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

ABSTRACT & COMMENTARY

Honey, Can You Stop Coughing?

By Martin S. Lipsky, MD

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

SYNOPSIS: In a meta-analysis, researchers found honey alleviates cough for patients with upper respiratory infections.

SOURCE: Abuelgasim H, Albury C, Lee J. Effectiveness of honey for symptomatic relief in upper respiratory tract infections: A systematic review and meta-analysis. *BMJ Evid Based Med* 2020; Aug 18;bmjebm-2020-111336. doi: 10.1136/bmjebm-2020-111336. [Online ahead of print].

Upper respiratory infections (URIs) are among the most common reasons for patients to visit their primary care providers. Despite evidence indicating antibiotics are ineffective, URIs also are the most common reason for physicians to prescribe an antibiotic.[1] Unnecessary antibiotics expose patients to side effects and drive up both costs and antimicrobial resistance.[2] A lack of effective alternatives may be one driving force behind these unnecessary prescriptions.

One possible alternative is honey. Long considered a "home remedy," Abuelgasim et al systematically reviewed the literature for evidence related to the use of honey and its effectiveness for URI symptoms. They identified 14 randomized, clinical trials or in-vivo observational studies that compared honey of any type or administered in any way (either alone or in conjunction with other treatments) to at least one other group (either no treatment, placebo, or usual therapy) for treating URI symptoms. They found that compared with usual care, honey improved combined symptom scores (three studies, mean difference, -3.96; 95% CI, -5.42 to -2.51; I^2 = 0%), cough frequency (eight studies, standardized mean difference [SMD], -0.36; 95% CI, -0.50 to -0.21; I^2 = 0%), and cough severity (five studies, SMD, -0.44; 95% CI, -0.64 to -0.25; I^2 = 20%).

They concluded honey was superior to usual care for the improvement of symptoms of URIs, but recommended further high-quality, placebo-controlled trials to confirm and assess the level of benefit.

■ COMMENTARY

Although personal anecdote and testimony is at the bottom of the evidence-based food chain, hot tea with honey is my personal go-to remedy when I have the

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"sniffles." This study adds credibility to my belief in honey. Known for its antibacterial properties, the lay media touts several health benefits related to honey.[3,4] This meta-analysis provides modest evidence supporting the use of honey to reduce the incidence of URI symptoms, especially for cough. One head-to-head study also revealed honey proved superior to dextromethorphan and diphenhydramine.[5]

How honey might work remains uncertain. In addition to its antimicrobial activity, it also seems to produce some antioxidant and antiviral activity.[6,7] Eccles proposed honey's natural sweetness causes reflex salivation and an increase in airway mucus, which might sooth the pharynx and larynx mucosa, thereby alleviating cough.[8] He also suggested that closely related sensory nerve fibers that initiate cough and the gustatory nerve fibers that taste sweetness may produce the antitussive effects of sweet substances via a central nervous system mechanism.

Since there is little to offer those with URIs, honey represents a low-risk, inexpensive, and easily accessible alternative that seems reasonable to suggest to patients. Adding that honey is a natural remedy also may appeal to many patients. Not only may honey offer some benefit, it might reduce the use of unnecessary antibiotics. Two caveats: First, avoid giving honey to those younger than age 1 year because of the risk of infant botulism.[9] Second, remember that honey largely is sugar, and that each teaspoon of honey contains about 15 calories. ■

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ABSTRACT & COMMENTARY

Vegan Diets May Cause More Fractures

By Joseph E. Scherger, MD, MPH

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

SYNOPSIS: In a large, prospective study of men and women in the United Kingdom, those following a vegan diet sustained more total and hip fractures than those eating animal products.

SOURCE: Tong TYN, Appleby PN, Armstrong MEG, et al. Vegetarian and vegan diets and the risks of total and site-specific fractures: Results from the prospective EPIC-Oxford study. *BMC Med* 2020;18:353.

Tong et al analyzed the data of men and women in the United Kingdom that were collected at baseline (between 1993 and 2001) and at follow-up (around 2010) as part of the EPIC-Oxford study. The information gathered concerned

participants' dietary habits. The authors identified four groups based on their diets: 29,380 meat eaters (full omnivore diet), 8,807 fish eaters (no meat intake), 15,499 vegetarians (ate one or both of eggs or dairy), and 1,982 vegans (plant foods only). Adjustments were made for socioeconomic, body mass index, and other lifestyle factors.

