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Hospital Medicine

Evidence-Based Information for Hospitalists Intensivists, and Acute Care Physicians [ALERT]

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ABSTRACT & COMMENTARY

Brain MRI Helpful for Identification of Causal Lesions in Adults with First Suspected Seizure

By Jennifer A. Best, MD, FACP, FHM
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Dr. Best reports no financial relationships in this field of study.

SOURCE: An Hakami T, et al. MRI-identified pathology in adults with new onset seizures. *Neurology* 2013;81:920-927.

In settings in which an admitting neurology service is unavailable, hospitalists may be called upon to care for and initiate an appropriate diagnostic evaluation for adult patients with new-onset seizures. Such a workup generally includes metabolic laboratory tests, toxicology screening, electroencephalography (EEG) and brain imaging with CT and/or MRI. The utility of brain MRI in evaluation of patients with first seizure has not been well established, although two clinical guidelines have estimated the yield for epileptogenic lesions to be between 1% and 47%.[1]

In this study, Hakami and colleagues prospectively evaluated a cohort of Australian patients evaluated in an ambulatory setting following a suspected first seizure event over a 9-year period with the goal of establishing the diagnostic efficacy of brain MRI, determining the incidence and types of identified lesions and evaluating whether specific MRI findings correlate with findings on EEG.

Study patients were referred to the First Seizure Clinic at the Royal Melbourne Hospital from the emergency department or by a primary care practitioner. This clinic was staffed by a consulting neurologist with seizure expertise. Patients with established epilepsy or acute symptomatic seizures were excluded from participation, in contrast to previous studies which have included these populations. EEG (ideally within 24 hours of the event) and MRI ("standard epilepsy" or "temporal lobe epilepsy" protocols, with addition of contrast or MR angiography in patients with history of stroke or tumor) were ordered unless previously obtained; many patients had computed tomography (CT) of

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the head prior to clinic presentation.

At the time of physician evaluation, each patient's event was classified as "epileptic" in nature, "nonepileptic" (including psychogenic and syncopal events) or "uncertain." "Epileptic" events were further stratified based on clinical history: "generalized convulsive," "generalized nonconvulsive," "focal convulsive," "focal nonconvulsive" or "unclassified."

MRI reports were reviewed by a neuroradiologist, and a random sample selected for review by a second neuroradiologist to ensure diagnostic congruency. Lack of agreement was identified in only 2% of cases; these files were reviewed by a third neuroradiologist, who established a consensus diagnosis. MRI findings were classified as 1) "epileptogenic" (structural lesions causally or possibly related to epilepsy), 2) "nonepileptogenic" (findings unlikely to be related to epilepsy or findings that were nonspecific) or 3) "normal" (no lesions). Drawing on previously published classification schemes, "epileptogenic" lesions were further categorized by radiologic appearance: "vascular," "developmental," "gliosis/encephalomalacia," "epilepsy-associated brain tumor" or "mesial temporal sclerosis." EEG findings were classified as "focal or generalized epileptiform," "focal or generalized slowing," or "normal."

Finally, the diagnoses suggested by MRI and EEG were correlated with clinical syndrome diagnoses, resulting in four categories: "lesional focal" (focal seizure with focal MRI), "nonlesional focal" (focal seizure with normal or nonepileptogenic lesion), "idiopathic generalized" (if generalized discharge seen on EEG) or "unclassified" (if uncertain type with normal MRI and EEG).

Following exclusions, 993 patients were included in the study cohort. Sixty-one percent were male; mean patient age was 42.2 years. Median time of presentation to clinic following the suspected seizure was 24 days. Seventy-two percent of patients presenting to the clinic were determined to have had an epileptic seizure (18% nonepileptic/10% uncertain) and classification of a specific epileptic syndrome was accomplished in 59%. Seventy-seven percent of study patients underwent MRI; the most common reasons for not completing MRI were failure to show for the appointment or a contraindication, such as indwelling metal. Incidentally, the majority of patients (79%) without MRI did undergo CT scan. Of the 764 patients who underwent MRI, 45% had a positive finding, and 23% of these findings were deemed potentially "epileptogenic." These lesions were most commonly identified as gliosis or encephalomalacia (48%); many of these patients had conditions predisposing to this development, such as trauma or stroke. Tumors were much less common at 15%. Potentially epileptogenic lesions were found to be more common in those who were diagnosed with epileptic events, those who had focal seizures and those with a syndrome diagnosis of focal epilepsy ($P<0.00001$); there was a nonsignificant trend toward higher incidence in patients greater than 65 years.

EEG was obtained in 94% of patients. Thirty-one percent of these tests were abnormal, with epileptiform discharges noted in 42%. A majority (52%) of patients with epileptogenic lesions had a normal EEG. Eighteen percent of patients had an abnormal MRI and EEG, although there was discordance on seizure foci location in 8% of subjects. Abnormal findings on MRI or EEG led to the start of an antiepileptic regimen in 6% of subjects.

In summary, although it is important to recall that this study was undertaken in a patient population presenting to an outpatient clinic at a single site and findings may not generalize to all settings, this evidence suggests that MRI with an epilepsy protocol (which may vary between institutions) should be added to EEG for evaluation of new-onset seizures in adults, as it has a high diagnostic yield, may supplement EEG which is frequently unrevealing, and may influence treatment planning. Furthermore, it is worth recall-

ing that identification of focal lesions may render certain patients candidates for surgical therapies when medical therapy is ineffective. Neurology consultation is essential in interpreting MRI and EEG findings, adjudicating conflicting results between the two where necessary, and considering the risks and benefits of specific therapies for a given patient. ■

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ABSTRACT & COMMENTARY

Fluoroquinolones and the Risk of Acute Kidney Injury

By Rahul Gupta, MD, MPH, FACP

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Dr. Gupta reports no financial relationships relevant to this field of study.

