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EARLY GOAL-DIRECTED THERAPY DOES NOT LOWER MORTALITY IN SEPTIC PATIENTS

- N Engl J Med 2017 Mar 21; [e‑pub].
  http://dx.doi.org/10.1056/NEJMoa1701380

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NOREPINEPHRINE SHORTAGE IS ASSOCIATED WITH HIGHER MORTALITY

- JAMA 2017 Apr 11; 317:1433.
  http://dx.doi.org/10.1001/jama.2017.2841
- JAMA 2017 Apr 11; 317:1415.
  http://dx.doi.org/10.1001/jama.2017.2826

THE DOWNSIDES OF SHORT-TERM CORTICOSTEROIDS

- BMJ 2017 Apr 12; 357:j1415.
  http://dx.doi.org/10.1136/bmj.j1415

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  http://dx.doi.org/10.1001/jama.2017.4360

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- Ann Intern Med 2017 Apr 18; [e‑pub].
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  http://dx.doi.org/10.1136/bmj.j791

MORE EVIDENCE THAT EXCESSIVE BP LOWERING CAN HEIGHTEN CV RISK

- Lancet 2017 Apr 5; [e‑pub].
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  http://dx.doi.org/10.1136/bmj.j909
  http://dx.doi.org/10.1136/bmj.j1340

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- Neurology 2017 Apr 4; 88:1313.
  http://dx.doi.org/10.1212/WNL.0000000000003788

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- JAMA 2016 Dec 6; 316:2204.
  http://dx.doi.org/10.1001/jama.2016.17424
- JAMA 2016 Dec 6; 316:2193.
  http://dx.doi.org/10.1001/jama.2016.16398

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- JAMA Intern Med 2017 Apr 10; [e‑pub].
  http://dx.doi.org/10.1001/jamainternmed.2017.0453

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- Radiology 2017 Feb 23; [e‑pub].
  http://dx.doi.org/10.1148/radiol.2017161659

AN INTERVENTION TO ENHANCE COMMUNICATION BETWEEN PATIENTS AND ONCOLOGISTS

  http://jamanetwork.com/journals/jamaoncology/fullarticle/2551984
  http://dx.doi.org/10.1200/JCO.2016.68.5651
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- Ann Rheum Dis 2017 Mar 17; [e‑pub].
  http://dx.doi.org/10.1136/annrheumdis-2016-210872

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- JAMA Intern Med 2017 Apr 21; [e‑pub].
  http://dx.doi.org/10.1001/jamainternmed.2017.1144
- JAMA Intern Med 2017 Apr 21; [e‑pub].
  http://dx.doi.org/10.1001/jamainternmed.2017.1676

IN-PERSON COGNITIVE-BEHAVIORAL THERAPY vs. AUTOMATED INTERACTIVE VOICE-RESPONSE CBT FOR CHRONIC BACK PAIN

- JAMA Intern Med 2017 Apr 3; [e‑pub].
  http://dx.doi.org/10.1001/jamainternmed.2017.0223

HPV VACCINE: LONG-TERM PROTECTION AFTER TWO DOSES

- JAMA 2017 Apr 25; 317:1687.
  http://dx.doi.org/10.1001/jama.2017.1840

DOES MATERNAL STRESS DURING PREGNANCY AFFECT LONGEVITY OF OFFSPRING?

- Proc Natl Acad Sci U S A 2017 Apr 18; 114:4201.
  http://dx.doi.org/10.1073/pnas.1617911114
Early goal-directed therapy for sepsis — which specifies somewhat arbitrary goals for physiologic parameters like central venous pressure and central venous oxygen saturation — had been the standard of care for more than a decade until roughly 2014. It was then that three large international trials found that the “usual care” of septic patients was as effective as early goal-directed therapy, at less cost and with fewer interventions (www.jwatch.org/na34016; www.jwatch.org/na35864; www.jwatch.org/na37396). In an impressive collaboration, the researchers from these three trials had prospectively standardized their enrollment criteria, protocols, and outcomes to facilitate a meta-analysis of their data. Now, on the website of the New England Journal of Medicine (http://dx.doi.org/10.1056/NEJMoa1701380), the researchers report the results of this meta-analysis, which included nearly 4000 septic patients at 140 hospitals.

All of the patients got early antibiotics and intravenous fluids. At 3 months, mortality was similar in the two groups, but length of stay in the intensive care unit was longer and more patients got vasopressors in the early goal-directed therapy group. In subgroup analyses, early goal-directed therapy conferred no benefit in patients with the most severe septic shock. Among the patients treated with early goal-directed therapy, 90-day mortality was higher in those with severe chronic liver disease than in those without liver disease, and lower in those who had severe liver disease, and lower in those who had severe liver disease, and lower in those who had severe liver disease, and lower in those who had severe liver disease, and lower in those who had severe liver disease, and lower in those who had severe liver disease, and lower in those who had severe liver disease, and lower in those who had severe liver disease, and lower in those who had severe liver disease, and lower in those who had severe liver disease, and lower in those who had severe liver disease, and lower in those who had severe liver disease, and lower in those who had severe liver disease, and lower in those who had severe liver disease, and lower in those who had severe liver disease, and lower in those who had severe
chronic lung disease than in those who did not. Cost was higher in the early goal-directed therapy group.

This meta-analysis makes it clear that the time for early goal-directed therapy 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. The focus moving forward should be on recognizing sepsis early, to allow for the prompt administration of antimicrobials and fluids.

