Therapeutic Phlebotomy for Testosterone-Induced Polycythemia

A Blood Center's Perspective

Nancy L. Van Buren, MD,[1] *Anita J. Hove, RN,*[1] *Tracy A. French, RN,*[2] *and Jed B. Gorlin, MD*[1]

From [1]Physician Services and [2]Collections Quality, Memorial Blood Centers, Innovative Blood Resources, Division of New York Blood Center, St Paul, MN.

Key Words: Therapeutic phlebotomy; Testosterone replacement therapy; Polycythemia; Patient management

Am J Clin Pathol 2020;XX:1–5

DOI: 10.1093/AJCP/AQAA019

ABSTRACT

Objectives: *To evaluate therapeutic phlebotomy (TP) requests for testosterone replacement therapy (TRT) and to highlight the impact to a blood center (BC) or service that provides TP for individuals on TRT.*

Methods: *Review of TP requests for individuals on TRT at our BC over a 3-year period from 2014 through 2016, as well as the total number of TP collections.*

Results: *Total TPs during 2014, 2015, and 2016 were 475, 500, and 569, respectively. Annual TP collections for patients on TRT were 193, 212, and 239, respectively. TRT patients with TP orders increased 71.4% during this period. After discontinuation of TP services for TRT at our BC, 32% continued to donate as volunteer blood donors at our BC.*

Conclusions: *Our BC observed increased TP requests for patients on TRT from 2014 through 2016. Our findings suggest that individuals on TRT may be presenting to BCs as volunteer blood donors to avoid charges for TP.*

Testosterone prescribing practices have significantly increased over the past 10 years in the United States and Canada.[1] In addition to the accepted indication of testosterone replacement therapy (TRT) for hypogonadism in men,[2] marketing strategies have significantly contributed to testosterone sales by promoting its use for hormonal rejuvenation, often times under the rubric "low T."[3,4] Polycythemia is a common adverse effect of TRT.[5] Several studies have raised concern that testosterone therapy increases the risk of cardiovascular events.[6-8] In fact, a placebo-controlled trial was terminated early due to concern of possible cardiovascular harm among men randomized to receive off-label prescription testosterone.[9] Publication of several observational studies also support this concern.[10,11] In 2014, the US Food and Drug Administration (FDA) issued a safety communication addressing cardiovascular risk investigation with the use of testosterone.[12] Concomitantly, the Endocrine Society also issued a statement warning about the cardiovascular risk of testosterone.[13] The FDA subsequently required label changes in 2015, adding a warning about possible increased risk of heart attack and stroke, as well as cautioning about the use of testosterone products for age-related hypogonadism.[14] Despite these concerns, a recent study found that many men get prescriptions for the hormone without evidence of T-deficiency, contributing to increased drug usage.[15] Another recently published study evaluating trends in testosterone prescribing practices using Medicare data found that off-label prescriptions for men with and without heart disease remain significantly

higher than on-label prescription expenditures, even after the publication of safety warnings, suggesting the need for more effective dissemination of label changes.[16] Until the results of an FDA-mandated randomized clinical trial assessing cardiovascular risk are available, caution should prevail.

Therapeutic phlebotomy (TP) is often requested for patients with testosterone-induced polycythemia to lower the hematocrit, at least as a temporary measure while adjusting the dose of medication.[2,17] The reported incidence of polycythemia in those on TRT, defined as hemoglobin (Hb) greater than 18 g/dL or hematocrit greater than 54%, ranges from 2.5% to 40% in the literature.[18] Men on higher dosages of testosterone are at greater risk for developing polycythemia, particularly those receiving injectable testosterone compared with transdermal drug administration.[15,19] In a recent Canadian study,[1] the Hb was greater than 18 g/dL at 25% of appointments in 39 male blood donors who self-identified or were found on donor screening to be on TRT. Of the 27 repeat donors, the Hb remained persistently elevated in 44%. The authors concluded that these findings raise concerns about persistent risk of vascular events in these donors, particularly when coupled with the misperception that blood donation will reduce or eliminate the risks of TRT-induced polycythemia.

