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ABSTRACT & COMMENTARY

Sexually Transmitted Diseases in the United States — Not a Happy Picture

By Stan Deresinski, MD, FACP, FIDSA

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

SYNOPSIS: Since reaching historically low rates, many sexually transmitted infections have re-emerged in the United States. Of particular concern is the continued emergence of antibiotic resistance in *Neisseria gonorrhoeae*.

SOURCE: Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2018. Available at: http://bit.ly/2pPBDf4. Accessed Oct. 9, 2019.

In 2018, the incidence of *Chlamydia trachomatis* infection, the most common notifiable condition in the United States, increased 2.9% over the previous year to 539.9 cases per 100,000 population. This increase was observed throughout the country, in both men and women, and among all ethnic groups. Adolescents and young adults were disproportionately affected, with two-thirds of cases occurring in individuals 15-24 years of age. In addition, infections were detected much more frequently in women (3,693 cases per 100,000) than in men, but this likely is related, at least in part, to the fact that women are targeted for screening. Nonetheless, the incidence of infections in men increased by 38% between 2014 and 2018. In 2018, gonorrhea was the second most common notifiable condition in the United States (583,405 cases). Although *Mycoplasma genitalium* infections are more common than gonorrhea, it is not a reportable disease. Since reaching an all-time low in 2009, the reported incidence increased by 82.6%, including a 5.0% increase between 2017 and 2018. The increase has affected both men and women. Antibiotic resistance among *Neisseria gonorrhoeae* isolates has been increasing, although almost uniform susceptibility to ceftriaxone remains — only 0.2% had an elevated minimal inhibitory concentration in 2018.

There has been an almost yearly increase in reported cases of syphilis since the lows observed in 2000 and 2001. The total number of cases reached 115,045 in

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2018, 30.4% of which involved primary or secondary syphilis and, therefore, were infectious. The rates of primary and secondary syphilis have increased in women and men. The increase among the latter largely has occurred in men who have sex with men (MSM), with approximately two-fifths of them known to be infected with HIV. At the same time, recent, dramatic increasing incidences in women have raised concerns about "a rapidly growing heterosexual epidemic." Of additional concern is a rise in cases of congenital syphilis, which reached a rate of 33.1 cases per 100,000 live births in 2018. The number of resultant deaths of newborns increased by 22% to 94.

■ COMMENTARY

These results demonstrate that STD public health in the United States is going backward, with the number of cases progressively increasing after previously reaching historic lows. Add to that the increasing number of antibiotics to which *N. gonorrhoeae* has become resistant, and it is obvious that we are facing a critical public health challenge. It is clear that additional resources must be provided to public health agencies to deal with the problem effectively. In addition, there must be assurance that ready access to healthcare will be made available to all. The Healthy People 2020 Sexually Transmitted Diseases Objectives include reducing the proportion of adolescents and young adults with *C. trachomatis* infections and reducing gonorrhea rates, as well as reducing the transmission of primary and secondary syphilis and the number of congenital syphilis cases.

Also targeted are young adults with genital HSV-2 infection and the proportion of women (age 15-44 years) who have ever required treatment for pelvic inflammatory disease. In dealing with *Chlamydia* infection, public health officials aim to increase comprehensive screening for *Chlamydia* infections in sexually active women with Medicaid or commercial health insurance. This limitation to women with a third-party payer reflects the lack of healthcare accessibility for a significant portion of Americans. ■

ABSTRACT & COMMENTARY

Consensus Position Statement on the Use of Testosterone in Women

By Jeffrey T. Jensen, MD, MPH

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Dr. Jensen reports that he is a consultant for and receives grant/research support from ObstetRx, Bayer, Merck, and Sebela; he receives grant/research support from AbbVie, Mithra, and Daré Bioscience; and he is a consultant for CooperSurgical and the Population Council.

SYNOPSIS: A task force of representatives from leading international societies issued guidance for appropriate prescribing of testosterone in women.