**NOREPINEPHRINE SHORTAGE IS ASSOCIATED WITH HIGHER MORTALITY**

During the past decade, drug shortages caused by production interruptions have increasingly affected hospitals in the United States. In 2011, there was a national shortage of norepinephrine. To evaluate the potential effect on patients with septic shock, researchers examined a large administrative database that contained data from before the shortage (2008–2010), during the shortage (2011), and after the shortage (2012–2013). Details appear in the April 11 issue of *JAMA* (http://dx.doi.org/10.1001/jama.2017.2841).

About 170,000 patients with septic shock were included in the analysis. “Shortage hospitals,” defined as those with at least a 20% decrease in norepinephrine use during 2011 (and a return to preshortage use in 2012), were compared with nonscarce hospitals. In a multivariate analysis, in-hospital mortality in the shortage hospitals declined overall during the 5-year study period, but during the norepinephrine shortage, the odds ratio for death (1.15) was significantly higher than during nonscarce times, and the use of phenylephrine increased. Neither an excess in mortality nor rises in phenylephrine use were seen in the nonscarce hospitals.

The message of this study is not that using phenylephrine to treat septic shock is harmful, although these data certainly suggest that that could be true. Instead, the results make tangible the changes in physician practice that happen in times of medication shortage and raise concern that alterations in usual care have significant effects on patient outcomes. As the accompanying editorial suggests (http://dx.doi.org/10.1001/jama.2017.2826), this is a wake-up call for more discussion about strategies to address and prevent drug shortages.

**THE DOWNSIDES OF SHORT-TERM CORticOSTEROIDS**

Although the adverse effects of long-term corticosteroids are clear, we don’t know much about short-term use. In a retrospective study on the website of *The BMJ* (http://dx.doi.org/10.1136/bmj.j1415), researchers in the United States used a nationwide commercial insurance claims dataset to determine the incidence of three adverse effects (namely, sepsis, venous thromboembolism, and fracture) that were associated with oral corticosteroid use for less than a month by almost 2 million patients between the ages of 18 and 64 (mean age, 45) continuously enrolled from 2012 through 2014.

In all, 20% of the patients got at least one short-term prescription for an oral corticosteroid (the median duration was 6 days and the median prednisone equivalent dose was 20 mg/day). Nearly half of the patients got a 6-day “dosepack” of methylprednisolone. Respiratory tract infections and disorders, spinal conditions, and allergies accounted for 60% of the prescriptions. In users compared with nonusers, the incidence rates for sepsis (1.8 vs. 1.0 per 1000 person-years), venous thromboembolism (4.6 vs. 2.4 per 1000 person-years), and fracture (21.4 vs. 14.3 per 1000 person-years) were significantly higher regardless of age. In a self-controlled case series, the risks for sepsis (incidence rate ratio, 5.3), venous thromboembolism (IRR, 3.3), and fracture (IRR, 1.9) were significantly higher during the 5 days to 30 days after the prescription date than the 5 days to 180 days before the prescription date.

An astonishing one in five commercially insured adults got a short course of oral corticosteroid therapy during this 3-year study period. Although the absolute excess risk for sepsis, venous thromboembolism, and fracture associated with short-term corticosteroid use was low, the cumulative number of affected patients was not trivial, so the widespread use of short-term oral corticosteroids has substantial public health implications. Clinicians should not administer short-term oral corticosteroids for conditions in which these agents are ineffective. For conditions in which corticosteroids might provide transient symptom relief, but are not essential, clinicians should think twice before prescribing these drugs.

**PERIOPERATIVE TROpONIN PREDICTS 30-DAY MORTALITY AFTER NONCARDIAC SURGERY**

In a study from 2014, researchers showed that even modestly elevated non–high-sensitivity troponin T levels during the 3 days after noncardiac surgery were independently associated with excess mortality at a month (www.jwatch.org/na33941). Now, the same researchers have performed a similar multicenter study using a high-sensitivity troponin T assay in more than 20,000 patients 45 or older undergoing inpatient noncardiac surgery with general or regional anesthesia. The patients’ high-sensitivity troponin T levels were measured 6 hours to 12 hours after surgery, and then daily for 3 days; the manufacturer considers levels of 14 ng/L or higher as abnormal (as an aside: The units for high-sensitivity troponin T are ng/L and the units for non–high-sensitivity troponin T are usually ng/mL). Findings appear in the April 25 issue of *JAMA* (http://dx.doi.org/10.1001/jama.2017.4360).
Overall, 1.2% of the patients died within a month. Elevated high-sensitivity troponin T significantly and independently predicted higher 30-day mortality. For example, among about 4000 patients with peak postoperative high-sensitivity troponin T levels between 20 ng/L and 65 ng/L, 30-day mortality was 3%. Mortality increased further at higher peak high-sensitivity troponin T levels, and several nonfatal cardiac outcomes correlated with elevated high-sensitivity troponin T levels. An absolute change of at least 5 ng/L in high-sensitivity troponin T levels across two measurements in an individual patient was also associated with a 3% mortality rate at 30 days. Importantly, more than 90% of the patients with high-sensitivity troponin T elevations in the range predicting elevated 30-day mortality had no symptoms of cardiac ischemia. Only 11% of the patients with elevated high-sensitivity troponin T levels had a potentially nonischemic etiology of the elevated high-sensitivity troponin T level (like sepsis or pulmonary embolism).

