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Internal Medicine

Evidence-based summaries of the latest research in internal medicine [ALERT]

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ABSTRACT & COMMENTARY

Long-term Use of Proton Pump Inhibitors and Earlier Death

By Joseph Scherger, MD, MPH

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

SYNOPSIS: An observational study of a Veterans Affairs population showed that the use of proton pump inhibitors over a median 5.7-year follow-up period increased the risk of death by 25% compared with the use of H2 blockers or no medication.

SOURCE: Xie Y, Bowe B, Li T, et al. Risk of death among users of proton pump inhibitors: A longitudinal observational cohort study of United States veterans. *BMJ Open* 2017;7:e015735.

Investigators studied patient data from the U.S. Department of Veterans Affairs (VA) collected between October 2006 and September 2008. Among 3.5 million veterans, about 350,000 received proton pump inhibitors (PPIs) for ongoing suppression of gastric acid. This cohort was compared with veterans who received histamine 2 (H2) blockers and with veterans who did not receive medication. Otherwise, the three groups were matched by age and overall health. The group that received PPIs demonstrated a higher relative risk of death (hazard ratio, 1.2-1.25, depending on the comparison group). The cause of death was not evaluated. The results of this study were reported widely as a 25% increase in death from PPI medications. To put the results in perspective, those given PPIs experienced a death rate of 4.7 per 100 veterans per year, comparted with 3.3 deaths per 100 in the group that took H2 blockers. The death rate for veterans on no medication was similar to those given H2 blockers.

■ COMMENTARY

Since their entry into the market decades ago, PPIs have been indicated for short-term use. PPIs are effective, and the main problem they treat, gastro-

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esophageal reflux disease (GERD), is a chronic health problem. Since PPIs do not produce immediate side effects in most patients, they often are taken long term. Adverse health consequences of long-term PPI use are piling up and are quite serious. An article published in *The New York Times* in March summarized the research documenting the complications of PPIs as nutrient deficiencies (vitamin B12, vitamin C, calcium, iron, and magnesium), joint pain, infections (including *C. difficile*) bone fractures, heart attacks, and dementia.[1] Studies published in the past two years described in greater detail the relationship between PPIs and many of these health complications.[2-4] Previous research revealed increased one-year mortality in institutionalized patients on PPIs.[5,6]

Xie et al carried out the first longitudinal study of a cohort over a longer period. Based on all this research, long-term use of PPIs should occur with great caution and with the patient's informed consent. Before PPIs, the H2 blockers were among the most prescribed drugs in the world. They are effective and, based on the Xie et al study, are as safe from mortality as no medication. However, H2 blockers suppress the acid environment of the stomach, which may produce adverse consequences over time, such as proliferation of *H. pylori* and other gastric flora as well as cellular changes that may lead to gastric cancer.[7,8] There is a nutritional solution to consider for patients with GERD, dyspepsia, and irritable bowel syndrome (IBS). These conditions are often a reflection of dysbiosis, an unhealthy gut microbiome. The gut microbiome depends on what we eat. Reducing or eliminating inflammatory foods such as those containing gluten and fructans have been shown to relieve these problems in some patients.[9,10] Gluten is an inflammatory protein complex found in wheat, barley, and rye. Fructans are oligosaccharides and polysaccharides that are in some vegetables, grains, and fruits. Fructans also are known as FODMAPS, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.

