



Hospitalist Review

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Disclosures

- ▶ No affiliations with industry of any kind
- ▶ No one is paying me to be here

- ▶ Hospitalist for past 10 years
- ▶ Was a hospitalist Director, Now a Nocturnist
- ▶ Never worked outside of the Hospital setting other than Residency Clinic

Objectives

- ▶ To look at recent articles that could change the way we practice when it comes to the care of hospitalized patients
- ▶ We will look at these from a systems based viewpoint
- ▶ We will review some data from the literature on COPD/Asthma and pneumonia, CHF/Cardiac care, and Sepsis

Format

- ▶ We will look at recent studies that have already been reviewed by experts in Medicine and review the findings
- ▶ We will then look at some of the previous studies that these build upon
- ▶ There have also been updates from specialty societies that warrant a discussion

The Marathon Paradigm

- ▶ A new presentation is like racing a marathon
- ▶ Preparing, training, but never doing the full 26.2 until race day
- ▶ I enjoy running and Hospital medicine, so the anxiety and preparation for both are exciting





COPD and Pneumonia

- ▶ One of the most common admission diagnosis
- ▶ Fall is here and respiratory illness admission are expected to rise



Oral Corticosteroids for Nonasthmatic Patients with Probable Viral Bronchitis?

- ▶ Thomas L. Schwenk, MD reviewing Hay AD et al. JAMA 2017 Aug 22.
- ▶ Take Home: **Steroid therapy didn't lessen severity or duration of symptoms.**
- ▶ Assumption for the study: If one excludes pneumonia, acute lower respiratory tract infections (LRTIs) usually are viral in origin (often labeled as “viral bronchitis”). Patients with non-pneumonia LRTIs often receive oral corticosteroids, probably because their symptoms are like those seen in asthma exacerbations.
- ▶ In this U.K. study, researchers evaluated 401 adults (mean age, 47; 17% smokers) with acute cough plus at least one of the following: sputum production, chest pain, wheezing, or shortness of breath. Patients with chronic lung disease or asthma were excluded. Patients who “required same-day antibiotics” also were excluded, which suggests that enrolled patients were presumed not to have pneumonia (although this was not explicitly stated in the study protocol). Enrolled patients were randomized to oral prednisolone (40 mg daily for 5 days) or placebo and were followed for 8 weeks.

COMMENT OF REVIEWER

- ▶ No significant differences were found between the groups in duration of moderately bad or worse cough (5 days), symptom severity, or peak flow. No patient experienced serious adverse events, and minor side effects were similar in both groups.
- ▶ These results clearly advise against using oral corticosteroids for treating nonasthmatic patients with uncomplicated acute LRTIs who are otherwise healthy and presumed to have viral bronchitis. Although half of these patients stated that they were wheezing, only 6% had wheezing or rhonchi on physical examination. This study doesn't address whether steroids would benefit patients without previously diagnosed asthma who present with acute bronchitis and marked expiratory wheezing on auscultation.

- ▶ EDITOR DISCLOSURES AT TIME OF PUBLICATION

- ◀ **Disclosures for Thomas L. Schwenk, MD at time of publication** Editorial boards UpToDate

- ◀ CITATION(S):

- ◀ Hay AD et al. Effect of oral prednisolone on symptom duration and severity in nonasthmatic adults with acute lower respiratory tract infection: A randomized clinical trial. JAMA 2017 Aug 22; 318:721. (<http://dx.doi.org/10.1001/jama.2017.10572>)

Importance: Acute lower respiratory tract infection is common and often treated inappropriately in primary care with antibiotics. Corticosteroids are increasingly used but without sufficient evidence.

Objective: To assess the effects of oral corticosteroids for acute lower respiratory tract infection in adults without asthma.

Design, Setting, and Participants: Multicenter, placebo-controlled, randomized trial (July 2013 to final follow-up October 2014) conducted in 54 family practices in England among 401 adults with acute cough and at least 1 lower respiratory tract symptom not requiring immediate antibiotic treatment and with no history of chronic pulmonary disease or use of asthma medication in the past 5 years.

Interventions: Two 20-mg prednisolone tablets ($n = 199$) or matched placebo ($n = 202$) once daily for 5 days.

Main Outcomes and Measures: The primary outcomes were duration of moderately bad or worse cough (0 to 28 days; minimal clinically important difference, 3.79 days) and mean severity of symptoms on days 2 to 4 (scored from 0 [not affected] to 6 [as bad as it could be]; minimal clinically important difference, 1.66 units). Secondary outcomes were duration and severity of acute lower respiratory tract infection symptoms, duration of abnormal peak flow, antibiotic use, and adverse events.

Results: Among 401 randomized patients, 2 withdrew immediately after randomization, and 1 duplicate patient was identified. Among the 398 patients with baseline data (mean age, 47 [SD, 16.0] years; 63% women; 17% smokers; 77% phlegm; 70% shortness of breath; 47% wheezing; 46% chest pain; 42% abnormal peak flow), 334 (84%) provided cough duration and 369 (93%) symptom severity data. Median cough duration was 5 days (interquartile range [IQR], 3-8 days) in the prednisolone group and 5 days (IQR, 3-10 days) in the placebo group (adjusted hazard ratio, 1.11; 95% CI, 0.89-1.39; $P = .36$ at an $\alpha = .05$). Mean symptom severity was 1.99 points in the prednisolone group and 2.16 points in the placebo group (adjusted difference, -0.20; 95% CI, -0.40 to 0.00; $P = .05$ at an $\alpha = .001$). No significant treatment effects were observed for duration or severity of other acute lower respiratory tract infection symptoms, duration of abnormal peak flow, antibiotic use, or nonserious adverse events. There were no serious adverse events.

Adding Prednisone to Pneumonia Therapy: Sufficient Evidence?

- ▶ Mary E. Wilson, MD reviewing Blum CA et al. Lancet 2015 Jan 18. Annane D. Lancet 2015 Jan 18.
- ▶ *Addition of oral prednisone to usual treatment shortened time to clinical stability in patients hospitalized with community-acquired pneumonia.*
- ▶ Pneumonia remains a common cause of hospitalization and death globally. In a recent multicenter, double-blind trial, investigators assessed whether adjunctive corticosteroid therapy might reduce time to clinical stability in patients hospitalized with community-acquired pneumonia. Previously published studies have produced mixed results.

- ▶ Patients aged ≥ 18 at seven tertiary care hospitals in Switzerland were randomized to receive usual treatment plus either oral prednisone (50 mg daily) or placebo for 7 days. Exclusion criteria included severe immunosuppression, cystic fibrosis, and active tuberculosis. The primary endpoint was “clinical stability” (as defined by the authors and determined by measures of temperature, respiratory rate, heart rate, oxygenation, oral intake, and mental status) for ≥ 24 hours.

