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ABSTRACT & COMMENTARY

Antibiotic Therapy: How Long Is Long Enough?

By Stan Deresinski, MD, FACP

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SYNOPSIS: The CDC and the American College of Physicians have provided advice on the best practice regarding the duration of antibiotic therapy for several common infections.

SOURCE: Lee RA, Centor RM, Humphrey LL, et al. Appropriate use of short-course antibiotics in common infections: Best practice advice from the American College of Physicians. *Ann Intern Med* 2021; Apr 6. doi: 10.7326/M20-7355. [Online ahead of print].

The CDC and the American College of Physicians have provided best practice advice addressing the duration of antibiotic therapy for several infections commonly encountered in primary care. These include acute bacterial exacerbations of COPD, community-acquired pneumonia, uncomplicated urinary tract infections, and non-purulent cellulitis. Their recommendations:

- Acute bacterial exacerbations of COPD: five days. The authors refer to this entity as acute bronchitis in adults with COPD and describe clinical signs of bacterial infection. These are listed as "increased sputum purulence in addition to increased dyspnea and/or increased sputum volume."
- Community-acquired pneumonia: five days. This recommendation refers to non-immunocompromised adults who achieve clinical stability and follows the Infectious Diseases Society of America/American Thoracic Society guideline.
- Uncomplicated bacterial cystitis in nonpregnant adult women: nitrofurantoin for five days, trimethoprim-sulfamethoxazole for three days, or fosfomycin as a single dose.
- Uncomplicated pyelonephritis in nonpregnant adults: depending on susceptibility test results, a fluoroquinolone for five to seven days, or trimethoprim-sulfamethoxazole for 14 days.
- Non-purulent cellulitis in all adults: an antibiotic active against streptococci for five to six days.

■ COMMENTARY

This best practice advisory is useful, but some of its recommendations are perhaps more conservative than necessary. One important example is illustrated by a

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recently published randomized trial that showed three days of antibiotic therapy was noninferior to eight days in hospitalized patients with moderately severe community-acquired pneumonia who achieved clinical stability after three days of therapy.[1] On the other hand, the recommendation for the FDA-approved use of fosfomycin as a single dose may be insufficient in women with uncomplicated lower urinary tract infection, as shown in a recent randomized trial demonstrating this to be significantly less effective than a five-day course of nitrofurantoin.[2]

This advisory serves as a good starting point in convincing clinicians to shorten unnecessarily prolonged durations of antibiotic therapy, thus reducing the selective pressure leading to the evolution of antimicrobial resistance. However, there is a long way to go. ■

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ABSTRACT & COMMENTARY

The Cost-Effectiveness of HPV Vaccination for Adults Age 30 to 45 Years

By Rebecca B. Perkins, MD, MSc

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SYNOPSIS: Researchers found extending the upper limit of HPV vaccination to age 30 to 45 years is not cost-effective.

SOURCE: Kim JJ, Simms KT, Killen J, et al. Human papillomavirus vaccination for adults aged 30 to 45 years in the United States: A cost-effectiveness analysis. *PLoS Med* 2021; Mar 11. doi.org/10.1371/journal.pmed.1003534.

Human papillomavirus (HPV) vaccination is considered a powerful tool for cancer prevention. Clinical trials and long-term population-level follow-up studies have demonstrated decreases in precancers and cancers.[1-3] However, these findings are based largely on HPV vaccination in adolescence, before exposure to oncogenic HPV types.

