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ABSTRACT & COMMENTARY

CDC's Updated 2021 Sexually Transmitted Infections Treatment Guidelines

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SYNOPSIS: The CDC updated their sexually transmitted infections treatment guidelines with new recommendations for *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, pelvic inflammatory disease, and *Mycoplasma genitalium*.

SOURCE: Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep* 2021;70:1-187.

Highlights from the CDC Sexually Transmitted Infections (STI) Treatment Guidelines, 2021 are as follows:

For women, *Chlamydia trachomatis* and *Neisseria gonorrhoeae* urogenital infection can be diagnosed by vaginal or cervical swabs or first-void urine with nucleic acid amplification tests (NAATs). NAATs that are FDA-approved for use with vaginal swab specimens can be collected by a provider or patient in the clinic. Patient-collected vaginal swab specimens are equivalent in sensitivity and specificity to those collected by a provider. Vaginal swabs are more sensitive than first-void urine testing and, therefore, are the optimal route of sample collection. Annual screening of all sexually active women younger than age 25 years is recommended, as is screening of older women at increased risk for infection (e.g., women age 25 years or older) who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has an STI).

The recommended regimen for the treatment of *C. trachomatis* in women has changed to a dose of doxycycline 100 mg orally twice a day for seven days. Alternative regimens are azithromycin 1 g orally once or levofloxacin 500 mg once daily for seven days. However, pregnant women still can be treated with azithromycin preferentially.

The recommended regimen for the treatment of *N. gonorrhoeae* urogenital infection in women is

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ceftriaxone 500 mg intramuscularly (IM) in a single dose for patients weighing less than 150 kg and, for those weighing more, 1 g of ceftriaxone should be administered. Alternative regimens are gentamicin 240 mg IM in a single dose with azithromycin 2 g orally in a single dose or cefixime 800 mg orally in a single dose. For pregnant women who are allergic to cephalosporins, because gentamicin cannot be given, consultation with an infectious disease expert is recommended.

Mycoplasma genitalium is increasingly recognized as a pathogen. There is one NAAT approved for use by the FDA for testing. However, screening of asymptomatic *M. genitalium* infection among women is not recommended. Nevertheless, women with recurrent cervicitis should be tested for *M. genitalium*, and testing should be considered among women with pelvic inflammatory disease (PID). Testing should be accompanied with resistance testing, if available. In clinical practice, if testing is unavailable, *M. genitalium* should be suspected in cases of persistent or recurrent cervicitis and considered for PID.

The recommended treatment for trichomoniasis among women has changed to metronidazole 500 mg orally twice a day for seven days. Two grams of metronidazole is no longer recommended. Tinidazole 2 g orally in a single dose is an alternative option but is more expensive. Topical metronidazole vaginal gel is not recommended because it does not reach therapeutic levels in the urethra and perivaginal glands. Importantly, we no longer need to counsel patients to avoid alcohol consumption while taking metronidazole, since a review found there was no convincing evidence of a disulfiram-like reaction.

Whereas before, the addition of metronidazole to the treatment regimens for PID was recommended in the case of tubo-ovarian abscess, the guidelines now recommend routine use of metronidazole with both intravenous and oral therapy for all cases of PID. The recommended outpatient IM/oral treatment regimens for PID now are ceftriaxone 500 mg IM in a single dose with doxycycline 100 mg orally twice a day and metronidazole 500 mg orally twice a day for 14 days. Alternative regimens include cefoxitin 2 g IM in a single dose and probenecid 1 g orally administered concurrently in a single dose with doxycycline 100 mg orally twice a day and metronidazole 500 mg orally twice a day for 14 days or other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime) with doxycycline 100 mg orally twice a day and metronidazole 500 mg orally twice a day for 14 days. The CDC also endorsed the recommendation from the United States Selected Practice Recommendations for Contraceptive Use that intrauterine devices (IUDs) do not automatically need to be removed during treatment of PID, stating "if no clinical improvement occurs within 48 to 72 hours of initiating treatment, providers should consider removing the IUD."

