Here are 25 trials that we feel are highly relevant for your practice as a future hospitalist. There's more to our practice than this, but here's a great start!

CARDIOLOGY

1. RACE II

Key findings: Among patients with permanent atrial fibrillation, lenient rate control (HR<110 bpm) is as effective as strict rate control (HR <80 bpm) in preventing cardiovascular events

Background:

- AFFIRM (2002) suggested a mortality benefit in management of AF with rate control over rhythm control.
- The 2010 Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II (RACE II) trial directly addressed the issue of optimal rate control for patients with permanent AF.

Study design:

- Multicenter, open-label, parallel-group, randomized controlled noninferiority trial
- N=614
    - Lenient rate control (n=311)
    - Strict rate control (n=303)
- Setting: 33 Dutch centers
- Enrollment: January 2005 to June 2007
- Median follow-up: 3 years
- Primary outcome: Composite of CV mortality, CHF, stroke, VTE, major bleeding, and arrhythmic events

Results:

- A lenient rate control strategy (resting HR <110 bpm) was noninferior to a strict rate control strategy (resting HR <80 bpm and HR during moderate exercise <110 bpm) in preventing the composite outcome of CV death, CHF hospitalization, stroke, systemic embolism, bleeding, and life threatening arrhythmic events over 3 years (estimated cumulative incidence of the primary outcome at 3 years was 12.9% in the lenient-control group and 14.9% in the strict-control group).

  The strict rate control group met their resting targets in 67% of cases (compared to 98% in the lenient rate control group) and required nine times as many visits (684 vs. 75) in order to achieve rate control targets.

Criticisms:

- The trial included physically active rather than sedentary patients
- It excluded patients with previous stroke, due to the decision to assess rate control by means of exercise testing in the strict-control group. This resulted in a low-risk study population and may have led to the lower-than-expected primary outcome event rate.
- In the strict-control group, the resting and exercise targets were achieved in 67.0% of the patients, whereas in the lenient-control group the target rate was virtually always reached.
- Therefore, the possibility that a significant difference might exist between the two groups had a more effective means of strict rate control been used, had the heart rates been kept just below 110 beats per minute in the lenient-control group, or had the study followed patients beyond 3 years.

Additional points:

- Based upon the results of RACE II, very stringent heart rate control is not necessary in many physically active patients with atrial fibrillation who are minimally symptomatic.
- A more lenient rate control strategy offers the advantages of less medication and fewer outpatient visits to achieve HR control.

Citation: Van Gelder IC, et al. "Lenient versus Strict Rate Control in Patients with Atrial Fibrillation". *The New England Journal of Medicine*. 2010. 362(15):1363-73.

2. ARISTOTLE

Key findings: In patients with nonvalvular atrial fibrillation and at ≥1 stroke risk factor (age ≥75 years; prior stroke, TIA, or embolism; symptomatic HF in prior 3 months or LVEF <40%; DM; HTN requiring medications), apixaban is associated with a greater reduction in rates of stroke or systemic embolism while having a lower rate of lower bleeding than warfarin.

Background:

- Vitamin K antagonist therapy had been established as the standard of care for prevention of stroke and systemic embolism in atrial fibrillation, but has multiple drawbacks including drug-drug interactions, need for frequent monitoring, and dietary modification.
- Several drugs, including dabigatran in RE-LY (2009) and rivaroxaban in ROCKET-AF (2011) (and later edoxaban in ENGAGE AF-TIMI 48) subsequently were proven efficacious as alternatives to VKA therapy in atrial fibrillation.

- Like these other drugs, apixaban, an oral factor Xa inhibitor, does not require monitoring, and has fewer drug-drug interactions. ARISTOTLE was the first large clinical trial establishing its efficacy.

Study design:

- Multicenter, double-blind, comparative trial
- N=18,201
    - Apixaban (n=9,120)
    - Warfarin (n=9,081)
- Setting: 1,034 centers in 39 countries
- Enrollment: 2006-2010
- Median follow-up: 1.8 years
- Analysis: Intention-to-treat and non-inferiority
- Primary outcomes:
    - Effectiveness: Stroke or systemic embolism
    - Safety: Major bleeding

Results: With a median follow-up of 1.8 years, apixaban was superior to warfarin in rates of stroke or systemic embolism (annual incidence 1.27% vs. 1.60%). It was also associated with less major bleeding (annual incidence 2.13% vs. 3.09%).
Criticisms:

- Patients in the warfarin group had an INR in the therapeutic range (2-3) for a mean of 62.2% of the time.

Additional points: The *2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation* released January 28, 2019 recommend non-vitamin K oral anticoagulants (NOACs) (including dabigatran, rivaroxaban, apixaban and edoxaban) as the preferred drug class over warfarin to reduce stroke risk in appropriate (nonvalvular) atrial fibrillation patients, unless patients have moderate-to-severe mitral stenosis or a mechanical heart valve.

Citation: Granger CB, et al. "Apixaban versus warfarin in patients with atrial fibrillation". *The New England Journal of Medicine*. 2011. 365(11):981-982.

3. TIMACS

Key findings: Among patients with unstable angina or NSTEMI, early intervention (≤24 h) does not result in a decrease in the composite of death, MI, or stroke at 6 months compared to delayed intervention (≥36 h) except in patients at high-risk (GRACE score >140).

Background:

- Numerous randomized controlled trials including FRISC-II, RITA-3, and TACTICS-TIMI 18 have demonstrated the benefit of early invasive intervention with angiography in high-risk patients with unstable angina (UA) and NSTEMI. However, the exact timing of intervention had not been clearly established.
- Prior to the TIMACS trial, observational studies had suggested lower rates of complications in patients undergoing PCI after ≥48 h of medical therapy with the hypothesis that this "cooling-off" strategy allows for plaque stabilization and better interventional outcomes.

Study design:

- Multicenter, blinded, parallel-group, randomized, controlled trial
- N=3,031 patients with UA/NSTEMI
    - Early intervention (n=1,593)
    - Delayed intervention (n=1,438)
- Setting: 152 sites in 19 countries
- Enrollment: 2003-2008
- Mean follow-up: 6 months
- Analysis: Modified Intention-to-treat
- Primary outcome: Composite of death, myocardial infarction, or stroke

Results:

- At 6 months, the primary outcome (composite of death, new MI, or stroke) occurred in 9.6% of patients in the early-intervention group compared to 11.3% in the delayed-intervention group (HR 0.95; 95% CI 0.68 to 1.06; P=0.15).
- There was a significant difference in the secondary outcome of death, MI, or refractory ischemia at 6 months in the early-intervention group (9.5%) versus delayed-intervention patients (12.9%) which was largely driven by a reduction in refractory ischemia (HR 0.72, CI 0.58 to 0.89, p=0.003).
- A prespecified subgroup analysis showed the highest risk patients (classified as having a GRACE risk score >140) undergoing early intervention had a significantly lower rate of the primary outcome compared to those in the
- delayed intervention arm (13.9% vs. 21.0% HR 0.65, CI 0.48 to 0.89, p=0.006). When this same subgroup analysis was applied to low- to moderate-risk patients, there was no significant difference in the primary outcome between early or delayed intervention.