SOURCE: Davis SR, Baber R, Panay N, et al. Global consensus position statement on the use of testosterone therapy for women. *Climacteric* 2019; Sep. 2. doi: 10.1080/13697137.2019.1637079. [Epub ahead of print].

Clinicians lack clearly established guidance and indications for testosterone therapy for women, which has led to considerable variation in practice patterns. The absence of clear indications and approved products for women has resulted in the use of compounded therapies or off-label prescription of testosterone formulations approved for men. To address concerns regarding current prescribing practice, representatives from the International Menopause Society, the European Menopause and Andropause Society, the International Society for Sexual Medicine, and the Endocrine Society

established a task force to conduct a systematic review and meta-analysis of the risks and benefits of testosterone therapy in women. The task force met in Berlin in May 2019 and drafted a consensus position paper that was published simultaneously in the several journals. The task force developed this consensus position statement to inform healthcare professionals of the known benefits and potential risks of testosterone therapy with the aim of providing clear guidance for treatment, considering benefit and risk. They also addressed conditions for which evidence does not support prescribing testosterone. Wherever possible, the task force based recommendations on findings from blinded placebo/comparator randomized, controlled trials (RCTs) of at least 12 weeks' duration. They reported findings with Levels of Evidence (e.g., Level I, experimental studies [RCTs]; Level II, quasi-experimental studies [prospective studies]; Level III, nonexperimental studies [case-control]; Level IV, opinion of respected authorities [clinical practice guidelines, consensus panels]; Level V, experiential and non-research [literature reviews, case reports]) and Grades of Recommendations (A = high quality [Level I] to recommend; B = good quality [Level II]; C = weak evidence).

Measurement of testosterone, female sexual dysfunction, and endogenous androgen levels. The task force noted that testosterone concentrations decline during reproductive years, but are maintained during menopause (Level IIB). They found direct assays highly unreliable (Level A) for diagnosis within the normal female range of values, but useful to exclude high baseline concentrations in the setting of suspected pathology or to rule out supra-physiologic doses during treatment (expert opinion). The task force recommended the use of high accuracy liquid/gas chromatography and tandem mass spectrometry (LC/GC-MS/MS) assays for total testosterone.

Recommendations for the terminology for female sexual dysfunction (FSD). Grade B evidence supports the categorization of hypoactive sexual desire disorder/dysfunction (HSDD) and female sexual arousal disorder (FSAD) as distinct conditions. They have different etiologies, risk factors, clinical features, and responses to psychological and biological interventions, including androgen therapy. The task force recommended basing the diagnosis of HSDD in clinical practice on a thorough clinical assessment[1] guided by diagnostic criteria, such as those proposed by the International Society for the Study of Women's Sexual Health (expert opinion).[2-4]

Recommendations pertaining to the associations between endogenous androgen concentrations and female sexual function. The task force categorized the evidence for using androgen concentrations as a diagnostic test for sexual function as "insufficient," and found no cutoff blood level for any measured circulating androgen to differentiate women with and without sexual dysfunction (Grade C).

Recommendations regarding systemic testosterone therapy. The task force found insufficient evidence to make any recommendations regarding the use of testosterone in *premenopausal women* for treatment of sexual function or any other outcome. In contrast, high-quality (Level I, Grade A) evidence supports the beneficial effect of testosterone replacement at physiologic levels on sexual function in naturally or surgically *postmenopausal women with HSDD*. The benefit over placebo includes an average of one satisfying sexual event per month, and increases in the subdomains of sexual desire, arousal, orgasmic function, pleasure, and sexual responsiveness, along with a reduction in sexual concerns, including sexual distress. The experts found insufficient evidence to support using testosterone to enhance cognitive performance or delay cognitive decline in postmenopausal women. They found high-quality evidence that testosterone does not improve bone density or increase lean body mass (Level I, Grade A). They also found systemic testosterone therapy in postmenopausal women at physiologic levels was associated with mild side effects in some women (acne, increased body/facial hair) but not with alopecia, clitoromegaly, or voice change (Level I, Grade A).