Background

Our blood center began providing TP services without charge in the 1970s, with many collections performed for individuals with hereditary hemochromatosis (HH). So when the opportunity came to obtain a variance from the FDA to collect blood for transfusion from individuals with HH who met all the allogeneic blood donation criteria other than frequency,[20] it was readily incorporated into our TP program in 2001, which allowed us to avoid labeling the resulting RBC units with the TP indication while discarding the others.

In recent years, some blood centers have also obtained a variance for patients on testosterone. Without a variance, all collections from therapeutic phlebotomies must be discarded and are not allowed for transfusion regardless of whether the patient otherwise meets requirements for volunteer blood donation. Notably, our blood center does not have an FDA variance under 21 Code of Federal Regulations 640.3 to allow for individuals on prescription testosterone to donate blood and blood components more frequently than 8 weeks without special labeling about the donor's disorder, provided the donor is referred with a prescription by a physician containing instructions regarding frequency of phlebotomy and hematocrit or Hb limits, as long as all other criteria for allogeneic blood donation are met.

Alternatively, many hospitals and health care facilities, as well as some blood centers, are able to charge a fee or bill the patient's health care insurance. Our blood center has not invested in the infrastructure to bill patients and has traditionally provided free TP services. Given the above concerns and alternatives, our blood center ultimately decided to discontinue TP services for patients on TRT. We sent letters of notification to patients and ordering providers, completing TP orders that were currently in place, which provided adequate time for alternative arrangements to be made (eg, hospitals, doctor offices, or outpatient clinics).

Materials and Methods

We reviewed the total number of TP collections, as well as TP requests for patients on TRT at our blood center over a 3-year period from January 2014 through December 2016. TP collections are scheduled through our main facility and performed at our fixed donor center sites but not on mobile operations. The patients' medical providers submit orders to our blood center with documentation of the medical condition requiring TP. We require annual renewal of the order with the indication and requested collection frequency, as well as acceptable Hb limits. Special process and deferral codes based on the medical condition are applied after approval by the blood center physician. TP orders must be renewed annually, and a temporary deferral of 1 year is placed on these patients, unless a longer deferral period is required based on medical conditions identified during the predonation interview. Retrospective evaluation was performed to determine whether patients with previous TP orders for TRT returned as regular blood donors.

Results

The total number of TPs during 2014, 2015, and 2016 was 475, 500, and 569, respectively. Of those, the TP collections for TRT during this same period of time were 193, 212, and 239, respectively. In addition to TPs from patients with HH and other hematologic diseases, the number of TP collections from patients on testosterone increased 24% during this timeframe **Figure 1**. The total number of TRT patients increased 71.4% over the 3-year period: 63 in 2014, 85 in 2015, and 108 in 2016. The number of TPs per registered TRT patient varied widely,

DOI: 10.1093/AJCP/AQAA019

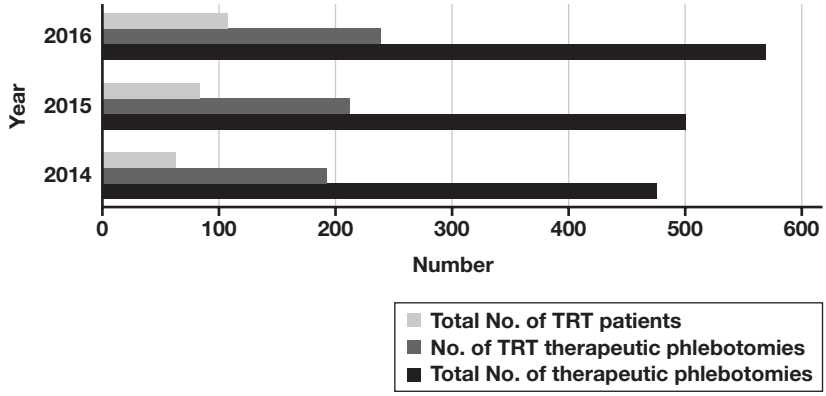

Figure 1 Therapeutic phlebotomies for testosterone replacement therapy (TRT) patients.

ranging from one to 12 TPs per calendar year. Further analysis revealed that 62% of the patients on TRT had TP performed fewer than six times per year, and 38% had TP performed six or more times per year. Overall, the average number of TP collections for patients on TRT varied from 3.8 to 2.8 per year during this timeframe.