■ COMMENTARY

The last update of the CDC sexually transmitted disease treatment guidelines occurred in 2015. One important change this time is the title. The CDC changed "disease" to "infection" to reduce the stigma associated with sexually transmitted infections and recognize that "disease" refers to the condition that results from an infection in some, but not all, cases.

The rationale for the change in chlamydia treatment from a single dose of azithromycin to a seven-day course of doxycycline stems from the fact studies show doxycycline is more effective for rectal chlamydia in both men and women.[1] However, the CDC acknowledges adherence to this regimen is more difficult than with a single dose. Nevertheless, they state concomitant rectal chlamydia infection can occur in women and place them at risk for repeat urogenital infection through autoinoculation from the rectal site. Interestingly, in one study, *C. trachomatis* was detected at the anorectal site among 33% to 83% of women who had urogenital *C. trachomatis* infection. Its detection was not associated with a report of receptive anorectal sexual activity.[2] The CDC states "when nonadherence to doxycycline regimen is a substantial concern, azithromycin 1 g regimen is an alternative treatment option but might require post-treatment evaluation and testing because it has demonstrated lower treatment efficacy among persons with rectal infection."

For gonorrhea treatment, the dose of ceftriaxone rose from 250 mg to 500 mg (the CDC had released this already) to

maximize efficacy against any isolates with elevated minimal inhibitory concentrations. For trichomoniasis treatment, the single 2-g dose of metronidazole was eliminated after trials found it was inferior to the seven-day regimen.[3]

Currently, the CDC believes *M. genitalium* can cause cervicitis and may contribute to PID, but routine screening of asymptomatic women is not warranted. Rather, the organism should be suspected in cases of recurrent cervicitis and should be considered in PID. The treatment of *M. genitalium* is difficult, and while the CDC recommends resistance testing, this may not be routinely available. Treatment without resistance testing involves doxycycline 100 mg orally twice a day for seven days, followed by moxifloxacin 400 mg orally once daily for seven days. The doxycycline reduces the load of the organism and the moxifloxacin eradicates it. Although current PID treatment regimens do not cover *M. genitalium*, the CDC does not recommend routinely adding moxifloxacin; rather, it recommends only treating the organism if it happens to be detected. They state, "No data have been published that assess the benefits of testing women with PID for *M. genitalium*, and the importance of directing treatment against this organism is unknown."

Finally, the CDC now recommends the routine addition of metronidazole to PID treatment regimens because this regimen eradicates anaerobic organisms more effectively from the upper genital tract.[4]

There are other important changes to the guidelines regarding novel treatments for bacterial vaginosis, human papillomavirus vaccine recommendations and counseling messages, expanded risk factors for syphilis testing among pregnant women, and two-step testing for serologic diagnosis of genital herpes simplex virus. All these should be incorporated into clinical practice as needed. The app for the 2021 guidelines for iOS or Android is not yet available from the CDC; however, there are posters and pocket guides that can be downloaded from the website. ■

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ABSTRACT & COMMENTARY

Why Exercise Alone Does Not Result in Fat Loss

By Joseph E. Scherger, MD, MPH

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SYNOPSIS: To lose body fat, a ketogenic weight loss diet must be combined with exercise.

SOURCE: Careau V, Halsey LG, Pontzer H, et al. Energy compensation and adiposity in humans. *Curr Biol* 2021;S0960-9822(21)01120-9. doi: 10.1016/j.cub.2021.08.016. [Online ahead of print].

Careau et al studied the data on adult total energy expenditure (TEE) and basal energy expenditure (BEE) in 1,754 people living normal lives. They found a typical person averages a 28% decrease in BEE with more exercise, negating much of the increased energy expenditure with exercise. Those with more adiposity recorded the greatest decline in BEE, making losing fat among the overweight and obese harder.

■ COMMENTARY

I tell patients that once it is there, the body wants to keep excess fat. This likely is an evolutionary survival adaptation that allowed our ancestors to keep hunting and survive famines. This biological adaption seems cruel to the overweight and obese population today. Energy expenditure alone (i.e., exercise) is not a successful weight loss approach.