Recently, HPV vaccination received FDA approval for use in adults age 26 to 45 years, and the CDC Advisory Committee on Immunization Practices recommended shared decision-making in this age group.[4] The recommendation is based on study findings of a reduced composite endpoint for genital HPV disease among previously uninfected women, and notes vaccination is not routinely recommended for this age group because of a lack of anticipated population-level benefit.[4]

The study by Kim et al describes the findings of two microsimulation models of HPV infection. In these models, which have been validated previously against several population-level datasets, individuals can move between states of no infection, infection, precancer, and cancer. HPV-related diseases in the models included cervical, anal, oropharyngeal, vulvar, vaginal, and penile cancers, as well as genital warts. The models compared the cost effectiveness of HPV vaccination in women through age 26 years and in men through age 21 years with vaccination through ages 30, 35, 40, and 45 years. Over a wide range of model assumptions and sensitivity analysis, HPV vaccination at older ages was not cost-effective. Incremental cost-effectiveness ratios (ICERs) ranged from $315,700 to $440,600 per quality-adjusted life year (QALY) gained, which exceeds the commonly accepted

upper threshold of $200,000 per QALY. This supports current CDC recommendations not to routinely recommend HPV vaccination for this age group.

■ COMMENTARY

This study adds important evidence to help providers, patients, and policymakers decide when to discuss, accept, and reimburse HPV vaccination among patients age 27 to 45 years. The effectiveness of HPV vaccination at preventing precancer and cancers declines in older adolescence, with several studies demonstrating significant drops in effectiveness after age 18.[5,6] The people to most likely to benefit from HPV vaccination are those who have not been exposed to oncogenic HPV, and are likely to be exposed in the future. This applies broadly to adolescents who have not begun sexual activity. However, since most people acquire HPV within a few years of beginning intercourse, relatively few adults are in this category.[7-9]

Primary care clinicians discuss health maintenance with patients, including cancer screenings, flu vaccination, smoking cessation, and cardiovascular disease prevention.[10] The Kim et al study supports current guidelines (i.e., clinicians should not discuss HPV vaccination routinely with adult patients).[4] Guidance is limited regarding which patients may benefit from HPV vaccination as adults. The American College of Obstetricians and Gynecologists (ACOG) supports CDC recommendations against routine vaccination. ACOG notes women most likely to benefit from vaccination include younger women, those not in committed monogamous relationships, and those recently diagnosed with sexually transmitted infections.[11] One specific population that may benefit from HPV vaccination is patients who have been treated for cervical intraepithelial neoplasia, since data indicate post-treatment vaccination may be beneficial to prevent recurrence.[12,13] One meta-analysis showed a 64% reduction in recurrence of cervical intraepithelial neoplasia grade 2 or higher.[14] The creators of a randomized, controlled trial in the Netherlands are exploring this question, which should provide more definitive data on whether vaccination should be recommended routinely after precancer treatment.[15] ■

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ABSTRACT & COMMENTARY

Loneliness and Type 2 Diabetes Incidence

By Lindsey N. Clark, MD, and Nancy J. Selfridge, MD

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SYNOPSIS: Loneliness appears to be an independent risk factor for type 2 diabetes, although further research to identify the causal relationship between loneliness and type 2 diabetes development is needed.

SOURCE: Hackett RA, Hudson JL, Chilcot J. Loneliness and type 2 diabetes incidence: Findings from the English Longitudinal Study of Ageing. *Diabetologia* 2020;63:2329-2338.

Loneliness, or the perception of unmet social needs and dissatisfying social relationships, is a common experience. Forty percent of adults older than age 65 years report feelings of loneliness, and studies show loneliness tends to increase with advancing age.[1]

In addition to the feeling of a persistent negative emotional experience, loneliness appears to affect physical and mental health. Various studies have established loneliness can be a predictor for all-cause mortality and has been associated with chronic diseases, such as coronary heart disease, hypertension, metabolic syndrome, cognitive decline, and dementia.[1,2]

Despite the growing body of literature reporting the associations between loneliness and chronic inflammatory diseases, the relationship between loneliness and type 2 diabetes remains understudied, particularly examinations of loneliness as a potential risk factor for type 2 diabetes. With estimates showing 462 million individuals affected by type 2 diabetes globally, diabetes is ranked as the ninth leading cause of mortality.[3,4] At the same time, there is growing global concern over a "loneliness epidemic" that is infiltrating society. Studies have showed social networks and household size are shrinking, one-third of adults in the United States older than age 45 years have reported feeling lonely, and the prevalence of loneliness can be expected to increase as the population ages.[5] Additionally, given that loneliness has been linked to several risk factors for type 2 diabetes, such as aging, obesity, and metabolic syndrome, identifying the prospective association between loneliness and type 2 diabetes is of great importance.