This article originally appeared in the September 15, 2013, issue of Internal Medicine Alert. *It was edited by Stephen Brunton, MD, and peer reviewed by Gerald Roberts, MD. Dr. Brunton is Adjunct Clinical Professor, University of North Carolina, Chapel Hill, and Dr. Roberts is Senior Attending Physician, Long Island Jewish Medical Center, NS/LIJ Health Care System, New Hyde Park, NY. Dr. Brunton serves on the advisory board for Abbott, Amarin, Boehringer Ingelheim, Duchesnay, Janssen, Lilly, Novo Nordisk, Sunovion, and Teva; he serves on the speakers bureau of Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, and Teva. Dr. Roberts reports no financial relationship to this field of study.*

Synopsis: In men taking oral fluoroquinolone antibiotics, the risk of acute renal failure is doubled, and when combined with renin-angiotensin-system blockers, the risk increases by 4.5 fold.

Source: Bird ST, et al. Risk of acute kidney injury associated with the use of fluoroquinolones. *CMAJ* 2013;185:E475-E482.

Fluoroquinolones are commonly prescribed bactericidal agents with a wide spectrum of activity. In addition to the coverage against conventional gram-negative organisms, newer agents in this class have an expanded spectrum of activity against a variety of gram-positive and atypical organisms. One agent, moxifloxacin, even has increased activity against anaerobic bacteria. Additionally, fluoroquinolones are a promising new class of drugs for the treatment of tuberculosis.[1] Fluoroquinolones are also associated with a variety of known adverse effects. These include gastrointestinal, neurological, dermatological, respiratory, and cardiovascular effects. Similar to other antimicrobials, it is not uncommon to observe newer side effects with more extensive clinical use after regulatory approval. Case reports of tendon rupture and retinal detachment have indicated that these drugs may damage collagen and connective tissue.[2] Similarly, reports of acute kidney injury with the use of fluoroquinolones have been published, and it is often included in the product label in the list of potential, but uncommon, adverse reactions.[3] Since acute kidney injury is serious and potentially a fatal adverse event, it is essential that we attempt to quantify this risk.

In their study, Bird et al analyzed a Health Plan Claims Database that contained fully adjudicated medical and pharmacy claims for more than 68 million patients from U.S. health care plans. A nested case-control design of men aged 40-85 years between 2001 and 2011 was used for primary analysis. Data were extracted for 2 million men who had both prescription and medical coverage. Those men who met the inclusion criteria between January 1, 2001, and June 30, 2011, and who had 365 days of enrollment with no acute kidney injury were included. Men with a history of chronic kidney disease or dialysis were excluded since they may be more prone to acute kidney injury. Cases were defined as those admitted to hospital for acute kidney injury, and controls were admitted to hospital with a different presenting diagnosis. Drug exposure to oral fluoroquinolones such as ciprofloxacin, gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin, and norfloxacin was included. Ophthalmic, topical, and intravenous fluoroquinolones were excluded as the study was focused on outpatient-dispensed preparations with significant systemic absorption. Current use was defined as having a supply of or stopped taking a fluoroquinolone within a week of hospitalization. Recent users were those who had a prescription termination up to 60 days before admission and no drug taken within the week prior to admission. Past users had a prescription termination 61-180 days prior to admission and had no active prescriptions during days 0-60.

Researchers found that current fluoroquinolone use was associated with a 2.18 fold (95% confidence interval [CI] 1.74-2.73) higher adjusted relative risk (RR) of acute kidney injury compared with no use. The study researchers did not find any association between acute kidney injury and recent or past

fluoroquinolone use. The researchers observed one additional case per 1529 patients given fluoroquinolones. Additionally, the dual use of fluoroquinolones and renin-angiotensin-system blockers was associated with a 4.46 fold (95% CI, 2.84-6.99) higher adjusted RR for acute kidney injury. The use of amoxicillin or azithromycin was not associated with acute kidney injury.

The limitations of this study included a lack of information on kidney injury severity, an inability to assess the risk associated with the dosage or duration of treatment, and residual confounding inherent in observational research.

■ COMMENTARY

There is no doubt that when serious infections occur, a variety of wide-spectrum antibiotics, including fluoroquinolones, are appropriate and required to be prescribed in order to save lives. However, this study finds more than a two-fold increased risk of acute kidney injury requiring hospital admission with the use of fluoroquinolone antibiotics among adult men. In clinical practice, when oral fluoroquinolones are prescribed, the potential for acute kidney injury is generally not a clinical consideration. However, the study results mean that physicians need to be aware of the risks of acute kidney injury when prescribing these drugs, albeit much lower in prevalence. Additionally, it is also a concern that a strong interaction with concurrent use of fluoroquinolones and renin-angiotensin-system blockers was found. Renin-angiotensin-system blockers are a widely prescribed and popular class of cardiovascular medications used for a variety of diagnoses. This certainly requires taking a cautious approach against the concomitant use of these two drug classes when possible. Interestingly enough, the findings of absence of an increased risk of acute kidney injury with other antibiotics such as amoxicillin and azithromycin would support the hypothesis that this potential adverse association of fluoroquinolones with acute kidney injury is not a class effect of all antibiotics. That would allow physicians to use other classes of antibiotics in high-risk patients such as those on renin-angiotensin-system blockers or with pre-existing renal disease. ■

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ABSTRACT & COMMENTARY

Shorter Door-to-Balloon Times — No Change in Mortality

By Andrew J. Boyle, MBBS, PhD

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Dr. Boyle reports no financial relationships relevant to this field of study.