The leading obesity researchers have shown that a low carbohydrate diet with intermittent fasting is required to achieve sustained weight loss, with or without exercise.[1-3] Unfortunately, the food industry often resists this biological evidence, since most of the food profits come from processed carbohydrates. Sadly, many academic experts depend on food industry funding. ■

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ABSTRACT & COMMENTARY

Localized Slow Wave Sleep in the Awake but Inattentive Brain

By Alan Z. Segal, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

SYNOPSIS: Electroencephalogram studies of humans during periods of "mind wandering" and "mind blanking" have shown regional changes that suggest parts of the brain may be asleep while other areas are activated.

SOURCE: Andrillon T, Burns A, Mackay T, et al. Predicting lapses of attention with sleep-like slow waves. *Nat Commun* 2021;12:3657.

With every hour spent awake over the course of a day, our "sleep pressure" mounts. It has been believed that falling asleep is the only way for the brain to restore homeostatic balance. However, more recent research suggests that even while awake, localized areas of the brain can rest. This process has been well documented using depth electrodes in rodents and it has been demonstrated to a lesser extent on surface electroencephalogram (EEG) in humans. When local sleep occurs, a specific signature is observed on EEG, showing regional zones of high amplitude slow waves (delta frequency), closely mimicking deep (stage 3), non-rapid eye movement (REM) sleep. Importantly, this pattern is distinct from drowsiness, in which more global changes occur on EEG. The drowsy state more closely resembles stage 1 sleep — showing a global dampening rather than a rise in EEG amplitude and showing brain wave frequencies in the low alpha to upper theta range, rather than 1 Hz to 3 Hz delta waves.

Behaviorally, local sleep may be associated with lapses of attention. When subjects are asked to stay on task, especially a boring one, their mind may turn inward, wandering into unrelated thoughts or even becoming vacant entirely. In the Andrillon et al study, states of mind wandering (MW) and mind blanking (MB) are distinguished from the fully attentive state of being "on-task" (ON). Both MW and MB are found to be different from ON, but more importantly, MW and MB are shown to be distinct from each other.

Participants (n = 32) were placed in a dimly lit room and asked to perform go/no-go tasks. In one paradigm, they were shown a series of faces and asked to press a button for all neutral faces (go) and avoid this response (no-go) for any smiling faces. Similarly, they were shown digits (one through nine) and asked to press the button for any digit (go) that was not the digit three (no-go). The task was interrupted at random intervals during which participants also were asked whether they felt they were "task focused" (ON) or whether they were "off task," either focusing on some other thoughts (MW) or focusing on nothing (MB). Also, they rated their level of vigilance on a scale between one (extremely sleepy) to four (extremely alert).

The results of this investigation showed there was more inattention in the MB state, since misses were recorded when go responses were required. Reaction time also was slower. By contrast, the MW state suggested hyperarousal, with an increase in false alarm activations when no-go responses were required. Reaction times were shortened correspondingly. Overall, MB was a sluggish mental state, while MW suggested impulsivity.

The investigators also used larger pupil size as a measure of vigilance. While both MW and MB showed smaller pupils than ON, there was no difference when MW and MB were compared directly. This occurred despite the observation that subjects reported they were more vigilant when in MW.

However, more striking were the EEG data. When MW was compared to ON, there was an increase in high amplitude, slow frontal lobe activity. This suggests that in MW, the frontal lobe might be downregulated, shifting focus and allowing the mind to wander off topic. MB also showed this frontal lobe activity, but, in addition, it showed slow wave activity in central-parietal areas, suggesting a more widespread distribution of sleep-like brain waves. When comparing MW and MB, frontal lobe, high-amplitude activity was more pronounced with MW, and parietal waves were more pronounced with MB. This parietal activity, with a sharp upward deflection, followed by a wider downward wave, exhibited the morphology of K-complexes as seen in stage 2 non-REM sleep.