Hackett et al used data from the English Longitudinal Study of Ageing (ELSA) to conduct a prospective, longitudinal, observational study focused on assessing loneliness as an independent risk factor for type 2 diabetes. Started in 2002, ELSA collects data on people older than age 50 years living in England with the goal of understanding all aspects of aging. Every two years, data are collected on the same set of ELSA participants. As of 2020, more than 18,000 individuals have participated in ELSA.[6] Participants were selected from the ELSA database, and the authors followed the same study design as ELSA by collecting questionnaire data from participants in "waves" occurring every two years.

Overall, there were eight waves of data collection spanning 15 years. Wave 1 data collection began in 2002-2003 to identify potential participants, with wave 2 (2004-2005) used to collect data on participant loneliness and diabetes diagnosis status at baseline, as well as covariate data on age, sex, ethnicity, smoking status, alcohol consumption, frequency of physical activity, body mass index (BMI), hypertension diagnosis, and household non-pension wealth (indicator of socioeconomic status.) Participants in wave 2 also completed a nurse visit during which covariate data were confirmed, blood pressure readings were taken, and HbA1c was measured. Participants who indicated a diagnosis of type 2 diabetes or who recorded an HbA1c in the diabetic range of ≥ 6.5% were excluded from the study. During the follow-up period of wave 3 (2006-2007) through wave 8 (2016-2017), self-reported information on participant incidence of type 2 diabetes was collected. Participants who provided a complete data set on loneliness in wave 2 and type 2 diabetes status in the follow-up period were included in the final analysis.

Loneliness, the primary predictor variable, was assessed using the University of California Los Angeles Loneliness Scale, a 20-item scale presenting various feelings of loneliness and isolation that participants could rate according to frequency.[6] Participants were given three numerical options for rating each item: 1 (hardly ever/never), 2 (some of the time), and 3 (often). Participant ratings were averaged, with higher values associated with greater loneliness. Cronbach's alpha of 0.82 was reported in the study sample. Secondary predictor variables included social isolation, living alone, and depressive symptoms. Social isolation was measured based on frequency of contact with children, family, and friends. Participants were given a social isolation score from 0-4, with higher scores indicating greater isolation. Living

alone was based on a self-reported yes/no question. Depressive symptoms were measured using an eight-item Centre for Epidemiological Studies Depression Scale, where participants could score 0-7, with scores ≥ 6 considered signs of severe depression.

Cox proportional hazards regression was used to test the association between loneliness and type 2 diabetes after controlling for age, sex, wealth, ethnicity, smoking, physical activity, alcohol consumption, BMI, hypertension, cardiovascular disease, and HbA1c. Loneliness was inserted as a continuous variable, where the hazard ratio (HR) and 95% confidence intervals (CI) represented a 1 U increase. The secondary analysis consisted of adding covariates and secondary predictor variables to the statistical model to test the independent effect of loneliness on diabetes incidence. Ultimately, five models were created, with covariate data added in Model 1, depression added in Model 2, living alone added in Model 3, and social isolation score indexes added in Model 4. Model 5 was the final model and included loneliness, all covariates, depression, living alone, and social isolation as type 2 diabetes predictors.

Results showed 8,780 participants identified as eligible at the conclusion of wave 2, with 4,112 participants providing a complete data set that could be used in the final analysis. In the follow-up period, 262 participants reported developing type 2 diabetes. Cox regression modeling showed loneliness to be a significant predictor of type 2 diabetes incidence (HR, 1.46; 95% CI, 1.15-1.84; $P = 0.027$) independent of covariates, including age, sex, ethnicity, wealth, smoking, physical activity, alcohol consumption, BMI, HbA1c, hypertension, and cardiovascular disease. Additionally, Model 2 through Model 4 showed loneliness as an independent predictor; depressive symptoms, living alone, and social isolation were not significant predictors of type 2 diabetes incidence. Model 5 (final results) also continued to show loneliness to be an independent predictor of type 2 diabetes (HR, 1.41; 95% CI, 1.04-1.90; $P = 0.027$). An additional analysis showed loneliness was associated with a greater likelihood of smoking and physical inactivity, and a reduced likelihood of regular alcohol consumption.