This article originally appeared in the October 2013 issue of Clinical Cardiology Alert. *It was edited by Michael H. Crawford, MD, Professor of Medicine, Chief of Clinical Cardiology, University of California, San Francisco, and peer reviewed by Ethan Weiss, MD, Assistant Professor of Medicine, Division of Cardiology and CVRI, University of California, San Francisco. Dr. Crawford reports no financial relationships relevant to this field of study, and Dr. Weiss is a scientific advisory board member for Bionovo.*

Source: Menees DS, et al. Door-to-balloon time and mortality among patients undergoing primary PCI. *N Engl J Med* 2013;369:901-909.

Primary percutaneous coronary intervention (PCI) is the preferred strategy for treating ST-segment elevation myocardial infarction (STEMI). The goal is reperfusion of the infarct-related artery as quickly as possible, and the national benchmark is to achieve this within 90 minutes of the patient's arrival at the hospital (i.e., door-to-balloon time [D2B] < 90 mins). Considerable attention has been placed on the publicly reported metric of a hospital's D2B time. It has been assumed that achieving shorter D2B times will reduce mortality associated with STEMI. Menees and colleagues took advantage of the American College of Cardiology's National Cardiovascular Data Registry (NCDR) CathPCI Registry to examine recent temporal trends in D2B times and the corresponding in-hospital mortality rates. They analyzed 96,738 admissions for patients undergoing primary PCI for STEMI from July 2005 through June 2009 at 515 hospitals throughout the country participating in the CathPCI Registry. The primary outcome of the study, in-hospital mortality, is recorded for all patents in the CathPCI Registry. They excluded patients who were transferred from another facility to receive primary PCI and patients whose D2B time was > 3 hours. In a subgroup analysis using a linked Medicare dataset, they also assessed 30-day mortality.

The mean age of the study population was 60.8 years, 28.0% were female, 61.0% had hyperten-

sion, 59.2% had dyslipidemia, 43.3% were current smokers, and 18.8% had diabetes. The prevalence of diabetes, hypertension, and dyslipidemia increased in each year of the study. The proportion of patients with a prior MI and previous PCI increased slightly each year. The mean ejection fraction was 46.8% and was unchanged from year to year. Patients presenting with cardiogenic shock accounted for 9.9% of all patients and it remained constant throughout the study.

Median D2B times declined from 83 minutes in 2005-2006 to 67 minutes in 2008-2009 ($P < 0.001$). The proportion of patients whose D2B was < 90 minutes increased from 59.7% in 2005-2006 to 83.1% in 2008-2009 ($P < 0.001$). However, despite improvements in D2B times, there was no change in unadjusted in-hospital mortality (4.8% in 2005-2006 and 4.7% in 2008-2009, $P = 0.43$) or in risk-adjusted in-hospital mortality (5.0% in 2005-2006 and 4.7% in 2008-2009, $P = 0.34$), nor was a difference observed in 30-day mortality ($P = 0.64$). They repeated the analyses in three high-risk subgroups: patients > 75 years of age, anterior MI, and cardiogenic shock. In all subgroups, D2B decreased over the study interval but in-hospital mortality did not change. The authors conclude that although national D2B times have improved significantly for patients undergoing primary PCI for STEMI, in-hospital mortality has remained virtually unchanged.

■ COMMENTARY

This is a very interesting study that makes us question the validity of using D2B times as a quality metric. There is an entrenched knowledge that reperfusion of the occluded infarct-related artery is beneficial, and that sooner is better than later. However, one is left to ponder just how much must we shorten the duration of ischemia to realize the maximal benefit of reperfusion? Have we already made all the gains that are possible? Is shaving off a few extra minutes of in-hospital time to reperfusion going to further improve outcomes? As the in-hospital ischemic time (i.e., D2B time) becomes shorter, it makes up less of the total ischemic time (i.e., symptom onset to balloon time). Therefore, incremental gains in D2B time are subject to the law of diminishing returns. Perhaps our focus should now shift to reducing total ischemic time, not just D2B time.

This study is strengthened by its rigorous statistical design and the large number of patients included in the analyses. There are several limitations in the data that should be acknowledged when interpreting its significance. First, this is a retrospective, observational study. There is always the potential for unmeasured confounders in observational datasets. Second, public reporting of D2B times and outcomes became more widespread during the study period. Public reporting has been shown to lead to risk-averse behavior, and it is possible that some of the sicker patients, whose outcomes are worse but who gain more benefit from primary PCI, were never offered PCI for their STEMI. Third, over the time period of the study, the patients became higher risk with more having prior MI and diabetes. Although the authors adjusted for risk with known parameters, risk adjustment is an inexact science and the cohorts may not have been directly comparable. Fourth, we are not told of the long-term effects on left ventricular function, subsequent heart failure, quality of life, or readmission rates. Mortality is not the only important endpoint. If shorter D2B time results in less heart failure or better quality of life, then the considerable resources devoted to shortening D2B time may be justified. Further long-term studies are needed.

