¹

Rheumatology

41. Acute monoarthritis: what is the cause of my patient's painful swollen joint?

Ma L, Cranney A, Holroyd-Leduc JM.

CMAJ. 2009 Jan 6; 180(1):59-65. PMID: 19124791

Key points:

- The differential diagnosis for acute monoarthritis includes crystal-induced arthritis (gout or pseudogout) (18-27%), septic arthritis (8-27%), degenerative osteoarthritis (5-17%), rheumatoid arthritis (11-16%), trauma (11%), other rheumatologic disease (5-7%), spontaneous hemarthrosis (3%), and aseptic necrosis (3%). In 16-36% of cases, the cause is not identified.
- History and physical examination are important but are usually not adequate to make a diagnosis. The next step should be analysis of synovial fluid for gross appearance, presence of crystals, leukocyte count and differential, Gram staining, and culture.
- Risk factors for gout include male sex (RR = 7.6), chronic kidney disease (RR = 5), hypertension (RR = 3.9), and obesity (RR = 3.8). A diagnosis of gout is established by the presence of ≥ 7 of 13 criteria established by the American Rheumatism Association.

²¹ Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clin Infect Dis* 2011;52:e56-93. PMID: 21258094

- Risk factors for septic arthritis include age >80 (RR = 3.5), recent joint surgery (RR = 6.9), hip or knee prosthesis (RR = 3.1), prosthesis with skin infection (RR = 15), diabetes (RR = 2.7), and rheumatoid arthritis (RR = 2.5). Using synovial fluid culture as the gold standard (sensitivity 75-95%), the most useful laboratory finding for early diagnosis of septic arthritis is synovial fluid leukocyte count >50 x 10⁹/L (positive likelihood ratio = 7.7, negative LR = 0.42) with at least 90% neutrophils (positive LR 3.4, negative LR 0.34).
- The American College of Rheumatology has developed 3 different sets of criteria for diagnosis of osteoarthritis: clinical, clinical and radiographic, and clinical and laboratory.

42. Laboratory testing in the rheumatic diseases: a practical review.

Colglazier CL, Sutej PG.

South Med J. 2005 Feb; 98(2):185-91. PMID: 15759949

Key points:

- ESR is elevated in many inflammatory conditions and is therefore nonspecific. CRP tends to rise and fall more quickly and is also nonspecific.
- ANA is highly sensitive for SLE, and a negative ANA makes SLE very unlikely (negative likelihood ratio = 0.11). However, a positive ANA is less helpful with a positive predictive value of only 11% for SLE. ANA is also seen in healthy patients (especially with advancing age) and in other inflammatory conditions. ANA staining patterns are not sensitive or specific and have generally been replaced by other tests; however, ANA titers may be clinically useful.
- The presence of anti-dsDNA is very specific for SLE (97.4%) but is not very sensitive (57.3%), and a negative test does not exclude the possibility of SLE (negative LR = 0.49).
- Anti-Smith antibody is highly specific for SLE but is only seen in 25-30% of SLE patients. Anti-U1-RNP is associated with mixed connective tissue diseases. Anti-histone antibodies are found in 95% of drug-induced lupus.
- Anti-Ro/SS-A and anti-La/SS-B antibodies are found in 75% of patients with primary Sjogren syndrome and 50% of patients with SLE. These antibodies are also associated with congenital heart block when present in the mother.
- Anti-Scl-70 antibodies are found in 20% of diffuse systemic sclerosis patients. Anti-centromere antibodies are associated with limited cutaneous systemic sclerosis (formerly CREST). Anti-U3-RNP antibodies are found in 12% of patients with scleroderma.
- The sensitivity of rheumatoid factor for RA is 50-85%, but rheumatoid factor is also seen in healthy individuals and in other inflammatory conditions. Anti-CCP antibodies have similar sensitivity for RA but are more specific (90-95%).
- c-ANCA is highly sensitive for Wegener's granulomatosis, whereas p-ANCA is associated with microscopic polyarteritis and isolated pauci-immune glomerulonephritis.

Neurology

43. Carotid stenosis.

Grotta JC.