COMMENT

► The median age of study participants was 74; 62% were men. In the intent-to-treat population (n=802), time to clinical stability was significantly shorter in the prednisone group than in the placebo group (median, 3.0 vs. 4.4 days). Results were similar in the per-protocol population (n=785). Time to hospital discharge was 1 day shorter in the steroid-treated group than in the control group. As of 30-day follow-up, pneumonia-associated complications and adverse events were similar between groups, except prednisone-treated patients had a higher incidence of in-hospital hyperglycemia needing insulin treatment.

► EDITOR DISCLOSURES AT TIME OF PUBLICATION

- ◄ **Disclosures for Mary E. Wilson, MD at time of publication** Editorial boards UptoDate; Clinical Infectious Diseases; RSTMH International Health; Infectious Diseases in Clinical Practice; Travel Medicine and Infectious Diseases
- ◄ CITATION(S): Blum CA et al. Adjunct prednisone therapy for patients with community-acquired pneumonia: A multicenter, double-blind, randomized, placebo-controlled trial. *Lancet* 2015 Jan 18; [e-pub ahead of print]. ([http://dx.doi.org/10.1016/S0140-6736\(14\)62447-8](http://dx.doi.org/10.1016/S0140-6736(14)62447-8))
- ◄ Annane D. Corticosteroids and pneumonia: Time to change practice. *Lancet* 2015 Jan 18; [e-pub ahead of print]. ([http://dx.doi.org/10.1016/S0140-6736\(14\)62391-6](http://dx.doi.org/10.1016/S0140-6736(14)62391-6))

- ▶ The authors note that their study involved only hospitalized patients and that critically ill patients were underrepresented. An editorialist believes that steroids improve pneumonia outcomes by reducing inflammation without causing immune suppression. Issues not addressed by this study are possible late complications in steroid-treated patients and treatment of ambulatory patients. Larger trials should focus on the effect on mortality (a more common primary outcome) and on potential benefits or risks in selected subgroups.

A Feather in the CAP: Steroids for Community-Acquired Pneumonia

- ▶ *Daniel D. Dressler, MD, MSc, SFHM, FACP* reviewing Siemieniuk RAC et al. *Ann Intern Med* 2015 Oct 6. Restrepo MI et al. *Ann Intern Med* 2015 Oct 6.
- ▶ A meta-analysis of corticosteroids for hospitalized CAP patients reveals significant treatment benefits.
- ▶ As many as 20% of patients with community-acquired pneumonia (CAP) worsen despite guideline-adherent antimicrobial therapy; in fact, some cases are caused by viruses ([NEJM JW Gen Med Sep 1 2015](#) and *N Engl J Med* 2015; 373:415). Systemic corticosteroids might reduce the cytokine and inflammatory responses that can lead to some CAP treatment failures. In two recent randomized controlled trials, researchers found outcome improvements with steroid therapy ([NEJM JW Infect Dis Mar 2015](#) and *Lancet* 2015; 385:1511; [NEJM JW Infect Dis Apr 2015](#) and *JAMA* 2015; 313:677); however, these trials were not powered to detect mortality differences.

- In a meta-analysis of 13 randomized, placebo-controlled trials (>2000 hospitalized CAP patients), moderate systemic corticosteroids doses (20–60 mg of prednisone or equivalent total daily dose) significantly lowered incidences of in-hospital mortality (5.3% vs. 7.9%; number needed to treat [NNT], 38), acute respiratory distress syndrome (0.4% vs. 3.0%; NNT, 38), and mechanical ventilation (3.1% vs. 5.7%; NNT, 38) and shortened hospital length of stay (by 1.0 days). Mortality benefit seemed to occur only in the subgroup of patients with severe pneumonia (7.4% vs. 22.0%; NNT, 7), whereas steroids improved other outcomes regardless of disease severity. Hyperglycemia that required treatment was more common in the corticosteroid group.

COMMENT

- ▶ This meta-analysis establishes corticosteroids as a valuable intervention in hospitalized CAP patients, especially those with severe pneumonia. A large randomized trial, scheduled to be completed in 2018, will help clarify dose and duration, but clinicians should consider a brief course (3–7 days) of daily moderate-dose (20–60 mg of prednisone or equivalent) systemic corticosteroids for hospitalized CAP patients.

- ▶ EDITOR DISCLOSURES AT TIME OF PUBLICATION

- ◀ **Disclosures for Daniel D. Dressler, MD, MSc, SFHM, FACP at time of publication** Editorial boards Hospital Medicine Practice (EBMedicine); Journal of Hospital Medicine (Wiley); Principles and Practice of Hospital Medicine (McGraw-Hill) Leadership positions in professional societies American College of Physicians, Georgia Chapter (Hospitalist Committee Chair)

- ◀ CITATION(S):

- ◀ Siemieniuk RAC et al. Corticosteroid therapy for patients hospitalized with community-acquired pneumonia: A systematic review and meta-analysis. *Ann Intern Med* 2015 Oct 6; 163:519. (<http://dx.doi.org/10.7326/M15-0715>)
PubMed abstract (Free)

- ◀ Restrepo MI et al. Corticosteroids for severe community-acquired pneumonia: Time to change clinical practice. *Ann Intern Med* 2015 Oct 6; 163:560. (<http://dx.doi.org/10.7326/M15-1805>)

More Evidence That Steroids Are Beneficial in Community-Acquired Pneumonia

- ▶ Daniel J. Pallin, MD, MPH reviewing Wu W-F et al. Am J Emerg Med 2017 Jul 15.
- ▶ A meta-analysis of randomized trials finds that steroids halve the risk of in-hospital mortality in patients with severe CAP.
- ▶ I previously recommended glucocorticoid therapy for patients admitted with severe community-acquired pneumonia (CAP), based on a meta-analysis of studies of all comers with CAP, which found a decreased incidence of acute respiratory distress syndrome (ARDS) but no mortality benefit (NEJM JW Emerg Med Dec 2015 and Chest 2016; 149:209). Now investigators report findings of a meta-analysis of randomized, controlled trials of adjuvant glucocorticoid therapy in patients with severe CAP.

- ▶ Ten trials including 729 patients with severe CAP met the criteria. Of these, three were considered good quality, seven fair, and one poor. All patients received standard therapy, including antibiotics, and were randomized to the addition of glucocorticoids. Type of glucocorticoid, dose, and duration of treatment varied among studies. The pooled in-hospital mortality estimate for patients treated with glucocorticoids was half that for patients not treated with glucocorticoids (relative risk, 0.49). Length of hospital stay also was lower in the glucocorticoid group. There was no significant difference in clinical efficacy or mechanical ventilation time between groups.