Should we change practice based on this study? No, I think patients with STEMI should still undergo primary PCI in the most rapid time feasible. However, this study gives us pause to consider whether resources that are aimed at further reducing D2B could be better spent reducing total ischemic time. ■

ABSTRACT & COMMENTARY

Mortality Decline With the Use of a Sepsis Treatment Bundle

By Eric C. Walter, MD, MSc

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Dr. Walter reports no financial relationships relevant to this field of study.

This article originally appeared in the October 2013 issue of Infectious Disease Alert. *It was edited by Stan Deresinski, MD, FACP, FIDSA, and peer reviewed by Timothy Jenkins, MD. Dr. Deresinski is Clinical Professor of Medicine, Stanford University, Associate Chief of Infectious Diseases, Santa Clara Valley Medical Center, and Dr. Jenkins is Assistant Professor of Medicine, University of Colorado, Denver Health Medical Center. Dr. Deresinski does research for the National Institutes of Health, and is an advisory board member and consultant for Merck, and Dr. Jenkins reports no financial relationships relevant to this field of study.*

SYNOPSIS: This large, multicenter, quality improvement project showed a dramatic reduction in mortality among patients with severe sepsis or septic shock after implementation of a sepsis treatment bundle.

SOURCE: Miller RR, et al. Multicenter implementation of a severe sepsis and septic shock treatment bundle. *Am J Respir Crit Care Med* 2013; 188:77-82.

Guidelines for the treatment of severe sepsis and septic shock over the last decade have focused on early recognition and rapid, aggressive resuscitative efforts. Implementation of these guidelines has consistently been shown to improve outcomes. However, the relative importance of different elements has been debated. As part of a multicenter quality improvement project, a sepsis treatment bundle was implemented for all patients admitted from the emergency department (ED) to the ICU in 11 hospitals within a single healthcare system (Intermountain Healthcare).

The sepsis treatment bundle was comprised of seven "resuscitative elements" and four "maintenance elements." The first three resuscitative elements — 1) measuring lactate, 2) blood cultures prior to antibiotic administration, and 3) administration of broad-spectrum antibiotics — had to be completed within 3 hours of ED arrival. The additional resuscitation elements were: 4) administration of fluids of 20-40 mL/kg for hypotension or lactate ≥ 4 mmol/L, 5) administration of vasopressors for hypotension despite appropriate fluid administration, 6) obtaining central venous pressure (CVP) and central venous oxygen saturation ($ScVO_2$) at regular intervals with a goal CVP ≥ 8 cm H_2O and $ScVO_2$ ≥ 70%, and 7) administration of inotropes and/or packed red cells (if hematocrit < 30%) if $ScVO_2$ was < 70% and CVP ≥ 8 cm H_2O. All had to be accomplished within 6 hours of ED admission. The four maintenance elements consisted of 1) mean glucose ≤ 180 mg/dL between 12-24 hours following admission, 2) administration of glucocorticoids for persistent hypotension despite adequate fluid resuscitation, or a high dose of a single vasopressor or requiring more than 1 vasopressor, 3) assessment of drotrecogin alfa eligibility (no longer part of the bundle), and 4) use of low tidal volume ventilation (6 mL/kg predicted body weight) if mechanically ventilated.

From 2004-2010, 4329 subjects were diagnosed with severe sepsis or septic shock. All-or-none total bundle compliance increased from 4.9% to 73.4% over the study period, showing that a sepsis treatment bundle could be effectively implemented. Over the same time period, in-hospital mortality declined from 21.2% to 8.7%. Interestingly, the decline in mortality did not appear to be due to 100% bundle adherence, as a similar decline in mortality was seen in subjects for whom not all bundle elements were implemented (21.7% to 9.7%). Throughout the study, however, the number of bundle elements successfully achieved per patient steadily increased.

The first three resuscitative elements were applied to all subjects. Additional elements were only applied if subjects were eligible (i.e., one could only be eligible for vasopressors, inotropes/red cell transfusion, glucocorticoids, or lung protective ventilation if one was hypotensive, had low $ScVO_2$, or was intubated). A 100% compliance with the first three elements was associated with ineligibility for inotropes/red cell transfusions, glucocorticoids, and lung protective ventilation. Another way of saying this is that in subjects for whom lactate was measured, blood cultures were drawn prior to antibiotics, and broad-spectrum antibiotics were provided within the first 3 hours of ED arrival were less likely to have persistent hypotension, low $ScVO_2$ or require mechanical ventilation. They were also less likely to die ($P < 0.0001$).

■ COMMENTARY

The authors should be commended on a tremendous amount of work put forth to implement this quality improvement project across 18 ICUs in 11 hospitals as well as to collate data from more than 4000 patients. The authors show that with an effective collaboration between the ED and ICU, a detailed sepsis treatment bundle can be effectively implemented. They also show that aggressive sepsis treatment should not be restricted to the first 6 hours; it should extend into comprehensive ICU care. The all-or-none measurement bar prevented providers from picking and choosing elements they felt were most beneficial. Supporters will argue that this demanding approach standardized care and led to the impressive decline in mortality. Detractors will argue the extensive bundle was "overkill" and not needed, as mortality declined equally among subjects in whom not all bundle elements were implemented. The truth probably lies somewhere in the middle. Like other pre-post studies evaluating practice changes, the outcome cannot be definitely attributed to the intervention. We may not definitely know what part or parts of the treatment bundle led to the mortality improvement, but clearly the implementation of this bundle achieved a very positive outcome.