I suspect we will hear much more about nutritional solutions in the future if the research is funded to generate high-quality clinical trials. Meanwhile, look for patients taking long-term PPIs and speak with them about alternatives. You may be saving their lives. ■

REFERENCES

1. Brody JE. Pop a Pill for Heartburn? Try Diet and Exercise Instead. *The New York Times*, March 20, 2017. Available at: http://nyti.ms/2n1BZd5. Accessed July 19, 2017.
2. Schoenfeld AJ, Grady D. Adverse effects associated with proton pump inhibitors. *JAMA Intern Med* 2016;176:172-174.
3. Xie Y, Bowe B, Li T, et al. Proton pump inhibitors and risk of incident CKD and progression to ESRD. *J Am Soc Nephrol* 2016;27:3153-3163.
4. Klepser DG, Collier DS, Cochran GL. Proton pump inhibitors and acute kidney injury: A nested case-control study. *BMC Nephrol* 2013;14:150. doi: 10.1186/1471-2369-14-150.
5. Bell JS, Strandberg TE, Teramura-Gronblad M, et al. Use of proton pump inhibitors and mortality among institutionalized older people. *Arch Intern Med* 2010;170:1604-1605.
6. Maggio M, Corsonello A, Ceda GP, et al. Proton pump inhibitors and risk of 1-year mortality and rehospitalization in older patients discharged from acute care hospitals. *JAMA Intern Med* 2013;173:518-523.
7. Sabesin SM. Safety issues relating to long-term treatment with histamine H2-receptor antagonists. *Aliment Pharmacol Ther* 1993;7(Suppl 2): 35-40.
8. Parikh N, Howden CW. The safety of drugs used in acid-related disorders and functional gastrointestinal disorders. *Gastroenterol Clin North Am* 2010;3:529-542.
9. Fedewa A, Rao SSC. Dietary fructose intolerance, fructan intolerance and FODMAPS. *Curr Gastroenterol Rep* 2014;16:370.
10. Ford AC, Lacy BE, Talley NJ. Irritable Bowel Syndrome. *N Engl J Med* 2017;376:2566-2578.

ABSTRACT & COMMENTARY

Glycemic Measures May Vary Depending on Race

By Seema Gupta, MD, MSPH

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

SYNOPSIS: In patients with type 1 diabetes, hemoglobin A1c levels overestimate the mean glucose concentration in black persons compared with white persons, possibly owing to racial differences in the glycation of hemoglobin.

SOURCE: Bergenstal RM, Gal RL, Connor CG, et al. Racial differences in the relationship of glucose concentrations and hemoglobin A1c levels. *Ann Intern Med* 2017;167:95-102.

Based on data from early studies, including the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study, it has been established that in patients with diabetes, intensive therapy targeting lower levels of glycemia delays onset effectively and slows the progression of microvascular complications such as diabetic retinopathy, nephropathy, and neuropathy.[1,2] Glycated hemoglobin A1c (A1c) measurement, as the standard glycemic marker for the assessment of diabetes and prediabetes status, remains the most widely used clinical test to estimate the degree to which this is achieved. A1c is hemoglobin with glucose attached to the N-terminal valine of the beta chain and is expressed as the proportion of total hemoglobin. The lifespan of red blood cells is about 120 days; therefore, A1c reflects mean blood glucose levels over the past two to three months.

Despite the broad acceptance of A1c as the gold standard of blood glucose control and its wide use to judge the efficacy of diabetes treatment and to adjust therapy, many recognize that levels may vary substantially between individuals, even those who exhibit similar blood glucose levels.[3] Several studies have shown that this glycation gap in terms of demonstrating higher A1c concentrations may be significant in some ethnic groups when compared to white patients with similar blood glucose concentrations. Genetic factors substantially determine A1c, and studies have shown that in patients with type 1 diabetes, genetic effects or heritability could explain approximately 62% of population variance in A1c, while the remainder may be attributable to the influence of unique environment and age.[4] Researchers have found that between-patient variation in derived mean red blood cell age may explain all glucose-independent variations in A1c.[5]

Bergenstal et al conducted a prospective, 12-week observational study across 10 diabetes centers in the United States to determine whether a racial difference exists in the relationship between mean glucose concentrations and A1c levels and to explain the observed differences in A1c levels between non-Hispanic black persons and non-Hispanic white persons with type 1 diabetes. The authors recruited 104 black participants and 104 participants ≥ 8 years of age who had suffered from type 1 diabetes for at least two years and presented with A1c levels between 6-12%. Investigators measured mean glucose concentrations using continuous glucose monitoring, then compared by race with A1c, glycated albumin, and fructosamine values.