COMMENT

- ▶ This study adds to building evidence that glucocorticoids benefit patients with pneumonia. It is time for a large definitive trial.
 - ▶ Note to readers: At the time we reviewed this paper, its publisher noted that it was not in final form and that subsequent changes might be made.
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- ▶ EDITOR DISCLOSURES AT TIME OF PUBLICATION
 - ◀ **Disclosures for Daniel J. Pallin, MD, MPH at time of publication** Consultant / advisory board: Paratek Pharmaceuticals; Grant / Research support: NIH—National Center for Advancing Translational Sciences; Editorial boards: Annals of Emergency Medicine; Academic Emergency Medicine; JAMA; New England Journal of Medicine; Clinical Infectious Diseases; Leadership positions in professional societies: Society for Academic Emergency Medicine (Chair, Program Committee, 2017–2018)
 - ◀ CITATION(S):
 - ◀ Wu W-F et al. Efficacy of corticosteroid treatment for severe community-acquired pneumonia: A meta-analysis. *Am J Emerg Med* 2017 Jul 15; [e-pub]. (<http://dx.doi.org/10.1016/j.ajem.2017.07.050>)

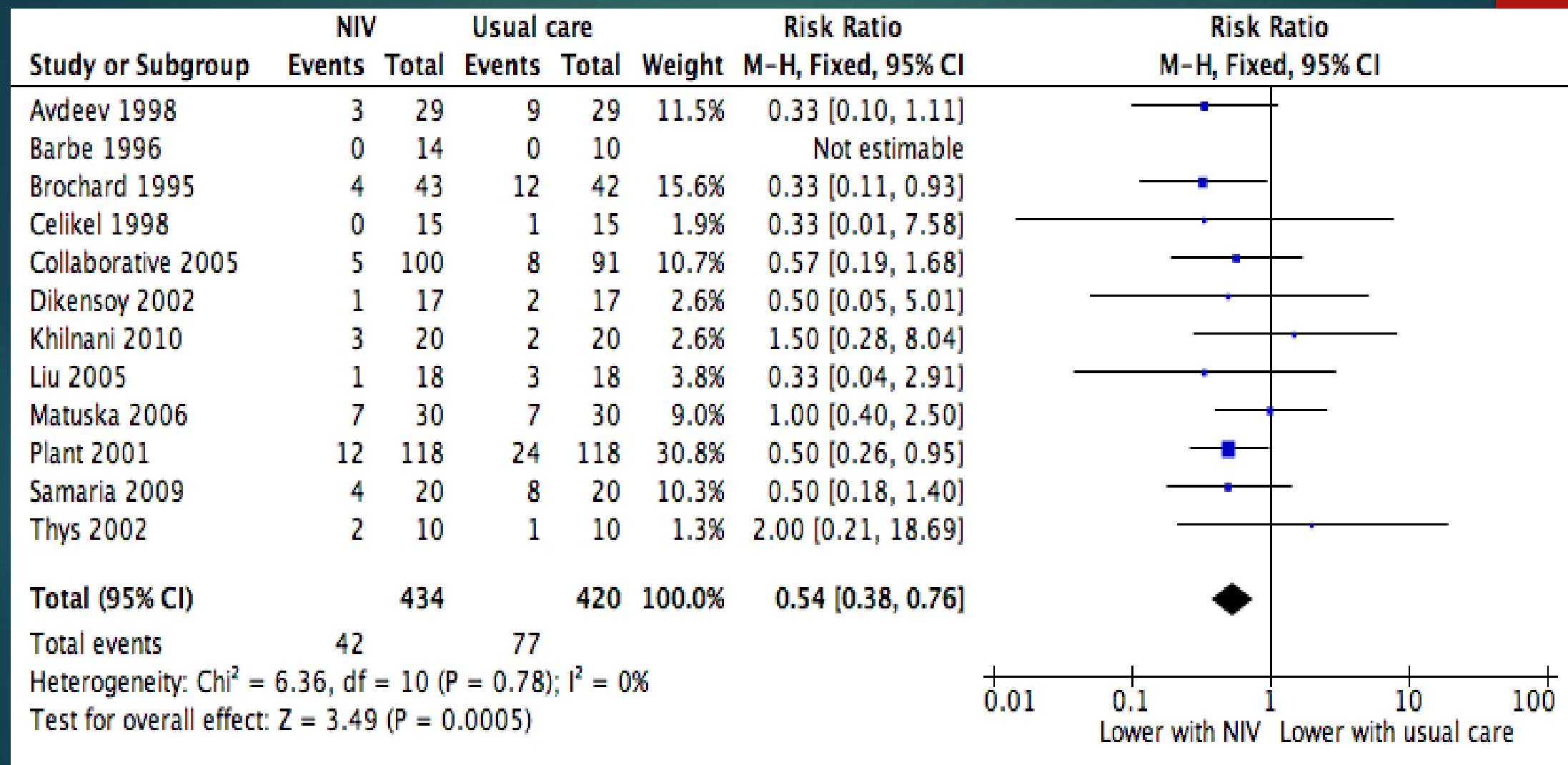


When Is Noninvasive Ventilation Indicated in Patients with COPD Exacerbations?

- ▶ *Daniel D. Dressler, MD, MSc, SFHM, FACP* reviewing Osadnik CR et al. Cochrane Database Syst Rev 2017 Jul 13.
- ▶ A meta-analysis reaffirms that noninvasive ventilation lowers mortality and shortens hospital stays in patients with chronic obstructive pulmonary disease and hypercapnic respiratory failure.

- ▶ International guidelines recommend noninvasive positive-pressure ventilation (NPPV) for patients with chronic obstructive pulmonary disease (COPD) exacerbations and acute hypercapnic respiratory failure (AHRF) based on symptoms or low serum pH ([NEJM JW Hosp Med Jul 2017](#) and *Am J Respir Crit Care Med* 2017; 195:557). To evaluate this recommendation, investigators aggregated results from 17 randomized controlled trials in which NPPV was compared with no NPPV in 1264 COPD patients with exacerbations and AHRF. Both groups received other standard therapies for COPD exacerbation.

- NPPV led to the following significant outcome improvements:
- In-hospital mortality: 10% with NPPV vs. 18% with no NPPV (number needed to treat [NNT], 12)
 - Subgroup with presenting pH <7.3: 11% vs. 20% (NNT, 11)
 - Subgroup with presenting pH 7.3–7.35: 8% vs. 17% (NNT, 12)
- Intubation: 12% with NPPV vs. 34% with no NPPV (NNT, 5)
 - Subgroup with presenting pH <7.3: 13% vs. 44% (NNT, 4)
 - Subgroup with presenting pH 7.3–7.35: 11% vs. 25% (NNT, 7)
- Length of stay (LOS): NPPV patients' LOS was a mean 3.4 days shorter than no-NPPV patients' LOS.



COMMENT

- ◀ Anecdotal experience suggests that NPPV is underused in admitted patients with COPD exacerbation and AHRF, especially when hypercapnic acidemia is only mild (pH 7.3–7.35). This meta-analysis affirms NPPV's benefits in limiting in-hospital mortality and intubation and in shortening LOS. Inpatient clinicians should apply this intervention liberally when patients meet criteria.