The strong association between 100% compliance of the first three resuscitation bundle elements and subsequent severity of illness and death is intriguing. Simply asking physicians to consider sepsis and treat early is vital. Future studies will help delineate the added importance of invasive monitoring, vasopressors, inotropes, and transfusions. In the absence of such studies, these data argue that adherence to most, if not all, sepsis treatment guidelines should be the go-to approach. ■

ECG REVIEW

Mobitz I or Mobitz II AV Block?

By Ken Grauer, MD

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Dr. Grauer is the sole proprietor of KG-EKG Press, and publisher of an ECG pocket brain book.

This article originally appeared in the September 15, 2013, issue of Internal Medicine Alert. *It was edited by Stephen Brunton, MD, and peer reviewed by Gerald Roberts, MD. Dr. Brunton is Adjunct Clinical Professor, University of North Carolina, Chapel Hill, and Dr. Roberts is Senior Attending Physician, Long Island Jewish Medical Center, NS/LIJ Health Care System, New Hyde Park, NY. Dr. Brunton serves on the advisory board for Abbott, Amarin, Boehringer Ingelheim, Duchesnay, Janssen, Lilly, Novo Nordisk, Sunovion, and Teva; he serves on the speakers bureau of Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, and Teva. Dr. Roberts reports no financial relationship to this field of study.*

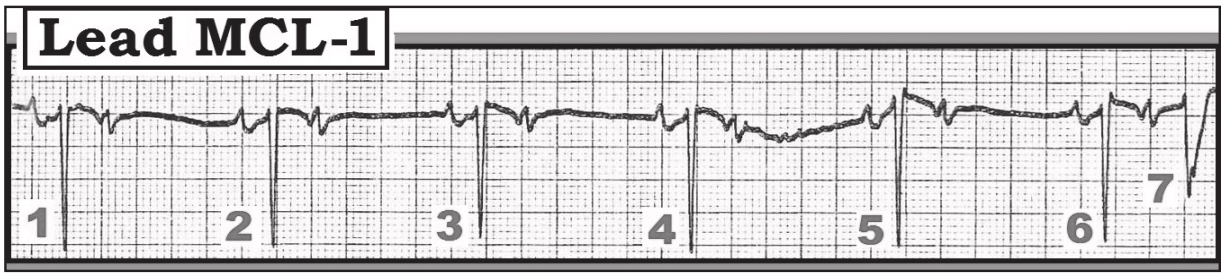

Figure — Lead MCL-1 rhythm strip. Is this Mobitz I or Mobitz II?

Scenario: Interpret the lead MCL-1 rhythm strip shown in the figure. Does this rhythm represent Mobitz I (*Wenckebach*) or Mobitz II AV block? Is a pacemaker likely to be needed?

Interpretation: Neither Mobitz I nor Mobitz II is present. Rather than AV block, the rhythm in the figure represents an insightful example of the "mischief" that *blocked* premature atrial contractions (PACs) can cause, especially when PACs are frequent.

All forms of AV block are characterized by the presence of similar morphology P waves that occur with a regular (or at least fairly regular) P-P interval. Requiring similar P wave morphology when assessing an arrhythmia for AV block eliminates other potential causes of bradycardia such as wandering pacemaker, sinus pauses, and sinus arrest. So while occasional PACs with differing P wave morphology may be seen, the presence of constantly changing P wave morphology should suggest some phenomenon other than AV block.

With regard to regularity of the atrial rate, slight variation in the P-P interval may be seen with AV block when there is underlying sinus arrhythmia. However, gross variation in the P-P interval is usually *not* seen when the primary problem is AV block.

Keeping these two points in mind allows us to rule out AV block as the cause of the rhythm disturbance in the figure. The P-P interval is clearly irregular. In fact, there is a pattern to this P-P variation (alternating *short-long* cycles) produced by the finding that every other P wave is early (premature). The underlying rhythm is atrial bigeminy (every other beat is a PAC). In addition, P wave morphology changes from one beat to the next. Sinus P waves are seen as a biphasic (positive-then-negative) deflection preceding beats 1, 2, 3, 4, 5, and 6. In contrast, P waves buried within the ST-T wave of beats 1 through 6 are triphasic (small negative, then positive, then narrow negative), deflections that clearly look *different* in morphology than the sinus P waves. These triphasic P waves arise from an atrial site other than the sinus node.

In summary, the underlying rhythm in the figure is atrial bigeminy. The very early occurring PACs (buried within the T waves of beats 1 through 5) are non-conducted because they occur during the absolute refractory period. In contrast, the PAC that occurs within the T wave of beat 6 *is* conducted, albeit with aberration (because it presumably occurs during the relative refractory period). No AV block is present. No pacemaker is needed. Clinically, blocked PACs are much more common than any form of heart block. They may be recognized by careful attention to P wave regularity, morphology, and careful search for the "telltale" notching of a hidden PAC within T waves preceding a relative pause on the tracing.