In their discussion, the authors noted their findings are robust and consistent over three complementary parameters: behavioral (false activations and misses), phenomenological (subject reporting of MW and MB), and physiological (EEG). Thus, attentional lapses were dichotomized into two distinct footprints. One showed false activations (impulsivity), MW, and impaired frontal lobe function (with high-amplitude slow wave mimicking sleep). The other showed misses (sluggish mentation), MB, and parietal slow waves, which mimicked stage 2 sleep.

■ COMMENTARY

It has been proposed that sleep allows for the clearance of toxic proteins (amyloid beta, among others) from the brain by enhancing the so-called "glymphatic" system. During deep sleep, there can be increased drainage of cerebrospinal fluid through channels in perivascular spaces and through widened gap junctions. Crucially, if focal slow wave EEG patterns can occur even in the waking state, as this paper suggests, it can be concluded that areas of the brain may rest and become restored even without the occurrence of sleep. As the authors noted, local sleep is achieved when attention is "turned inward" rather than focused on the external world. It could be suggested meditation (which has been part of the human experience for thousands of years) might help achieve this. By either letting the mind wander or by wiping our thoughts clean entirely, we actually may produce similar restoration of neural homeostatic balance as if we were actually asleep.

One weakness of this study is the authors did not address REM, a state of cortical activation during sleep (dreaming) that also is thought to be a crucial restorative stage. Following sleep deprivation, not only slow wave sleep but also REM can be observed to rebound. REM is a mixed state, since there is muscle relaxation but also upregulation of the sympathetic nervous system, with increases in heart and respiratory rates. If the concept of "daydreaming" were true to its name, it is possible that while some areas are slowed (such as the frontal lobe in MW), deep brain regions known to be involved in REM, such as the so-called peduncular pontine reticular formation, enter an activated state. ■

ABSTRACT & COMMENTARY

SARS-CoV-2 Rapid Antigen Testing in a Nursing Home Outbreak

By Joseph F. John, Jr., MD, FACP, FIDSA, FSHEA

Clinical Professor of Medicine and Microbiology, Medical University of South Carolina and Lowcountry Infectious Diseases, Charleston

SYNOPSIS: Rapid antigen testing was accurate in detecting SARS-CoV-2 antigen when compared to polymerase chain reaction.

SOURCE: McKay SL, Tobolowsky FA, Moritz ED, et al. Performance evaluation of serial SARS-CoV-2 rapid antigen testing during a nursing home outbreak. *Ann Intern Med* 2021;174:945-951.

The objective of this study was to determine the efficacy and role of rapid antigen testing for SARS-CoV-2 infection during a nursing home outbreak. The period was October and November 2020, with the first case identified on Oct. 7, 2020. During just a 13-day period, all staff and patients were tested up to three times if they were at the facility on the day of testing. The Abbott BinaxNOW COVID-19 Ag Card was used to perform antigen testing. Along with rapid antigen testing of samples from each nare, a reverse transcription polymerase chain reaction (RT-PCR) for COVID-19 analysis also was conducted to determine the relative usefulness of a rapid antigen test. Results showed 107 staff and 127 residents took part in at least one round of testing, and there were 234 total participants. Among residents, the median age was 75 years; 43% were female and 60% were Black. During the three testing periods, 522 paired specimens, including 388 from persons who were not tested previously, were tested.

The percentage positive agreement (PPA) and the percentage negative agreement (PNA) were determined for each sample, and the antigen test had an 84% to 99% PPA and a near 100% PNA. When antigen was compared to RT-PCR, 133 of 532 paired samples were positive by one of the methods. Of those who were positive, 64% were positive by both methods. Only 33 of 113 were RT-PCR positive and antigen negative. Of all the 532 paired samples, the PPA between antigen and PCR was 69% and the PNA was 98%. For those who were not positive previously, the PPA was 63%. Importantly, for all groups, the PNA between antigen and PCR remained near 100%.