- ◀ EDITOR DISCLOSURES AT TIME OF PUBLICATION

- ◀ **Disclosures for Daniel D. Dressler, MD, MSc, SFHM, FACP at time of publication** Royalties McGraw-Hill Editorial boards Journal of Hospital Medicine (Frontline); Principles and Practice of Hospital Medicine (McGraw-Hill)

- ◀ CITATION(S):

- ◀ Osadnik CR et al. Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2017 Jul13; 7:CD004104.
[\(<http://dx.doi.org/10.1002/14651858.CD004104.pub4>\)](http://dx.doi.org/10.1002/14651858.CD004104.pub4)



CHF/Cardiac

- ▶ New Heart failure guidelines have been released, let's take a look
- ▶ The new anticoagulants have been raising some practical questions

Managing Heart Failure: A Focused Update

- ▶ Frederick A. Masoudi, MD, MSPH, FACC, FAHA reviewing Yancy CW et al. *Circulation* 2017 Aug 08.
- ▶ *The update addresses treatment changes for patients with either preserved or reduced systolic function.*
- ▶ **Sponsoring Organizations:** American College of Cardiology (ACC) Foundation, American Heart Association (AHA), and the Heart Failure Society of America in collaboration with American Academy of Family Physicians, American College of Chest Physicians, and International Society for Heart and Lung Transplantation

- ◀ **Target Audience:** Cardiovascular specialists, cardiac surgeons, and primary care clinicians providing care to patients with heart failure (HF).
- ◀ **Background and Objective**
- ◀ This update of the 2013 ACC/AHA guideline is based on a review of clinical trials that were presented at national and international scientific meetings and published in the peer-reviewed literature between April 2013 and November 2016.

Key Points

- ▶ 1. **Biomarkers:** Natriuretic peptides are useful for diagnosis in patients with suspected HF or for prognosis (Class I [strong recommendations]) and might help to identify patients at risk for HF who might benefit from team-based preventive care (Class IIa [moderate recommendation]).
- ▶ Troponin levels at the time of hospitalization are also useful for prognostication (Class I).
- ▶ The value of using biomarkers in guiding therapy is not clear.

- ↳ 2. **Renin-Angiotensin System Inhibition:** This strategy is recommended to reduce morbidity and mortality in all patients with HF and reduced ejection fraction (HFrEF) and no contraindications, in addition to optimal therapy that includes beta blockers and aldosterone antagonists in those without contraindications as well as device therapy (implantable cardioverter-defibrillator cardiac resynchronization therapy, or both) in those with an indication.
- ↳ Angiotensin-converting enzyme (ACE) inhibitors (Class I) or
- ↳ Angiotensin receptor blockers (ARBs, Class I) or
- ↳ Angiotensin receptor–neprilysin inhibitor (ARNI) to replace ACE inhibitors or ARBs in patients who have tolerated either agent (Class I, but with a lower level of evidence than ACE or ARB). ARNI should not be used within 36 hours of the last dose of an ACE inhibitor or in patients with angioedema (Class III [harm]).

- ← 3. **Ivabradine:** Consider using this drug to reduce HF hospitalizations for symptomatic HFrEF and resting heart rate ≥ 70 bpm in patients on optimal therapy, including a beta blocker at the maximal tolerated dose (Class IIa).
- ← 4. **Therapy for HF with Preserved Ejection Fraction (HFpEF):** Therapy remains largely targeted at coexisting conditions, including hypertension, coronary disease, and atrial fibrillation. Aldosterone receptor antagonists or ARBs in appropriately selected patients might reduce hospitalization risk (Class IIb [weak recommendation]). Routine nitrates or phosphodiesterase-5 inhibitors are discouraged (Class III [no benefit]).

- ◀ 5. **Anemia and Iron Deficiency:** Intravenous iron to improve health status is recommended for symptomatic patients with HF and iron deficiency (Class IIb). Erythropoietin-stimulating agents should not be used (Class III [no benefit]).
- ◀ 6. **Hypertension:** Recommended optimal levels (Class I) are <130/80 mm Hg for those at risk for HF (stage A) or systolic <130 mm Hg in patients with HFrEF or HFpEF.
- ◀ 7. **Sleep-Disordered Breathing:** Screening (Class IIa) and treatment of obstructive sleep apnea (Class IIb) to reduce sleepiness are recommended. Adaptive servo-ventilation in patients with central sleep apnea should be avoided (Class III [harm]).

What's Changed

- ◀ This update includes new recommendations on substituting ARNI for ACE or ARB in HFrEF and selective use of ivabradine in optimally managed patients with HFrEF, plus a modest recommendation for aldosterone antagonists for HFpEF. The dos and don'ts for treating coexisting conditions integrate data from other randomized trials.
- ◀ COMMENT
- ◀ Many clinicians might be uncomfortable using ARNI for HFrEF because of concerns about adverse effects; this document provides helpful guidance. HFpEF treatment remains frustrating because of the lack of definitive positive trials. The recommendations for treating coexisting conditions remind us of the complexity of caring for patients with HF. The best care considers issues well beyond the heart.

EDITOR DISCLOSURES AT TIME OF PUBLICATION

- ◀ Dr. Masoudi was a member of the writing committee for this guideline update.
- ◀ **Disclosures for Frederick A. Masoudi, MD, MSPH, FACC, FAHA at time of publication**
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- ◀ CITATION(S):
- ◀ Yancy CW et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation* 2017 Aug 08; 136:e137.
(<http://dx.doi.org/10.1161/CIR.0000000000000509>)

Prothrombin Complex Concentrate for Bleeding from Direct Oral Anticoagulants

- ▶ David Green, MD, PhD reviewing Majeed A et al. *Blood* 2017 Aug 23.
- ▶ Treatment was effective for 70% of hemorrhages associated with apixaban or rivaroxaban.
- ▶ Direct oral anticoagulants (DOACs) are infrequently associated with major bleeding. Hemorrhages in patients receiving dabigatran are managed with idarucizumab (NEJM JW Oncol Hematol Oct 2017 and *N Engl J Med* 2017; 377:431), but for those on other DOACs, a new agent, andexanet (NEJM JW Oncol Hematol Oct 2016 and *N Engl J Med* 2016; 375:1131), is still under evaluation and not yet approved.

- ↳ To determine whether a four-factor prothrombin complex concentrate (PCC) can safely control major bleeding in patients receiving apixaban or rivaroxaban, investigators conducted an observational study of patients who had taken one of these DOACs within 24 hours. Of 84 patients, 70% had intracranial hemorrhages and 15.5% had gastrointestinal bleeding. The PCC was given in a dose of 1500 IU for patients weighing less than 65 kg and 2000 IU for those weighing more than 65 kg.

- ↳ Treatment was considered effective for 70% of hemorrhages, irrespective of whether the patient had received apixaban or rivaroxaban. Treatment failures occurred mainly in patients with intracranial bleeding; most of the 15 deaths that occurred were in these patients. Only three suspected thrombotic events were recorded.

