ABSTRACTS IN URGENT CARE

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Each month, Dr. Nahum Kovalski reviews a handful of abstracts from, or relevant to, urgent care practices and practitioners. For the full reports, go to the source cited under each title.

Metabolic Consequences of Insufficient Sleep

Key point: A small, randomized, controlled crossover study demonstrates changes in a critical insulin-signaling pathway in peripheral tissue.

Citations: Broussard JL, Ehrmann DA, Van Cauter E, Tasali E, Brady MJ. Impaired insulin signaling in human adipocytes after experimental sleep restriction: A randomized, crossover study. *Ann Intern Med* 2012;157(8):549-557. and Cappuccio FP, Miller MA. A new challenge to widely held views on the role of sleep. *Ann Intern Med* 2012;157(8):593-594.

Small experimental studies have revealed adverse effects of reduced sleep duration on glucose tolerance and insulin sensitivity. To explore the effects of sleep restriction on metabolic activity in peripheral tissue, investigators randomized seven lean, healthy young adults (aged 18–30) to undergo 4 weeks each of normal and restricted sleep (8.5 and 4.5 hours, respectively), in random order and under controlled conditions, 4 weeks apart. The primary endpoint was change in levels of phosphorylated Akt — an important step in the insulin-signaling pathway — in abdominal subcutaneous adipocytes.

Phosphorylation of Akt was 30% lower after restricted sleep than after normal sleep (P=0.01). This reduction coincided with a 16% reduction in total-body insulin sensitivity, as measured by frequently sampled intravenous glucose tolerance tests.

Published in *J Watch Card.* October 31, 2012 — Harlan M. Krumholz, MD, SM. ■

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Cardiovascular Effects of Sulfonylureas and Metformin in Patients with Type 2 Diabetes

Key point: Compared with metformin, sulfonylurea was associated with a higher rate of cardiovascular events or death in a large retrospective study.

Citations: Roumie CL, Hung AM, Greevy RA, Grijalva CG, et al. Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: A cohort study. *Ann Intern Med.* 2012;157(9):601-610 and Nissen SE. Cardiovascular effects of diabetes drugs: Emerging from the dark ages. *Ann Intern Med.* 2012;157(9): 671-672.

Cardiovascular disease (CVD) is the primary cause of death in patients with diabetes. Two common classes of drugs used in treating type 2 diabetes are sulfonylureas and metformin. Their impact on cardiovascular outcomes is not well known. Using a database from the national Veterans Health Administration, researchers conducted a retrospective cohort study comparing the effects of sulfonylureas and metformin on the composite endpoint of acute myocardial infarction, stroke, or death.

Among 253,690 patients (97% men; 75% white), metformin was prescribed in 61% and sulfonylureas in 39% (55% glyburide; 45% glipizide). Those who used both medications, rosiglitazone, or pioglitazone were excluded. Differences between the metformin and sulfonylurea groups were median follow-up (0.80 years vs. 0.61 years), median age (62 vs. 67), and

hemoglobin A_{1c} levels (7.0 vs. 7.3). Characteristics of the two groups were similar after propensity score matching of 80,648 patients in each treatment group. Unadjusted rates of the composite endpoint were 18.2 per 1000 person-years for sulfonylurea users and 10.4 per 1000 person-years among metformin users. The adjusted hazard ratio was 1.21 and was similar with glyburide and with glipizide. The authors estimated 2.2 more CVD events or deaths and 1.2 more CVD events per 1000 person-years in sulfonylurea versus metformin recipients. Results were similar in analyses stratifying patients by CVD history, age, body-mass index, and proteinuria.

Published in *J Watch Card*. November 21, 2012 — Joel M. Gore, MD. ■

No Benefit of Multivitamins for Preventing Cardiovascular Disease in Men

Key point: A randomized, controlled trial showed that myocardial infarction, stroke, and death were not affected.

Citation: Sesso HD, Christen WG, Bubes V, et al. Multivitamins in the prevention of cardiovascular disease in men: The Physicians' Health Study II randomized controlled trial. *JAMA*. 2012;308(17):1751-1760.