■ COMMENTARY

Hackett et al presented a first-of-its-kind study that prospectively examined loneliness as a risk factor for type 2 diabetes. To date, other researchers have conducted cross-sectional analyses demonstrating a relationship between loneliness and type 2 diabetes. However, these studies were limited in their ability to determine whether loneliness stimulates the development of type 2 diabetes or if type 2 diabetes onset and management lead to a strain on the quality of social relationships, ultimately resulting in loneliness.[7,8] Based on their work, Hackett et al concluded loneliness can be considered a predictor of type 2 diabetes independent of other social and mental health variables, such as depressive symptoms, living alone, and social isolation.

Potential limitations in the study design include selection bias and the inability to generalize findings to non-white populations (the authors noted the ELSA database, from which participants were selected, contains few ethnic minority participants). An analysis of the baseline covariate data of participants lost to follow-up showed poorer health, lower financial status, and higher rates of loneliness when compared to participants who completed the study. Thus, selection bias caused by non-random exclusion may have occurred.

Patients identified as experiencing loneliness may benefit from interventions that address improving the quality of social relationships and treating maladaptive thought processes. Literature reviews identify a key characteristic of loneliness as an individual's hypervigilance to perceived social threats and negative social information. Interventions focused on providing patients with therapy to recognize the internal cognitive biases caused by loneliness, along with tactics to improve perceptions of social interactions, may be more beneficial than interventions aimed at improving social skills or simply increasing opportunities for social interaction.[1,2]

Additionally, a recent study showed online cognitive behavioral therapy for individuals experiencing loneliness showed a decrease in loneliness and anxiety and an increase in quality of life, with benefits sustained at a two-year follow-up.[9] While further research is needed to determine the physiological mechanisms by which loneliness may lead to the development of type 2 diabetes, physicians now can consider loneliness as an independent risk factor for type 2 diabetes, adding to the knowledge of the effects of loneliness on the development of chronic inflammatory diseases. Hackett et al provide strong evidence for clinicians taking time to ask patients about their sense of social support, loneliness, and feelings of isolation, as well as considering referrals to psychologists for appropriate therapy to help alleviate loneliness. ■

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PHARMACOLOGY UPDATE

Dapagliflozin Tablets (Farxiga)

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.

The FDA has approved dapagliflozin tablets to treat adults with chronic kidney disease (CKD) at risk for disease progression. The drug is a sodium-glucose cotransporter-2 (SGLT2) inhibitor approved in 2014 to improve glycemic control in type 2 diabetes mellitus (T2DM). In April 2021, the FDA gave fast-track, breakthrough therapy, and priority review for the new indication. Dapagliflozin is marketed as Farxiga.

INDICATIONS

Dapagliflozin can be prescribed to lower the risk of hospitalization for heart failure in adults with CKD at risk for progression, end-stage kidney disease, cardiovascular (CV) death, and sustained estimated glomerular filtration rate (eGFR) decline.[1]

Farxiga also can be prescribed to cut the risk of hospitalization for heart failure and CV death in adults with heart failure with reduced ejection fraction (New York Heart Association class II-IV) and to improve glycemic control in patients with T2DM.

DOSAGE

The recommended dose is 10 mg orally once daily.[1] Initiation of treatment is not recommended if eGFR is < 25 mL/min/1.73m^2. Dapagliflozin is available as 5 mg and 10 mg tablets.