COMMENT

◀ Kcentra is the only four-factor PCC available in the U.S. As used in this study, it appears to be safe and effective for DOAC-associated bleeding. Very few thrombotic events were recorded, despite the fact that two thirds of the patients also received tranexamic acid. Alternatives for patients not responding to initial dosing are a second dose of the PCC or recombinant factor VIIa.

◀ EDITOR DISCLOSURES AT TIME OF PUBLICATION

◀ **Disclosures for David Green, MD, PhD at time of publication**Nothing to disclose

◀ CITATION(S):

◀ Majeed A et al. Management of rivaroxaban or apixaban associated major bleeding with prothrombin complex concentrates: A cohort study. *Blood* 2017 Aug 23; [e-pub]. (<http://dx.doi.org/10.1182/blood-2017-05-782060>)

Rivaroxaban, Aspirin, or Both in Stable Coronary Disease

- ▶ Joel M. Gore, MD reviewing Eikelboom JW et al. *N Engl J Med* 2017 Aug 27. Braunwald E. *N Engl J Med* 2017 Aug 27.
- ▶ The combination of rivaroxaban plus aspirin was shown to improve outcome, even when bleeding was factored in.
- ▶ Aspirin remains the mainstay of secondary prevention for coronary artery disease; vitamin K antagonists are superior when added to aspirin or used alone for patients with acute myocardial infarction (MI), but excess bleeding has limited their use. In the manufacturer-sponsored, double-blind COMPASS trial, investigators enrolled 27,395 patients (mean age, 68; 22% women) with stable coronary artery disease to the direct-acting oral anticoagulant rivaroxaban (2.5 mg twice a day) plus aspirin (100 mg daily), rivaroxaban (5 mg twice a day), or aspirin (100 mg daily). The primary outcome was cardiovascular death, stroke, or MI.

- ◀ The study was stopped after 23 months of follow-up because of a significant advantage in efficacy for rivaroxaban plus aspirin. The primary outcome occurred in 4.1% of patients who received rivaroxaban plus aspirin, 4.9% who received rivaroxaban alone, and 5.4% who received aspirin alone. When bleeding events (3.1%, 2.8%, and 1.9%, respectively) were included in the analysis, the net clinical benefit remained significantly greater with rivaroxaban plus aspirin than with aspirin alone; rivaroxaban alone did not have a significant advantage over aspirin alone. Results were consistent across predefined subgroups including age, sex, geographic region, and race or ethnicity.

RESULTS

- The primary outcome occurred in fewer patients in the rivaroxaban-plus-aspirin group than in the aspirin-alone group (379 patients [4.1%] vs. 496 patients [5.4%]; hazard ratio, 0.76; 95% confidence interval [CI], 0.66 to 0.86; $P<0.001$; $z=-4.126$), but major bleeding events occurred in more patients in the rivaroxaban-plus-aspirin group (288 patients [3.1%] vs. 170 patients [1.9%]; hazard ratio, 1.70; 95% CI, 1.40 to 2.05; $P<0.001$). There was no significant difference in intracranial or fatal bleeding between these two groups. There were 313 deaths (3.4%) in the rivaroxaban-plus-aspirin group as compared with 378 (4.1%) in the aspirin-alone group (hazard ratio, 0.82; 95% CI, 0.71 to 0.96; $P=0.01$; threshold P value for significance, 0.0025). The primary outcome did not occur in significantly fewer patients in the rivaroxaban-alone group than in the aspirin-alone group, but major bleeding events occurred in more patients in the rivaroxaban-alone group.

COMMENT

◀ For patients with stable coronary artery disease, it appears that rivaroxaban plus aspirin improves cardiovascular outcomes at 2 years. Many patients who might benefit from this combination are already taking aspirin and other medications, and their ability to add another twice-daily drug to their regimen long-term may bear on how readily rivaroxaban plus aspirin is adopted in clinical practice. The current recommendation for patients with atherosclerotic disease is to remain on aspirin for life; it's unclear whether patients would need to remain on rivaroxaban plus aspirin for life as well. Furthermore, the additional cost of rivaroxaban is not insignificant.

◀ EDITOR DISCLOSURES AT TIME OF PUBLICATION

◀ **Disclosures for Joel M. Gore, MD at time of publication** Grant / Research support NIH–National Heart, Lung, and Blood Institute

◀ CITATION(S):

◀ Eikelboom JW et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017 Aug 27; [e-pub]. (<http://dx.doi.org/10.1056/NEJMoa1709118>)

◀ Braunwald E. An important step for thrombocardiology. *N Engl J Med* 2017 Aug 27; [e-pub]. (<http://dx.doi.org/10.1056/NEJMe1710241>)

Dual Antithrombotic Therapy Is Safe for Patients with AF and a New Stent

- ▶ Mark S. Link, MD reviewing Cannon CP et al. *N Engl J Med* 2017 Aug 27.
- ▶ A direct anticoagulant plus a P2Y12 inhibitor — without aspirin — did not increase bleeding risk.
- ▶ For stented patients with atrial fibrillation (AF), triple antithrombotic therapy — warfarin, a P2Y12 inhibitor, and low-dose aspirin — is effective in preventing systemic embolism and stent thrombosis, but bleeding risk is markedly elevated. In the PIONEER-AF trial, rivaroxaban at doses lower than that approved for stroke prevention, plus a single P2Y12 inhibitor, did not increase stent-thrombosis risk and lowered bleeding risk, compared with standard triple therapy.

- In the manufacturer-funded RE-DUAL trial ([NCT02164864](#)), researchers randomized 2725 patients with AF and a new stent to receive either dual therapy with dabigatran (110 or 150 mg twice daily) plus clopidogrel or ticagrelor — or triple therapy with warfarin, clopidogrel or ticagrelor, and ≤100-mg daily aspirin (for 1 or 3 months depending on stent type). Consistent with product labeling in those countries, elderly patients outside the U.S. could not receive 150-mg dabigatran. Mean follow-up was 14 months.

- Incidence of the primary endpoint — major or clinically relevant nonmajor bleeding — was significantly lower with 110-mg dabigatran dual therapy than with triple therapy (15% vs. 27%; hazard ratio, 0.52) and with 150-mg dabigatran dual therapy than with triple therapy (20% vs. 26%; HR, 0.72), demonstrating dual therapy's noninferiority at either dabigatran dose. A composite endpoint of thromboembolic events (myocardial infarction, stroke, or systemic thromboembolism), death, or unplanned revascularization did not differ significantly between the dual-therapy groups combined (13.7%) and the triple-therapy group (13.4%). All groups had low stent-thrombosis rates (0.8%–1.5%).