Retrospective data analysis revealed that 37 (32%) of 117 patients with previous TP orders for TRT returned to donate as voluntary whole blood donors. Of those, none had subsequent deferrals for disease markers, but seven of the donors were deferred from at least one donation for an elevated Hb above the acceptable limit of 19 g/dL, all of whom subsequently returned for blood donation with acceptable Hb levels. Of those who continued to donate as regular blood donors, 32 (86%) donated fewer than six times per year and five (14%) donated six or more times per year (at no less than 56-day intervals). The mean and median Hb values measured prior to discontinuation of TP for patients on TRT were similar to the values sampled in the individuals who returned to donate as volunteer blood donors **Table 1**.

Table 1
Patients With TP Orders for TRT and Subsequent Blood Donations

Characteristic	2014-2016	July 2017 to July 2019
No. of TRT TP patients/blood donors	117	37
No. (%) with <6 donations/year	73 (62)	32 (86)
Mean Hb, g/dL	17.6	17.4
Median Hb, g/dL	17.7	17.5
No. (%) with ≥ 6 donations/year	44 (38)	5 (14)
Mean Hb, g/dL	17.8	17.6
Median Hb, g/dL	17.8	17.8

Hb, hemoglobin; TP, therapeutic phlebotomy; TRT, testosterone replacement therapy.

Discussion

Our blood center experienced an increased number of TPs during the study period, which was accompanied by increased TP orders for patients on TRT. We considered requesting an FDA variance for patients with testosterone-induced polycythemia; however, unlike TP collections from those with HH, which is an inherited disease, polycythemia due to TRT is an iatrogenic condition resulting from an excess dose of testosterone, and the benefits of TP are unproven. In addition, documentation of HH based on results of genetic studies is easy to obtain and well defined. We found it much more difficult to obtain documentation of appropriate indications for TRT from providers requesting TP for their patients, particularly from providers located in other states, so this was another obstacle that affected our decision to discontinue TP services for TRT patients.

The management of individuals on TRT is problematic for blood centers, because testosterone is not on the medication deferral list; hence, it is difficult to monitor how frequently patients with TRT-induced polycythemia present as regular blood donors. This is a concern for blood centers, since it alters the altruistic motivation for donation and may possibly affect blood safety. Of the 32% of men who continued to donate blood after discontinuation of TP services for patients on TRT, none developed positive infectious disease markers on our screening assays. The findings that the baseline Hb remained high before and after the change in our policy suggest that most of these individuals remained on testosterone, but those previously presenting for TP more frequently than the allowable 56-day interval for blood donation (six or more times yearly) may have adjusted their dosage to be able to continue to donate. No follow-up surveys were conducted to determine whether others had TPs arranged by their health care provider.

DOI: 10.1093/AJCP/AQAA019

Although we report a single blood center's experience, our findings likely reflect the increased trend of testosterone prescription practices. The limitations of this study include capillary Hb analysis using point-of-care testing, which may overestimate Hb compared with venous samples.[21] Nonetheless, the values were at the high end of the range for male volunteer blood donors (13-19 g/dL). In addition, in the course of reviewing patient orders, it was not part of our process to contact clinicians to try to educate them about adjusting the dosage to decrease the need for TP, nor was it our practice to determine whether the patient was on TRT for a medically confirmed indication for treatment. We also did not specifically inform the ordering physicians that they should not direct their patients to become volunteer blood donors, nor did we attempt to contact individuals with previous TP orders to determine whether they were still on testosterone, which is suggested by persistent elevation of Hb values in those who continued to donate blood.