Researchers found that the mean A1c level was higher among black participants (9.1%) than white participants (8.3%), and the mean glucose concentration for a given A1c was significantly lower in black participants than in white participants ($P = 0.013$). This lower concentration level was reflected in mean A1c values among black participants, which were 0.4% higher than those among white participants (95% confidence interval, 0.2-0.6) for a given mean glucose concentration. However, the researchers observed no significant racial differences in the relationship of glycated albumin and fructosamine levels with the mean glucose concentration ($P > 0.2$ for both comparisons).

■ COMMENTARY

There has been a long debate about why African-American patients with diabetes exhibit a higher A1c than their white counterparts. Is it because of biological differences, or do African-Americans demonstrate higher blood glucose because they may not have the same access to care or insurance? Or is it some combination of several factors? Bergenstal et al certainly provided evidence that in addition to environmental and other socioeconomic factors, biological factors play a critically significant role in this difference. This is noteworthy because we should no longer dismiss these differences as normal and inconsequential. The findings of this study should help us provide some direction in the clinical management of certain populations. For patients with difficult-to-control

diabetes, it may be essential to spend more time studying the individual blood glucose readings to help better personalize the patient's blood glucose management. At the same time, it's important to understand that intrapatient variability, interpatient variability, and racial variability are critical factors of which all clinicians should be aware, including the differences between black and white patients. Finally, it is important to note that there were too few participants in the study with A1c levels < 6.5% to generalize the results to such individuals. ■

REFERENCES

1. Diabetes Control and Complications Trial Research Group; Nathan DM, Genuth S, Lachin J, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977-986.
2. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:837-853.
3. Wilson DM, Xing D, Cheng J, et al. Persistence of individual variations in glycated hemoglobin: Analysis of data from the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Randomized Trial. *Diabetes Care* 2011;34:1315-1317.
4. Snieder H, Sawtell PA, Ross L, et al. HbA(1c) levels are genetically determined even in type 1 diabetes: Evidence from healthy and diabetic twins. *Diabetes* 2001;50:2858-2863.
5. Malka R, Nathan DM, Higgins JM. Mechanistic modeling of hemoglobin glycation and red blood cell kinetics enables personalized diabetes monitoring. *Sci Transl Med* 2016;8:359ra130.

BRIEF REPORT

Atypical Transient Symptoms Require Aggressive Investigation for Cause

By Matthew Fink, MD

Professor and Chairman, Department of Neurology, Weill Cornell Medical College; Neurologist-in-Chief, New York Presbyterian Hospital

Dr. Fink reports he is a consultant for Procter & Gamble.

SOURCE: Lavallee PC, Sissani L, Labreuche J, et al. Clinical significance of isolated atypical transient symptoms in a cohort with transient ischemic attack. *Stroke* 2017;48:1495-1500. doi: 10.1161/STROKEAHA.117.016743.

Atypical transient symptoms, such as partial sensory deficit, dysarthria, vertigo and unsteadiness, unusual visual deficits, and diplopia, usually are not classified as transient ischemic attacks, and they frequently are not investigated in the same fashion. Investigators undertook detailed evaluation of these patients admitted to their TIA clinic from 2003 until 2008, and investigated them with systematic brain, arterial, and cardiac investigations. They compared the prevalence of recent brain infarction on imaging, as well as evidence of intracranial or extracranial atherosclerosis, cervical artery dissection, or a source of cardiac embolism. They then quantified the one-year risk of major vascular events in patients who had isolated typical or atypical transient symptoms.