COMMENT

- ◀ The findings from RE-DUAL, which used standard dabigatran doses, should kill triple antithrombotic therapy for stent recipients with AF, building on PIONEER and WOEST. RE-DUAL was underpowered to assess thromboembolism prevention, but the larger RE-LY trial (dabigatran vs. warfarin in AF) has already done that work. I am finally comfortable with using a direct anticoagulant plus a P2Y12 inhibitor for my patients with AF and stents; however, I will use the recommended direct-anticoagulant dose and, if possible, clopidogrel.

- ◀ EDITOR DISCLOSURES AT TIME OF PUBLICATION

- ◀ **Disclosures for Mark S. Link, MD at time of publication** Editorial boardsUpToDate; Heart Rhythm; Circulation; EP Lab Digest Leadership positions in professional societies Heart Rhythm Society (Chair, CME Compliance Committee); American Heart Association (Chair, ACLS Writing Group; Member, Emergency Cardiovascular Care)

- ◀ CITATION(S):

- ◀ Cannon CP et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med* 2017 Aug 27; [e-pub]. (<http://dx.doi.org/10.1056/NEJMoa1708454>)



Sepsis

- ▶ The new sepsis definition and the ever changing guidelines from the Surviving Sepsis Campaign
- ▶ A novel new adjunctive treatment for Sepsis?

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

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- ▶ [Author Affiliations](#) [Article Information](#)
- ▶ JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287
- ▶ Abstract
- ▶ **Importance** Definitions of sepsis and septic shock were last revised in 2001. Considerable advances have since been made into the pathobiology (changes in organ function, morphology, cell biology, biochemistry, immunology, and circulation), management, and epidemiology of sepsis, suggesting the need for reexamination.

Objective

- ↳ To evaluate and, as needed, update definitions for sepsis and septic shock.
- ↳ **Process** A task force ($n = 19$) with expertise in sepsis pathobiology, clinical trials, and epidemiology was convened by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. Definitions and clinical criteria were generated through meetings, Delphi processes, analysis of electronic health record databases, and voting, followed by circulation to international professional societies, requesting peer review and endorsement (by 31 societies listed in the Acknowledgment).
- ↳ **Key Findings From Evidence Synthesis** Limitations of previous definitions included an excessive focus on inflammation, the misleading model that sepsis follows a continuum through severe sepsis to shock, and inadequate specificity and sensitivity of the systemic inflammatory response syndrome (SIRS) criteria. Multiple definitions and terminologies are currently in use for sepsis, septic shock, and organ dysfunction, leading to discrepancies in reported incidence and observed mortality. The task force concluded the term severe sepsis was redundant.

Recommendations Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10%. Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L ($>18 \text{ mg/dL}$) in the absence of hypovolemia. This combination is associated with hospital mortality rates greater than 40%. In out-of-hospital, emergency department, or general hospital ward settings, adult patients with suspected infection can be rapidly identified as being more likely to have poor outcomes typical of sepsis if they have at least 2 of the following clinical criteria that together constitute a new bedside clinical score termed quickSOFA (qSOFA): respiratory rate of 22/min or greater, altered mentation, or systolic blood pressure of 100 mm Hg or less.

Conclusions and Relevance These updated definitions and clinical criteria should replace previous definitions, offer greater consistency for epidemiologic studies and clinical trials, and facilitate earlier recognition and more timely management of patients with sepsis or at risk of developing sepsis.

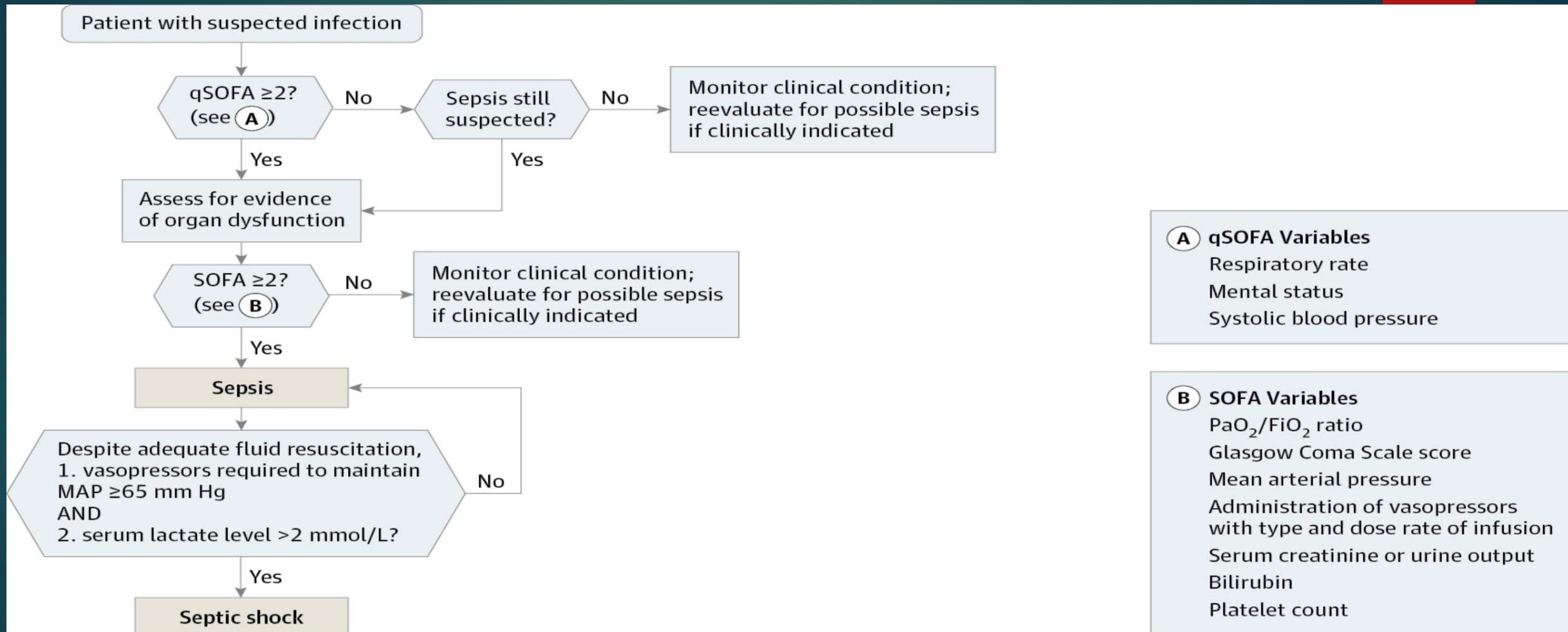


Figure Legend:

Operationalization of Clinical Criteria Identifying Patients With Sepsis and Septic Shock The baseline Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score should be assumed to be zero unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection.

qSOFA indicates quick SOFA; MAP, mean arterial pressure.