Meat eaters exhibited the lowest risk for hip fractures, with some increased risk for fish eaters (hazard ratio, 1.26) and vegetarians (hazard ratio, 1.25). Vegans were much more likely to sustain hip fractures (hazard ratio, 2.31) vs. meat eaters. Vegans also were at higher risks for total and other site fractures vs. meat eaters.

■ COMMENTARY

Advocates for exclusive plant-based diets are quite vocal. They cite studies showing how eating only plants results in lower cancer rates and all-cause mortality.[1,2] The American College of Lifestyle Medicine strongly advocates for plant-based diets among its leaders.[3] Many vegans and vegetarians believe eating animal products is unhealthy, even immoral, and bad for the environment.

Evolutionary biologists note *Homo sapiens* survived through omnivorous habits, and that our large brains and intestinal tracts reflect eating animal foods.[4,5] Studies have shown vegetarians exhibit lower bone mineral density than nonvegetarians.[6] Vegan diet adherents intake less calcium and protein,[7] and vegans often record a lower body mass index.[8] One author who lived for 20 years as a staunch vegan shared details about the musculoskeletal complications she suffered as a result of eating only plant foods.[9]

Living as a vegan or vegetarian is a choice and can benefit one's health. However, clinicians should educate patients about potential risks, including bone fractures. Appropriate supplementation might prevent these complications. ■

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ABSTRACT & COMMENTARY

Virtual Visits and Antibiotic Prescribing

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: Compared to in-person visits, virtual visits were associated with improved antibiotic prescribing practices for women with uncomplicated urinary tract infections.

SOURCE: Johnson KL, Dumkow LE, Salvati LA, et al. Comparison of diagnosis and prescribing practices between virtual visits and office visits for adults diagnosed with uncomplicated urinary tract infections within a primary care network. *Infect Control Hosp Epidemiol* 2020; Oct 29:1-6. doi: 10.1017/ice.2020.1255. [Online ahead of print].

Johnson et al retrospectively examined the appropriateness of outpatient treatment of uncomplicated urinary tract infections in women ages 18-65 years who were encountered either via virtual or actual visits between Jan. 1 and Dec. 31, 2018. After screening of records, the authors selected 350 cases (175 in each group) using a random number generator.

Virtual visits to providers in this large primary care practice health system start with a patient entering information into an existing system. On electronic notification, the provider examines the information, including patient answers to a questionnaire, makes a diagnosis, and selects a treatment plan from a drop-down menu with antibiotic (dose and duration) and supportive care choices based on national recommendations. Antibiotics were prescribed during 100% and 96.6% of virtual and in-person visits, respectively. Guideline-concordant antibiotic selection occurred significantly more frequently during virtual

visits: 74.9% vs. 59.4% ($P = 0.002$). Nitrofurantoin was the most frequently prescribed antibiotic in both groups. The prescribed duration of antibiotic therapy was more likely to be guideline-concordant for virtual visits (100% vs. 53.1%; $P < 0.001$).

A urinalysis was ordered during 97.1% of office visits and 0% of virtual visits, while urine cultures were ordered during 73.1% and 0%, respectively. The bacteria isolated in culture from the office visitors was susceptible to nitrofurantoin 94.8% of the time in those given this drug but was susceptible to the alternative agents administered to the others only 76.3% of the time ($P = 0.011$). An unplanned interval revisit in the following seven days occurred more frequently in those with an initial office visit: 18.9% vs. 5.1%; $P < 0.001$.

■ COMMENTARY

Progress has been made in the implementation of effective antimicrobial stewardship in the outpatient setting. This has resulted in more appropriate use of antibiotics during in-person patient visits. However, there has been a significant shift from in-person to virtual patient visits. Although the shift was, to some extent, already occurring, the emergence of the COVID-19 pandemic and the CMS waiver of its previously existing payment limitations has shifted telemedicine into high gear. Although the CMS waiver is planned to only be temporary, it seems clear that telemedicine will continue to be a significant part of clinical practice. This raises the question of whether and how to implement antimicrobial stewardship practice into the management of patients during virtual visits. Johnson et al have provided useful information in this regard.