Among 1,850 patients with possible ischemic diagnoses, 43% had isolated transient symptoms, with 34% being typical TIAs and 9.6% being atypical. The presence of brain infarction on imaging was similar in both groups of patients. One-year risk of recurrent major vascular events was not significantly different between patients who had typical TIA symptoms or atypical isolated or non-isolated symptoms. Therefore, these patients should be investigated intensively in a manner similar to patients with classical TIA symptoms. ■

PHARMACOLOGY UPDATE

Delafloxacin Tablets (Baxdela)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco. Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved a new fluoroquinolone for the treatment of skin and skin structure infections. Delafloxacin is a broad-spectrum agent with activity against gram-positive and gram-

negative organisms. The FDA granted delafloxacin priority review because of the drug's designation as a Qualified Infectious Disease Product. It is marketed as Baxdela.

INDICATIONS

Delafloxacin is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible organisms.[1] Gram-positive organisms include *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates), *Staphylococcus haemolyticus*, *Staphylococcus lugdunensis*, *Streptococcus agalactiae*, the *Streptococcus anginosus* group (including *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*), *Streptococcus pyogenes*, and *Enterococcus faecalis*. Gram-negative organisms include *Escherichia coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.

DOSAGE

The recommended dose is one tablet (450 mg) orally or 300 mg by IV infusion every 12 hours for five to 14 days. Clinicians can switch patients from a 300 mg IV dose to a 450 mg oral dose to complete the treatment course. The tablets may be taken without regard to meals. Delafloxacin is available as 300 mg in a single dose vial and 450 mg tablets.

POTENTIAL ADVANTAGES

The physicochemical properties of delafloxacin enhances its ability to penetrate bacterial cells and enhance activity in acidic pH, such as cutaneous infections.[2] Delafloxacin offers IV and oral dosing flexibility with interchangeability of the two dosage forms.

POTENTIAL DISADVANTAGES

Delafloxacin carries the fluoroquinolone class box warning for tendinitis and tendon rupture, peripheral neuropathy, central nervous system effects, and exacerbation of muscle weakness in patients with myasthenia gravis.[1] The most frequent adverse reactions are nausea (8%) and diarrhea (8%).

COMMENTS

The safety and efficacy of delafloxacin were evaluated in two double-blind, double-dummy, noninferiority studies in subjects with ABSSSI.[1] This condition includes cellulitis, wound infections, burn infections, and major cutaneous abscesses. The overall mean surface area of the infected lesion was 307 cm^2 to 353 cm^2. In study 1, subjects were randomized to delafloxacin 300 mg via IV infusion every 12 hours (n = 331) or vancomycin (15 mg/kg) and aztreonam (n = 329). In study 2, subjects received six doses of IV delafloxacin and were then switched to oral 450 mg (n = 423) or vancomycin/aztreonam (n = 427). Clinical response was defined as a ≥ 20% decrease in lesion size at 48-72 hours. Investigator assessment of treatment success also was made at follow-up day 14. Success was defined as "cure + improved," whereby subjects had complete or near resolution of signs and symptoms with no further antibacterial needed.

Response rates at 48-72 hours were 78.2% for delafloxacin, compared to 80.9% for vancomycin/aztreonam in study 1, and 83.7% and 80.6%, respectively, for study 2. Success rates at follow-up were 81.6% for delafloxacin and 83.3% for vancomycin/aztreonam in study 1, and 87.2% compared to 84.8%, respectively, for study 2. These met the FDA criteria for noninferiority (10% margin).[3] The most common baseline pathogen was *S. aureus* (319 isolates) with MRSA, representing 144 isolates. Clinical response and success at follow-up were similar for delafloxacin and comparator vancomycin for these organisms.