Criticisms:

- Finding of benefit with early intervention in high-risk patients came out of subgroup analysis

- Trial was relatively underpowered to detect differences in the primary end point
- High crossover rate into the early intervention arm
- Anticoagulant used was heparin rather than low-molecular weight heparin, the latter associated with improvements in outcomes among patients with ACS

Additional points:

- The overall findings from this trial suggest that in patients with UA/NSTEMI, an early intervention strategy is not superior to delayed intervention except in those patients at highest risk determined by the GRACE risk score tool.
- Early intervention was associated with a significant decrease in refractory ischemia suggesting that in patient's presenting to a PCI-capable institution, early intervention may be more favorable but not critical.
- Based on the results of this trial, 2014 AHA/ACC guidelines on NSTEMI suggest that it may be reasonable to choose an early invasive strategy (within 24 hours of admission) over a delayed one (within 25 to 72 hours) in patients with high-risk UA/NSTEMI.

Citation: Mehta SR, et al. "Early versus Delayed Invasive Intervention in Acute Coronary Syndromes". *The New England Journal of Medicine*. 2009. 360:2165-2175.

4. CANVAS

Key findings: Among patients with type 2 diabetes mellitus at high risk for cardiovascular events, canagliflozin had a lower risk of cardiovascular events and reduced the rate of renal decline and heart failure hospitalization compared to those who received placebo but a greater risk of amputation.

Background:

- Type 2 diabetes mellitus is associated with significant risk of cardiovascular and renal disease. While standard medications such as insulin, sulphonylureas, and DPP4 inhibitors all effectively reduce blood glucose, these agents have not been associated with improvements in a cardiovascular disease or survival.
- The use of inhibitors of sodium–glucose cotransporter 2 (SGLT2) had been shown to have favorable effects on biomarkers, including glycemia, weight, blood pressure, intrarenal hemodynamics, and albuminuria.
- CANVAS was designed to assess the effects of treatment with canagliflozin on cardiovascular, renal, and safety outcomes.

Study design:

- Two multicenter, randomized, double-blind, placebo-controlled trial
- N=10,142 (4330 in CANVAS and 5812 in CANVAS-R; 96% completed trial)

        - Canagliflozin 100mg vs. 300mg daily vs. Placebo
        - Canagliflozin 100mg then 300mg daily vs. Placebo
    - Setting: 667 centers in 30 countries involved in two trials
    - Enrollment: 2009-2013
    - Median follow-up: 126 weeks; mean follow-up: 188 weeks
    - Analysis: Intention-to-treat
    - Primary outcome: CV mortality, nonfatal MI, or nonfatal stroke

Results:

- At mean follow-up of 188 weeks, canagliflozin was associated with a reduction in death from CV causes, nonfatal MI, or nonfatal stroke (26.9 vs. 31.5 per 1,000 patient-years; HR 0.86; 95% CI 0.75-0.97) with a possible benefit with respect to the progression of albuminuria (HR 0.73; 95% CI 0.67-0.79), the composite outcome of reduction in GFR, need for renal-replacement therapy or death from renal causes (HR 0.60; 95% CI 0.47-0.77), and hospitalization for heart failure (HR 0.67; 95% CI, 0.52-0.87).
- There was a greater incidence of genital infections and canagliflozin was also associated with a significant doubling in the risk of amputations (6.3 vs. 3.4 per 1000 patient-years; HR 1.97; 95% CI, 1.41 to 2.75), primarily of the toe or metatarsal.

Criticisms:

- Low number of events of end-stage kidney disease observed and large number of analyses, which could increase the risk of false positive findings
- The trial also had a relatively small proportion of patients with established kidney disease, which limits generalization of the results to that population

Additional points: Since this trial, use of SGLT2 inhibitors has been incorporated into the treatment algorithms in both the ACC and ADA guidelines.

Citation: Neal B, et al. "Canagliflozin and cardiovascular and renal events in type 2 diabetes". *The New England Journal of Medicine*. 2017. 377(7):644-657.

NEUROLOGY

5. POINT

Key findings: Among patients with acute TIA or minor ischemic stroke, starting aspirin/clopidogrel within 12h of symptom onset reduces the 90-day stroke incidence at the cost of increasing bleeding rates, when compared to aspirin monotherapy.

Background:

- Aspirin and other antiplatelet agents are the mainstays of therapy in patients with non-thromboembolic ischemic stroke and TIA, and there has been interest in combining antiplatelet agents to improve efficacy.
- Prior studies in which patients received long-term treatment with aspirin/clopidogrel in CHARISMA, MATCH, and SPS3 suggested that dual antiplatelet therapy increases bleeding risk without significantly reducing the risk of stroke. However, since the risk of stroke recurrence after TIA or minor stroke is front-loaded, there continued to be interest in investigating the efficacy of a short course of dual antiplatelet therapy immediately following stroke or high-risk TIA.
- CHANCE demonstrated in a Chinese population that the combination of aspirin/clopidogrel for 21 days followed by clopidogrel monotherapy was superior to single-agent aspirin for reducing stroke recurrence at 90 days, without a difference in bleeding rate between the two groups.
- Despite these promising results, many European and North American clinicians were reluctant to apply this data to their patients. A randomized study of a broader population was necessary.

Study design:

- Multicenter, randomized, double-blind, placebo-controlled trial
- N=4,881 patients with acute ischemic stroke or high-risk TIA
    - Aspirin (n=2,432)
    - Aspirin/clopidogrel (n=2,449)
- Setting: 269 centers in North America, Europe, Australia, and New Zealand
- Enrollment: 2010-2017
- Follow-up: 90 days
- Analysis: Intention-to-treat
- Primary outcome: Composite of ischemic stroke, MI, or ischemic vascular death

Results:

- The study was halted after 83.6% of planned enrollment when a safety signal for excess major hemorrhage was noted in the aspirin/clopidogrel group.

- Among patients in the aspirin/clopidogrel group, fewer primary efficacy outcome events occurred (5.0% vs. 6.5%; P=0.02; NNT=66), but with more major bleeding (0.9% vs. 0.4%; P=0.02; NNH=200).
- POINT demonstrates that 90 days of DAPT reduces the rate of recurrent stroke and increases rates of major bleeding among patients with minor ischemic stroke and high-risk TIA. Further analysis suggests that 90 days of DAPT is unnecessarily long.
- The majority of efficacy events occurred during the first 7 days, and 80-90% occurred within the first 30 days, while the bleeding rate was roughly stable during the 90-day follow-up.

Criticisms:

- Compared to CHANCE, the trial included a longer duration of dual anti-platelet therapy (90 vs. 21 days) and the loading dose for clopidogrel used was higher (600 mg vs. 300 mg), which may have affected bleeding rates
- Patients with moderate-to-severe stroke, those with cardioembolic stroke, and those who are candidates for thrombolysis or thrombectomy were not represented in the trial
- Although discontinuation rates were similar in the two groups, a trial drug was discontinued permanently in 29% of the patients before the follow up period was complete

Additional points:

- The 2019 American Heart Association/American Stroke Association (AHA/ASA) guidelines, which focus on early management of ischemic stroke, strongly recommend the administration of aspirin within 24 to 48 hours of acute ischemic stroke (AIS).
- For patients with minor noncardioembolic ischemic stroke (NIHSS score ≤3) who did not receive IV alteplase, the guidelines also strongly recommend the use of 21 days of DAPT with aspirin and clopidogrel started within 24 hours of presentation.

Citation: Johnston SC, et al. "Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA". *The New England Journal of Medicine*. 2018. 379(3):215-225.

6. ECASS III

Key findings: Intravenous alteplase improved neurologic outcomes within 4.5 hours of stroke onset among patients with acute ischemic stroke. Despite an increased incidence of intracranial hemorrhage, there was no difference in mortality between alteplase and placebo groups.