These same investigators previously performed a similar study in adults with acute sinusitis and found that virtual visits were associated with a significantly greater likelihood of guideline-concordant diagnoses as well as a significant decrease in antibiotic prescriptions.[1]

The improved adherence to antibiotic prescribing guidelines during virtual visits may be the result of a number of factors, perhaps most importantly the use of a drop-down menu giving recommendations. Regarding the results in patients with sinusitis, it could easier for the provider to say "no" to a remote patient's request for an antibiotic prescription than it is to say "no" to a patient in person. At any rate, it would appear telemedicine may prove to be an important element in the armamentarium of antimicrobial stewardship programs. ■

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ABSTRACT & COMMENTARY

Using Sacubitril/Valsartan to Treat Heart Failure with Preserved Ejection Fraction

By Jamie L. W. Kennedy, MD, FACC

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

SYNOPSIS: An analysis of renal outcomes in the PARAGON-HF trial revealed sacubitril/valsartan slows progression of kidney disease in patients with heart failure with preserved ejection fraction compared to valsartan alone.

SOURCE: McCausland FR, Lefkowitz MP, Claggett B, et al. Angiotensin-neprilysin inhibition and renal outcomes in heart failure with preserved ejection fraction. *Circulation* 2020;142:1236-1245.

Heart failure with preserved ejection fraction (HFpEF) is common, accounting for half of heart failure diagnoses. However, evidence-based treatment options remain elusive — and not for lack of effort. Historically, HFpEF was understood to be the result of left ventricular hypertrophy and fibrosis caused by long-standing hypertension, diabetes, and (often) coronary disease. But, increasingly, the contribution of endovascular dysfunction has been recognized. Furthermore, diseases such as cardiac amyloidosis and variant forms of hypertrophic cardiomyopathy are diagnosed more often. It is likely that unintentional inclusion of these patients in early HFpEF trials blunted the effect of potentially efficacious therapies.

Neprilysin inhibitors increase the concentration of natriuretic peptides, which results in coronary vasodilation and inhibition of cardiomyocyte hypertrophy. Renal effects include higher glomerular filtration rate (eGFR), inhibition of sodium reabsorption, and suppression of

renin and aldosterone. Preliminary studies revealed the combination of sacubitril/valsartan lowered NT-proBNP, shrank left atrial size, and improved New York Heart Association (NYHA) functional class compared to valsartan alone, prompting the PARAGON-HF study.

The PARAGON-HF study authors enrolled 4,822 patients with left ventricular ejection fraction (LVEF) 45% or higher. Patients presented with stable NYHA class II-IV symptoms requiring treatment with diuretics, age ≥ 50 years, left atrial enlargement or left ventricular hypertrophy, and elevated NT-proBNP on a sliding scale based on sinus rhythm vs. atrial fibrillation and recent heart failure hospitalization. Patients with hypotension (systolic blood pressure < 110 mmHg), severe chronic kidney disease (eGFR < 30 mL/min/1.73 m^2), or hyperkalemia (> 5.2) at baseline were excluded.

Patients with potential alternative explanations for functional limitations, such as severe pulmonary disease, anemia (hemoglobin < 10 g/dL), or morbid obesity, were excluded. Patients with a history of reduced ejection fraction (< 40%), congenital heart disease, constrictive pericarditis, or significant valvular heart disease were excluded, as were patients with known infiltrative, genetic, hypertrophic, peripartum, viral, or chemotherapy-induced cardiomyopathies. Patients were randomized to either valsartan (target dose = 160 mg twice daily) or sacubitril/valsartan (target dose = 97/103 mg twice daily) after a run-in period to ensure tolerance of both agents.

Patients were, on average, age 72.8 years, and 51.7% were women. Most were NYHA class II (77%) or III (19%). Race was predominantly white (81.5%), followed by Asian (12.7%) and Black (2.2%). Most enrolled patients lived in Central or Western Europe, followed by Asia-Pacific, North America, and Latin America. The baseline BMI was 30 kg/m^2, the eGFR was measured as 63 mL/min/1.73m^2, systolic blood pressure was measured as 130 mmHg, LVEF was 58%, and NT-proBNP was 910 pg/mL. Most patients were hypertensive (95%), half had been hospitalized for heart failure, 43% were diabetic, 37% were living with coronary disease, and one-third exhibited atrial fibrillation or flutter.

The median duration of follow-up was 35 months. The primary outcome was a composite of heart failure hospitalizations and cardiovascular death. Overall, the rate of the primary outcome was 12.8 per 100 patient-years in the sacubitril/valsartan group and 14.6 per 100 patient-years in the valsartan group (rate ratio, 0.87; 95% CI, 0.75-1.01). Interestingly, a subgroup analysis suggested women benefited from sacubitril/valsartan (rate ratio, 0.73; 95% CI, 0.59-0.90) while men did not (rate ratio, 1.03; 95% CI, 0.85-1.25). Other secondary analyses revealed more patients in the sacubitril/valsartan arm demonstrated improved quality of life and NYHA class.