Observational studies of multivitamins for preventing cardiovascular disease (CVD) have yielded inconsistent and mostly negative results, as have randomized controlled trials of individual vitamins and minerals (including -carotene, selenium, and vitamins B, C, and E). This randomized controlled trial that involved nearly 15,000 male physicians (mean age, 64) who were randomized to commercial daily multivitamins (Centrum Silver) or placebo is a companion analysis to a recently published study that showed a small benefit of multivitamin supplementation for preventing. Follow-up continued for a median of 11 years.

No difference was found between the groups in risk for any major adverse CVD event, including myocardial infarction, stroke, or cardiac-related mortality. Multivitamin supplementation also was not beneficial in the small subgroup of men with histories of CVD at study entry (5% of participants).

Published in *J Watch Gen Med*. November 15, 2012 — Thomas L. Schwenk, MD. ■

Clindamycin vs. Trimethoprim/Sulfamethoxazole for Soft-Tissue Infections — A Clinical Trial That Needs Some Marketing

Key point: A clinical trial on treatment of skin and soft-tissue infections using clindamycin vs. trimethoprim/sulfamethoxazole has widespread clinical applications, yet may receive little if any attention. The drugs were fairly evenly matched in terms of efficacy. These drugs are VERY inexpensive.

Citation: http://blogs.jwatch.org/hiv-id-observations/index.php/clindamycin-vs-tmpsmx-for-soft-tissue-infections-a-clinical-trial-that-needs-some-marketing/2013/09/13/

This was a randomized, double-blind trial, to compare Clindamycin vs. Trimethoprim/Sulfamethoxazole. Eligible subjects had a skin infection (abscess and/or cellulitis), were not systemically ill, diabetic, or needing hospitalization. If abscesses were present, they were drained. Participants were then randomized to clindamycin 300 mg three-times daily or TMP/SMX 1 DS tablet twice daily for 10 days, along with matching placebos. 524 study subjects enrolled at 4 US sites; they had a mean age of 27, with 30% younger than 13. 45% had purulent drainage, and virtually all had I and D as part of their management; the remainder had cellulitis alone. Among those who had cultures, more than half had MRSA; 14% of the *Staph aureus* isolates had resistance to clindamycin.

14 days after enrollment, 80% of the clinda and 78% of the TMP/SMX group were cured. (About half of the "failures" were really loss to follow-up.) Diarrhea was more common in the clindamycin arm; there were no cases of *C diff*, and no severe rashes to TMP/SMX.

How to choose? Here are some pros and cons.

- **Clindamycin** is famously good for beta strep, and active against most (but not all) *Staph aureus*, including MRSA. But, there's that diarrhea nastiness, with or without *C diff*.
- **TMP-SMX** is active against virtually all *Staph aureus*, but whether it's a beta-strep drug depends on whom you ask (many think it isn't). And of course, it rarely can cause severe rashes and systemic hypersensitivity reactions. ■

Possible Future of Evaluating Febrile Infants

Key point: Rapid molecular analysis of blood may soon replace standard cultures in the management of young febrile infants.

Citation: Mahajan P, Ramilo O, Kuppermann N. The future possibilities of diagnostic testing for the evaluation of febrile infants. *JAMA Pediatr.* 2013;167(10):888-898.

One of the major issues in acute care pediatrics is management of febrile infants, especially those aged >3 months. Although most such episodes are not caused by serious bacterial infection (SBI), the rapidity with which life-threatening infections can develop in infants who appear only mildly ill often results in unnecessary hospitalization and use of broad-spectrum intravenous antibiotics.

Investigators have attempted to develop clinical criteria that—used in combination with laboratory screening tests—can define a group of infants who are unlikely to have SBI and thus do not require hospitalization or empirical antibiotics, but no criteria or clinical prediction rules have been sufficiently definitive to rule out SBI. False-positive results with blood and cere-

brospinal fluid cultures and the ensuing need for additional, unnecessary tests and possible hospitalization may outweigh the possible benefits of these measures.

A solution to this problem requires tests that can positively recognize patterns of bacterial disease with high sensitivity and few false-positives. Mahajan and colleagues propose that molecular assays in current development have such characteristics. Although polymerase chain reaction has become the standard for detecting many viruses, it has not yet proven sufficiently sensitive for detection of bacteria in the blood. However, microarray analysis of the RNA of blood leukocytes can reveal distinct host responses to various classes of pathogens and allow differentiation among them (e.g., bacteria vs. viruses, gram-positive vs. gram-negative bacteria) without requiring pre-incubation or culture. Based on promising small studies that have already been published, the authors call for prospective evaluation of this approach. ■

Clinical Practice Guidelines Require Scrutiny for Quality

Key point: Two studies revealed problems with endocrine and oncology guidelines.