Follow-Up Studies Support New Sepsis-3 Definitions' Prognostic Value

- ▶ Patricia Kritek, MD reviewing Freund Y et al. JAMA 2017 Jan 17. Raith EP et al. JAMA 2017 Jan 17. Lamontagne F et al. JAMA 2017 Jan 17.
- ▶ SOFA (sequential organ failure assessment) score performed best in the intensive care unit, and quick SOFA performed best in the emergency department.
- ▶ Sepsis-3 Validation Studies
- ▶ In 2016, new definitions for sepsis and septic shock (Sepsis-3) were published, including endorsement for using sequential organ failure assessment (SOFA) and quick SOFA (qSOFA) scores to assess prognosis (NEJM JW Gen Med Mar 15 2016 and JAMA 2016; 315:801). In two new studies, investigators examined use of these scores in emergency department (ED) and intensive care unit (ICU) populations (Figure).

- ◀ In one study, European investigators examined 879 patients who presented to the ED with clinically suspected, potentially serious infections. Overall mortality for the cohort was 8%; however, 24% of patients with qSOFA scores ≥ 2 died. Compared with ≥ 2 systemic inflammatory response syndrome elements (SIRS), severe sepsis (SIRS + organ dysfunction), or SOFA score ≥ 2 , qSOFA ≥ 2 was best at predicting in-hospital death. Results were similar for predicting ICU admission and long ICU stay (≥ 72 hours). Adding lactate level measurement to qSOFA did not improve its prognostic value.

- ▶ Investigators from Australia and New Zealand performed similar studies in a population of 185,000 patients admitted to ICUs with infection-related diagnoses. In contrast to qSOFA's superior performance in an ED population (as described above), qSOFA did not perform well in this ICU population. Instead, an increase of ≥ 2 points in SOFA score within 24 hours of admission to the ICU was the best predictor of in-hospital mortality. The same was true for predicting long ICU stays.

Sepsis-3 Validation Studies

Sepsis-3 ED Validation Study

- 900 patients with suspected infection in 30 European emergency departments
- In-hospital mortality, 8%

Criteria	Mortality in patients with finding	Mortality in patients without finding
qSOFA ≥ 2	24%	3%
SOFA ≥ 2	18%	3%
SIRS ≥ 2	11%	2%
SIRS ≥ 2 + lactate >2 mmol/L	20%	6%

Sepsis-3 ICU Validation Study

- 185,000 patients with infection-related diagnoses in 182 Australia and New Zealand intensive care units
- In-hospital mortality, 19%

Criteria	Mortality in patients with finding	Mortality in patients without finding
SOFA increase ≥ 2	20%	4%
qSOFA ≥ 2	23%	14%
SIRS ≥ 2	20%	10%

COMMENT

- ▶ These two studies support the findings published with the unveiling of Sepsis-3. In the ED, qSOFA works well as an indicator of who is really sick. What we need to know now is whether qSOFA scores help providers intervene earlier and modify outcomes in patients who present with sepsis; studies to examine this question likely will be forthcoming. In the ICU, qSOFA is of limited value: I would argue that, although calculation of a SOFA score might help with prognostication, I'm not convinced its use will change management and improve survival.

EDITOR DISCLOSURES AT TIME OF PUBLICATION

- ◀ **Disclosures for Patricia Kritek, MD at time of publication** Speaker's Bureau American College of Chest Physicians (Critical Care Board Review Course)
- ◀ CITATION(S):
- ◀ Freund Y et al. Prognostic accuracy of Sepsis-3 criteria for in-hospital mortality among patients with suspected infection presenting to the emergency department. JAMA 2017 Jan 17; 317:301. (<http://dx.doi.org/10.1001/jama.2016.20329>)
- ◀
- ◀ Raith EP et al. Prognostic accuracy of the SOFA score, SIRS criteria, and qSOFA score for in-hospital mortality among adults with suspected infection admitted to the intensive care unit. JAMA 2017 Jan 17; 317:290. (<http://dx.doi.org/10.1001/jama.2016.20328>)
- ◀
- ◀ Lamontagne F et al. qSOFA for identifying sepsis among patients with infection. JAMA 2017 Jan 17; 317:267. (<http://dx.doi.org/10.1001/jama.2016.19684>)

Lactate Clearance Measures Efficacy of Goal-Directed Therapy in Sepsis (the History Lesson)

- ▶ Diane M. Birnbaumer, MD, FACEP reviewing Jones AE et al. JAMA 2010 Feb 24. Lewis RJ. JAMA 2010 Feb 24.
- ▶ Mortality did not differ significantly when lactate clearance or central venous oxygen saturation was used to measure tissue oxygen delivery.
- ▶ Goal-directed resuscitation for severe sepsis focuses on three targets: (1) fluid resuscitation to a central venous pressure of 8–12 mm Hg, (2) pressure support to a mean arterial pressure of at least 65 mm Hg, and (3) adequate oxygen delivery (via blood transfusion, dobutamine infusion, or both) to central venous oxygen saturation (ScvO_2) of at least 70%. Measurement of ScvO_2 , however, requires a special catheter. These authors tested the hypothesis that use of lactate clearance $>10\%$ is not inferior to use of $\text{ScvO}_2 \geq 70\%$ for assessing the adequacy of oxygen delivery.

- ▶ In a prospective study conducted at the emergency departments of three U.S. medical centers, 300 patients with severe sepsis and septic shock were randomized to resuscitation to a target central venous pressure of 8–12 mm Hg, mean arterial pressure of >65 mm Hg, and either ScvO₂ ≥70% or lactate clearance >10% at 2 hours after initiation of resuscitation. The primary outcome was absolute in-hospital mortality. Overall, 23% of patients in the ScvO₂ group died, compared with 17% in the lactate clearance group; the 6% difference between groups did not reach the predetermined statistical threshold of a 10% difference. Rates of adverse events were similar between groups.

COMMENT

- Early goal-directed therapy in patients with sepsis reportedly decreases mortality by as much as 46%, but the need for a special catheter to measure ScvO₂ can be an obstacle to its implementation. This study's findings suggest that a serum lactate decrease of 10% within 2 hours after initiation of sepsis resuscitation is not inferior to an ScvO₂ of 70% for measuring adequate oxygen delivery and that lactate measurement might substitute for ScvO₂ measurement.

- Dr. Birnbaumer works in the same department as Dr. Lewis, the editorialist. However, Dr. Lewis did not participate in Dr. Birnbaumer's coverage of this article.
- CITATION(S):
- ↳ Jones AE et al. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: A randomized clinical trial. JAMA 2010 Feb 24; 303:739.
[PubMed abstract \(Free\)](#)[Web of Science](#)
- ↳ Lewis RJ. Disassembling goal-directed therapy for sepsis: A first step. JAMA 2010 Feb 24; 303:777.
[PubMed abstract \(Free\)](#)[Web of Science](#)

Early Goal-Directed Therapy Does Not Lower Mortality in Septic Patients

- ▶ Patricia Kritek, MD reviewing *The PRISM Investigators. N Engl J Med 2017 Mar 21.*
- ▶ A meta-analysis confirms no benefit, even for patients with the most severe septic shock.
- ▶ Early goal-directed therapy (EGDT) for sepsis — which specifies somewhat arbitrary goals for physiologic parameters such as central venous pressure and central venous oxygen saturation —had been the standard of care for more than a decade until 2014–2015. Then, three international trials found that “usual care” of septic patients was as effective as EGDT, at less cost and with fewer interventions. In an impressive collaboration, the investigators from these trials had standardized enrollment criteria, protocols, and outcomes to facilitate a meta-analysis of their data. Now, researchers report results of this meta-analysis, which included 3723 septic patients at 138 hospitals.