For more information on the basics of AV block, please visit: https://www.kg-ekgpress.com/av_block_pdf_file/. ■

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To earn credit for this activity, please follow these instructions:

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CME QUESTIONS

1. According to the study by Hakami et al., the incidence of potentially epileptogenic lesions found on MRI was statistically significantly higher in all groups, EXCEPT the following:

a. Age greater than 65
b. Patients with epileptic events
c. Patients with a clinical syndrome of focal epilepsy
d. Patients with focal seizures

2. In the nested case-control study by Bird et al., which of the following observations were made in relationship to men admitted to the hospital for acute kidney injury?

a. Current use of oral fluoroquinolones was associated with an increased risk of mortality.
b. Current use of oral fluoroquinolones was associated with a two-fold increased risk of acute kidney injury.
c. Current use of amoxicillin or azithromycin was associated with a nearly three-fold increased risk of acute kidney injury.
d. Renin-angiotensin-system blockers decreased the risk of acute kidney injury in men taking fluoroquinolones.

3. The study by Menees and colleagues looked at the association of door-to-balloon times and various outcomes for patients undergoing percutaneous coronary intervention (PCI) for STEMI. As door-to-balloon times decreased, which of the following outcomes improved?

a. Risk-adjusted in-hospital mortality
b. 30-day mortality
c. Development of cardiogenic shock
d. None of the above.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss pertinent safety, infection control and quality improvement practices;
- explain diagnosis and treatment of acute illness in the hospital setting; and;
- discuss current data on diagnostic and therapeutic modalities for common inpatient problems.

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Finasteride for Prevention of Prostate Cancer: 18 Years of Follow-up

Source: Thompson I, et al. *N Engl J Med* 2013;369:603-610.

THE PROSTATE CANCER PREVENTION TRIAL (PCPT) was a randomized, double-blind, placebo-controlled trial (n = 18,880) performed to evaluate the efficacy of the 5-alpha-reductase inhibitor finasteride (FIN) for prevention of prostate cancer. At the end of 7 years, the good news was a 25% reduction in total prostate cancer; the bad news was that there was a 27% *increase* in higher-grade prostate cancers, intimating that although the total amount of prostate cancer was reduced, overall outcomes could possibly be worsened by the increase in more aggressive cancers. Mitigating explanations for the increased risk of higher-grade tumors included alpha-reductase inhibitor-induced shrinkage of healthy prostate tissue (thereby increasing the likelihood of biopsy-positive results) and alteration of tissue architecture induced by FIN; insufficiently reassured by these explanations, most primary care clinicians have opted not to use FIN for prostate cancer prevention.

The outcomes of this population in very long-term follow-up can better answer the question of whether the risk-benefit balance was indeed unfavorably tipped by high-grade prostate cancers. Reviewing the outcomes of patients originally enrolled in PCPT, the survival rates at 18 years were essentially identical among men who had been randomized to FIN or placebo. Although FIN treatment did not appear to reduce mortality, the increased incidence of higher-grade Gleason scores among FIN-treated patients did not appear to increase mortality either. In the absence of mortality improvement, unless men are seeking alpha-reductase treatment for symptomatic benign prostatic hyperplasia, FIN treatment for prevention of prostate cancer would appear unwarranted, albeit otherwise safe. ■

Addressing Diabetic Neuropathy

Source: Tesfaye S, et al. *Diabetes Care* 2013;36:2456-2465.

TYPE 2 DIABETES (T2DM) REMAINS THE No. 1 cause of atraumatic limb loss in the United States. Neuropathy is a primary culprit in the process beginning with undetected foot injury that progresses to deep-seated infection and, ultimately, limb loss. Hence, it is hoped that early identification and management of diabetic peripheral neuropathy (DPN) might improve outcomes. Unfortunately, of the microvascular consequences of T2DM, neuropathy appears to be the most recalcitrant to glucose control: Glucose control appears to forestall progression of neuropathy, but not improve nerve function or reverse neuropathy.

In clinical practice, it is recommended that the diagnosis of DPN should be based on typical symptoms and physical examination (e.g., lower extremity deep tendon reflex changes). On the other hand, clinical trials usually employ sophisticated techniques such as nerve conduction testing. Comparison of tuning fork testing vs monofilament testing found the former to be the most sensitive test for identification of neuropathy. The postulated pathophysiology of DPN is uncertain and may be multifactorial, but there is some support for dysfunction of the neural microvasculature.

FDA-approved agents for DPN pain are duloxetine and pregabalin, although venlafaxine, gabapentin, carbamazepine, and alpha-lipoic acid have also demonstrated some efficacy. A recently published algorithm created by the Toronto International Neuropathy Consensus Group suggests that when traditional agents are not effective, opioid analgesia may be considered. ■

When Metformin and Sulfonylurea Are Not Enough: Canagliflozin or Sitagliptin?

Source: Schernthaner G, et al. *Diabetes Care* 2013;36:2508-2515.

MANY TYPE 2 DIABETES (T2DM) PATIENTS are unable to achieve or maintain their A1c goals even when appropriately treated with oral agents. Currently, the combination of metformin with a sulfonylurea (MET/SFU) is a very commonplace initial combination. Because T2DM is a progressive disorder, and because some agents lose efficacy over time, most patients must recognize that augmentation of treatment is usually required. But which next step is best when MET/SFU is insufficient?

Canaglifozin (CAN) is the first approved member of a new class of agents for T2DM, known as the SGLT2 inhibitors, which work by blocking renal reabsorption of excess glucose, leading to increased urinary glucose excretion. Sitagliptin (SIT) is one of three approved

DPP-4 inhibitors that work by increasing blocking glucagon and stimulating insulin production when glucose is elevated.