Regarding cardiovascular health, oral testosterone therapy results in adverse changes in lipid profiles, but these effects are not seen with transdermal therapy (Level I, Grade A). Short-term transdermal testosterone therapy does not increase mammographic breast density or affect breast cancer risk (Level I, Grade A), but insufficient data exist to assess long-term breast cancer risk or to support safety in women with hormone-sensitive breast cancer (expert opinion). The experts found high-quality evidence supporting an absence of serious adverse events associated with physiologic testosterone replacement in postmenopausal women, but noted safety data do not exist beyond 24 months of treatment.

Considerations for clinical care of postmenopausal women with FSAD. The task force noted that clinicians should consider the multiple biopsychosocial etiologies (neuroendocrine imbalance, health status, interpersonal difficulties, psychological distress, and sexually repressive cultural or religious values) that contribute to FSAD (Grade C), and offer treatments that follow this biopsychosocial model, including pharmacologic options (hormone therapies and other pharmacologic

agents), psychotherapy, or multimodal treatments that combine both (Grade B). The only evidence-based female indication for the use of testosterone is HSDD in postmenopausal women (Level I, Grade A). Use of supraphysiologic doses of testosterone is not recommended (expert opinion). To keep levels in the physiologic range, the task force recommended measurement of a baseline total testosterone prior to initiation of treatment, and a repeat level three to six weeks later (Level II, Grade C). They further recommended monitoring patients for signs of androgen excess, measuring testosterone levels every six months to screen for overuse (expert opinion), and discontinuing treatment at six months in the absence of benefit. The group found high-quality evidence to recommend against the use of systemic DHEA for the treatment of HSDD (Level I, Grade A).

■ COMMENTARY

This statement provides useful guidance to clinicians considering using androgen therapy to treat FSD. The task force reviewed the available literature to determine the quality of evidence both for and against the use of testosterone. For many recommendations, little data exist, and for this reason, many recommendations are conservative and based on expert opinion only. The take-home recommendation is that postmenopausal women with a diagnosis of HSDD benefit from testosterone (T) replacement in the physiologic range of normal premenopausal women. This recommendation is based on a meta-analysis of seven RCTs by Achilli et al.[5] The testosterone-treated women reported significantly more satisfying sexual episodes, sexual activity, orgasms, and desire; a decrease in Personal Distress Scale score; and minor androgenic adverse events vs. the placebo group. Most studies used transdermal doses of T at 150-300 mcg per day. As only postmenopausal women meeting the criteria of HSDD have been shown to benefit from T therapy, the task force cautioned clinicians not to generalize the findings to other groups.

Another caveat is that more is not better. In fact, more T may be worse from the perspective of side effects. Measure T levels and keep these in the normal range of premenopausal women for the reference lab. Use a lab that measures T using state-of-the-art LC/GC-MS/MS methods, if possible. Another consideration is that RCTs of T therapy have excluded women at high risk for cardiovascular disease, and that most studies have included women taking concurrent estrogen therapy.

Furthermore, all studies have been of relatively short duration. Therefore, we have much less information regarding risks and benefits of T therapy than with estrogen only or combined estrogen/progestogen treatment. Keeping up to date on this evolving literature remains important. ■

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BRIEF REPORT

Urine Cultures: A Gateway to Antibiotic Overuse

By Carol A. Kemper, MD, FACP

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

SOURCE: Brown KA, Daneman N, Schwartz KL, et al. The urine-culturing cascade: Variation in nursing home urine culturing and association with antibiotic use and *C. difficile* infection. *Clin Infect Dis* 2019. doi: 10.1093/cid/ciz482. [Epub ahead of print].