Background:

- The National Institute of Neurological Disorders and Stroke (NINDS) trial in 1995 demonstrated that administration of alteplase in patients with acute ischemic stroke within 3 hours of symptom onset resulted in improvements in functional outcomes at 3 months.
- However, prior to ECASS III, the efficacy and safety of alteplase administered more than 3 hours after the onset of symptoms had not been established.

Study design:

- Multi-center, double-blind, parallel-group, randomized, placebo-controlled trial
- N=821
    - Alteplase (n=418)
    - Placebo (n=418)
- Setting: 130 centers in 19 European countries
- Follow-up: 3 months
- Median time for administration: 3 hours 59 minutes

Results:

- The primary outcome was disability at 3 months, and ECASS III found a greater proportion of patients randomized to alteplase with complete or near complete neurologic recovery (NNT 14).
- Despite a 10-fold increase in symptomatic intracerebral hemorrhage, there was no difference in mortality between alteplase and placebo groups.

Criticisms:

- Placebo group had higher rates of previous stroke (7.7% vs. 14.1%; P=0.003), which could account for the worsened outcome of the placebo group.
- Study excluded patients with severe stroke signs.
- The study protocol was changed during the trial.

Additional points: The window for administration of IV alteplase was extended to up to 4.5 hours for selected patients per the AHA/ASA guidelines as a result of the ECASS III trial.

Citation: Hacke W, et al. "Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke". *The New England Journal of Medicine*. 2008. 359(13):1317-1329.

ENDOCRINOLOGY

7. RABBIT 2

Key findings: In non-critically ill inpatients with type 2 diabetes mellitus who were insulin-naive, a basal-bolus insulin regimen was more effective for glycemic control as compared to sliding-scale regular insulin. There were no significant differences in the incidence of hypoglycemia and length of stay between the two treatment strategies.

Background:

- Poor glycemic control is associated with worse outcomes in critical and non-critically ill patients with diabetes mellitus (DM). At the time of the trial, the optimal management strategy for glycemic control of hospitalized patients was unclear.
- Although sliding-scale insulin (SSI) was widely used, there are significant disadvantages associated with this reactive strategy which attempts to treat rather than prevent hyperglycemia.
- Queale *et al.* reported that SSI is associated with a 3-fold increase in the risk of hyperglycemia as compared to patients not receiving glycemic therapy.

Study design:

- Multicenter, prospective, randomized, controlled trial
- N=130 non-critically ill inpatients with DM
    - Basal-bolus insulin (n=65)
    - SSI (n=65)
- Setting: 2 centers in Atlanta and Florida
- Follow-up: Length of hospital stay
- Analysis: Not specified
- Primary outcome: Glycemic control as measured by the mean daily blood glucose concentration

Results:

- Patients treated with basal-bolus insulin had greater improvement in glycemic control than those treated with SSI, with lower mean fasting glucose (147 ± 36 vs. 165 ± 41 mg/dl, $P < 0.01$), mean random glucose (164 ± 35 vs. 189 ± 42

mg/dl, $P < 0.001$), and mean glucose during the hospital stay (166 ± 32 vs. 193 ± 54 mg/dl, $P < 0.001$).
- There were no differences in the incidence of hypoglycemia or length of stay between the two strategies.

Criticisms:
- Patients without documented DM before admission were excluded
- Patients treated with insulin and corticosteroids were excluded due to the higher risk of hyperglycemia if they were treated with SSI
- The study was not powered to determine differences in mortality or clinical outcome between basal-bolus insulin regimen and SSI groups
- There was crossover of 9 (14%) SSI patients to basal-bolus regimen. It is unclear if these were analyzed as intention-to-treat.
- Small sample size, conducted at only 2 sites, which limits generalizability
- There were significantly more males in the basal-bolus insulin group as compared to the SSI group (64.6% vs. 32.3%). However, the significance of this is unclear.
- The SSI group received a significantly less total daily insulin dose as compared to the basal-bolus group (12.5 vs. 42 units; P<0.001). It is unclear if the difference in insulin dose is related to the difference in outcomes observed between these treatments.

Additional points: As a result of these and other studies, the American Diabetes Association recommends a basal-bolus insulin approach over a SSI-only approach for hospitalized patients with DM.

Citation: Umpierrez GE, et al. "Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 trial)". *Diabetes Care*. 2007. 30(9):2181-2186.

8. NICE SUGAR

Key findings: In medical ICU patients, intensive glycemic control (target 81-108 mg/dL) led to more deaths compared to conventional control (target≤180).

Background:
- The impact of glycemic control on inpatient mortality has been long debated. The 2001 Leuven Surgical Trial was one of the first to demonstrate a mortality benefit among predominantly surgical ICU patients treated with intensive glycemic control (targeting a blood glucose of 80-110 mg/dL, 4.4-6.1 mmol/L).

- This mortality benefit with intensive glycemic control was not replicated in the same Belgian center among medical ICU patients in the 2006 Leuven Medical Trial.

Study design:

- Multicenter, non-blinded, parallel group, randomized, controlled trial
- N=6,104
    - Intensive (n=3,054)
    - Conventional (n=3,050)
- Setting: 42 centers
- Enrollment: 2004-2008
- Analysis: Intention-to-treat
- Primary outcome: 90-day mortality

Results:

- Intensive glycemic control arm had a higher 90-day mortality and more hypoglycemic events.
- There was no difference between medical or surgical ICU patients, and there were no differences in LOS, duration of ventilator therapy, or need for renal replacement therapy.

Criticisms:

- The target in NICE-SUGAR's conventional therapy arm (target 140-180 mg/dL) differs from the arm in the Leuven studies (target 180-215 mg/dL)
- Patients received enteral nutrition exclusively (compared to supplemental parenteral nutrition as in the Leuven studies), in which case undernourished patients may have been harmed by insulin administration
- Subjective inclusion criterion of expected length of stay
- Inability to blind treating staff

Additional points: Guidelines now recommend to follow a glucose control protocol targeting levels ≤180 mg/dL rather than ≤110 mg/dL (strong recommendation, high quality of evidence)

Citation: Finfer S, et al. "Intensive versus conventional glucose control in critically ill patients". *The New England Journal of Medicine*. 2009. 360(13):1283-1297.

INFECTIOUS DISEASE

9. ADRENAL

Key findings: In patients with septic shock on mechanical ventilation and receiving vasopressors, a week of hydrocortisone 200 mg/day did not reduce 90 day mortality but may be associated with time until reversal of shock, time to extubation, length of ICU stay, and blood transfusion.

Background:

- Multiple RCTs have investigated the potential role for steroid therapy in patients with septic shock.
- The Annane Trial in 2002 with 299 patients demonstrated a short-term mortality benefit with IV hydrocortisone and fludrocortisone among patients with evidence of adrenal insufficiency on ACTH stimulation testing.
- CORTICUS with 499 patients in 2008 investigated hydrocortisone in patients with and without adrenal insufficiency and found a faster reversal of shock but no benefit in either subgroup with suggestion of increased infection rates in patients receiving hydrocortisone.
- HYPRESS in 2016 with 380 patients showed no difference in mortality but showed decrease time to reversal of shock.