CLINICAL IMPLICATIONS

The FDA defines the disease manifestation of ABSSSI as cellulitis/erysipelas, wound infections, and major cutaneous abscesses.[4] It does not include less serious conditions such as impetigo or more complicated conditions such as chronic wound infections. The most common pathogens are *S. pyogenes* and *S. aureus* including MRSA. This classification does not exactly correspond to practice guidelines developed by the Infectious Diseases Society of America (IDSA), which divided skin and skin structure infections into non-purulent and purulent, with cellulitis and erysipelas falling in the former, and abscesses falling in the latter.[4,5] For severe purulent infections, the IDSA lists vancomycin, linezolid, tigecycline, daptomycin, ceftaroline, and telavancin as drugs of choice. Two single-dose IV glycopeptide regimens (dalbavancin and oritavancin) have been approved since the guidelines were published. In the two clinical trials, delafloxacin was found to be noninferior to vancomycin, thus, providing another therapeutic option. Because of the limited clinical experience and the availability of numerous options, the role for delafloxacin remains to be determined. Delafloxacin is under evaluation in comparison to moxifloxacin in community-acquired pneumonia.[6] The cost for delafloxacin was not available at the time of this review. ■

REFERENCES

1. Baxdela Prescribing Information. Melinta Therapeutics. June 2017.
2. Van Bambeke F. Renaissance of antibiotics against difficult infections: Focus on oritavancin and new ketolides and quinolones. *Ann Med* 2014;46:512-529.
3. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry. Acute Bacterial Skin

and Skin Structure Infections: Developing Drugs for Treatment. Available at: http://bit.ly/2tDArfU. Accessed July 24, 2017.
4. Russo A, Concia E, Cristini F, et al. Current and future trends in antibiotic therapy of acute bacterial skin and skin-structure infections. *Clin Microbiol Infect* 2016;22(Suppl 2):S27-36. doi: 10.1016/S1198-743X(16)30095-7.
5. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2014;59:147-159.
6. ClinicalTrials.gov. Study to Compare Delafloxacin to Moxifloxacin for the Treatment of Adults With Community-acquired Bacterial Pneumonia (DEFINE-CABP). Available at: http://bit.ly/2tucrI2. Accessed July 24, 2017.

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CME QUESTIONS

1. **Which of the following long-term approaches to treating gastroesophageal reflux disease is the safest?**
   a. Omeprazole
   b. Ranitidine
   c. Famotidine
   d. A diet low in Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols.

2. **Based on the results of study by Bergenstal et al, which of the following statements is true?**
   a. A1c overestimates mean blood glucose in black patients compared to white patients.
   b. A1c overestimates mean blood glucose in white patients compared to black patients.
   c. Glycated albumin overestimates mean blood glucose in black patients compared to white patients.
   d. Glycated albumin overestimates mean blood glucose in white patients compared to black patients.

CME OBJECTIVES

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

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

[IN FUTURE ISSUES]

B-type Natriuretic Peptide Is Less Useful in Elderly Patients with Dyspnea

Dual Antibiotic Therapy Is Not Routinely Necessary for Uncomplicated Cellulitis

Omega-3 Polyunsaturated Fatty Acid Supplementation and Cognitive Decline

Clinical Briefs

By Louis Kuritzky, MD

NSAID-associated Recurrent Gastrointestinal Bleeding

SOURCE: Chan FKL, Ching JYL, Tse YK, et al. *Lancet* 2017;389:2375-2382.

Gastrointestinal bleeding (upper and/or lower) is a well-recognized adverse effect of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs). The COX-2 inhibitors (e.g., celecoxib) were offered to clinicians as an alternative to "non-selective" COX inhibitors (NSAIDs such as ibuprofen, diclofenac, naproxen, and many others). The putative advantage of celecoxib was an anticipated reduced risk of gastrointestinal bleeding, since relatively less COX-1 (the enzyme necessary to maintain gastric mucosal protection integrity) inhibition was occurring than with "traditional" non-selective NSAIDs. While the CLASS trial corroborated that during a six-month period, celecoxib incurred fewer serious bleeding events than non-selective NSAID therapy. This trial drew criticism later after an analysis of the study data at one year showed no meaningful differences between treatment arms.