McCausland et al more completely analyzed the effect on renal function. There was a prespecified composite secondary renal endpoint: 50% or greater decline in eGFR from baseline, the development of end-stage renal disease, or death from kidney disease. Additional analyses concerned the rate of decline in renal function over time. At baseline, the average eGFR measurement was 63 ± 19 mL/min/1.73m^2. The composite renal outcome occurred in 1.4% of the sacubitril/valsartan group vs. 2.7% of the valsartan group (HR, 0.50; P = 0.001). This outcome was driven primarily by the reduction in eGFR component: 1.1% of sacubitril/valsartan patients vs. 2.5% of valsartan patients (HR, 0.44; 95% CI, 0.28-0.69). There was no statistical difference in the rate of progression to end-stage renal disease or death from renal causes.

In a time-based analysis, the eGFR measurement declined 2 mL/min/1.73m^2 annually in the sacubitril/valsartan group compared to 2.7 mL/min/1.73m^2 in the valsartan group (P < 0.001). When the outcomes were analyzed by baseline renal function, there was no significant difference. The authors concluded sacubitril/valsartan slows progression of kidney disease in patients with HFpEF.

■ COMMENTARY

PARAGON-HF was a negative trial, although several intriguing findings may lead to positive trials in the future. Chronic kidney disease complicates half of heart failure; thus, preventing progressive renal dysfunction is an important goal.

The series of disappointing HFpEF trials continues with the recent publication of VITALITY-HFpEF (vericiguat) and CAPACITY HFpEF (praliciguat).[1,2] The results of PARAGON-HF suggests treatment with sacubitril/valsartan slows progression of renal disease in patients with HFpEF compared to valsartan, in addition to the suggestion of benefit in women, improvement in NYHA class, and quality of life.

A wise friend asked me if SGLT2 inhibitors are efficacious in systolic heart failure because we all are prediabetic. He might be on to something. I am disappointed McCausland et al did not break down outcomes by presence or absence of diabetes. I also am disappointed the authors did not assess proteinuria. Trials of SGLT2 inhibitors dapagliflozin and empagliflozin in patients with HFpEF are in progress. I suspect they will demonstrate clear benefit. For now, clinicians should consider substituting sacubitril/valsartan for ACE or ARB in HFpEF patients in whom borderline renal function is present. ■

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PHARMACOLOGY UPDATE

Remdesivir Injection and Baricitinib Tablets

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

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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 issued another emergency use authorization (EUA) for a new COVID-19 treatment. The EUA was issued for baricitinib in combination with remdesivir for treating hospitalized COVID-19 patients who require supplemental oxygen.[1] Baricitinib (Olumiant) is a kinase inhibitor that targets the intracellular signaling pathway of cytokines. It was approved in 2018 for moderate to severe active rheumatoid arthritis. Remdesivir is an antiviral agent that was approved in October 2020.

INDICATIONS

Baricitinib/remdesivir should be used to treat suspected or laboratory-confirmed COVID-19 in hospitalized adults and pediatric patients ≥ age 2 years who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[1,2]

DOSAGE

The recommended dose for baricitinib in adults and pediatric patients (≥ age 9 years) is 4 mg orally once daily for 14 days of total treatment or until hospital discharge, whichever happens first.[2] The dose for pediatric patients (age 2 to 9 years) is 2 mg. For patients who cannot swallow an oral medication, baricitinib can be given as an oral dispersion, by gastrostomy tube, or nasogastric tube. The dose can be adjusted for reduced renal function and interrupted because of low absolute lymphocytic count, absolute neutrophil count, or elevated liver aminotransferases. Because of a drug-drug interaction with organic anion transporter 3 inhibitors (i.e., probenecid), the dose of baricitinib should be lowered. Remdesivir is administered by intravenous infusion for 10 days. Baricitinib is available as 1 mg and 2 mg tablets.

POTENTIAL ADVANTAGES

Baricitinib/remdesivir appeared to be more effective than remdesivir alone in shortening recovery time and improving clinical status in hospitalized COVID-19 patients who require supplemental oxygen.[2,4]

POTENTIAL DISADVANTAGES

Based on animal studies, baricitinib poses a potential embryo-fetal toxicity. Therefore, potential benefit must justify potential risk when used during pregnancy.[2] The combination is not recommended for patients on dialysis, those with end-stage renal disease, or those with acute renal injury.