Study design:

- Multicenter, double-blind, parallel-group, randomized, controlled trial
- N=3,658 patients with septic shock requiring vasopressors and mechanical ventilation
    - Hydrocortisone (n=1,832)
    - Placebo (n=1,826)
- Setting: Australia (45 sites), UK (12), New Zealand (8), Saudi Arabia (3), and Denmark (1)
- Enrollment: 2013-2017
- Follow-up: 90 days
- Analysis: Intention-to-treat
- Primary Outcome: 90-day mortality

Results:

- There was no difference at the primary outcome of death from any cause at 90 days, nor were any difference found in any of the six prespecified subgroups.
- The hydrocortisone group had faster time to reversal of shock, shorter time to discharge from the ICU, time to extubation, and decreased number of blood

transfusion. These additional outcomes may best be regarded as hypothesis-generating.

Criticisms:

- Adverse events were recorded based on clinical judgement and were not centrally adjudicated. Similarly, appropriateness of antimicrobials was not centrally adjudicated.
- The trial excluded those who had received etomidate, an anesthetic with some adrenal suppression. This limits generalizability.
- Long-term neuromuscular weakness not assessed.
- Cost analysis not performed.
- ACTH stimulation testing was not performed.
- Prior trials used bolus doses of corticosteroids. Given importance of rapid reversal of shock, is unclear if a slower infusion may have delayed onset of action of the medication and, thus, attenuated any true association between the intervention and primary outcome. The authors note that they chose an infusion over bolus dosing because of theoretical safety benefits (lower hyperglycemia and impacts on the inflammatory response).

Additional points:

- As of February 2018, no guidelines had been published that reflect the results of this trial.
- The 2016 Surviving Sepsis Campaign severe sepsis and septic shock suggests using IV hydrocortisone if hemodynamics cannot be stabilized using fluids and vasopressors. This recommendation was made before the release of the large ADRENAL trial and may lead to re-evaluation of this recommendation.
- This trial likely puts to rest steroids for all-comers in sepsis, however, does not settle if steroids would be beneficial in patients that are non-responders to initial fluid resuscitation and vasopressor administration, as recommended in the guidelines.

Citation: Venkatesh B, et al. "Adjunctive glucocorticoid therapy in patients with septic shock". *New England Journal of Medicine*. 2018. Epub 2018-01-19:1-12.

10. 7 vs 14 day Treatment for GNR Bacteremia

Key findings: In patients hospitalized with gram-negative bacteremia achieving clinical stability before day 7, an antibiotic course of 7 days was noninferior to 14 days.

Reducing antibiotic treatment for uncomplicated gram-negative bacteremia to 7 days is an important antibiotic stewardship intervention.

Background: Gram-negative bacteremia is a major cause of morbidity and mortality in hospitalized patients. Data to guide the duration of antibiotic therapy are limited.

Study design:

- This was a randomized, multicenter, open-label, noninferiority trial.
- Inpatients with gram-negative bacteremia, who were afebrile and hemodynamically stable for at least 48 hours, were randomized to receive 7 days (intervention) or 14 days (control) of covering antibiotic therapy.
- Patients with uncontrolled focus of infection were excluded.
- The primary outcome at 90 days was a composite of all-cause mortality; relapse, suppurative, or distant complications; and readmission or extended hospitalization (>14 days). The noninferiority margin was set at 10%.
-

Results:

- The primary outcome occurred in 140 of 306 patients (45.8%) in the 7-day group vs 144 of 298 (48.3%) in the 14-day group (risk difference, -2.6% [95% confidence interval, -10.5% to 5.3%]).
- No significant differences were observed in all other outcomes and adverse events, except for a shorter time to return to baseline functional status in the short-course therapy arm.

Criticisms:

- The dominance of Enterobacteriaceae as the offending pathogens (~90%) limits the applicability of the results for gram-negative nonfermenters such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii*
- This study was unable to show the impact of reducing antibiotic use on resistance
- caution should be practiced when applying these results in the immunocompromised or BSIs caused by non-Enterobacteriaceae

Citation: Yahav D, Franceschini E, Koppel F, et al; Bacteremia Duration Study Group. “Seven versus 14 days of antibiotic therapy for uncomplicated gram-negative bacteremia: a noninferiority randomized controlled trial”. *Clin Infect Dis.* 2019;69(7):1091-1098.

11. RECOVERY (Covid-19)

Key findings: In patients hospitalized with Covid-19, dexamethasone 6 mg/d for up to 10 days improved 28-day survival in the subset of patients receiving supplemental oxygen or mechanical ventilation.

Background:

- In the early days of the Covid-19 pandemic, clinicians and investigators scrambled to develop effective therapies for patients, particularly those with severe disease in whom the case fatality rate was very high.
- Authors of mechanistic studies, case reports, retrospective studies, and clinical guidelines advocated for remdesivir, hydroxychloroquine, antiretrovirals, anticoagulants, and other therapies on the basis of limited data which at best was hypothesis-generating.
- As randomized data became available, it became clear that many of these treatments were modestly effective if at all: remdesivir improved time to recovery but did not impact survival, hydroxychloroquine did not improve clinical outcomes when given as Covid-19 therapy or as postexposure prophylaxis, and the antivirals lopinavir-ritonavir were ineffective.
- Steroids had been proposed as well, but a well designed, randomized study was needed to demonstrate their efficacy in Covid-19.

Study design:

- Open label, randomized, multi-center trial
- N=6,425 patients hospitalized with Covid-19
    - Dexamethasone (n=2,104)
    - Placebo (n=4,321)
- Setting: 176 National Health Service organizations in the UK
- Enrollment: March-June 2020
- Analysis: Intention-to-treat
- Primary outcome: 28-day mortality

Results:

- Patients in the dexamethasone arm had a significantly lower 28-day mortality, which was the primary endpoint of the study (22.9% vs. 25.7%; RR 0.83; $P<0.001$).
- A subgroup analysis demonstrated that this benefit was limited to patients receiving supplemental oxygen (23.3% vs. 26.2%; RR 0.82) or mechanical ventilation (29.3% vs. 41.4%; RR 0.64).

- Consequently, the number needed to treat to save one life at 28 days was 34 among patients receiving supplemental oxygen, and 8 among patients receiving mechanical ventilation.
- The authors note the lack of benefit, and possibility of harm, of dexamethasone in patients not receiving respiratory support.

Criticisms:

- Around a third of patients in the trial were still in hospital at the end of the 28-day trial period, so their final outcomes were not known
- As an immunosuppressive drug, there are fears that dexamethasone could make the illness worse, and prolong the infection in patients where the immune system has not yet overreacted and caused inflammation
- The preprint authors themselves warned that "the results are consistent with possible harm" in patients who did not require oxygen at the time of enrolment. The trial observed a 22% *increase* in mortality in these patients (rate ratio 1.22 [95% Confidence Interval 0.93 to 1.61]; p=0.14), though this observation may still be due to chance.
- Responding to the publication, the WHO emphasized that dexamethasone should only be used for patients with severe or critical disease, under close clinical supervision, stating that "There is no evidence this drug works for patients with mild disease or as a preventative measure, and it could cause harm.

Additional points:

- NIH Covid-19 Treatment Guidelines (2020, adapted) recommends dexamethasone 6 mg/d for up to 10 days for the treatment of Covid-19 in patients receiving mechanical ventilation (recommendation level A, evidence I) and in patients receiving supplemental oxygen but who are not mechanically ventilated (BI).
- The panel recommends against dexamethasone for patients who do not require supplemental oxygen (AI).
- If dexamethasone is unavailable, the panel recommends an alternative agent such as prednisone, methylprednisolone, or hydrocortisone (AIII).

Citation: Horby P, et al. "Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report". *The New England Journal of Medicine*. 2020. e-pub 2020-07-17:1-11.