In a 1-year trial comparing the addition of CAN or SIT to MET/SUF (n = 755), A1c reduction with CAN was substantially greater (-1.03 vs -0.66) and both agents were well tolerated. SGLT2 inhibitors are potentially useful when A1c goals are not attained or maintained with MET/SUF. ■

Wedge Insoles for Knee Osteoarthritis: Probably Not

Source: Parkes MJ, et al. *JAMA* 2013;310:722-730.

In the United States, osteoarthritis is the No. 1 cause of disability. The "graying" of America, in concert with an ever-growing prevalence of obesity, portends an equally expanding population of osteoarthritis.

Osteoarthritis of the knee (OA-K) can be particularly disabling, and currently available medical treatments, such as NSAIDs, topical analgesics, and opioids, each have limitations. Hence, short of surgical intervention, alternatives — such as non-pharmacologic treatment — are sought.

Medial OA-K is one of the most common subtypes. In theory, load reduction on the medical compartment might alleviate symptoms, disease progression, or both. By placing an angulated wedge under the sole of the foot, such load reduction can be achieved. A meta-analysis was performed (n = 885) by Parkes et al to evaluate the efficacy of mechanical interventions intended to unload the medial knee compartment including wedges or structured shoes.

Overall, studies did confirm a positive effect of devices to unload the medial compartment, although the effect size was not large. Additionally, trials with an active control (such as a neutral vs an offloading wedge) failed to confirm positive effects. These mixed results call into question whether clinicians can be confident in the efficacy of wedge insoles. ■

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Post-Stroke Blood Pressure Targets: Recent Lacunar Stroke

Source: The SPS3 Study Group. *Lancet* 2013;382:507-515.

Cerebral infarction related to small vessel disease, known as lacunar stroke, is strongly associated with hypertension (HTN). Numerous clinical trials have confirmed that control of HTN provides substantial stroke reduction overall (≥ 40%), without specifically distinguishing the effects on lacunar stroke.

The Secondary Prevention of Small Subcortical Strokes trial compared two levels of systolic blood pressure (SBP) among patients with a recent MRI-confirmed lacunar stroke for impact on recurrent stroke. Because of concern that excessive SBP lowering in the face of acute cerebral ischemia might be detrimental, subjects were randomized at least 2 weeks after the identifying event. Subjects (n = 3020) were randomized to one of two groups: SBP goal 130-149 mmHg or SBP goal < 130 mmHg. Clinicians were allowed to use whatever medications they preferred to attain SBP goals.

At 3.7 years, there was no statistically significant difference in the primary outcome of the study: all stroke. On the other hand, a secondary endpoint (which must be considered "hypothesis generating" since the primary endpoint failed) of hemorrhagic stroke was reduced by almost two-thirds in the SBP < 130 group. This finding prompted the consideration by the authors that since there was no difference in overall outcomes, but the suggestion of substantial reduction in hemorrhagic stroke by more strict blood pressure control, some clinicians might consider the more stringent SBP at least potentially beneficial. ■

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Can We Identify Persons on Zolpidem at Risk for Driving Mishap?

Source: Farkas RH, et al. *N Engl J Med* 2013;369:689-691.

Benzodiazepines can impair consciousness. It has been recognized that the elderly — and anyone with renal impairment because they metabolize zolpidem (ZOL) more slowly — should receive a lower dose (ZOL 5 mg) than other adults (ZOL 10 mg). Soon after the advent of immediate-release ZOL, a controlled-release formulation became available. Prospective studies of ZOL indicated that plasma levels > 50 ng/mL were associated with impairment in driving skills. As formulations of ZOL evolved, pharmacokinetic studies found that the 10 mg approved dose of immediate-release ZOL was associated with ZOL levels > 50 ng/dL in as many as 15% of women (who metabolize ZOL more slowly).

Recognition of the potential for ZOL to produce impairment in driving has resulted in FDA recommendations for dose reductions in various ZOL formulations, especially in women.

Insomnia and other sleep disorders are, of course, associated with an increased risk of auto accidents due to excessive daytime sleepiness. Clinicians should maintain vigilance that appropriate dose limitations are observed — since patients often do not perceive the impairment induced by benzodiazepines — and that patients do not drive sooner than the recommended interval after taking their dose of medication. ■

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Medications for Risk Reduction of Breast Cancer in Women

In this issue: USPSTF issues new guidelines for risk reduction of breast cancer; safety of Chantix in patients with depression; polypills for cardiovascular disease; and FDA actions.

Risk reduction of breast cancer

The U.S. Preventive Services Task Force (USPSTF) has published new guidance regarding medications for risk reduction of primary breast cancer in women. The group reviewed evidence on the effectiveness, adverse effects, and subgroup variations of medications to reduce breast cancer, specifically the selective estrogen receptor modulators tamoxifen and raloxifene (Evista). The USPSTF recommends that clinicians engage in shared, informed decision making with women who are at increased risk for breast cancer about medications to reduce the risk. Women who are at increased risk for breast cancer and have a low risk for adverse medication effects should be offered one of the risk-reducing medications (B recommendation). However, the group recommends against the routine use of these medications in women who are not at increased risk of breast cancer. High-risk women are defined as those with a 5-year risk of ≥ 3% based on the National Cancer Institute's Breast Cancer Risk Assessment Tool (www.cancer.gov/bcrisktool/). Tamoxifen and raloxifene are shown to reduce the risk of estrogen receptor-positive breast cancer, but not estrogen receptor-negative cancer, which is more difficult to treat. Tamoxifen is associated with a moderate benefit for breast cancer but a slightly higher risk of endometrial cancer. Raloxifene is associated with a slightly smaller benefit for breast cancer but no risk for endometrial cancer. Both drugs may reduce the risk of nonvertebral fractures with greater benefit for raloxifene. Both drugs also increase the risk of venous thromboembolism with the risk being age-dependent (*Ann Intern Med* published online September 24, 2013). ■