COMMENTS

The rationale for coupling baricitinib with remdesivir is to modulate the dysregulated inflammatory response associated with COVID-19. The clinical evidence supporting the EUA was a randomized, double-blind, placebo-controlled trial sponsored by the National Institute of Allergy and Infectious Diseases (Adaptive COVID-19 Treatment Trial 2, ACTT-2).[2,4] Hospitalized subjects were COVID-19-positive and exhibited at least one of the following: radiographic evidence of infiltrates, SpO_2 ≤ 94% on room air, requirement for supplemental oxygen, or requirement for mechanical ventilation. Subjects were randomized to baricitinib/remdesivir (n = 515) or placebo plus remdesivir (n = 518). The primary efficacy endpoint was time to recovery within 29 days after randomization. Recovery was defined as: discharged with no limitation on activities, discharged with limitation and/or requiring home oxygen, or hospitalized but not requiring oxygen and no longer requiring medical care. A key secondary outcome was change in clinical status according to an 8-point ordinal scale on day 15 based mainly on need for hospitalization and need for oxygen.

The median times to recovery were seven days for baricitinib/remdesivir vs. eight days for remdesivir alone. This represented a 15% faster recovery (P = 0.047).[2] Patients on noninvasive ventilation or high-flow oxygen recovered after a median 10 days vs. 18 days for remdesivir alone.[4] Other findings associated with those randomized to baricitinib/remdesivir included: 26% more likely to have a better clinical status (P = 0.044) and lower risk of death or noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation by day 29 (23% vs. 28%; P = 0.039).[2] Mortality at day 29 was numerically lower for baricitinib/remdesivir (4.7% vs. 7.1%) but did not reach statistical significance. The adverse event (AE) profiles for baricitinib/remdesivir generally were similar to remdesivir alone, although

AEs leading to discontinuation of the study drug and serious AEs were less frequent with the combination (7% vs. 12%) and (15% vs. 20%).[2,4]

CLINICAL IMPLICATIONS

Baricitinib/remdesivir provides measurable benefit to certain hospitalized patients with COVID-19 who require supplemental oxygen, especially those receiving high-flow oxygen or noninvasive ventilation. Currently, there are no recommendations from the Infectious Diseases Society of America or the National Institutes of Health (NIH) for baricitinib/remdesivir.[5,6] Current NIH COVID-19 treatment guidelines recommend dexamethasone with or without remdesivir as options for patients hospitalized and requiring supplemental oxygen or oxygen delivery through a high-flow device or noninvasive ventilation, and dexamethasone alone for patients requiring invasive mechanical ventilation or ECMO.[6] Dexamethasone has been reported to reduce 28-day mortality among patients receiving either invasive mechanical ventilation or oxygen alone (29.3% vs. 41.4%).[7] Baricitinib/remdesivir provides another therapeutic option in this COVID-19 population. ■

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CME QUESTIONS

1. **Which possible benefit of honey has the most compelling evidence?**
   a. It alleviates congestion.
   b. It alleviates cough.
   c. It lowers the risk of secondary sinus infections.
   d. It limits fever.

2. **Which diet results in the lowest bone density?**
   a. Eating meat, fish, and all plant foods
   b. Eating fish and plant foods, but no meat
   c. Eating plant foods and eggs
   d. Eating only plant foods

3. **Sacubitril/valsartan compared to valsartan alone in patients with heart failure and preserved ejection fraction showed significant beneficial effects in:**
   a. heart failure hospitalization.
   b. cardiac death.
   c. progression of renal disease.
   d. men.

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.

Internal Medicine [ALERT]