POTENTIAL ADVANTAGES

Dapagliflozin lowers the risk of composite endpoints of sustained decline in eGFR, end-stage kidney disease, or death from renal or CV causes vs. placebo, regardless of the presence or absence of T2DM.[1,2]

POTENTIAL DISADVANTAGES

Effectiveness in patients with type 1 diabetes, polycystic kidney disease, lupus nephritis, or antineutrophil cytoplasmic antibody-associated vasculitis has not been established because these were excluded from the clinical trial.[1]

COMMENTS

The efficacy of dapagliflozin on renal outcomes and CV mortality in patients with CKD was evaluated in a randomized, double-blind, placebo-controlled study (DAPA-CKD).[1,2] Subjects with CKD were defined as eGFR between 25 mL/min/1.73m^2 and 75 mL/min/1.73m^2 and urine albumin to creatinine ratio (UACR) between 200 mg/g and 5,000 mg/g on standard background therapy (i.e., maximally tolerated dose of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker). At baseline, 67.5% had T2DM, 53% were white, and 67% were men (mean eGFR = 43 mL/min/1.73m^2; median UACR = 950 mg/g). Subjects were randomized to placebo (n = 2,152) or dapagliflozin 10 mg daily (n = 2,152). The median follow-up time was 28.5 months. The primary endpoint was first time to the composite of ≥ 50% sustained decline in eGFR, progression to end-stage kidney disease (eGFR < 15 mL/min/1.73m^2, initiation of chronic dialysis, or renal transplantation), or CV or renal death.

The study ended early when researchers found the evidence of efficacy was overwhelming. Dapagliflozin reduced the primary composite endpoint by 39% (9.2% vs. 14.5%; HR, 0.61; 95% CI, 0.51-0.72). The main contribution to the composite endpoint was decline in eGFR (5.2% vs. 9.3%). In a prespecified subgroup analysis, dapagliflozin was efficacious in patients with diabetes (HR, 0.64; 95% CI, 0.52-0.79) and patients without diabetes (HR, 0.50; 95% CI, 0.35-0.72).[3]

In an additional prespecified subgroup analysis, dapagliflozin also was efficacious independent of the presence or absence of concomitant CV disease.[4]

CV disease was defined as the presence of coronary heart disease, cerebrovascular disease, peripheral artery disease, heart failure, valvular heart disease, cardiac arrhythmias, or presence of cardiac devices other than cardiac resynchronization therapy. The primary outcome was a composite of ≥ 50% reduction in eGFR and onset of end-stage kidney disease or death from renal or CV causes. HRs were identical for each subgroup (0.61).

CLINICAL IMPLICATIONS

SGLT2 inhibitors have become first-line agents in the treatment of T2DM. In addition to their antihyperglycemic effect, improved CV and renal outcomes have been shown with three in the class so far (canagliflozin, empagliflozin, and dapagliflozin).[5] The favorable effects on renal hemodynamics appears to be independent of their glucose-lowering effects.[6] Current evidence shows dapagliflozin is effective in both patients with or without T2DM, prompting the FDA's approval for CKD at risk for disease progression regardless of diabetes status. Few options are available to slow the progression of CKD. Dapagliflozin adds a new option for these patients. ■

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CME QUESTIONS

1. **Which is correct regarding the recent CDC/American College of Physicians recommendation for the usual duration of antibiotic therapy for the following common infections?**
   a. Bacterial exacerbation of chronic obstructive lung disease: 14 days
   b. Community-acquired pneumonia in non-immunocompromised adults: five days
   c. Non-purulent cellulitis in adults: 10 days
   d. Uncomplicated cystitis in nonpregnant adult women: nitrofurantoin for seven days

2. **Which statement about the Kim et al study is true?**
   a. Human papillomavirus (HPV) vaccination of mid-adults is not cost-effective.
   b. Only cervical cancer was considered in the modeling.
   c. The two models showed different results.
   d. HPV vaccination of adults is recommended routinely.

3. **Based on the study by Hackett et al, which statement about loneliness is true?**
   a. Both loneliness and living alone can be considered significant risk factors for type 2 diabetes development.
   b. Loneliness is best defined as low quantity of social interactions in an individual's environment.
   c. The mechanism by which loneliness may contribute to inflammatory disease development is known to be via dysregulation of glucocorticoid pathways.
   d. Loneliness can be considered a risk factor for type 2 diabetes independent of a patient's HbA1c.