The assumption here is that relatively modest elevations in high-sensitivity troponin T levels during or just after noncardiac surgery can represent potentially clinically important ischemic myocardial injury that’s often initially asymptomatic or unrecognized. The question is whether perioperative troponin levels should be routinely measured (or in selected high-risk subgroups) after noncardiac surgery. Evidence-based interventions shown to improve outcomes in patients with asymptomatic perioperative troponin elevations are lacking, but a clinical trial examining the use of dabigatran for this purpose is underway (https://clinicaltrials.gov/ct2/show/NCT01661101).

A NEGATIVE HIGH-SENSITIVITY TROPOVIN AND NONISCHEMIC ECG CAN RULE OUT ACUTE MI

High-sensitivity cardiac troponin T assays, combined with electrocardiograms, can rapidly rule out acute myocardial infarction in patients presenting to the emergency department with chest pain (www.jwatch.org/em201004160000004/2010/04/16/high-sensitivity-troponin-assays; www.jwatch.org/na41510/2016/06/01/high-sensitivity-troponin-assays-can-rule-out-mi-1-hour; www.jwatch.org/na41965/2016/07/29/can-single-negative-high-sensitivity-troponin-t-level-rule). In a meta-analysis on the website of the Annals of Internal Medicine (http://annals.org/aim/article/2619006/rapid-rule-out-acute-myocardial-infarction-single-high-sensitivity-cardiac), researchers examined 11 studies to determine the accuracy of a single negative high-sensitivity cardiac troponin T plus a nonischemic electrocardiogram for ruling out acute MI in these patients. Of more than 9000 patients who met inclusion criteria, 30% were deemed to be at low risk (hs-cTnT<0.005 µg/L and nonischemic ECG). Only 14 low-risk patients (0.5%) had acute MI during the hospital admission; in half of them, blood was drawn for the single high-sensitivity cardiac troponin T test less than 3 hours after symptom onset. Sensitivity was 98%, specificity was 64%, negative predictive value was 99%, and positive predictive value was 22%. Nine studies were judged to have a high or unclear risk of bias.

These results support the use of a single negative high-sensitivity cardiac troponin T result and a nonischemic electrocardiogram to rule out acute myocardial infarction in adult patients in the emergency department with chest pain. But high-sensitivity cardiac troponin T must be measured at least 3 hours after symptom onset (which can be difficult to define), and considerable overtesting will likely be a consequence of false positive results, given that the positive predictive value was only 22%. Notably, the high-sensitivity cardiac troponin T cutoff used in this meta-analysis (less than 0.005 µg/L) is slightly lower than that approved by the Food and Drug Administration (which is lower than 0.006 µg/L), so sensitivity might be slightly lower for the United States version of the assay.

SERUM CREATININE ELEVATIONS AFTER STARTING ANGIOTENSIN-RENIN BLOCKADE SIGNAL HIGH RISK

National Kidney Foundation guidelines (https://www2.kidney.org/professionals/kdoqi/guidelines_bp/guide_11.htm) recommend stopping angiotensin–converting–enzyme inhibitors or angiotensin-receptor blockers if serum creatinine increases by at least 30% after starting treatment. But the rationale for this 30% threshold is unclear. In a cohort study on the website of The BMJ (http://dx.doi.org/10.1136/bmj.j791), researchers in the United Kingdom evaluated outcomes associated with rises in serum creatinine concentrations in 120,000 patients during the first 2 months after they began treatment with ACE inhibitors or angiotensin-receptor blockers.

About 2100 patients (1.7%) had serum creatinine increases of 30% or more after starting treatment. Compared with the patients in whom creatinine increased by less than 30%, those with larger increases were more likely to die (adjusted incident rate ratio, 1.84) or to develop end-stage kidney disease (IRR, 3.43), heart failure (IRR, 1.37), or myocardial infarction (IRR, 1.46) during about 10 years of follow-up. Plus, dose-response associations between serum creatinine and these outcomes were seen even when creatinine rose by 10% to 19% or by 20% to 29% following the start of therapy with an ACE inhibitor or an angiotensin-receptor blocker.

In this real-world study, which was subject to residual confounding, any increase in serum creatinine after starting ACE inhibitor or angiotensin-receptor blocker therapy was associated with higher risks for death,
end-stage kidney disease, heart failure, and myocardial infarction — with no distinct cutoff at 30%. Whether ACE inhibitors or angiotensin-receptor blockers directly cause adverse outcomes or just unmask underlying pathophysiology is unknown. Even so, patients with increases in serum creatinine after starting these drugs should be recognized as a high-risk group and monitored closely.

MORE EVIDENCE THAT EXCESSIVE BP LOWERING CAN HEIGHTEN CV RISK

The optimal target blood pressure for patients who are taking antihypertensive therapy remains controversial; it’s been suggested that an excessive lowering of blood pressure can increase the risk for some adverse cardiovascular events. But in the SPRINT trial, targeting a systolic blood pressure of lower than 120 mm Hg lowered the incidence of adverse cardiovascular events more than did less-aggressive treatment, although the average achieved systolic blood pressure actually remained slightly higher than 120 mm Hg (www.jwatch.org/na39551). To further elucidate the association between blood pressure and adverse cardiovascular outcomes, researchers analyzed pooled data from more than 30,000 high-risk patients (with an age of 55 or older and a history of cardiovascular disease or diabetes with organ damage; 70% had hypertension) who were assigned to take ramipril, telmisartan, both, or neither for a median of nearly 5 years in two trials funded by the manufacturer of telmisartan. Outcomes included a composite endpoint (namely, cardiovascular-related death, myocardial infarction, stroke, or hospitalization for heart failure), individual cardiovascular endpoints, and all-cause death. Details appear on the website of The Lancet (http://dx.doi.org/10.1016/S0140-6736(17)30754-7).