ECG Review

By Ken Grauer, MD

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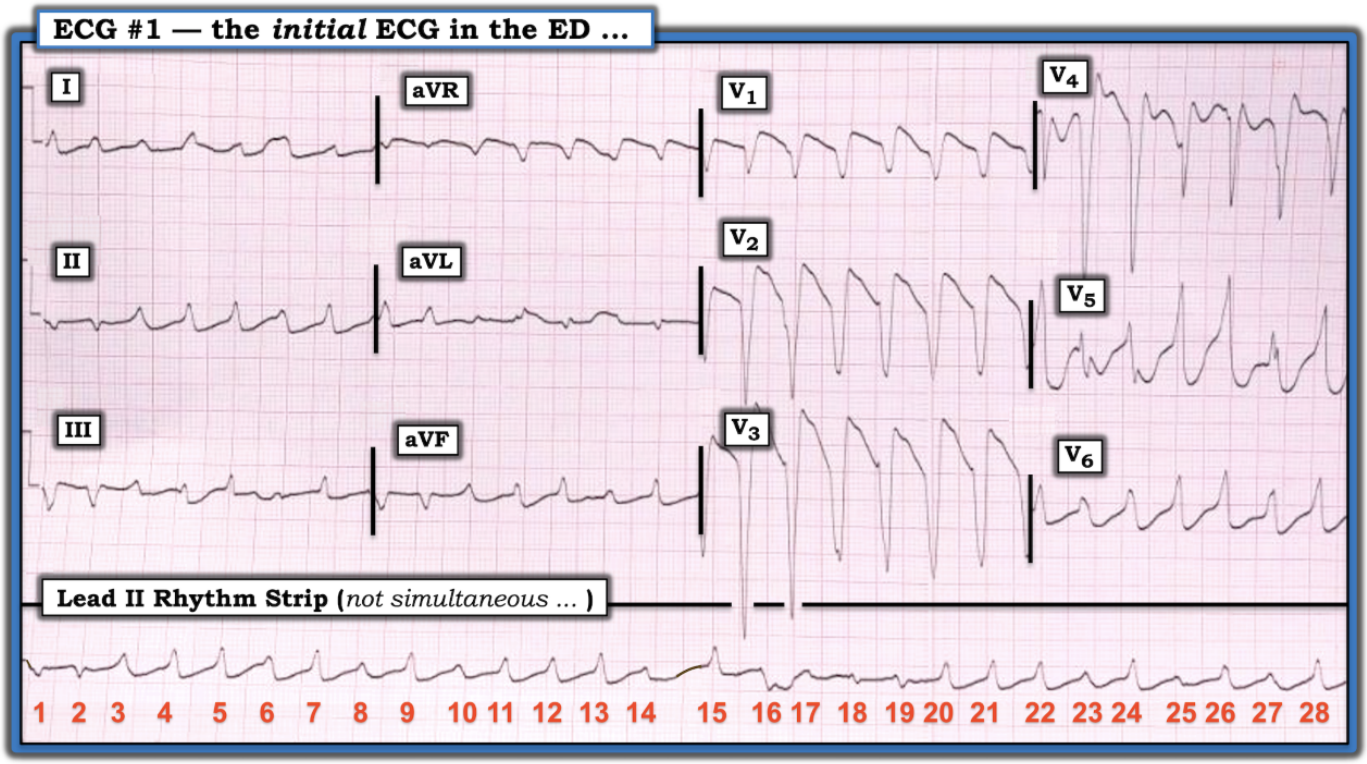
Dr. Grauer reports no financial relationships relevant to this field of study.

Why Does This WCT Change Its Shape?

Imagine there was no history for the ECG shown in the figure below. How would one interpret this tracing?



My immediate impression on seeing the 12-lead ECG with simultaneously obtained long lead II rhythm strip is the rhythm is fast, irregular, and manifests changing QRS morphology. No sign of atrial activity is seen. I thought the differential diagnosis was either polymorphic ventricular tachycardia (PMVT) or rapid atrial fibrillation in a patient with Wolff-Parkinson-White (WPW) syndrome. Looking closer, I was surprised to find that other than for beats 15, 16, and 17, the R-R interval remained constant throughout the long lead II rhythm strip. This ruled out the possibility of atrial fibrillation in a patient with WPW.

I was left with the possibility that the rhythm must be some form of ventricular tachycardia (VT). The changing QRS morphology ruled out the possibility of the most common form of VT, which is monomorphic — there is a nearly identical QRS morphology for all VT beats. The other common form of VT is PMVT, in which QRS appearance and/or the frontal plane axis changes continually from one beat to the next throughout the tracing. In addition to constantly changing QRS morphology, PMVT is an irregular rhythm, which is not what we see for the rhythm in the figure. A lesser known form of VT is pleomorphic VT, in which the overall rhythm is fairly regular, and there are runs of VT of varying duration — QRS morphology is similar, punctuated by runs of VT showing different QRS morphologies. This is precisely what we see in the figure. For example, it appears the eight QRS complexes seen in simultaneously recorded leads V1, V2, and V3 are similar in morphology.

Pleomorphic VT is not common. Usually, it is seen in patients with severe underlying heart disease. It may be caused by either shifting conduction properties that alter the myocardial activation sequence or shifting VT circuit exit sites. The response to antiarrhythmic therapy often is poor, as is the prognosis. Unfortunately, the patient in this case did not respond to either antiarrhythmic therapy or multiple defibrillation attempts.

For more information about and further discussion of this case, please visit: https://bit.ly/2JJbVTs.