Internal Medicine [ALERT]

ECG Review

By Ken Grauer, MD

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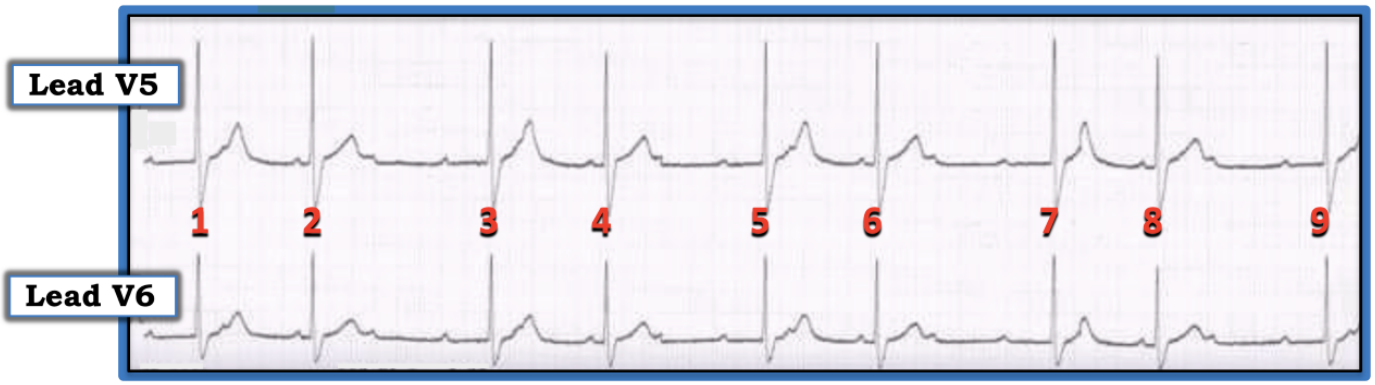
What Form of Heart Block?

How would one interpret the rhythm disturbance shown in the figure below? Unfortunately, no history was available. Does the rhythm in the figure represent Mobitz II second-degree AV block, complete AV block, or Wenckebach? Does the patient need a pacemaker?



This is a challenging tracing. That said, there are several observations that can be made that significantly narrow the diagnostic possibilities. Group beating is present in the form of alternating short-long intervals. Although several arrhythmias (e.g., atrial bigeminy or trigeminy) also may produce group beating, recognition of this phenomenon should prompt one to consider some form of Wenckebach conduction. Several beats are non-conducted. For example, two P waves in a row (without any intervening QRS complex) are seen within the R-R intervals of beats 2-3, 4-5, 6-7, and 8-9.

At least some beats are conducted because one can see an identical PR interval preceding the first QRS complex at the end of each brief pause (i.e., the PR interval preceding beats 1, 3, 5, 7, and 9 is the same). The atrial rhythm appears to be regular. This is not easy to appreciate without using calipers. This is because on-time P waves are hiding within the ST segments of beats 1, 3, 5, and 7. But three P waves in a row in each group are not visible. For example, a P wave with a short PR interval immediately precedes beat 2, another P wave immediately follows the ST-T wave of beat 2, and a third consecutive P wave appears before beat 3. This appearance of consecutive P waves reveals what the P-P interval is and allows one to verify that subtle notching within the ST segments of beats 1, 3, 5, and 7 represents on-time, regular atrial activity.

These observations strongly suggest some form of Wenckebach conduction is present. The rhythm in the figure is not complete AV block because the constant PR intervals preceding the first QRS complex at the end of each pause proves there is at least some conduction. The rhythm also is not Mobitz II second-degree AV block because the PR interval never remains constant for two conducted beats in a row. Finally, a pacemaker will not necessarily be needed because the rhythm appears to be AV Wenckebach, in which the overall ventricular response is not overly slow. Instead, clinical correlation will be needed to determine the best course of management.

For more information about and further discussion of this case, please visit: https://bit.ly/2R3iFz3.