Inappropriate antibiotics use in nursing homes across North America continues driving antibacterial resistance and the risk of *Clostridioides difficile* infection (CDI) in the elderly. In my experience, one of the greatest offenses is the misinterpretation of urinalysis and culture results (a problem also

common to the clinic and the acute care setting). Brown et al conducted a retrospective review of nursing home residents in Ontario, Canada, from 2014 to 2017. An assessment of nursing home residents was made once quarterly, documenting the proportion with a urine culture within 14 days of the assessment, the receipt of antibiotics within 30 days, and the incidence of CDI within 90 days. The researchers examined specific antibiotic use and noted those antibiotics commonly used for urinary tract infection (UTI), including ciprofloxacin, nitrofurantoin, and trimethoprim-sulfamethoxazole (TMP-SMX). Considering the national healthcare system, information about diagnosis and antibiotic use was available for about 91% of all nursing home residents in the province. CDI was based on both a diagnosis and the use of medication prescribed for CDI.

The analysis included 131,218 residents from 591 nursing homes. Of these, 71% were women, and 55% were > 85 years of age. Of these, 7.9% had a urine culture obtained within 14 days of the quarterly assessment (ranging from 3.4% for the lowest 10th percentile of facilities and up to 14.3% for the 90th percentile). Seventeen percent of residents received an antibiotic within 30 days, and 5.4% received an antibiotic commonly used for UTI. Antibiotic use within 30 days of assessment included, in decreasing order, ciprofloxacin (2.7%), cephalexin (2.6%), TMP-SMX (2.5%), nitrofurantoin (2.2%), Augmentin (2.1%), and other fluoroquinolones combined (2.6%). Urine culturing strongly predicted an increased use of antibiotics and explained 40% of the variability in antibiotic use between facilities, especially the use of nitrofurantoin. With every doubling of urine culturing, there was a 1.22-fold increase in total antibiotic use and a 1.36-fold increase in the use of antibiotics for UTI. CDI was diagnosed in 2,181 residents within 90 days. After adjusting for various factors, the rate of urine culturing at a facility was associated with a risk of CDI (for every doubling of culturing, the IRR for CDI was 1.18). Within 30 days of the quarterly assessment, 2.6% of residents died. Urine culturing was associated weakly with mortality.

These data suggest that different nursing homes have "a culture" of culturing urine, which drives the use of antibiotics at that facility. It is amazing to me that 17% of nursing home residents received an antibiotic every three months. The use of interventions and education to ensure appropriate collection of urine specimens and the interpretation of those results would go a long way to reducing inappropriate antibiotic use in nursing homes. For one thing, I always maintain that obtaining a clean catch in an elderly person is virtually impossible. Imagine you are older than 85 years of age, balancing yourself while holding your labia open with one hand, cleaning yourself with the other hand, and then catching the midstream urine without toppling over. My guess is that most of these specimens represent simple contamination. Furthermore, asymptomatic bacteriuria in elderly patients is not uncommon and does not require treatment. ■

PHARMACOLOGY UPDATE

Omeprazole Magnesium, Amoxicillin, and Rifabutin Delayed-Release Capsules (Talicia)

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 fixed-dose combination, rifabutin-based (RFB) regimen to treat *Helicobacter pylori* infection. RFB is combined with amoxicillin (AMX), an antibiotic, along with omeprazole (OMEP), a proton pump inhibitor.

This regimen is designed to address clarithromycin-resistant *H. pylori*. It received a Qualified Infectious Disease Product designation and a priority review. The combination will be distributed by RedHill Biopharma as Talicia.

INDICATIONS

OMEP/AMX/RFB is indicated for the treatment of *H. pylori* infection in adults.[1]

DOSAGE

The recommended dose is four capsules every eight hours (120 mg OMEP, 3 g AMX, 150 mg RFB) with food for 14 days. It should not be taken with alcohol. Each delayed-release capsule contains OMEP magnesium 10.3 mg (the equivalent of 10 mg of OMEP), AMX 250 mg, and RFB 12.5 mg.