12. ACTT 1

Key findings: Among patients with Covid-19 hospitalized with lower respiratory tract involvement, remdesivir reduced the median time to recovery by approximately four days. There was no difference in 14-day survival between remdesivir and placebo groups. The report of 28-day mortality is pending (later found to have no benefit).

Background:

- Originally developed as a treatment for the Ebola virus, remdesivir is a prodrug adenosine analogue that inhibits RNA-dependent RNA polymerases of several RNA viruses.
- Remdesivir was identified as a potentially promising therapeutic agent for the treatment of Covid-19 after preclinical investigations discovered *in vitro* inhibitory activity against SARS-CoV-2 as well as related coronaviruses SARS-CoV and MERS-CoV.

Study design:

- International, multicenter, double-blind, placebo-controlled, randomized control trial
- N=1,063 patients with Covid-19
    - Remdesivir (n=541)
    - Placebo (n=522)
- Setting: 60 trial sites and 13 subsites in the United States, Denmark, the United Kingdom, Greece, Germany, Korea, Mexico, Spain, Japan, and Singapore
- Enrollment: 21 Feb 2020 to 19 Apr 2020
- Analysis: Intention-to-treat
- Primary outcome: Time to recovery

Results:

- The preliminary report of the ACTT-1 trial demonstrates that a 10-day course of remdesivir in hospitalized patients with severe Covid-19 is superior to placebo in reducing the the time to recovery, with a medial time to recovery of 11 days in the remdesivir group compared to 15 days in the placebo group.
- However, although there is a trend to overall reduced mortality with remdesivir (7.1% in the remdesivir group compared to 11.9%) at 14 days, this difference was not statistically significant.
- Subgroup analyses demonstrated that the reduction in time to recovery is driven by patients requiring supplemental oxygen. This subgroup has a statistically significant reduction in mortality at 14 days (HR 0.22, 95% CI 0.08-0.58).

Criticisms:

- Prior to the start of the trial, the primary outcome was defined as the difference in clinical status at day 15, based on baseline disease category. This initial primary outcome was changed to a key secondary outcome upon the recommendation of trial statisticians, who were blinded to treatment assignments, to make time to recovery the primary outcome. At the time of this proposal, 72 patients had been enrolled in the trial. The authors write that this change in the primary outcome was made in response to developing information that Covid-19 had a more protracted course than previously thought. Ultimately, both statistically significant differences were observed in both the original and new primary outcomes.
- A shortage of matching placebos occurred at some sites such that normal saline was used in its place. This situation may have compromised blinding.

Additional points:

- As a result of the preliminary data presented in the ACTT-1 trial, the NIH Covid-19 Treatment Guidelines recommends the use of remdesivir for the treatment of hospitalized Covid-19 patients with severe disease (defined as SpO2 ≤94% on ambient air or requiring supplemental oxygen, mechanical ventilation, or ECMO).
- This guideline does not recommend remdesivir for the treatment of mild or moderate Covid-19 outside the setting of a clinical trial.

Citation: Beigel JH, et al. "Remdesivir for the Treatment of Covid-19 - Preliminary Report". *The New England Journal of Medicine*. 2020. (e-pub 2020-05-22):1-12.

13. ID Consultation for Staph Aureus Bacteremia

Key findings: In this large, multicenter cohort study of 31 002 patients with *S aureus* bacteremia, infectious diseases consultation during the index hospital stay was associated with reduced risk of all-cause mortality and recurrence of bacteremia for 5 years after discharge.

Background:

- *Staphylococcus aureus* bacteremia (SAB) is common and associated with poor long-term outcomes.

- Previous studies have demonstrated an association between infectious diseases (ID) consultation and improved short-term (ie, within 90 days) outcomes for patients with SAB, but associations with long-term outcomes are unknown.

Study design:

- This cohort study included all patients (N = 31 002) with a first episode of SAB who were discharged alive from 116 acute care units of the nationwide Veterans Health Administration where ID consultation was offered.
- Data were collected from January 2003 to December 2014, with follow-up through September 30, 2018. Data analysis was conducted from February to December 2019.

Results:

- Approximately half of patients (15 360 [49.5%]) received ID consultation during the index hospital stay; ID consultation was associated with prolonged improvement in the composite outcome (adjusted hazard ratio at 5 years, 0.71; 95% CI, 0.68-0.74; $P < .001$).
- Infectious diseases consultation was also associated with improved outcomes when all-cause mortality without recurrence and SAB recurrence were analyzed separately (all-cause mortality without recurrence: adjusted hazard ratio at 5 years, 0.77; 95% CI, 0.74-0.81; $P < .001$; SAB recurrence: adjusted hazard ratio at 5 years, 0.68; 95% CI, 0.64-0.72; $P < .001$).

Criticisms:

- As in any observational study, a limitation is the potential for unmeasured confounding. Administrative data was relied on for diagnoses of comorbidities, which may be inaccurate and allow residual confounding.
- It is conceivable that ID consultation had differential associations with outcomes based on primary sites of infection, such as endocarditis or osteomyelitis.
- Most patients with SAB in VHA hospitals were men, which may limit the generalizability of these findings to female populations, although there is little biological plausibility to speculate that this association would be different between sexes.

Additional points: Having an ID consultation during the index hospital stay among patients with SAB was associated with improved postdischarge outcomes for at least 5 years, suggesting that contributions of ID specialists to management during acute infection may have a substantial influence on long-term outcomes.

Citation: Goto M, Jones MP, Schweizer ML, et al. Association of Infectious Diseases Consultation With Long-term Postdischarge Outcomes Among Patients With *Staphylococcus aureus* Bacteremia. *JAMA Netw Open.* 2020;3(2):e1921048.

HEME/ONC

14. AMPLIFY

Key finding(s) - Apixaban is noninferior to LMWH and vitamin K antagonist-based therapy for VTE recurrence and VTE mortality. Apixiban therapy has a greater reduction in rates of bleeding.

Background: The conventional treatment for VTE includes a heparin derivative such as LMWH followed by a vitamin K antagonist (warfarin). New DOACs had shown promise as alternative regimens for PE/DVT. Apixaban (a factor Xa inhibitor) had not yet been demonstrated in a large trial to be noninferior to heparin derivatives of vitamin K antagonists.

Study Design:

- Prospective, randomized, double-blinded trial with enrollment between 2008 and 2012.
- Age ≥18 years with symptomatic VTE
- N=5,395, Apixaban n=2,691, conventional therapy n=2,704.
- 358 centers in 28 different countries
- Intention-to-treat analysis
- Primary outcomes included recurrent symptomatic VTE or VTE mortality, major bleeding events, major bleeding or clinically-relevant non-major bleeding

Results:

- Recurrent symptomatic VTE or VTE mortality:
    - 2.3% vs 2.7% (RR 0.84, 95% HR 0.60-1.18) p<0.001 for noninferiority
- Major bleeding:
    - 0.6% vs 1.8% (RR 0.31, 95% CI 0.17-0.55) p<0.001 for superiority, NNT 100
- Major bleed or clinically relevant non-major bleeding
    - 4.3% vs 9.7% (RR 0.44; 95% CI 0.36-0.55) p<0.001 for superiority, NNT 19
- All cause mortality: 1.5% vs 1.9% (RR 0.79, 95% CI 0.53-1.19)

Criticisms: Unclear if outcomes would be affected if patients had cancer, were underweight, or had a decreased creatinine clearance of <50 mL/min

Additional Points: Apixaban is a safe, effective agent for treatment of PE and DVT and has lower risks of bleeding events than heparin and vitamin K antagonists and thus is preferred in eligible patients

Citation: Agnelli G, et al. “Oral apixaban for the treatment of acute venous thromboembolism”. *The New England Journal of Medicine.* 2013. 369(9):799-808

15. TRICC

Key finding(s): Restrictive strategies of red cell transfusion (goal hgb 7-9 g/dL) is at least as effective as and possibly superior to a liberal transfusion strategy (goal hgb 10-12 g/dL) in critically ill patients, with the possible exception of patients with acute MI and unstable angina.