Average blood pressure achieved on treatment was a stronger predictor of cardiovascular outcomes than was baseline blood pressure or the last recorded blood pressure before an adverse cardiovascular event occurred. For most outcomes, the risk was lowest at an average achieved systolic blood pressure of 120 mm Hg to 140 mm Hg and a diastolic blood pressure of 70 mm Hg to 80 mm Hg. The composite outcome, cardiovascular-related death, hospitalization for heart failure, and all-cause death all happened significantly more commonly at lower systolic blood pressures, and all of the outcomes, except stroke, were more frequent at lower diastolic blood pressures.

Statistical adjustments could not completely eliminate the possibility of reverse causality in this observational study. Optimal blood pressure targets might vary for preventing specific adverse cardiovascular outcomes, but, for most patients at high cardiovascular risk, targets of 120/70 mm Hg to 140/80 mm Hg are probably safest and most effective.

MODERATE ALCOHOL DRINKERS EXPERIENCE FEWER ADVERSE CV OUTCOMES

It’s been shown that both drinking no alcohol and heavy alcohol consumption are associated with a higher risk for cardiovascular morbidity and mortality compared with moderate drinking — a “U-shaped” association. But some studies on the topic categorized both never drinkers and former drinkers as nondrinkers — that’s a methodological flaw that could have biased results, because former drinkers might have an excess risk for cardiovascular disease. In a population-based cohort study on the website of The BMJ (http://dx.doi.org/10.1136/bmj.j909), researchers in the United Kingdom evaluated the associations between specific categories of alcohol consumption and multiple adverse cardiovascular outcomes in nearly 2 million adults without known cardiovascular disease at baseline.

During a median follow-up of 6 years, 115,000 patients experienced incident cardiovascular events. Three associations were noted in analyses adjusted for possible confounders (like smoking); they were:

- Compared with moderate drinkers (defined as “alcohol intake within recommended sensible limits”), never, former, and occasional drinkers were significantly more likely to develop various adverse cardiovascular endpoints (including coronary disease and heart failure), with adjusted hazard ratios in the 1.2 to 1.6 range; the risks for all-cause and cardiovascular-related mortality were also higher.

- Compared with moderate drinkers, heavy drinkers were significantly more likely to develop heart failure and several noncoronary cardiovascular endpoints, but their coronary risk was not elevated. These patients also had higher all-cause and cardiovascular-related mortality.

- Only heavy drinkers had a significant excess risk for adverse cerebrovascular outcomes.

This study supports the U-shaped association between alcohol intake and cardiovascular disease. Both teetotalers and heavy drinkers had higher risks for various adverse cardiovascular outcomes than did moderate drinkers.

Whether clinicians should endorse alcohol intake in the generally accepted moderate range (meaning 1 drink/day to 2 drinks/day for men, and 1 drink/day for women) for carefully selected patients remains controversial (http://dx.doi.org/10.1136/bmj.j1340).

CERVICAL ARTERY DISSECTION CAN BE EASILY MISSED IN OLDER PATIENTS

Although generally uncommon, cervical artery dissection is a major cause of stroke in young adults, with most patients aged 40 to 50 at the time of dissection. Reports of cervical artery dissection in older patients are few (and
their clinical characteristics are largely unknown), raising concern that older patients with cervical artery dissection might be missed.

In a study in the April 4 issue of *Neurology* ([http://dx.doi.org/10.1212/WNL.0000000000003788](http://dx.doi.org/10.1212/WNL.0000000000003788)), researchers in Europe reviewed a multicenter database and found that 7% of 2400 patients with cervical artery dissection were 60 or older; of these, two thirds were male. Compared with patients younger than 60, those 60 or older were less likely to present with cervical pain (adjusted odds ratio, 0.47), headache (AOR, 0.58), or a history of mechanical triggers (AOR, 0.53), but hypercholesterolemia, hypertension, and diabetes were more common in the older patients. Horner syndrome and other localizing signs of cervical artery dissection were seen in similar proportions in the two age groups, and the sites of dissection were no different. Although the rates of antithrombotic drug use were similar between the younger and the older patients, anticoagulants were more commonly administered to younger patients (63.9% vs. 50.0%). In an adjusted analysis, older patients had a lower likelihood of favorable neurological outcomes than did younger patients (AOR, 0.45).

The risk for underdiagnosing cervical artery dissection in older patients is heightened if diagnostic investigation is not pursued when the symptoms commonly seen in younger patients are absent. This study shows that being 60 or older is independently associated with less favorable outcomes in cervical artery dissection, underscoring the importance of awareness about the risk for this condition in older patients.

**ARE END-OF-ROTATION RESIDENT TRANSITIONS OF CARE DANGEROUS?**

Transitions of patient care, including handoffs, are associated with adverse patient outcomes, but not much evidence has been collected on the association between end-of-rotation resident transitions and patient outcomes ([http://dx.doi.org/10.1097/ACM.0b013e3181f51a6](http://dx.doi.org/10.1097/ACM.0b013e3181f51a6)). In a retrospective cohort study in the December 6, 2016 issue of *JAMA* ([http://dx.doi.org/10.1001/jama.2016.17424](http://dx.doi.org/10.1001/jama.2016.17424)), researchers examined data from more than 200,000 patients at 10 university-associated Veterans Affairs hospitals in which interns (first-year residents) and upper-level residents managed patients under the supervision of attending physicians. Patients who were admitted just before an end-of-rotation resident transition and were discharged or died within the week following that transition (transition group) were compared with all other discharged patients (control group).

