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EXPERT OPINION

# A Critique of the AUA Guidelines on Testosterone Deficiency

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## INTRODUCTION

The publication of the first American Urological Association (AUA) guidelines regarding the evaluation and management of testosterone deficiency (TD) in 2018 ("Guidelines") was a landmark event, serving to recognize the importance of this condition for US urologists.[1] Urologists play an outsized role in the treatment of men with TD because presenting symptoms are usually sexual. Urologists also have nearly 80 years of experience observing the effects of androgen deprivation.

The creation of clinical guidelines is a rigorous process intended to distill the best available evidence into a set of recommendations to guide health care providers in management of a condition. We congratulate the AUA Guidelines Committee for producing an excellent, useful document for the evaluation and management of men with TD. In particular, the Guidelines have advanced the field by acknowledging the utility of testosterone (T) therapy (TTh) in selected men with prostate cancer. As experienced clinicians and investigators in the field, we welcomed the *Journal*'s invitation to provide a critique of the Guidelines. Below, we comment on a number of topics where our perspective differs from that of the Guideline authors.

### What Is the Utility of Guidelines?

The purpose and utility of clinical guidelines are widely misunderstood by health care providers and the public. Contrary to popular opinion, guidelines are *not* rigid rules and do *not* establish standards of care; rather, "these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment."[1] This is a welcome comment, as any deviation from guideline recommendations in medicolegal cases is considered an indication of substandard practice. Given this reality, it is incumbent on guidelines committees to avoid making their own constituent members "wrong" via overly restrictive recommendations, as those recommendations may be used to harm practitioners practicing good medicine. This is particularly important for a first iteration of guidelines on a clinical condition, as a range of successful clinical practices may have existed for years before the introduction of new, unproven guideline recommendations.

These Guidelines, as do all others, emphasize reliance on evidence to support recommendations; yet, as Powers noted, "… guidelines are not just summaries of the evidence. They are also interpretations of that evidence by guideline authors who bring to the process their own conscious and unconscious biases."[2] Further, many aspects of clinical decision-making have never been tested experimentally. Together, these limitations mean that many recommendations represent opinions rather than clear interpretations of high-quality data. This is a general feature of all guidelines. A study of cardiology guidelines found that of more than 7,000 recommendations a median of only 11% were based on data from randomized controlled trials, and 48% were based on expert opinion.[3] The challenge for new guidelines is to incorporate solid existing practices with the best research evidence. It is no wonder that numerous studies across many fields show poor compliance with guidelines.

## COMMENTS ON SPECIFIC RECOMMENDATIONS AND TOPICS

### Purpose

The authors suggest that developing guidelines is necessary because too many men are treated improperly, and others who need treatment may not be receiving it due to unwarranted fears. Surely the most important goal is to provide an effective and evidence-based set of recommendations for the evaluation and management of a clinically important condition regularly encountered by urologists. We disagree that as many as 25% of men have never received a T test before receiving a T prescription, suggesting high levels of mismanagement.[1] Although this result was indeed reported, the study was based on electronic health records only, without verification of any individual chart. The nearly 20% rate of absent testing associated with endocrinology visits makes the accuracy of these results suspect.[4]

#### 1. Clinicians should use a total testosterone level below 300 ng/dL as a reasonable cutoff in support of the diagnosis of low testosterone (moderate recommendation; evidence level: grade B)

The single most critical item in any testosterone guideline is what total T concentration justifies treatment of a symptomatic man. Despite its importance in clinical practice, scant research

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has been performed to identify a discrete T threshold at which symptoms resolve, hence the lack of consensus on this threshold. Various guidelines recommend a range of thresholds from 264 ng/dL to 350 ng/dL.[5,6] The AUA Guidelines authors selected 300 ng/dL "as a reasonable cutoff." The history of 300 ng/dL as a threshold is that it was arbitrarily set by the US Food and Drug Administration (FDA) for pharmaceutical manufacturers of T products as the lower limit of normal. Experts in sexual medicine and the T field recognize that a threshold of 300 ng/dL is too stringent, as many symptomatic men with TD have total T values above this threshold and respond nicely to TTh. Application of such a low value will result in many appropriate candidates being denied valuable treatment.

The Guidelines are silent on the diagnostic use of free T. Data from the European Male Aging Study indicate that free T is a more reliable indicator of symptoms than total T.[7] This makes sense, as it is free T that enters target cells via their lipid bilayers and not T bound to large carrier molecules, such as sex hormone-binding globulin (SHBG). Although total T is a reasonable test of a man's androgen status, its interpretation is greatly impacted by SHBG concentrations. Recent data show wide interindividual variation in SHBG concentrations in young and older men,[8] and this variability confounds interpretation of total T. We believe that free T, calculated or directly measured, is an important diagnostic test in the evaluation of men with possible TD.[9] In our practices, we offer TTh to symptomatic men with low free T even if total T is normal. In most cases, this will be associated with a high-normal or elevated SHBG. Note that, when using an online calculator, for any given total T value changing the SHBG concentration from the lowest to the highest limits of normal will reduce the free T concentration by half.[8] We believe a trial of TTh is merited in symptomatic men with total T $<$ 350 ng/dL and in men with low free T (calculated $<$ 100 pg/mL or direct $<$ 1.5 ng/dL)[9] even if total T is normal.