POTENTIAL ADVANTAGES

Worldwide *H. pylori* antibacterial resistance to RFB is low compared to other antibacterials.[2] Rifabutin-based triple therapy with a lower dose of AMX and OMEP (2 g AMX and 80 mg of OMEP) has been shown to be effective in patients with triple-resistant (clarithromycin, metronidazole, and levofloxacin) *H. pylori*, achieving an 83% cure rate.[3]

POTENTIAL DISADVANTAGES

RFB is an inducer of and substrate for CYP3A isoenzymes, and OMEP is a substrate and inhibitor for CYP2C19 and a substrate for CYP3A4.[1] Clinically important drug-drug interactions may occur with concomitant treatment. Avoid concomitant use with 2C19 and 3A4 inducers and inhibitors. The most frequently reported (vs. placebo) adverse reactions were diarrhea (10-14% vs. 10%), headache (8-16% vs. 10%), and chromaturia (13% vs. 2%).[1]

COMMENTS

The approval of OMEP/AMX/RFB was based, in part, on two phase III studies: one with an active control arm to confirm the added benefit of RFB and the other a placebo-controlled study.[1] Participants were treatment-naïve, *H. pylori*-positive adult patients with complaints of epigastric pain/discomfort. Infection was confirmed with 13C urea breath test and follow-up upper endoscopy.

In study 1, participants were randomized to OMEP/AMX/RFB or AMX (3 g) and OMEP (120 mg) daily for 14 days. Treatment eradication/success was confirmed with a negative 13C urea breath test or fecal antigen test conducted ≥ 28 days post-therapy. Eradication rates were 83.8% for OMEP/AMX/RFB (n = 228) vs. 57.7% (n = 227) for OMEP/AMX. In study 2, the eradication/success rates for OMEP/AMX/RFB (n = 77) vs. placebo (n = 41) were 76.6% and 2.4%, respectively.

CLINICAL IMPLICATIONS

H. pylori infection is a common (usually lifelong) infection. The prevalence of the infection is much higher outside of North America (79.1% in Africa, 63.4% in Latin America and the Caribbean).[4] In North America, the prevalence is 37.1% and varies with socioeconomic status and race/ethnicity.[4,5] The World Health Organization classifies *H. pylori* as a group 1 carcinogen leading to gastric adenocarcinoma.[5] Worldwide *H. pylori* antibacterial resistance has increased for clarithromycin and metronidazole, with higher prevalence in women vs. men.[2] In vitro effectiveness for RFB against multidrug-resistance has been reported in 76% of isolates tested (n = 33).[5]

Currently, the American College of Gastroenterology recommends clarithromycin-based triple therapy (clarithromycin, a proton pump inhibitor, and AMX or metronidazole) for 14 days where *H. pylori* clarithromycin resistance is less than 15%.[6] For patients with high levels of clarithromycin resistance or history of macrolide use, bismuth-based quadruple therapy (bismuth, proton pump inhibitor, tetracycline, nitroimidazole) for 10-14 days is recommended.[6,7] OMEP/AMX/RFB provides an effective alternative to first-line therapy for drug-resistant *H. pylori* infections. The product is expected to be available in the first quarter of 2020. ■

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CME INSTRUCTIONS

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CME QUESTIONS

1. **Which was recommended by the Global Consensus Position Statement on the Use of Testosterone Therapy Task Force?**
   a. Treatment with testosterone at physiologic levels in postmenopausal women diagnosed with hypoactive sexual desire disorder/dysfunction
   b. Treatment with estrogen with testosterone at pharmacologic levels in premenopausal women with arousal disorder
   c. Treatment with testosterone at pharmacologic levels to increase bone density in breast cancer survivors
   d. Treatment with testosterone at pharmacologic levels in postmenopausal women diagnosed with hypoactive sexual desire disorder/dysfunction

2. **Which is correct regarding the incidence of sexually transmitted infections in the United States in recent years?**
   a. The incidence of syphilis has increased, but that of gonorrhea has decreased.
   b. The incidence of *Chlamydia* infection has increased, but that of syphilis has decreased.
   c. The incidences of gonorrhea, *Chlamydia* infection, and syphilis all have increased.
   d. The incidence of congenital syphilis has decreased.