Virus culture was not particularly sensitive in detection of virus in antigen-positive subjects. Viral cultures were positive when tested for only 21% of positive specimens. Viral culture was attempted only for subjects who were considered likely to have positive cultures (i.e., those

with a cycle threshold [CT] of < 34). Antigen performed best with early infections compared to late infections, with PPA 86% in early infection and 51% in late infection. Antigen positivity generally related to lower CT values.

■ COMMENTARY

This study in a Georgia nursing home population among residents who had been infected and those who had not showed rapid antigen testing was useful in detecting infected persons. It was not quite as good as RT-PCR, but good enough to be used in the setting of such healthcare facilities. The critical issue is whether rapid antigen testing can be used to identify those residents or patients within health facilities who need to be cohorted or receive early treatment with monoclonal antibodies to reduce disease progression and virus spread. The Abbott BinaxNOW antigen kit was used in this study, and it will be interesting to see if newer antigen methodology can improve on the data reported in this article.

Because antigen testing was more sensitive, perhaps fortuitously, in early vs. late infection, future studies can focus on just how early rapid antigen testing could be used to reduce subsequent spread. The proliferation of virus likely peaks between two to four days, suggesting to the hospital epidemiologist that tools like point prevalence surveys at a given frequency, say weekly, may detect additional infected persons in facilities like this Georgia nursing home. False-positives were stated to number only eight at a time when PNA was 98%. Several of those false-positives were in residents who had tested positive by PCR. Rapid COVID-19 antigen detection likely will assume more use because of ease of use, low cost, and reliability that a negative result correlates well with more expensive time-consuming tests. ■

PHARMACOLOGY UPDATE

Difelikefalin Injection (Korsuva)

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 the first-in-class selective kappa opioid receptor (KOR) agonist for the treatment of moderate-to-severe pruritus in adults undergoing hemodialysis (i.e., uremic pruritus). Difelikefalin is a synthetic peptide marker. It received a breakthrough therapy designation and priority review. It is marketed as Korsuva.

INDICATIONS

Difelikefalin can be prescribed to treat moderate-to-severe pruritus associated with chronic kidney disease in adults undergoing hemodialysis.[1] Difelikefalin has not been studied for use in peritoneal dialysis and is not recommended for use in this population.[1]

DOSAGE

The recommended dose is 0.5 mcg/kg given by intravenous bolus into the venous line of the dialysis circuit at the end of each hemodialysis treatment.[1] Difelikefalin is available as a single dose (65 mcg in a 1.3 mL vial).

POTENTIAL ADVANTAGES

Difelikefalin is the first approved pharmacological treatment for uremic pruritus. In clinical trials, difelikefalin improved itch intensity and itch-related quality of life, including sleep.[1-3] Difelikefalin produces no detectable activity at mu or delta opioid receptors that might be associated with dependency.[2]

POTENTIAL DISADVANTAGES

Adverse reactions reported with greater frequency than placebo were diarrhea (9% vs. 5.7%), dizziness (6.8% vs. 3.8%), nausea (6.6% vs. 4.5%), gait disturbance (including falls; 6.6% vs. 4.5%), mental status change (3.1% vs. 1.4%), and hyperkalemia in subjects on concomitant opioids (11.7% vs. 6.2%).[1]

COMMENTS

KORs are believed to play an important role in chronic pruritus.[4] Therefore, KORs are a reasonable target for pharmacological intervention. The efficacy of

difelikefalin was evaluated in two randomized, double-blind, placebo-controlled, 12-week trials in adults (≥ age 18 years) with moderate-to-severe pruritus undergoing hemodialysis.[1,2] Subjects (n = 378 in Trial 1, n = 472 in Trial 2) were randomized to difelikefalin or placebo three times weekly. Efficacy was based on the percentage of subjects achieving a 4-point or greater improvement from baseline in the weekly mean of the daily 24-hour, 11-point, Worst Itch Numeric Rating Scale (WI-NRS) score at week 12. Baseline was defined as the mean of the scores collected during the seven days before randomization. Rating of itch ranged from 0 (no itch) to 10 (worst itch imaginable). Percentages achieving efficacy endpoint were 40% vs. 21% in Trial 1 (baseline mean, 7.1 ± 1.5) and 37% vs. 26% in Trial 2 (baseline mean, 7.2 ± 1.4) for difelikefalin and placebo, respectively. Reduction in itch was observed by week 4 and sustained through week 12.