Background:

- Red-cell transfusions are used to augment delivery of oxygen in hope of avoiding complications from oxygen deprivation. An important concern in thinking of how to address anemia in the ICU setting was whether critically ill patients could tolerate anemia.
- To determine whether a restrictive strategy of red-cell transfusion and a liberal strategy produced equivalent results in critically ill patients, the authors compared the rates of death from all causes at 30 days and the severity of organ dysfunction between the two groups.

Study Design:

- Multicenter, 22 tertiary centers and 3 community ICUs in Canada; non-blinded, parallel-group, randomized controlled trial
- Enrollment period 1994-1997 (terminated early due to low enrollment)
- N=838 critically ill patients with anemia
    - Restrictive strategy (n=418)
    - Liberal strategy (n=420)
- Primary outcome was 30 day all cause mortality
- Randomly assigned to restrictive (hgb 7-9 g/dL) vs liberal (hgb 10-12 g/dL) strategy

Results: (*restrictive* vs *liberal*)

- Primary outcome, 30-day mortality
    - 18.7% vs 23.3% (ARR 4.7%; p=0.11)
- Secondary outcomes:
    - ICU mortality: 13.9% vs 16.2% (ARR 2.3%; p=0.23)
    - Inpatient mortality: 22.2% vs 28.1% (ARR 5.8%; p=0.05)

    - Multiple-organ dysfunction score: 3.2 vs 4.2 (p=0.04)
    - Change in organ dysfunction from baseline: 3.2 vs 4.2 (p=0.04)
    - 60 day mortality: 22.7% vs 26.5% (ARR 3.7%; p=0.23)
    - ICU cardiac events: 13.2% vs 21% (ARR 7.8%; p<0.01)

Criticisms:

- Reduced enrollment in patients with cardiac disease decreases the generalizability of results to this population.
- Altitude may be a factor not accounted for in the study. Only 13% of screened patients were included in the study, putting external validity into question.

Additional Points:

- There was a trend towards decreased 30-day mortality among patients treated according to the restrictive strategy, and rates of organ dysfunction all favored the restrictive strategy. These patients were also exposed to fewer blood products and this preserved red cells.
- The simple intervention of lowering the transfusion threshold appears to improve clinical outcomes and reduce unnecessary use of blood products.

Citation: Hebert PC, *et al*. “A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care”. *The New England Journal of Medicine*. 1999. 340(6):409-417.

16. PREPIC 2

Key finding(s) - In patients with pulmonary embolism at high risk of recurrence, the routine placement of a retrievable IVC filter does not reduce the risk of recurrent pulmonary embolism when compared to anticoagulation alone.

Background:

- Observational studies showed a sharp increase in IVC filter placement over preceding 30 years, including use as an add-on to anticoagulation therapy in patients with acute VTE.
- Previous studies had shown placing a permanent IVC filter in addition to anticoagulation reduced risk of recurrent pulmonary embolism compared with AC alone, however this was offset by delayed risk of recurrent DVT, often associated with filter thrombosis.
- Temporary IVC filter placement became feasible, so this study evaluated whether short term IVC filter (3 months) plus anticoagulation would prevent early PE recurrence in those at high risk while avoiding the complications of delayed DVT.

Study Design:

- Multicenter, randomized controlled trial, blinded endpoint performed at 17 healthcare settings in France
- Enrollment was between 2006-2012 with followup at 3-6 months.
- N=399 patients with acute PE and high risk of recurrence
    - IVC filter (n=200)
    - No IVC filter (n=199)
- Intention-to-treat analysis
- Primary outcome was recurrent symptomatic PE at 3 months
- Secondary outcomes included all cause mortality at 6 months, recurrent PE at 6 months, & major bleeding
- IVC filter removal was mandatory at 3 months and AC continued for at least 6 months in all patients

Results: (*IVC vs AC alone*)
Primary outcome was symptomatic or fatal recurrent PE at 3 months:

- 3% in IVC filter group vs 1.5% in anticoagulation group alone (RR 2.0; 95% CI 0.51-7.89; p=0.5)

Secondary outcomes:

- All-cause mortality at 6 months: 10.6% vs 7.5% (RR 1.40; 95% CI 0.74-2.64; p=0.29)
- Recurrent PE at 6 months: 3.5% vs 2.0% (RR 1.75; 95% CI 0.52-5.88; p=0.54)
- Major bleeding: 6.5% vs 7.5% (RR 0.87; 95% CI 0.42-1.77; p=0.69)

Criticisms:

- Filter retrieval rates during RCT are probably higher than in real world conditions.
- Patients varied with respect to clinical conditions putting them at risk, thus difficult to apply to a specific subgroup.

Additional Points: Overall, placing a retrievable (3 month) IVC filter in addition to anticoagulation does not confer mortality benefit or decrease risk of recurrent PE in at-risk patients, and thus should not be routinely performed.

Citation:
Mismetti P, *et al.* “Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism: a randomized clinical trial”. *The Journal of the American Medical Association*. 2015. 313(16):1627-35.

17. SOME

Key finding(s) - The addition of comprehensive CT scanning of the abdomen and pelvis to routine age-appropriate screening did not result in a difference in time to occult cancer diagnosis or cancer-related mortality in patients with initial unprovoked VTE.

Background:

- VTE may be the earliest sign of malignancy, and there is a wide variability in how physicians screen patients with VTE for previously undiagnosed cancer.
- This study evaluated whether adding a comprehensive CT of the abdomen and pelvis would be an efficacious way to detect occult malignancy in patients presenting with their first unprovoked DVT.

Study Design:

- Multicenter, open-label randomized controlled trial from 2008 to 2014, conducted at nine Canadian institutions, with intention-to-treat analysis
- Patients were assigned to undergo limited occult-cancer screening (basic blood testing, chest radiography, breast, cervical, and prostate cancer screening) or a limited occult-cancer screening in combination with CT.
- N=862 patients, with 431 in the limited group and 423 in the extended screening group
- Follow up at 1 year after diagnosis of unprovoked VTE
- Primary outcome: confirmed cancer within one year of follow up that was missed by screening strategy employed after the initial VTE diagnosis

Results:

- Primary Outcome: Of 854 patients who were randomized, 3.9% (33 patients) had a new diagnosis of occult cancer between randomization and the 1-year follow up. There were 14 in the limited screening group and 19 in the extended screening group.
    - 4 of 14 occult cancers (29%, 95% CI 8-58) in limited group were missed by initial screening strategy
    - 5 of 19 occult cancers (26%, 95% CI 9-51) (p=1.0) in extended screening group were missed in the initial screening strategy (limited plus CT)
- Secondary outcome (*limited vs extended)*:
    - Mortality at one year: 1.4% vs 1.2% (p=1.0)
    - Cancer-related mortality at one year: 1.4% vs 0.9% (p=0.75)
    - Time to cancer diagnosis: 4.2 months vs 4.0 months (p=0.88)
    - Incidence of recurrent VTE: 3.3% vs 3.4% (p=1.0)

Criticisms:

- CT abdomen/pelvis was the additional screening used, but this might not be the best appropriate test; given the low rates of occult malignancy the study was likely underpowered; they excluded those with a CrCl <60 ml/min which makes the study's findings less generalizable

Additional Points: Overall, the prevalence of occult malignancies is low among patients with a first unprovoked VTE. Adding a CT abdomen/pelvis to routine cancer screening for patients with unprovoked DVT may not be beneficial in detecting early cancers.
Citation:
Carrier M, *et al.* "Screening for Occult Cancer in Unprovoked Venous Thromboembolism". *The New England Journal of Medicine.* 2015. 373(8):697-704.