Patients who have experienced a gastrointestinal bleed on NSAIDs are at particularly high risk to bleed again. Additionally, concern about cardiovascular risks associated with NSAIDs becomes problematic for our vasculopathic patients (post-stroke, myocardial infarction, stenting, etc.) who require antiplatelet treatment (e.g., clopidogrel, aspirin). Nonetheless, many such patients require both antiplatelet and NSAID treatment concomitantly. Chan et al reported on their double-blind study of *Helicobacter*-negative subjects (n = 514) randomized to celecoxib or naproxen, all of whom had experienced and resolved an episode of upper gastrointestinal bleeding. Because of prior cardiovascular events, all subjects also were taking 80 mg of aspirin per day. At 18 months, there was a clear advantage to the celecoxib/aspirin group vs. naproxen/aspirin: 5.6% cumulative bleeding events for the former vs. 12.3% for the latter. Persons who have experienced an NSAID-related upper gastrointestinal bleed would be better served by taking celecoxib than naproxen if continuation of NSAID treatment is required. ■

Rheumatoid Arthritis Disease Activity and Calprotectin Levels

SOURCE: Bae SC, Lee YH. *Postgrad Med* 2017;129:531-537.

Clinicians who see patients with inflammatory bowel disease (IBD), such as Crohn's disease or ulcerative colitis, likely will be familiar with using fecal calprotectin levels as a diagnostic tool. Indeed, some experience suggests that because of "skip areas" observed in IBD, fecal calprotectin may be as or even more sensitive to diagnose IBD than endoscopy. Calprotectin also is measurable in plasma and synovial fluid, and has been recognized recently as a good marker of disease activity in rheumatoid arthritis (RA).

There are several validated metrics for assessment of disease activity in RA, including C-reactive protein (CRP) and Disease Activity in 28 Joints (DAS28). Bae and Lee performed a meta-analysis of RA patients (n = 849) to evaluate the correlation of calprotectin with CRP and DAS28. Significant positive correlations were demonstrated. Common treatment for RA patients includes biologic agents such as TNF-inhibitors. Calprotectin levels have been demonstrated to be good indicators of disease activity in patients on TNF treatment. Hence, calprotectin may provide a metric for confirmation of optimized control of RA, providing additional insight into disease activity beyond clinical symptoms alone. ■

Identification of Pneumococcal Pneumonia

SOURCE: Ceccato A, Torres A, Cilloniz C, et al. *Chest* 2017;151:1311-1319.

In approximately half of the cases of community-acquired pneumonia (CAP), an etiologic agent is not identified. CAP caused by *Streptococcus pneumoniae* (pneumococcal pneumonia) often is categorized as "invasive" (the bacteria was cultured from body fluids such as blood or pleural fluid) vs. "noninvasive" (body fluid cultures were negative, but urine antigen testing for *S. pneumoniae* was positive). Curiously, only pneumonia confirmed by invasive methodology has been incorporated into epidemiologic reporting of CAP traditionally. Cecatto et al noted that clinicians probably are significantly underestimating the burden of CAP by limiting the "gold standard" definition to cases identified "invasively."

The authors studied all cases of CAP (n = 5,132) in non-immunocompromised adults treated at their Barcelona, Spain, emergency department over a 14-year interval. Of these, only 15% were confirmed to be pneumococcal. Slightly more patients were confirmed to be infected by *S. pneumoniae* through urinary antigen testing (54%) than by body fluid cultures (46%). Additionally, the 30-day mortality was the same regardless of which tool confirmed the diagnosis, dispelling the notion that CAP diagnosed though the "invasive" path is more lethal. Both methods of diagnosis are valid indicators of the pathogen, but there is no reason to consider urine antigen positivity as indicative of less pneumonia lethality. ■

Internal Medicine [ALERT]