CLINICAL IMPLICATIONS

Pruritus is highly prevalent in patients with chronic kidney disease and end-stage renal disease.[5] It affects more than 60% of patients on hemodialysis, with 20% to 40% experiencing moderate-to-severe pruritus.[2] Pruritus is associated with worse quality of life, poor sleep, depression, and higher mortality rates.[5] The pathogenesis is poorly understood, with various proposed mechanisms involved, including immune-mediated effect, increase in the level of histamine, eosinophils and mast cells, peripheral nervous system dysfunction, and imbalance in mu and kappa receptor activity.[5] Current off-label pharmacologic interventions include oral antihistamines and gabapentin/pregabalin, with limited and some benefit, respectively.[5,6] Difelikefalin provides a new agent that targets KOR and is the only FDA-approved drug for this condition. An oral form of difelikefalin is under evaluation. The cost for difelikefalin was unavailable at the time of this review. ■

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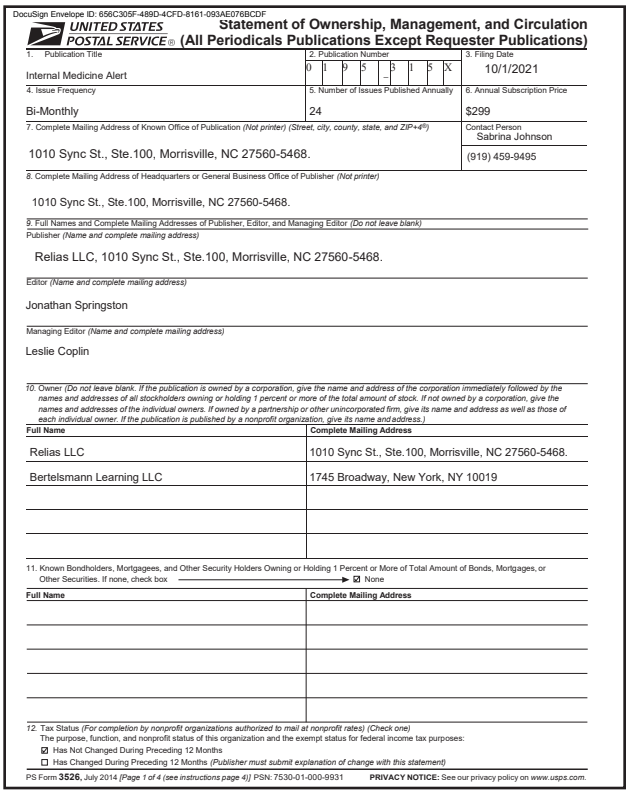

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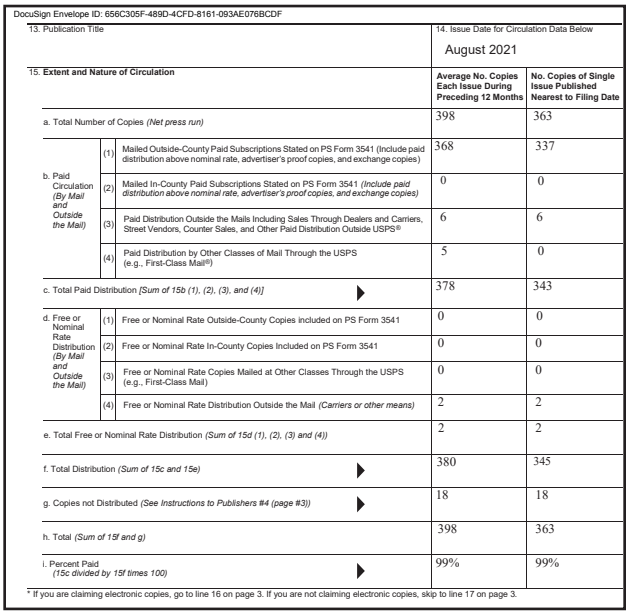