### 2. The diagnosis of low testosterone should be made only after 2 total testosterone measurements are taken on separate occasions, with both conducted in an early morning fashion (strong recommendation; evidence level: grade A)

This recommendation creates additional work for patients and clinicians for an uncertain benefit. The rationale has been that some men with an initial serum T $<$ 300 ng/dL will have a second test result that is $>$300 ng/dL. If one rigidly follows guideline recommendations, such a man would not be a candidate for treatment. However, is there really any meaningful difference between a value of 290 ng/dL vs 310 ng/dL? Not all blood tests require replication before intervention. Consider the recommendation for prostate biopsy in most men based on a single abnormally elevated prostate-specific antigen value. The current insurance requirement for repeated blood tests represents an obstacle to treatment and leads to considerable frustration for patients and physicians.

### 21. All men with testosterone deficiency should be counseled regarding lifestyle modifications as a treatment strategy (conditional recommendation; evidence level: grade B)

Although marked weight loss with bariatric surgery has been shown to increase testosterone and improve sexual symptoms, the amount of weight loss required for meaningful increases in T is difficult to achieve via lifestyle changes alone. On the other hand, TTh has been shown to be associated with reductions in fat mass and with progressive weight loss over several years. Although we agree with the recommendation to consider lifestyle modification, we also believe TTh may be a useful adjunct in some men to improve fitness and achieve weight loss.

### 22. Clinicians should adjust testosterone therapy dosing to achieve a total testosterone level in the middle tertile of the normal reference range (conditional recommendation; evidence level: grade C)

This recommendation is contradicted by extensive clinical experience. The authors recommend a treatment goal of 450–600 ng/dL. Because the goal of treatment is to alleviate symptoms, dosing should be adjusted until symptoms are relieved while maintaining serum T concentrations within the normal range. Although some men feel greatly improved at 400 ng/dL others require higher levels of 750–1000 ng/dL. This is easily understood by wide interindividual variability of SHBG concentrations and CAG repeats in the androgen receptor gene, which influence concentrations of biologically available T fractions and androgen receptor activity. Both of these may influence the biological response for any given T concentration. Treatment must therefore be individualized. Note also that many forms of TTh produce levels that change hourly or daily, adding to the challenge of specifying a specific target value while actual concentrations vary widely over a treatment cycle.

### 24. Testosterone therapy should not be commenced for a period of 3 to 6 months in patients with a history of cardiovascular events (expert opinion)

As Guideline authors acknowledge, this recommendation represents mere opinion, as there is inadequate evidence on this topic. Despite contradictory reports regarding cardiovascular risks of TTh, the weight of evidence suggests that men with normal T concentrations have a reduced cardiovascular risk compared to men with low levels, and mortality is reduced in men with higher T levels.[10] Two studies showed that mortality was reduced by half in T-deficient men who received TTh compared to men who did not. Although we recognize that it may be prudent to defer initiation of any new treatment immediately following a cardiovascular event, we are not aware of data indicating that this is of greater importance for TTh. We recommend individualizing decisions regarding initiation of TTh following cardiovascular events.

28. Commercially manufactured testosterone products should be prescribed rather than compounded testosterone, when possible (conditional recommendation; evidence level: grade C)

We disagree with this recommendation. With increasing denials by health insurers for TTh coverage, physicians and our patients have accumulated a large experience with compounding pharmacies for affordable testosterone formulations. Many of these compounding pharmacies have registered as 503B facilities, placing them under direct oversight by the FDA, similar to pharmaceutical manufacturers. Although we agree that there may be variability in non-FDA-registered testosterone compounded products, proper monitoring and titration can allow many patients to achieve symptomatic improvement with a significant costs saving and without compromising safety.

### Items Not Covered by Guidelines

We would add therapeutic phlebotomy to the options available to patients with erythrocytosis due to TTh, in addition to dose reduction or cessation of treatment, as discussed in recommendation 11. Although we agree with the recommendation to intervene if the hematocrit rises above 54%, we also note there is no good evidence that this specific threshold or any other represents a medical risk when erythrocytosis is caused by TTh. The Guidelines offer no recommendations regarding TTh and benign prostatic hyperplasia (BPH). Many clinicians fear that initiating TTh will result in worsening of lower urinary tract symptoms in hypogonadal men. Package inserts of testosterone products state that "patients with BPH treated with androgens are at an increased risk for worsening of signs and symptoms of BPH." Although androgen deprivation therapy does cause reduced prostate volume, restoring androgens merely returns prostates to their euvolemic state. Several studies show improved lower urinary tract symptoms and stable urodynamics with TTh.

## CONCLUDING COMMENTS

The AUA Guidelines for evaluation and management of men with TD are an important step forward for US urologists and our patients. These recommendations represent a useful playbook for novice and somewhat experienced clinicians to identify and manage men with TD. As with all guidelines, these recommendations are of less use to experts and specialists, who incorporate invaluable experience as well as additional clinical and research information in their decision making. We were particularly gratified to note the recognition in the Guidelines that TTh may be reasonably offered to some men with prostate cancer.

Our greatest area of disagreement is with the overly conservative diagnostic threshold of 300 ng/dL. This threshold is not followed by most experienced clinicians, and its application will result in many men suffering from classic symptoms of TD being denied treatment. We hope this threshold value will be liberalized in future Guidelines. We also believe that free testosterone plays an important role in diagnosing TD, and we encourage ordering this test as well as SHBG to evaluate the man presenting with symptoms suggestive of TD.

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