In analyses that were adjusted for baseline differences in patient characteristics (including comorbidities), inpatient mortality was significantly higher for the patients in the transition group when only interns were involved (3.5% vs. 2.0% in the control group) or when interns and upper-level residents were involved (4.0% vs. 2.1%), but not when only upper-level residents were involved (3.3% vs. 2.0%). Adjusted 30-day and 90-day mortalities were also significantly higher in the transition patients, regardless of the level of training of the residents.

This study adds to the growing body of evidence that provider handoffs are associated with worse patient outcomes — specifically, higher patient risk at rotation transitions by less-experienced physicians (namely, interns). The excess mortality in the intern-plus-resident group suggests that interns did the bulk of the transition work during the discharge process, possibly without adequate supervision. These less-experienced physicians deserve more direct observation of their rotation transition communication and processes; a structured approach to rotation transitions might improve patient outcomes ([http://dx.doi.org/10.1001/jama.2016.16398](http://dx.doi.org/10.1001/jama.2016.16398)).

**WHAT INTERVAL BETWEEN A POSITIVE FIT AND FOLLOW-UP COLONOSCOPY IS SAFE?**

How quickly after a positive fecal immunochemical test should colonoscopy be performed? In a retrospective cohort study in the April 25 issue of *JAMA* ([http://dx.doi.org/10.1001/jama.2017.3634](http://dx.doi.org/10.1001/jama.2017.3634)), researchers looked at the risk for any colorectal cancer or advanced (stage III or stage IV) colorectal cancer in patients with positive FIT screening who underwent follow-up colonoscopies in a large California healthcare system. Among more than a million screened patients, about 100,000 had positive fecal immunochemical tests, about 70,000 underwent colonoscopy, and 2200 cancers were found. The median time to follow-up colonoscopy was a little longer than a month.

When colonoscopy was performed during the 30 days after a positive fecal immunochemical test, any colorectal cancer was detected in 3% of the patients and advanced colorectal cancer was detected in 0.8% of the patients. These detection rates remained similar for colonoscopies performed during the next 9 months. But these rates increased to 4.9% and 1.9%, respectively, at 10 months to 12 months after FIT, and increased even further to 7.6% and 3.1%, respectively, beyond a year after FIT. This study did not include the actual clinical outcomes associated with various follow-up intervals, but outcomes can be inferred from the detected colorectal cancer stages. Adjusted analyses accounted for many patient, demographic, and clinical factors, but could not account for more subtle reasons (like patient anxiety or the presence of symptoms) for why colonoscopy was performed sooner rather than later after a positive fecal immunochemical test result. In any case, it’s reassuring to know that a delay of as long as 10 months ([http://dx.doi.org/10.1001/jama.2017.3629](http://dx.doi.org/10.1001/jama.2017.3629)) — whether for logistical, financial, or personal reasons — does not confer an excess risk for colorectal cancer.
PHYSICIAN NONADHERENCE TO BREAST CANCER SCREENING GUIDELINES

Breast cancer screening guidelines from the American College of Obstetricians and Gynecologists (www.jwatch.org/wh201107280000001), the American Cancer Society (www.jwatch.org/na39390), and the United States Preventive Services Task Force (www.jwatch.org/na40133) disagree on the age at which to begin and discontinue routine screening mammography. To see whether the screening recommendations of physicians reflect these differences, researchers studied national survey data from 900 primary care physicians (namely, family medicine and general practice physicians, internists, and gynecologists). Their findings appear on the website of JAMA Internal Medicine (http://dx.doi.org/10.1001/jamainternmed.2017.0453).

More than 80% of physicians recommended screening to women in their 40s, and two thirds recommended it to women 75 or older. Among the physicians who trusted the American College of Obstetricians and Gynecologists guidelines the most, more than 90% recommended screening in younger women, between the ages of 40 and 44; among those who most trusted the American Cancer Society and the Task Force guidelines (neither of which recommend routine screening in this age group), nearly 90% and 60%, respectively, endorsed such screening. Among the physicians who most trusted the American College of Obstetricians and Gynecologists and the American Cancer Society guidelines, which give no age for stopping screening, roughly three quarters recommended screening to women 75 or older, but 40% of the physicians who most trusted the Task Force guideline (which recommends stopping after the age of 74), also supported screening in older women.

Despite some influence of different breast cancer screening guidelines on physician recommendations, a large proportion of physicians who most trust the United States Preventive Services Task Force guideline continue to recommend screening in women who are younger (in their early 40s) or older (75 or older) than the age range routinely recommended in that guideline.

GUIDELINE WATCH: MANAGEMENT OF PULMONARY NODES FOUND INCIDENTALLY ON CT SCANS

As clinicians, you may have seen computed tomography scan reports in which the words “according to the Fleischner Society guidelines…” appear during the discussion of an incidentally found small pulmonary nodule. These widely cited guidelines, initially published in 2005, give recommendations on follow-up intervals for repeat imaging. Now, on the website of Radiology (http://dx.doi.org/10.1148/radiol.2017161659), the Society has published a revision.