ECG Review

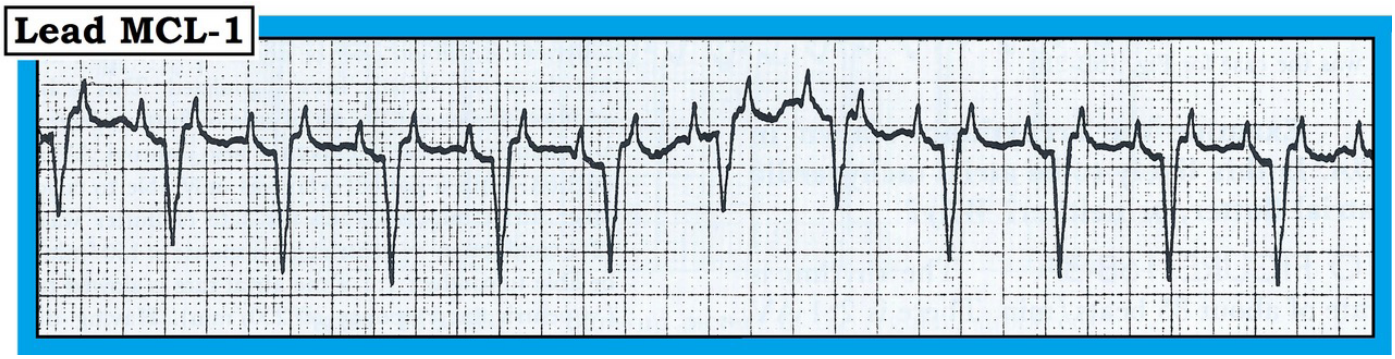
By Ken Grauer, MD

Professor Emeritus in Family Medicine, College of Medicine, University of Florida

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

Atrial Flutter or Atrial Tachycardia?

How would you interpret the rhythm in the figure below? What is your differential diagnosis? Can you be sure of your answer from looking at this lead MCL-1 rhythm strip? Why is it important to know if the patient is on digoxin?



The rhythm in the figure is regular, with a ventricular rate of ~115/minute. P waves outnumber QRS complexes by two to one, making the atrial rate ~230/minute. The QRS complex is narrow, implying a supraventricular mechanism, and each QRS complex is preceded by a P wave with a constant PR interval. Thus, P waves are related to the QRS complexes, albeit only one of every two P waves conducts to the ventricles. Therefore, this is a supraventricular tachycardia (SVT) rhythm with 2:1 AV conduction. The differential diagnosis is between atrial flutter and atrial tachycardia.

In favor of atrial flutter: Regular and rapid atrial activity with a peaked upward deflection in this right-sided MCL-1 monitoring lead. That said, the atrial rate of 230/minute is a bit below the usual atrial rate range for untreated atrial flutter (of 250-350/minute), and the expected "sawtooth" pattern of atrial flutter is missing in this lead.

In favor of atrial tachycardia: The atrial rate (below 250/minute) and the isoelectric baseline (rather than sawtooth) in this lead.

We do not know if this patient is taking an antiarrhythmic agent (such as flecainide, amiodarone, sotalol, etc.) that might slow the atrial rate of flutter. We do not know if this patient is taking digoxin. This is important because SVT with 2:1 conduction in a patient taking digoxin strongly suggests digitalis toxicity. Despite the greatly reduced use of this drug at the current time (atrial tachycardia with block because of digitalis toxicity is no longer seen commonly), it remains, nevertheless, important to inquire about this medication since it is still prescribed occasionally.

It is impossible to be certain of the rhythm diagnosis solely from the rhythm strip seen in the figure without the benefit of additional information (i.e., previous clinical history, knowing what medications the patient is taking). Seeing a full 12-lead ECG might help by revealing a typical sawtooth pattern in other leads. That said, the clinical reality is that neither rate nor baseline appearance (sawtooth vs. isoelectric baseline) have been shown to reliably distinguish between atrial tachycardia and atrial flutter. Fortunately, from a non-cardiologist's perspective, both initial and long-term management of these two SVT rhythms is similar (once you have ruled out the possibility of digitalis toxicity). Initial efforts entail slowing the ventricular response, with consideration of electrophysiology referral if the arrhythmia is persistent or recurs.

For further discussion of this case, please visit: http://bit.ly/2tFJxnE.