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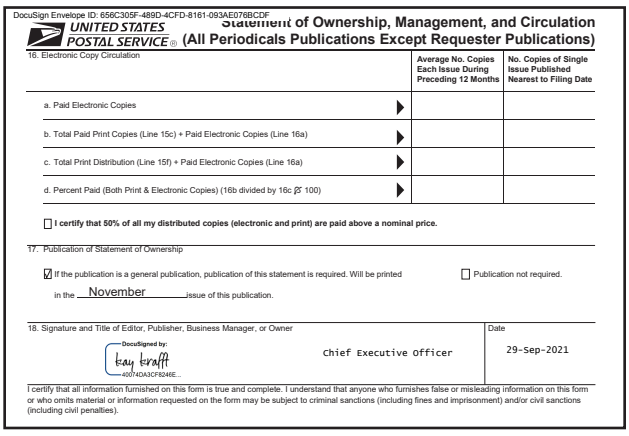
(4) Paid Distribution by Other Classes of Mail Through the USPS (e.g., First-Class Mail®)	5	0
c. Total Paid Distribution *[Sum of 15b (1), (2), (3), and (4)]* ▶	378	343
d. Free or Nominal Rate Distribution *(By Mail and Outside the Mail)* (1) Free or Nominal Rate Outside-County Copies included on PS Form 3541	0	0
(2) Free or Nominal Rate In-County Copies Included on PS Form 3541	0	0
(3) Free or Nominal Rate Copies Mailed at Other Classes Through the USPS (e.g., First-Class Mail)	0	0
(4) Free or Nominal Rate Distribution Outside the Mail *(Carriers or other means)*	2	2
e. Total Free or Nominal Rate Distribution *(Sum of 15d (1), (2), (3) and (4))*	2	2
f. Total Distribution *(Sum of 15c and 15e)* ▶	380	345
g. Copies not Distributed *(See Instructions to Publishers #4 (page #3))* ▶	18	18
h. Total *(Sum of 15f and g)*	398	363
i. Percent Paid *(15c divided by 15f times 100)* ▶	99%	99%

* If you are claiming electronic copies, go to line 16 on page 3. If you are not claiming electronic copies, skip to line 17 on page 3.



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b. Total Paid Print Copies (Line 15c) + Paid Electronic Copies (Line 16a) ▶		
c. Total Print Distribution (Line 15f) + Paid Electronic Copies (Line 16a) ▶		
d. Percent Paid (Both Print & Electronic Copies) (16b divided by 16c × 100) ▶		

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CME QUESTIONS

1. **According to the CDC's 2021 Sexually Transmitted Infection Treatment Guidelines, the first-line treatment for urogenital chlamydia infection in nonpregnant women is:**
   a. azithromycin 1 g orally once.
   b. doxycycline 100 mg orally twice a day for seven days.
   c. levofloxacin 500 mg orally once a day for seven days.
   d. moxifloxacin 400 mg orally once a day for seven days.

2. **What happens to most adults when energy expenditure rises during exercise?**
   a. There is a compensatory decrease in resting energy expenditure to compensate that results in preserving body fat.
   b. There is an additional increase in resting energy expenditure, adding to the weight loss benefits of exercise.
   c. There is no significant change in resting energy expenditure, resulting in fat loss only from exercise.
   d. Exercise is highly effective for burning body fat.

3. **The human electroencephalogram shows which change during periods of inattention (mind wandering)?**
   a. Generalized slowing, in the 1 Hz to 3 Hz range
   b. High-amplitude, slow-wave activity in the frontal lobes
   c. Normal posterior alpha rhythms
   d. Parietal lobe slow waves

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]

Intensive Lowering of Blood Pressure Does Not Affect the Progression of Small Vessel Disease

First-Line Therapy for Hypertension