Key points of the update are:

- The guidelines address pulmonary nodules detected incidentally on CT scans ordered for other reasons. They do not apply to nodules found on CT scans ordered explicitly for lung cancer screening, nor to immunosuppressed patients or patients with known cancer.
- The guidelines include two sets of recommendations, one for solid nodules and one for subsolid nodules (namely, ground glass or partly solid). Nodules are classified by size (smaller than 6 mm, between 6 mm and 8 mm, and larger than 8 mm); by whether a single nodule or multiple nodules are detected; and by whether the nodule, the patient, or both are considered to be low-risk or high-risk. Risk factors include nodule morphology, nodule location, the presence of emphysema or fibrosis, smoking history, and family history.
- Nodules are divided into 18 categories that reflect various combinations of size, morphology, and risk factors. Follow-up recommendations vary, from “no routine follow-up” (for single low-risk nodules smaller than 6 mm) to “consider CT at 3 months” (for selected larger nodules). Between these extremes, 6-month or 12-month follow-up scans are recommended in specified categories. For some nodules larger than 8 mm, tissue sampling or combined positron emission tomography plus CT should be considered.

Inevitably, any clinician who orders chest CT scans will need to manage patients with incidental pulmonary nodules. Consulting the Fleischner Society guidelines is a reasonable first step in these cases.

AN INTERVENTION TO ENHANCE COMMUNICATION BETWEEN PATIENTS AND ONCOLOGISTS

Recent research on patient-physician communication near the end of life has focused particularly on the role of palliative care consultation (www.jwatch.org/na43775). In contrast, researchers have now examined an intervention to enhance communication between oncologists and patients. The participants were 40 oncologists and nearly 300 of their patients with stage III or stage IV nonhematologic cancer; patients were eligible if their oncologists said they “would not be surprised” if the patient died within the year.

Half of the oncologists got two training sessions that addressed four communication domains, namely:

1. Engaging patients to be active participants in their care
2. Responding to patients’ emotions
3. Informing patients about prognosis
4. The “balanced framing” of possible treatment outcomes

This was the intervention group. Up to 10 patients per intervention-group oncologist got 1-hour coaching sessions (conducted by social workers) to help patients express their concerns during an upcoming oncology visit. The remaining oncologists and patients served as controls. At the first patient-oncologist encounter after the training intervention (or after study entry for the controls), standardized communication measures were documented from audio recordings of the visit. The results were published in three separate articles in the January 2017 (http://jamanetwork.com/journals/jamaoncology/fullarticle/2551984) and the November 2016 (http://dx.doi.org/10.1001/jamaoncol.2016.1861) issues of JAMA Oncology and the March 10, 2017 issue of the Journal of Clinical Oncology (http://dx.doi.org/10.1200/JCO.2016.68.5651).

A composite score that captured the four communication domains was significantly higher in the intervention group than in the control group. Plus, the intervention patients were more likely than were the controls (70% vs. 32%) to raise at least one topic from a “question prompt list” reviewed in their coaching sessions. But many specific topics (including prognosis, fears, goals of treatment, and end-of-life concerns) were discussed relatively rarely in both of the groups. After the audiotaped visits, the patients and their oncologists were asked to estimate patients’ 2-year survival in seven possible categories, namely: A 100% chance of survival at 2 years, a 90% chance, a 75% chance, a 50% chance, a 25% chance, a 10% chance, and a 0% chance of survival at 2 years. The estimates were discordant (meaning that they differed by at least 2 categories) in 70% of the patient-oncologist dyads in both the intervention and control groups.

In this study, relatively brief training sessions for patients with advanced cancer and their oncologists seemed to enhance communication between them. Even so, the participants avoided many difficult topics, and discordant prognostic estimates were common. The researchers note that the reluctance to discuss prognosis openly can come from either the patient or the physician, and that “the current productivity-oriented practice environment” presents barriers to communication. One limitation is that this study captured only single patient-oncologist visits, whereas trusting communication often evolves over multiple visits.

ALLOPURINOL DOSE ESCALATION IN PATIENTS WITH GOUT IS SAFE

Serum uric acid–lowering, generally to lower than 6 mg/dL, is critical in managing patients with gout. The Food and Drug Administration has approved allopurinol, the most commonly used urate-lowering therapy, for dosing as high as 800 mg/day, but most prescriptions don’t exceed 300 mg/day, partly because of concerns about safety. To evaluate the safety and urate-lowering efficacy of dose escalation, researchers in New Zealand enrolled 180 patients with gout and an average age of 60. The patients’ average baseline serum urate level was 7.2 mg/dL; half of them had a creatinine clearance lower than 60 mL/minute and 13% had a creatinine clearance lower than 30 mL/minute. The patients had been taking creatinine clearance-based allopurinol doses for at least a month. The researchers randomized these patients either to continue allopurinol at their current doses (this was the control group; their average baseline dose was 276 mg/day) or to allopurinol dose escalation (monthly escalation by 50 mg in those with creatinine clearances lower than 60 mL/minute and by 100 mg in those with creatinine clearances of 60 mL/minute or higher, until urate levels were lower than 6 mg/dL). Findings appear on the website of the Annals of the Rheumatic Diseases (http://dx.doi.org/10.1136/annrheumdis-2016-210872).

At a year, average urate levels had dropped by significantly more in the dose-escalation group than in the controls (1.5 mg/dL vs. 0.34 mg/dL), and significantly more of the dose-escalation patients had urate levels lower than 6 mg/dL (69% vs. 32%). The average allopurinol dose for those at target in both of the groups was 390 mg/day compared with 290 mg/day for those not at target. Serious adverse events were similar in the two groups; only one event was related to allopurinol.

Understandably, many clinicians are concerned about allopurinol dosing, especially in patients with renal insufficiency. But these results show that allopurinol doses can be substantially increased, and that higher-than-creatinine clearance–based doses are safe if dose escalation is done gradually. In this study, the two groups were similar in the number of gout flares, but the study was not primarily designed to evaluate that endpoint.