- ▶ All patients received early antibiotics and intravenous fluids. At 90 days, mortality was similar between groups; however, length of stay in intensive care was longer and more patients received vasopressors in the EGDT group. In subgroup analyses, EGDT conferred no benefit in patients with the most severe septic shock. Among EGDT-treated patients, 90-day mortality was higher in those with severe chronic liver disease than in those without the disease and lower in those who had severe chronic lung disease than in those who did not. Cost was higher in the EGDT group.

COMMENT

- ▶ This meta-analysis makes it clear that the time for EGDT has passed. Early appropriate antibiotics and adequate fluid resuscitation are essential in treating patients with sepsis and septic shock, but targeting arbitrary goals doesn't make sense. Our focus moving forward should be on recognizing sepsis early, to allow prompt administration of antimicrobials and fluids.

- ▶ EDITOR DISCLOSURES AT TIME OF PUBLICATION

- ◀ **Disclosures for Patricia Kritek, MD at time of publication** Speaker's Bureau of American College of Chest Physicians (Critical Care Board Review Course)Editorial boards American Journal of Respiratory and Critical Care Medicine Leadership positions in professional societies American Thoracic Society (Chair of the Nominating Committee, Section on Medical Education)

- ◀ CITATION(S):

- ◀ The PRISM Investigators. Early, goal-directed therapy for septic shock — A patient-level meta-analysis. *N Engl J Med* 2017 Mar 21; [e-pub]. (<http://dx.doi.org/10.1056/NEJMoa1701380>)

Further Evidence

- ▶ Published very recently.....
- ▶ In a study out of Africa, EGDT actually increased mortality in patients with HIV/AIDS and sepsis

Vitamin C, Thiamine, and Hydrocortisone for Sepsis Patients

- ▶ Patricia Kritek, MD reviewing Marik PE et al. *Chest* 2017 Jun.
- ▶ A single-center study showed remarkable mortality reduction with this cocktail.
- ▶ A myriad of interventions for sepsis have been studied; the vast majority have been disappointing. Despite such setbacks, the search persists for the right combination of agents to stop inflammatory dysregulation.

During 6 months, all patients admitted to the medical intensive care unit (MICU) in a Norfolk, VA, hospital with severe sepsis or septic shock and elevated procalcitonin levels (≥ 2 ng/mL), received intravenous high-dose vitamin C (6 g daily), hydrocortisone (50 mg every 6 hours), and thiamine. In a before–after study design, 47 intervention patients were compared with 47 patients who had been admitted to the MICU in the 6 months prior to implementation. Patients in the two groups had remarkably similar baseline characteristics.



Mortality was markedly lower in the patients treated with vitamin C, hydrocortisone, and thiamine (9% vs. 41% in the earlier group). Intervention patients also had faster resolution of shock with shorter mean duration of vasopressor use and less need for renal replacement therapy.

COMMENT

- With such a striking mortality difference, this study received considerable coverage in the lay press and a lot of discussion in ICUs. The authors discuss theoretical reasons for their choice of agents; for example, vitamin C has antioxidant properties, and thiamine deficiency is reportedly common in septic patients. They suggest that, although the study is small, single-center, and not randomized, this intervention is ready for implementation, because the potential benefits outweigh the risks. I don't agree. We have learned the harms of early adoption in critical care (e.g., tight glucose control, activated protein C); although vitamin C and thiamine probably have fewer downsides, they are not without risk or cost. Researchers are evaluating vitamin C in sepsis patients in an ongoing randomized controlled trial, and adoption should await confirmatory results.

EDITOR DISCLOSURES AT TIME OF PUBLICATION

- ◀ **Disclosures for Patricia Kritek, MD at time of publication**
- ◀ Speaker's BureauAmerican College of Chest Physicians (Critical Care Board Review Course)
Editorial boardsAmerican Journal of Respiratory and Critical Care Medicine
Leadership positions in professional societiesAmerican Thoracic Society (Chair of the Nominating Committee, Section on Medical Education)
- ◀ CITATION(S):
- ◀ Marik PE et al. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: A retrospective before-after study. *Chest* 2017 Jun; 151:1229. (<http://dx.doi.org/10.1016/j.chest.2016.11.036>)



High-Fat Diets Were Associated with Lower 7-Year Mortality

- ▶ Bruce Soloway, MD reviewing Dehghan M et al. *Lancet* 2017 Aug 28.
- ▶ Higher fat and lower carbohydrate intake was associated with lower mortality and no change in adverse cardiovascular events in this global study.
- ▶ Standard dietary advice to restrict total fat and saturated fatty acids (<30% and <10% of total energy, respectively) is based largely on a few observational studies conducted years ago in North America and Europe. However, recent meta-analyses have shown no association, or an inverse relation, between saturated fatty acid intake and total mortality and adverse cardiovascular (CV) events.

- Researchers conducted detailed analyses of the diets of more than 135,000 people with a range of income levels in 18 countries on five continents. Participants were sorted into quintiles based on percentage of dietary energy derived from carbohydrates; protein; and total, saturated, monounsaturated, and polyunsaturated fats. Median follow-up was 7.4 years.
- After adjustment for education, smoking, physical activity, diabetes, urban versus rural location, total energy intake, and geographic region, higher carbohydrate intake was associated with higher risk for overall mortality and non-CV-related death but was not associated with major adverse CV events assessed individually or as a group. Conversely, higher intakes of total, saturated, monounsaturated, and polyunsaturated fats were associated with lower risk for overall and non-CV-related death and were not associated with adverse CV events (other than an inverse relation between saturated fat intake and stroke).

COMMENT

- Data from this large, diverse international cohort does not support current dietary guidelines that recommend restricting total and saturated fats. The findings suggest that people who eat high carbohydrate diets might benefit from substituting fats for some of their carbohydrates.

- EDITOR DISCLOSURES AT TIME OF PUBLICATION
- ◀ **Disclosures for Bruce Soloway at time of publication** Nothing to disclose
- ◀ CITATION(S):
- ◀ Dehghan M et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): A prospective cohort study. *Lancet* 2017 Aug 28; [e-pub]. ([http://dx.doi.org/10.1016/S0140-6736\(17\)32252-3](http://dx.doi.org/10.1016/S0140-6736(17)32252-3))





LATER I'LL GO RUNNING



AND BURN THIS OFF