Chantix safe in patients with depression

Varenicline (Chantix) was approved in 2006 to treat smoking addiction. Since its approval, the drug has been plagued by reports of worsening depression and increases in suicidality, prompting the FDA to issue an alert in 2008 noting "serious neuropsychiatric symptoms" associated with the drug. But a new study suggests that varenicline may be safe and effective in smokers with a history of depression. In a study sponsored by Pfizer, 525 adult smokers with stably treated current or past major depression and no recent cardiovascular events were randomized to varenicline 1 mg twice daily or placebo for 12 weeks with 40 weeks of nontreatment follow-up. The primary outcome was carbon monoxide-confirmed continuous absence rate (CAR) for weeks 9-12. Other outcomes included ratings of mood, anxiety, and suicidal ideation or behavior. About two-thirds of patients in both groups completed the study. Patients treated with varenicline had double the quit rate at weeks 9-12 (CAR 35.9% vs 15.6%; odds ratio, 3.35; 95% confidence interval [CI], 2.16-5.21; $P < 0.001$). The quit rates were also approximately double from weeks 9-24 and from weeks 9-52, with the CAR at week 52 for the varenicline group at

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20.3% vs 10.4% for placebo. There were no clinically relevant differences between groups in suicidal ideation or behavior, or overall worsening depression or anxiety. About 27% of the treatment group experienced nausea as the most frequent adverse event. The authors conclude that varenicline increased smoking cessation in smokers with stably treated current or past depression without exacerbating depression or anxiety (*Ann Intern Med* 2013;159:390-400). ■

Polypills for cardiovascular disease

Is a "polypill" the answer to adherence in patients with cardiovascular disease (CVD)? Long-term medication adherence is notoriously poor in these patients. Even in high-income countries, adherence rates are only 50% in patients with coronary disease and 35% in those with those a history of stroke. Polypills combine several cardiovascular medications in one, including aspirin, a statin, and one or more blood pressure medications. A recent study was designed to see if these fixed-dose combination (FDC) pills would improve compliance, LDL cholesterol, and blood pressure levels compared to usual care. Two polypills were evaluated in the study. The first pill contained aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, and atenolol 50 mg. The second pill substituted hydrochlorothiazide 12.5 mg for atenolol. About 1000 patients received one of the FDCs with about 1000 controls continuing on usual care. After an average follow-up of 15 months, adherence was higher with the FDC vs usual care (86% vs 65%, $P < 0.001$), but there were only modest reductions in systolic blood pressure with FDC of about 2.6 mmHg and also modest reductions in LDL cholesterol of 4.2 mg/dL vs usual care. Subgroups of patients who showed poor adherence at baseline had higher levels of improvement in blood pressure and LDL cholesterol. There was no significant difference in cardiovascular events (5% FDC vs 3.5% usual care; relative risk, 1.45; 95% CI, 0.94-2.24; $P = 0.09$). The authors conclude that among patients at high risk of CVD, use of a FDC "polypill" improved medication adherence with small improvements in systolic blood pressure and LDL cholesterol (*JAMA* 2013;310:918-929). ■

FDA actions

Treatment of chronic pain has changed dramatically in the last 3 years, shifting from concern about undertreating patients with chronic pain to concern about the safety of overuse of extended-release and long-acting opioid analgesics. With overdoses of prescription opioids skyrocketing and far outnumbering overdoses from illegal drugs, the FDA has decided to take action. The agency is requiring labeling changes and new postmarketing study requirements for these drugs, including oxycodone (Oxycontin), controlled-release and extended-release morphine (MS Contin and Avinza), and fentanyl patches (Duragesic). The labeling changes are being required to "combat the crisis of misuse, abuse, addiction, overdose, and death from these drugs that have harmed too many patients and devastated too many families and communities." The updated indications for the extended-release and long-acting opioids state that these drugs are indicated "for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate." The goal of the postmarketing studies is to further assess the known serious risks of these drugs, including misuse, abuse, hyperalgesia, addiction, overdose, and death.

The FDA is also requiring additional labeling changes to fentanyl patches due to 32 accidental pediatric exposures, including 12 deaths in the last 16 years. The labeling requirements include printing the drug's name and strength in the clearly visible, long-lasting ink on the patch, in a color that is clearly visible to the patient and caregivers. The FDA also recommends that for disposal the patch be folded in half, sticky sides together, and flushed down the toilet immediately. These labeling changes apply to both generic fentanyl patches and brand-name Duragesic patches.

The FDA has approved the first generic version of the anticancer drug capecitabine (Xeloda), an oral chemotherapy agent used to treat metastatic colorectal cancer and metastatic breast cancer. The new generic is manufactured by Teva Pharmaceuticals while the branded product is manufactured by Roche. Two years ago, Roche settled a patent infringement case against Mylan over the same drug. It is unclear whether Mylan will now also launch its own generic. ■

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