N Engl J Med. 2013.Sep 19; 369(12):1143-50. PMID: 24328480

Carotid stenosis causes 10-20% of strokes due to atherosclerosis, dissection and fibromuscular dysplasia. Typical means of detection include ultrasonography, MRA, CTA or catheter angiography. Direct interventions include carotid endarterectomy (CEA) or carotid stenting with distal protection, with a slightly improved outcome for older patients with the former and improved outcome for younger patients with the latter.

Symptomatic patients with carotid stenosis > 70% benefit most from direct intervention (and those undergoing CEA appear to have the most benefit when performed within 2 weeks of neurologic symptoms). Patients with >50-69% stenosis also benefit from CEA but to a lesser degree, whereas patients with <50% stenosis derive no benefit. Asymptomatic patients, even those with >70% stenosis, receive less benefit than symptomatic patients although still had improved outcomes compared to medical therapy. The studies defining these stenosis criteria for appropriateness of CEA^{22, 23} were performed in the early 1990's, therefore outcomes may have improved with medical therapy in the era of statins and additional antiplatelet agents. CEA and stenting have been found to have equivalent outcomes in the modern era of medicine.

44. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack.

Johnston C, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, Sidney S.

Lancet. 2007 Jan 27; 369(9558):283-92. PMID 17258668.

Objective: Data from 2,893 patients presenting to the ED with TIA was evaluated to validate 2 similar existing prognostic scores for early risk of stroke after TIA (ABCD score = 7-day risk, California score = 90-day risk) and to develop a unified prognostic score to predict 2-day risk of stroke.

Conclusions: Stroke occurred in 9.2% of individuals within 90 days, 7.5% within 30 days, 5.5% within 7 days, and 3.9% within 2 days. The 2 existing prognostic scores predicted the risk of stroke similarly at 2, 7, and 90 days. The unified score (ABCD2) was based on 5 factors: age ≥60 (1 point); blood pressure ≥140/90 (1); clinical features: unilateral weakness (2), speech impairment without weakness (1); duration ≥60 minutes (2) or 10-59 minutes (1); and diabetes (1). This score validated well with a 2-day stroke risk of 8.1% for a score of 6-7 (high risk), 4.1% for 4-5 (moderate risk), and 1% for 0-3 (low risk).

²² Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* 1998;351: 1379-87.

²³ Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med.* 1991 Aug 15;325(7):445-53. PMID: 1852179

45. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke.

Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D, von Kummer R, Wahlgren N, Toni D; ECASS Investigators.

N Engl J Med. 2008 Sep 25; 359(13):1317-29. PMID: 18815396

Objective: A randomized controlled trial compared intravenous alteplase to placebo between 3 and 4.5 hours after onset of stroke. The primary outcome was disability at 90 days based on the Rankin scale.

Conclusions: 821 patients were enrolled after exclusion of patients with brain hemorrhage, severe stroke, seizure, stroke or head trauma within the past 3 months, anticoagulation within the past 48 hours, platelet count <100,000, and systolic blood pressure >185. The median time for administration of alteplase was 3 hours 59 minutes. More patients in the alteplase had a favorable outcome than in the placebo group (52.4% vs. 45.2%). There was no difference in mortality between the 2 groups (7.7% vs. 8.4%). The rate of intracranial hemorrhage was higher in the alteplase group (for any hemorrhage, 27% vs. 17.6%; for symptomatic hemorrhage, 2.4% vs. 0.2%). There was no significant difference in the rate of other adverse events.

Healthcare Quality

46. An intervention to decrease catheter-related bloodstream infections in the ICU.

Pronovost P, Needham D, Berenholtz S, Sinopoli D, Chu H, Cosgrove S, Sexton B, Hyzy R, Welsh R, Roth G, Bander J, Kepros J, Goeschel C.

N Engl J Med. 2006 Dec 28; 355(26):2725-32. PMID: 17192537

Objective: A quasi-experimental study was performed to determine the impact of implementation of an evidence-based “bundle” intervention on the incidence of catheter-related bloodstream infections in Michigan ICUs. The Keystone bundle consisted of the following: hand hygiene, use of full barrier precautions during the insertion of central venous catheters, cleansing of the skin with chlorhexidine, avoiding the femoral site if possible, and removal of unnecessary catheters.