GASTROENTEROLOGY

18. Albumin for SBP

Key finding(s) - Among patients with cirrhosis and spontaneous bacterial peritonitis on IV antibiotics, IV albumin reduces the incidence of renal impairment and mortality when compared to antibiotics alone.

Background: In patients with cirrhosis, SBP is a common infection with high morbidity and mortality. SBP is associated with a high incidence of renal dysfunction, thought to be related to reduction in effective arterial blood volume. This study evaluated whether plasma volume expansion with IV albumin prevents renal impairment and reduces mortality.
Study Design:

- Randomized controlled trial; 126 patients with cirrhosis and SBP randomized to receive cefotaxime (N=63) vs cefotaxime + IV albumin (N=63).
- Renal impairment defined as irreversible deterioration of renal function during hospitalization

Results:

- Primary Outcomes: *(antibiotics vs. antibiotics+albumin)*
  - Renal impairment: 33% vs. 10% (P=0.002; **NNT=4**)
  - Hospital mortality: 29% vs. 10% (P=0.01; **NNT=5)**
  - All-cause mortality at 3 months: 41% vs. 22% (P=0.03; **NNT=5**)
- Secondary Outcomes:
  - Resolution of infection: 94% vs 98% (p=0.36)
  - Duration of antibiotics: 6 vs 5 days (p=0.48)
  - Hospital stay: 13 vs. 14 days (p=0.48)

Criticisms:

- Study was not blinded, possibly leading to bias. Because renal impairment is related to compound effects of sepsis and cirrhosis on renal function, albumin infusion thus may be serving the role of fluid resuscitation rather than providing a specific benefit to renal function.
- No details for fluid management in the control group were provided, nor were the details of utilization of vasoconstrictors.

Additional Points:

- Guidelines now recommend treating all patients with SBP with broad spectrum antibiotics and IV albumin.
- Administration of albumin at 1.5 g/kg at diagnosis and 1g/kg on day 3 is associated with a reduction in hepatorenal syndrome.
- Typically albumin infusion is given if the creatinine is >1 mg/dL, the blood urea nitrogen is >30 mg/dL, or the total bilirubin is >4 mg/dL.

Citation:

Sort P, *et al.* "Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis". *The New England Journal of Medicine.* 1999. 341(6):403-409.

19. Antibiotics in Cirrhosis with Hemorrhage

Key finding(s) - Among cirrhotic patients with GI bleed, ceftriaxone reduces the rate of bacterial infection by 67% but does not confer an increased survival benefit when compared to norfloxacin.

Background:

- In 1992, a trial showed norfloxacin reduced incidence of bacterial infections among cirhhotic patients with GI bleed; thus, norfloxacin had been the standard of care for prophylaxis of bacterial infections in these patients.
- However, quinolone resistance had been increasing in this population, and thus this RCT compared oral norfloxacin with IV ceftriaxone in the prophylaxis of bacterial infection.

Study Design:

- Between 2000-2004, a multicenter, double-blinded, parallel group, randomized controlled trial at 4 centers in Spain with intention-to-treat analysis
- Patients with cirrhosis who had GI bleed were randomized to receive norfloxacin 400 mg orally bid vs. ceftriaxone 1g IV daily
- 10-day follow up

- N=111
    - Ceftriaxone, N=54
    - Norfloxacin, N=57
- Primary Outcome: proven infections plus possible infections

Results:
- Primary Outcome: (*CTX vs norfloxacin)*
    - Proven infection plus possible infection: 11% vs 33% (p=0.003)
- Secondary Outcome:
    - Proven infection: 11% vs 26% (P=0.03)
    - SBP or bacteremia: 2% vs 12% (p=0.03)
    - 10-day mortality: 11% vs 9% (non-significant)
    - Inpatient mortality: 15% vs 11% (non-significant)

Criticisms:
- Not powered to detect mortality.
- Also, antibiotics compared were IV and PO, which may have favored ceftriaxone, as the majority of patients had NG tubes in place.

Additional Points: Ceftriaxone should be administered to prevent bacterial infections in cirrhotics presenting with GI bleed.

Citation:
Fernández J, et al. "Norfloxacin vs. ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage". *Gastroenterology*. 2006. 131(4):1049-56.

20. Prednisolone in Severe Alcoholic Hepatitis
Key finding(s) - In patients with severe alcoholic hepatitis, prednisolone improves 2-month survival.

Background: Alcoholic hepatitis carries a high mortality rate and involves mostly supportive treatment. Investigators have sought to find disease-modifying therapies.

Study Design:
- Double-blind, parallel group, randomized, placebo-controlled trial.
- 61 patients with severe, biopsy-proven alcoholic hepatitis were either randomized to prednisolone or placebo.

- Severe disease was defined by presence of hepatic encephalopathy or Maddrey's DF >32.

Results:

- At two months, survival was significantly better in the group that received prednisolone than placebo (88% vs 34%). NNT 3. They also had lower rates of GI bleeds and infections as compared to the placebo group. Benefit was still seen at six months out.

Criticisms:

- Pts in placebo group had higher bilirubin, Cr, and DF, which could indicate more severe disease than in those in steroid group. Majority of trial participants (70%) were female, which makes the results of the study difficult to generalize to the United States population, where the majority of those with alcoholic hepatitis are male.

Additional Points:

- Follow-up study STOPAH trial (Thursz et al, 2015) randomized participants with severe AH to placebo, prednisolone, or pentoxyphylline. Those who received prednisolone achieved slight reduction in mortality at 28 days. There was no change in mortality for those who received pentoxyphylline.

Citation: Ramond MJ, et al. "A randomized trial of prednisolone in patients with severe alcoholic hepatitis". *The New England Journal of Medicine*. 1992. 362(8):507-512.

21. Omeprazole in Peptic Ulcer Bleeding

Key finding(s) - This trial demonstrated a 70% reduction in rebleeding with intravenous omeprazole in patients with active GIB.

Background: Attempted to assess the effect of IV pantoprazole on recurrent bleeding in those hospitalized for bleeding peptic ulcer.

Study Design:

- N=240, adults ≥16 y, admitted for GI bleeding, underwent EGD within 24 hours of admission, found to have active bleeding ulcers or ulcers with visible non-bleeding vessels
- Single center, double-blinded, parallel-group, randomized, placebo-controlled trial
- N=120 in omeprazole group, n=120 in placebo group

- Primary outcome: recurrent bleeding by day 30, actively bleeding ulcers, ulcers with nonbleeding visible vessels, recurrent bleeding by day 7, recurrent bleeding by day 7

Results: Notable for significant decrease in rebleeding rates at both day 3 and day 30

Additional Points:

- Later trial determined that PPI BID was non-inferior to PPI continuous infusion

Citation: Lau JYW, et al. "Effect of Intravenous Omeprazole on Recurrent Bleeding after Endoscopic Treatment of Bleeding Peptic Ulcer". *The New England Journal of Medicine*. 2000. 343(5):310-316.