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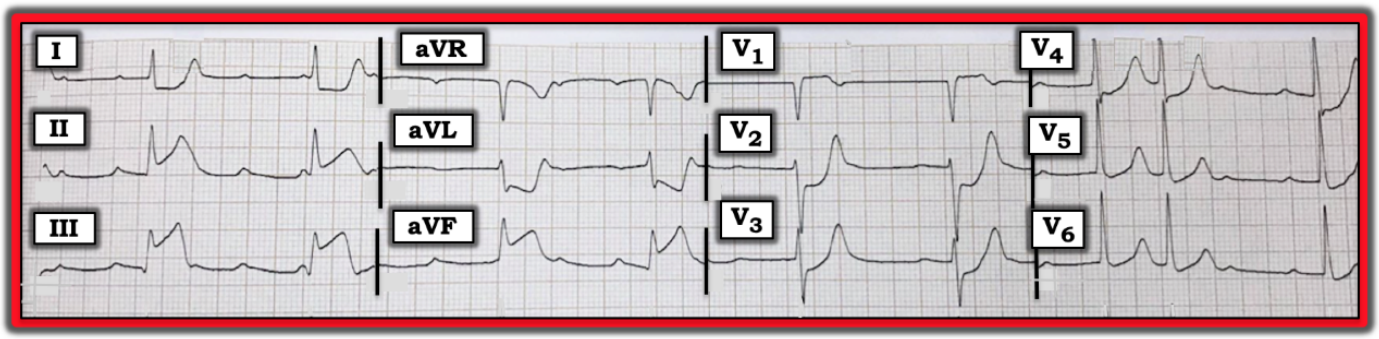
Dr. Grauer reports no financial relationships relevant to this field of study.

Why Was There Syncope?

The 12-lead ECG in the figure below was obtained from a middle-aged woman with syncope and hypotension but no chest pain. No long lead rhythm strip is available. What might be causing her syncope?



The cardiac rhythm is complex and virtually impossible to completely interpret from this 12-lead ECG without benefit of a long lead rhythm strip. However, there is bradycardia (heart rate is clearly below 60 beats/minute in many places). There are nine beats on this tracing. All QRS complexes are narrow. P waves are present, and many P waves are not conducted. Therefore, some form of high-grade AV block appears to be present.

That said, complete AV block is unlikely since the QRS rhythm is irregular (i.e., most of the time with complete AV block, the escape rhythm is at least fairly regular). It is hard to say more without a long lead rhythm strip.

As to interpretation of the rest of this ECG, there is a normal frontal plane axis, and there is no chamber enlargement. A small q wave is present in lead III. R wave progression is normal, with a transition occurring between leads V3 and V4. The most remarkable changes are seen in ST-T waves. There is marked ST elevation in each of the inferior leads, which manifest a hyperacute appearance. This is associated with reciprocal ST depression in high-lateral leads I and aVF. In the chest leads, there is ST depression that is most marked in leads V2 and V3, with overly peaked T waves. There is subtle-but-real ST elevation in lead V1.

ECG findings suggest high-grade, second-degree AV block with acute infero-postero ST-elevation myocardial infarction (STEMI). This more than explains this patient's syncope and hypotension. The "culprit" artery is almost certain to be the right coronary artery (RCA) because 80-90% of patients have a right dominant circulation, so acute occlusion of the left circumflex (LCx) artery is, overall, much less common than acute RCA occlusion. ST elevation is much more marked in lead III compared to lead II, which favors RCA rather than LCx occlusion. In the setting of acute infero-postero STEMI, ST elevation as seen here in lead V1 strongly suggests acute right ventricular involvement. It is the proximal RCA that virtually always provides blood supply to the right ventricle.

For more information about and further discussion on this case, please visit: http://bit.ly/2KEPKeX.