Citations: Brito JP, Domecq JP, Murad MH, et al. The Endocrine Society guidelines: When the confidence cart goes before the evidence horse. *J Clin Endocrinol Metab.* 2013;98(8): 3246-3252 and Reames BN, Ponto SN, Wong SL. Critical evaluation of oncology clinical practice guidelines. *J Clin Oncol.* 2013;10(31):2563.

In two critical evaluations, investigators have assessed the reliability of clinical practice guidelines.

The first study concerned guidelines issued by the Endocrine Society, which uses the GRADE system (each recommendation is rated as strong or weak, and the quality of evidence supporting each recommendation is rated as high, moderate, low, or very low). Among 357 recommendations in 17 guidelines issued between 2005 and 2011, 121 (34%) combined a strong recommendation with low-quality evidence. Such guidelines require scrutiny because they strongly advocate a particular practice despite relatively weak supporting evidence. Using an explicit process, the authors found 33 instances in which no compelling justification for a strong- recommendation/low-evidence guideline existed.

In a second study, researchers reviewed 169 guidelines on prostate, lung, breast, and colorectal cancer published between 2005 and 2010. To determine whether guidelines were trustworthy, each was scored according to 8 standards published by the Institute of Medicine. On average, guidelines fulfilled only 2.75 of the 8 standards. ■

Influenza Prevention and Control Recommendations: 2013–2014

Key point: Updated recommendations from the AAP for use of seasonal influenza vaccine and antiviral medications in infants and children.

Citation: Committee on Infectious Diseases. Recommendations for prevention and control of influenza in children, 2013–2014. *Pediatrics.* 2013 Sep 2; [e-pub ahead of print].

Influenza seasons vary in severity, and last year's season was associated with higher morbidity and mortality than the previous season. These recommendations apply to the 2013–2014 season.

Recommendations: The AAP recommends annual influenza vaccination for children and adolescents aged ≥6 months with either trivalent or quadrivalent vaccine.

- The number of vaccine doses depends on the child's age at the time of first dose as well as previous vaccine receipt
  - Children aged >9 years receive one dose.
  - Children aged 6 months to 9 years require two doses separated by 4 weeks unless they have previously received ≥2 vaccine doses since July 1, 2010
- Inactivated influenza vaccine (IIV) is available for intramuscular injection in both trivalent and quadrivalent formulations. These vaccines are available in both inactivated form and live attenuated intranasal form.
- These vaccines can be administered to children with mild egg allergy (hives). Children with severe egg allergy (anaphylaxis) should be referred to an allergist prior to vaccination
- Treatment with antiviral agents in children is recommended as follows (dosage and schedule recommendations for infants aged <12 months are provided):
  - Hospitalized children with presumed or proven influenza illness
  - All children with underlying conditions that predispose them to complication of influenza
  - Consider treatment for healthy children who may benefit from a shortened duration of symptoms, if the antiviral can be administered within 48 hours of illness

During the 2012–2013 season, 160 influenza-associated pediatric deaths were reported, and many of these deaths could have been prevented by the vaccine. Influenza virus is unpredictable, and infection in children frequently heralds community infection. Immunization of infants and children early in the season is crucial to reducing illness and deaths each year. Healthcare providers should be fierce advocates for this vaccine. ■

Management of Superficial Venous Thrombosis

Key point: Nearly 10% of untreated patients experienced symptomatic SVT extension.

Citation: Lizorovicz A, Becker F, Buchmuller A, Quere I, Prandoni P, and Decousus H for the CALISTO Study Group. Clinical relevance of symptomatic superficial-vein thrombosis extension: Lessons from the CALISTO study. *Blood*. 2013;122(10): 1724-1729.

Thrombi often arise in the superficial veins of the leg. Those forming near the saphenofemoral junction (SFJ) are treated by saphenous vein ligation, thrombectomy, or anticoagulation. But whether superficial vein thrombosis (SVT) distal to the SFJ requires more than analgesics and local measures has been controversial.