PULMONARY:

22. FLAME

Key finding(s) - Among patient with COPD and mMRC dyspnea grade ≥2 symptoms, indacaterol+glycopyrronium (LABA+LAMA) is associated with a reduction in the rate of annual COPD exacerbations when compared to salmeterol+fluticasone (LABA+ICS).

Background:

- The search for the ideal medication to reduce COPD exacerbations is ongoing.
- One popular intervention, ICS therapy, has been associated with increased risk of pneumonia.
- Combined LABA+ICS therapy (salmeterol+fluticasone) had a similar COPD exacerbation rate as LAMA monotherapy (tiotropium) in INSPIRE (2008).
- Whether LABA+LAMA therapy provides benefit over LABA+ICS was unknown.

Study Design:

- Randomized, double-blind, double-dummy, noninferiority trial
- Pts were treated with tiotropium for 4 weeks and then randomized to either LABA+LAMA group or LABA+ICS group (N=3362)
- 356 centers in 43 countries
- Primary outcome: annual rate of all COPD exacerbations (both those requiring and not requiring hospitalization); non-inferiority
- Participants remained on randomized medication for 52 weeks
- Rescue inhaler was the same for both groups (salbutamol 100mcg)

Results:

- Lower annual COPD exacerbation rate with LAMA+LABA group (RR=0.8)
- Longer time to first exacerbation with LAMA+LABA group

- Annual rate of moderate to severe exacerbations and increase in FEV1 were both greater in LAMA+LABA

Criticisms:

- The study excluded some potential participants who suffered from very frequent exacerbations, and they may have benefited from inhaled steroids.
- Study funded by Novartis, the makers of indacaterol+glyocpyrronium
- Trial required a washout period, which would be impractical in practice

Additional Points:

- Results of the trial were used to inform the 2017 GOLD COPD guidelines, which stated that LAMA was more effective than LABA at preventing COPD exacerbations and that combination therapy with LAMA+LABA increases FEV1 and decreases rates of exacerbations compared to either monotherapy.

Citation: Wedzicha JA, et al. "Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD". *The New England Journal of Medicine*. 2016. 374(23):2222-2234.

23. REDUCE

Key finding(s) - A 5-day course of glucocorticoids is non-inferior to a 14-day course for treatment of acute COPD exacerbations in prevention of re-exacerbations.

Background:

- Prior studies have shown that steroids can be used to effectively treat COPD exacerbations, and that parenteral and enteric administration were equivalent
- Before the publication of this trial, there were no major randomized controlled trials examining optimal duration of steroids.

Study Design:

- 314 patients in Switzerland with history of smoking, who presented with acute COPD exacerbation
- 87% of participants were GOLD Class III or IV
- Randomized to 5-day or 14-day course of glucocorticoids (with initial dose of IV methylprednisolone)
- Clinicians could give patients additional glucocorticoids at their discretion
- Patients also received antibiotics, inhaled steroids, inhaled tiotropium, and inhaled SABA
- Primary outcome: rate of re-exacerbation within 6 months

- Secondary outcomes (included, but not limited to): all-cause mortality, need for mechanical ventilation, steroid-associated adverse events, cumulative prednisone dose, median hospital stay

Results:

- Shorter course of steroids was non-inferior to longer course of steroids
- No difference in glucocorticoid-related adverse events
- Shorter steroid course was associated with shorter hospital stay

Criticisms:

- Extrapolation to milder COPD (lower GOLD classes) is limited since the vast majority of participants had severe COPD
- Extrapolation to non-smokers is limited

Additional Points: at this point, the majority of clinicians employ a 5-day steroid course, with additional corticosteroids for persistent or severe disease as deemed appropriate by the clinician.

Citation: Leuppi JD, et al. "Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial". *JAMA*. 2013. 309(21):2223-2231.

NEPHROLOGY:

24. SALT-ED

Key finding(s) - Among non-critically ill ED patients, initial fluid resuscitation with balanced crystalloids (Lactated Ringer's or Plasma-Lyte) does not reduce duration of hospitalization when compared to the isotonic crystalloid, normal saline. However, balanced crystalloid use is associated with a reduction in major kidney-related events.

Background:

- The SMART-MED and SMART-SURG trials (critical care equivalent of this trial) demonstrated that resuscitation with balanced crystalloids reduced the rate of death, need for renal replacement therapy, and persistent renal dysfunction.
- The physiologically hyperchloremic composition of normal saline has been thought to result in metabolic derangements and possible renal dysfunction.

Study Design:

- Pragmatic, open label, cluster-randomized, multiple-crossover, single center trial

- Included 13,347 participants in intention to treat analysis
- Inclusion criteria: age ≥ 18 years, received >500cc in ED, admitted to non-ICU setting
- All patients enrolled on a given month were given either balanced crystalloids (95% use of Lactated Ringer's) or isotonic crystalloids (NS), with the treatment of choice alternating on subsequent months

Results:

- There was no difference in median hospital-free days to day 28 (primary outcome) or in-hospital death (secondary outcome)
- However, LR was associated with significantly fewer instances of adverse kidney events (major secondary outcome)
- Subgroup analysis suggests greater treatment effect in those with preexisting renal disease (serum creatinine ≥1.5mg/dL) and hyperchloremia (>110mmol/L)

Criticisms:

- Single center, open label study
- The intervention fluid was only continued in the ED, and no fluid choice was specifically assigned once on the floor
- Adverse renal event was measured as a rise in creatinine as opposed to an event (i.e. reduction in urine output, need for renal replacement therapy, or mortality)

Additional Points: suggests that balanced crystalloid (perhaps LR over NS) results in decreased renal morbidity and fewer instances of hyperchloremic, non-gap, metabolic acidosis.

Citation: Self WH, et al. "Balanced crystalloids versus saline in noncritically ill adults". *The New England Journal of Medicine*. 2018. 378(10):819-828.

PALLIATIVE CARE:

25. Early Palliative Care

Key finding(s) - Early integration of palliative care improved quality of life, reduced aggressive care at the end of life, and improved survival among patients with metastatic NSCLC.

Background:

- Patients with stage I, II, or III NSCLC are generally treated with curative intent using surgery, chemotherapy, and/or radiation therapy. In contrast, patients with stage IV metastatic NSCLC may benefit from palliative systemic therapy.

- As of 2010 (when article was published), palliative care was not integrated as part of standard of care when treated advanced NSCLC.

Study Design:

- Randomized 151 patients with newly diagnosed metastatic NSCLC (within past 8 weeks) to palliative care treatment or standard care
- Patients were recruited from ambulatory setting
- Single center study in Boston
- Early palliative care arm met palliative care team within 3 weeks of enrollment and monthly until death thereafter
- Standard care arm could potentially meet with palliative care team if patient, family, or oncologist specifically requested their services
- Primary outcome: quality of life (assessed by composite score of validated surveys at study start and at 12 weeks)

Results:

- Early integration of palliative care services improved outcomes associated with mood and quality of life
- Median survival was significantly improved among patients in the early palliative care arm compared with patients in the standard care arm (11.6 months vs 8.9 months), despite receiving less chemotherapy.

Criticisms:

- Non-blinded study
- Homogenous study population (100% Caucasian from Boston)

Additional Points: early introduction of palliative care services may be beneficial for patients diagnosed with many types of advanced cancers, not just NSCLC.

Citation: Temel JS, et al. "Early Palliative Care for Patients with Metastatic Non-Small-Cell Lung Cancer". *The New England Journal of Medicine*. 2010. 363(8):733-742.