DOES PRICE TRANSPARENCY CHANGE PHYSICIAN ORDERING OF INPATIENT LAB TESTS?

Showing the price of laboratory tests when they’re ordered might be a way to reduce the number of tests ordered, on the assumption that it might prompt clinicians to reconsider whether a test is needed. Past studies have been limited and have shown mixed results. In a study on the website of JAMA Internal Medicine (http://dx.doi.org/10.1001/jamainternmed.2017.1144), researchers randomized 60 groups of inpatient blood tests that are common (like complete blood counts and basic metabolic panels), expensive, or both to be shown either with or without prices in the electronic medical record at the time of ordering for nearly 100,000 patients (roughly 140,000 hospital admissions) in three hospitals in Philadelphia. The prices were Medicare reimbursement rates; actual costs to patients could not be determined.
In both the intervention group (where prices were shown) and the control group (where no prices were shown), the average costs per patient-day and the number of tests ordered did not change during the intervention year, compared with the year before the intervention.

The lack of information about patients’ actual out-of-pocket costs, if any, for the tests ordered might be this study’s greatest weakness (http://dx.doi.org/10.1001/jamainternmed.2017.1676). That information would be even more relevant if expensive imaging tests were studied in this fashion. Simply showing Medicare reimbursement rates for common blood tests seems to have no effect on the ordering behavior of clinicians.

IN-PERSON COGNITIVE-BEHAVIORAL THERAPY vs. AUTOMATED INTERACTIVE VOICE-RESPONSE CBT FOR CHRONIC BACK PAIN

Cognitive-behavioral therapy can be effective for improving both pain and function in patients with chronic back pain, but this therapy is often difficult to provide, and patients’ adherence to cognitive-behavioral therapy visits is low. Interactive voice-response cognitive-behavioral therapy uses automated telephone technology to allow patients to report symptoms, pain, and function and provides pre-recorded messages of support and education.

In a Veterans Affairs study on the website of JAMA Internal Medicine (http://dx.doi.org/10.1001/jamainternmed.2017.0223), researchers randomized more than 100 patients with an average age of 58 and with an average duration of chronic back pain of 11 years, but without complicating medical or surgical comorbidities, either to in-person cognitive-behavioral therapy (30-minute to 40-minute sessions once/week) or to interactive voice-response cognitive-behavioral therapy for 10 weeks. All of the patients reported their symptoms every day through an interactive voice-response system. The interactive voice-response cognitive-behavioral therapy patients got weekly pre-recorded 2-minute to 5-minute personalized messages matched to their symptoms.

The interactive voice-response cognitive-behavioral therapy patients were more adherent than were the in-person–cognitive-behavioral therapy patients (means, 8.9 vs. 6.6 weekly sessions). At 3 months after baseline (about 2 weeks after the study was completed), average pain scores had improved in both of the groups by about 0.8 points on a 10-point scale; about a third of the patients in each group had “clinically meaningful” improvement in their pain at 3 months (defined as a 30% relative reduction in their pain score). But at 9 months, improvement had declined to about 0.5 points in both of the groups. Secondary outcomes (namely, sleep and function) were also similar in the two groups.

Although the average improvement in chronic back pain in this study was statistically significant at 3 months in both of the groups, this improvement is of questionable clinical importance. The potential value of interactive voice-response cognitive-behavioral therapy as a way to improve both access to care and meaningful clinical benefit for patients with longstanding low back pain will require further study.

HPV VACCINE: LONG-TERM PROTECTION AFTER TWO DOSES

Human papillomavirus vaccine was licensed as a three-dose series more than a decade ago, but based on the vaccine’s efficacy at 3 years, the recommended administration schedule was recently modified to only two doses for those who get the vaccine before the age of 15. As durability of protection is critical, researchers in Canada conducted a post hoc analysis of a phase 3 post licensure trial to evaluate the immunogenicity of the quadrivalent human papillomavirus vaccine at 5 years in 100 girls between the ages of 9 and 13 who were randomized to either two or three doses of the vaccine in the original study. Details appear in the April 25 issue of JAMA (http://dx.doi.org/10.1001/jama.2017.1840).

Immune responses to the four human papillomavirus serotypes were similar regardless of vaccine dosing, although seropositivity rates for human papillomavirus 18 were higher after three doses than after two doses (94% vs. 84%). The response to all of the serotypes generally declined from 3 years to 5 years, but titers at 5 years were similar for the 50 girls who got two doses compared with the 50 girls who got three doses.

Duration of protection is critically important if clinicians are to recommend the administration of human papillomavirus vaccine to young adolescent patients. This study provides reassurance that protection against human papillomavirus infection extends to at least 5 years — and hopefully beyond.

DOES MATERNAL STRESS DURING PREGNANCY AFFECT LONGEVITY OF OFFSPRING?

Stressors to a pregnant woman or her very young offspring can affect the child’s subsequent health. In a study in the April 18 Proceedings of the National Academy of Sciences of the United States of America (http://dx.doi.org/10.1073/pnas.1617911114), researchers in France explored the adult longevity of nearly 6000 children born from August of 1914 through December of 1916 (basically, during World War I), a time when 350 French women lost their husbands each day to combat. In an analysis matched for date of birth, sex, and mother’s age, adult mortality of the children who had lost their fathers (either before or after their birth) was
compared with the lifespans of those whose fathers were not killed.

People who did not lose their fathers lived longer than those whose fathers died in the war. But this shortened lifespan was seen only in those who lost their fathers when they still were in utero: These people lived 2.4 years less than their matched controls who didn’t lose their fathers. Those who lost their fathers within the first year or two after their birth had normal lifespans.