To examine the frequency of thrombus extension, deep vein thrombosis (DVT), and pulmonary embolism (PE) in patients with SVT who do not receive anticoagulants, investigators analyzed data from the industry-sponsored, placebo-controlled CALISTO trial (N Engl J Med 2010; 363:1222). In that study, 3002 patients were randomized to receive placebo or the synthetic low-molecular-weight heparin fondaparinux (2.5 mg subcutaneously per day) and were followed for up to 77 days.

Symptomatic extension of the index SVT occurred in 9.4% of placebo patients, of whom 6.4% had DVT and 2.7% had PE; proximity of the thrombus to the SFJ was unrelated to the incidence of DVT or PE. In contrast, only 1.9% of fondaparinux recipients developed SVT extension (relative risk, 0.21; *P*<0.001), and none developed DVT or PE. Fondaparinux recipients also used fewer healthcare resources, such as inpatient and outpatient visits, surgical treatment of the SVT, and therapeutic-dose anticoagulants. ■

Isolated Sternal Fractures May Not Warrant Hospital Admission

Key point: Most patients with isolated sternal fractures can be safely discharged after emergency department evaluation.

Citation: Odell DD, Peleg K, Givon Ad, et al. Sternal fracture: Isolated lesion versus polytrauma from associated extrasternal injuries-analysis of 1,867 cases. *J Trauma Acute Care Surg*. 2013;75(3):448-452.

Sternal fractures are usually associated with high-energy trauma. Conventional wisdom has been that patients with sternal fractures require hospitalization because of the injury mechanism (usually motor vehicle crash), potential for occult associated injury, and severity of pain. In this retrospective study of 1867 patients with sternal fracture who were admitted to Israeli trauma centers over a 12-year period, the authors compared in-hospital events between patients with isolated sternal fractures (26%) and those with sternal fractures associated with other injuries (polytrauma; 73%).

Patient characteristics and mechanisms of injury (mostly motor vehicle collisions and falls from significant height) were similar in the two groups. Compared with patients with polytrauma, those with isolated sternal fractures less frequently exhibited tachycardia, hypotension, tachypnea, Glasgow Coma Scale score ≤14, and Revised Trauma Score ≤11. No patients with isolated sternal fracture required endotracheal intubation, chest tube, thoracoscopy, or resuscitative thoracotomy; these procedures were performed in 17% of patients with polytrauma. ■

A Green Light for Colchicine to Treat Acute Pericarditis

Key point: When added to anti-inflammatory agents, the drug significantly improved outcomes after a first attack.

Citation: A randomized trial of colchicine for acute pericarditis. *N Engl J* Med 2013 Sep 1; [e-pub ahead of print]. (http://dx.doi.org/10.1056/NEJMoa1208536)

Although some experts have recommended the use of colchicine for acute pericarditis, the recommendation has not been based on strong clinical-trial evidence. To address this gap in knowledge, investigators conducted the randomized, double-blind, ICAP trial at five centers in Italy. They assigned 240 patients with a first episode of acute pericarditis to receive colchicine (0.5 mg twice/day for patients weighing >70 kg and 0.5 daily for those weighing ≤70 kg) or placebo for 3 months. All patients were treated with anti-inflammatory agents, mostly aspirin or ibuprofen.

The primary endpoint, incessant or recurrent pericarditis during 18-month follow-up, occurred significantly less frequently in the colchicine group than in the placebo group (17% vs. 38%; relative risk, 0.56; 95% confidence interval, 0.30–0.72). Also, fewer patients in the colchicine group had persistent symptoms at 72 hours (19% vs. 40%; P=0.001). The remission rate at 1 week was higher in the colchicine group than in the placebo group (85% vs. 58%; P<0.001). Adverse-event rates were similar in the two groups. ■

Undervaccination Linked to Increased Risk of Pertussis

Key point: Young children who do not receive age-appropriate vaccinations for pertussis are up to 30 times more likely to acquire pertussis than children who are fully vaccinated.

Citation:Glanz JM, Norwaney KJ, Newcomer SR, et al. Association Between Undervaccination With Diphtheria, Tetanus Toxoids, and Acellular Pertussis (DTaP) Vaccine and Risk of Pertussis Infection in Children 3 to 36 Months of Age. *JAMA Pediatr*. 2013;167(11):1060-1064.