Conclusions: 103 Michigan ICUs reported data, accounting for 85% of ICU beds in the state. The mean incidence of catheter-related bloodstream infection decreased from 7.7 infections/1,000 catheter-days at baseline to 2.3 at 3 months and 1.4 at 18 months. The median rate decreased from 2.7 at baseline to 0 at 3 and 18 months. A follow-up study in the BMJ²⁴ found that the lower infection rates continued 36 months after the intervention.

²⁴ Pronovost PJ, Goeschel CA, Colantuoni E, Watson S, Lubomski LH, Berenholtz SM, Thompson DA, Sinopoli DJ, Cosgrove S, Sexton JB, Marsteller JA, Hyzy RC, Welsh R, Posa P, Schumacher K, Needham D. Sustaining reductions in catheter related bloodstream infections in Michigan intensive care units: observational study. *BMJ* 2010;340:c309. PMID: 20133365

47. The Association of Registered Nurse Staffing Levels and Patient Outcomes: Systematic Review and Meta-Analysis.

Kane RL, Shamliyan TA, Mueller C, Duval S, Wilt TJ.
Med Care. 2007; 45(12):1195-1204. PMID 18007170

Key points:

- Higher RN staffing (1 additional RN full time equivalent per patient-day or per shift) is associated with reduced mortality in ICU patients (OR = 0.91), medical patients (OR = 0.94), and surgical patients (OR = 0.84).
- Higher RN staffing is associated with fewer adverse events, including hospital-acquired pneumonia (OR = 0.70), respiratory failure (OR = 0.4), unplanned extubation (OR = 0.49), and cardiac arrest (OR = 0.72) in ICUs. No studies reported adjusted odds ratios for pressure ulcers or patient falls with respect to RN staffing.
- Higher RN staffing is associated with 24% shorter length of stay in ICUs and 31% in surgical patients.

48.6 EZ Steps to Improving Your Performance (or How to Make P4P Pay 4U!).

Hayward RA, Kent DM.
JAMA. 2008; 30(3): 255-6. PMID: 18632535.

This article is a satirical guide to the “way to success” in a pay-for-performance model that deftly outlines the artificial pressures through which P4P can undermine thoughtful patient care and our commitment to serve all patients, regardless of medical or social complexity.

Medical Education

49. The art of pimping.

Detsky AS.
JAMA. 2009; 301(13): 1370-81. PMID 19336716

Key points:

- The term “pimping” was popularized in 1989 by Brancati²⁵, but the origins of the term date back to 17th century London.
- For the pimpee, effective defense mechanisms include avoidance (no eye contact with the pimper), eating during the pimping session, acting hostile, constantly checking your pager, pimping back (using a PDA helps with this), or answering a different question than is asked (the politician’s approach). Crying is not effective.
- Pimpers should follow proper pimping etiquette by obeying the following rules:
 - Always start at the bottom of the educational chain and work your way up.
 - Do not embarrass other attending physicians.
 - Attempt to draw in the pimpees by starting with easy questions and using humor.
 - Apologize when you embarrass a pimpee, and offer praise.

²⁵ The art of pimping. Brancati FL. *JAMA* 1989; 262(1):89-90. PMID: 2733128

- Pimping should be used to increased retention of key teaching points, and learning more often occurs from incorrect answers. Most important, pimping should not be taken too seriously.

Nephrology

50. A practical approach to acid-base disorders.

Haber RJ.

West J Med. 1991; 155(2): 146-51. PMID 1843849

Key points:

- Three simple rules can be used to recognize a primary acid-base disorder:
 - 1) Look at the pH. Whichever side of 7.40 the pH is on, the process or processes that caused it to shift to that side are the primary abnormalities.
 - 2) Calculate the anion gap. If the anion gap is ≥ 20 , there is a primary metabolic acidosis regardless of pH or serum bicarbonate concentration.
 - 3) Calculate the excess anion gap and add to the measured serum bicarbonate concentration. If the sum is greater than a normal serum bicarbonate, there is an underlying metabolic alkalosis, and if it is less than a normal serum bicarbonate, there is an underlying non-anion gap metabolic acidosis.

Once the primary acid-base disorder is known, the etiology should be determined. Clues to etiology include whether the disorder is chronic or acute (based on presence or absence of compensatory response), volume status for patients with metabolic alkalosis (determined by measuring urine chloride concentration), and presence or absence of an anion gap for patients with metabolic acidosis.