Consistent with other animal and human research, this study shows that maternal stress during pregnancy can negatively affect the health of her children decades later — specifically, by shortening lifespan. Animal studies suggest a mother’s stress during pregnancy can alter the expression of her offspring’s genes, particularly those involved in the stress response.

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1. In a meta-analysis on the website of the New England Journal of Medicine, researchers compared outcomes among patients hospitalized with sepsis who were randomized to early goal-directed therapy or usual care. They found that, compared with usual care, early goal-directed therapy was associated with:
   (A) Higher cost  
   (B) Lower mortality at 3 mo  
   (C) Similar rates of vasopressor use  
   (D) Shorter stay in the intensive care unit

2. In a retrospective study on the website of The BMJ, researchers assessed the risks for adverse events associated with use of oral corticosteroids for <1 mo. They found that, compared with nonuse, short-term use of steroids was associated with increased risk for:
   (A) Fracture  
   (B) Sepsis  
   (C) Venous thromboembolism  
   (D) All the above

3. In a multicenter study in the April 25 issue of JAMA, high-sensitivity troponin T was monitored for 3 days postoperatively in patients who underwent noncardiac surgery. The researchers found that elevated levels were associated with:
   (A) Asymptomatic cardiac ischemia  
   (B) Increased risk for 30-day mortality  
   (C) Increased rates of subsequent cancer diagnoses  
   (D) Neither A nor B

4. In a large cohort study on the website of The BMJ, researchers evaluated concentrations of serum creatinine during the first 2 mo after initiating treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), and then monitored patients for adverse outcomes over the next 10 yr. They found which of the following relationships between elevation in serum creatinine level and risk for end-stage kidney disease, heart failure, myocardial infarction, and death:
   (A) Increased risk in patients with elevations as low as 10% over baseline  
   (B) Significantly increased risk only in patients with elevations of ≥30% over baseline  
   (C) Significantly increased risk only in patients with elevations of ≥50% over baseline  
   (D) No association between risk and degree of elevation during the first 2 mo

5. In a study on the website of The Lancet, researchers sought to clarify the association between blood pressure (BP) achieved while on antihypertensive therapy and cardiovascular (CV) outcomes. After pooling data from 2 clinical trials in which patients with hypertension were treated with an ACE inhibitor (ramipril) and/or an ARB (telmisartan), they found that:
   (A) Baseline BP was a stronger predictor of risk for adverse CV outcomes than was average BP achieved on therapy  
   (B) Last recorded BP before an adverse CV event was a stronger predictor of risk for adverse CV outcomes than was average BP achieved on therapy  
   (C) Risk for adverse CV outcomes was lowest in patients who achieved an average systolic BP of 120 mm Hg to 140 mm Hg while on therapy  
   (D) There were consistent linear relationships between average BP and risk for most adverse CV outcomes

6. In a study in the April issue of Neurology, researchers reviewed a multicenter database to compare characteristics of cervical artery dissection in younger (age <60 yr) and older (age ≥60 yr) adults. Compared with younger patients, those ≥60 yr of age were more likely to:
   (A) Have dissection attributed to a mechanical trigger  
   (B) Have unfavorable neurologic outcomes  
   (C) Present with cervical pain and headache  
   (D) Present with Horner syndrome

7. In a large retrospective cohort study in the April 25 issue of JAMA, researchers assessed risk for colon cancer in patients who underwent follow-up colonoscopies after a positive fecal immunochemical test (FIT). They found that colonoscopy could be delayed as long as _______ after a positive FIT without increasing the incidence of subsequent cancer diagnoses.
   (A) 3 mo  
   (B) 6 mo  
   (C) 9 mo  
   (D) 12 mo

8. On the website of Radiology, updated guidelines by the Fleischner Society provide recommendations for working up pulmonary nodules found incidentally on computed tomography. In addition to nodule size, which of the following characteristics affect risk stratification and recommendations for follow-up?
   (A) Number of nodules  
   (B) Patient risk factors  
   (C) Radiographic characteristics of the nodule  
   (D) All the above

9. In a study on the website of the Annals of the Rheumatic Diseases, patients with gout who had been taking allopurinol for ≥1 mo, dose-adjusted for creatinine clearance, were randomized to continue taking the same dose of allopurinol or to gradually escalate the dose until urate levels were <6 mg/dL. The researchers show that gradual dose escalation is associated with:
   (A) Greater decreases in urate levels without increased risk for adverse events  
   (B) Increased risk for adverse events in patients with creatinine clearance <60 mL/min  
   (C) Significantly decreased risk for flares  
   (D) Unacceptably high risk for adverse events in patients with creatinine clearance <30 mL/min

10. In a post-hoc analysis in the April 25 issue of JAMA, researchers compared the immunogenicity of the human papillomavirus vaccine in patients who had been randomized to receive 2 or 3 doses. They found that:
    (A) At 5 yr, antibody titers were significantly higher in the girls who received 3 doses of the vaccine  
    (B) Immune responses to the 4 human papillomavirus serotypes were similar regardless of vaccine dosage  
    (C) Immune response to 2 of 4 serotypes was stronger and more durable after the 3-dose regimen compared with the 2-dose regimen  
    (D) The maximal immune response achieved after either dosing regimen was sustained without decrement for 3 to 5 yr after dosing

Answers to NEJM Journal Watch Audio General Medicine Volume 28, Issue 10: 1-B, 2-B, 3-A, 4-C, 5-D, 6-B, 7-A, 8-C, 9-D, 10-A