Roughly 70 children with pertussis aged 3 to 36 months were matched to nearly 300 disease-free control patients. Children who were undervaccinated — that is, they had fewer than the four recommended doses of the diphtheria, tetanus toxoids, and acellular pertussis (DTaP) vaccine — were more likely to have laboratory-confirmed pertussis than children who were vaccinated on schedule. Patients who had missed three or four doses were, respectively, 19 and 28 times more likely to acquire pertussis.

The authors estimate that over a third of all pertussis cases in this population were attributable to undervaccination.

They conclude: "Our data suggest that undervaccination, whether due to parental refusal of vaccines or other barriers to health care, is an important contributing factor." ■

Tylenol Overdoses Spotlighted

Key point: Acetominophen has a significant potential for causing harm and despite being OTC, controls should be enacted on the drug.

Citation: http://www.propublica.org/series/overdose

More than 150 Americans die each year from accidental acetaminophen poisoning, while tens of thousands are hospitalized for overdosing on the painkiller, according to an investigative series by ProPublica. The report says the FDA has been slow to act in protecting consumers, and the manufacturer has argued against restrictions.

The latest story lays out nine proposals that could reduce the drug's toll, including:

- lowering the maximum daily dose from 4 g (eight extra-strength pills) to 3 g (six pills)
- allowing only a single pediatric strength
- removing acetaminophen from prescription opioids
- restricting the number of pills consumers can buy at one time
- instructing those using extra-strength acetaminophen to start with one pill and increase to two if their pain does not improve. ■

U.S. Hospitalizations for Pneumonia after a Decade of Pneumococcal Vaccination

Key point: Children who receive a vaccine to prevent blood and ear infections may be reducing the spread of pneumonia to the rest of the population, especially their grandparents and other older adults.

Citation:Griffin MR, Zhu Y, Moore MR, et al. U.S. Hospitalizations for Pneumonia after a Decade of Pneumococcal Vaccination. *N Engl J Med*. 2013;369:155-163.

The introduction of 7-valent pneumococcal conjugate vaccine (PCV7) into the U.S. childhood immunization schedule in 2000 has substantially reduced the incidence of vaccine-serotype invasive pneumococcal disease in young children and in unvaccinated older children and adults. By 2004, hospitalizations associated with pneumonia from any cause had also declined markedly among young children. Because of concerns about increases in disease caused by nonvaccine serotypes, the authors wanted to determine whether the reduction in pneumonia-related hospitalizations among young children had been sustained through 2009 and whether such hospitalizations in older age groups had also declined.

The authors estimated annual rates of hospitalization for pneumonia from any cause using the Nationwide Inpatient Sample database. The reason for hospitalization was classified as pneumonia if pneumonia was the first listed diagnosis or if it was listed after a first diagnosis of sepsis, meningitis, or empyema. Average annual rates of pneumonia-related hospitalizations from 1997 through 1999 (before the introduction of PCV7) and from 2007 through 2009 (well after its introduction) were used to estimate annual declines in hospitalizations due to pneumonia.

The annual rate of hospitalization for pneumonia among children younger than 2 years of age declined by 551.1 per 100,000 children (95% confidence interval [CI], 445.1 to 657.1), which translates to 47,000 fewer hospitalizations annually than expected on the basis of the rates before PCV7 was introduced. The rate for adults 85 years of age or older declined by 1300.8 per 100,000 (95% CI, 984.0 to 1617.6), which translates to 73,000 fewer hospitalizations annually. For the three age groups of 18 to 39 years, 65 to 74 years, and 75 to 84 years, the annual rate of hospitalization for pneumonia declined by 8.4 per 100,000 (95% CI, 0.6 to 16.2), 85.3 per 100,000 (95% CI, 7.0 to 163.6), and 359.8 per 100,000 (95% CI, 199.6 to 520.0), respectively. Overall, the authors estimated an age-adjusted annual reduction of 54.8 per 100,000 (95% CI, 41.0 to 68.5), or 168,000 fewer hospitalizations for pneumonia annually.

Declines in hospitalizations for childhood pneumonia were sustained during the decade after the introduction of PCV7. Substantial reductions in hospitalizations for pneumonia among adults were also observed. ■