This study also brings to light the role that transfusion medicine specialists, pathologists, and laboratory professionals play in the delivery of health care, whether it is located in a blood center, hospital, or other medical facility. While our blood center could have made the decision to start charging for this service, we had to question whether participating in the treatment of the secondary effect of testosterone-induced polycythemia was passively supporting the real issue of broad overuse of TRT due to false advertising, which lacks sound scientific evidence.

The Choosing Wisely campaign was established in 2012 by the American Board of Internal Medicine Foundation to support medical professionalism and improve the quality of health care.[22] Efforts are targeted at helping patients make informed medical decisions supported by evidence and curtailing costs due to overutilization of tests and procedures. The American Society for Clinical Pathology in 2015 recommended against prescribing testosterone therapy, unless there is laboratory evidence of testosterone deficiency.[23] Other medical and health care–related professional societies have also made Choosing Wisely recommendations related to testosterone therapy. Persistent concerns about overuse of prescription testosterone for "low T" suggest an opportunity for continued efforts to improve prescribing practices.

Conclusions

Our blood center observed an increased number of TP requests for polycythemia secondary to TRT from 2014 through 2016, consistent with increased prevalence of TRT in recent years cited in the literature due to marketing efforts for hormonal rejuvenation in men. After discontinuation of providing TP services for patients on TRT, we discovered that 32% of individuals with previous orders returned to donate as voluntary blood donors without indicating a need for TP. Our findings suggest that patients with TRT-induced polycythemia may be presenting to blood centers as voluntary blood donors to avoid TP charges.

Corresponding author: Nancy L. Van Buren, MD; Nancy.VanBurenMD@innovativeblood.org.

Acknowledgments: We are grateful for the assistance to Leanda Williams, donor suitability specialist at Innovative Blood Resources (a division of New York Blood Center enterprise), who contributed valuable data collection for this project.

References

1. Chin-Yee B, Lazo-Langner A, Butler-Foster T, et al. Blood donation and testosterone replacement therapy. *Transfusion.* 2017;57:578-581.
2. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2018;103:1715-1744.
3. Braun SR. Promoting "low T": a medical writer's perspective. *JAMA Intern Med.* 2013;173:1458-1460.
4. Handelsman DJ. Global trends in testosterone prescribing, 2000-2011: expanding the spectrum of prescription drug misuse. *Med J Aust.* 2013;199:548-551.
5. Handelsman DJ. Androgen physiology, pharmacology and abuse. In: DeGroot LJ, Jameson JL, eds. *Endocrinology.* 7th ed. Philadelphia, PA: Elsevier Saunders; 2015:2368-2393.
6. Stergiopoulos K, Brennan JJ, Mathews R, et al. Anabolic steroids, acute myocardial infarction and polycythemia: a case report and review of the literature. *Vasc Health Risk Manag.* 2008;4:1475-1480.
7. Marchioli R, Finazzi G, Specchia G, et al; CYTO-PV Collaborative Group. Cardiovascular events and intensity of treatment in polycythemia vera. *N Engl J Med.* 2013;368:22-33.
8. Giovanni CG, Rastrrelli G, Maseroli E, et al. Testosterone replacement therapy and cardiovascular risk: a review. *World J Mens Health.* 2015;33:130-142.
9. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. *N Engl J Med.* 2010;363:109-122.
10. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS One.* 2014;9:e85805.
11. Vigen R, O'Donnell CI, Baron AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA.* 2013;310:1829-1836.
12. US Food and Drug Administration. FDA evaluating risk of stroke, heart attack and death with FDA-approved testosterone products. FDA Drug Safety Communication. 2014. https://www.fda.gov/downloads/Drugs/DrugSafety/UCM383909.pdf. Accessed November 17, 2019.

DOI: 10.1093/AJCP/AQAA019

13. Endocrine Society. The risk of cardiovascular events in men receiving testosterone therapy. 2014. https://www.endocrine.org/-/media/endosociety/files/advocacy-and-outreach/position-statements/other-statements/the-risk-of-cardiovascular-events-in-men-receiving-testosterone-therapy-pdf?1a=en. Accessed November 18, 2019.
14. US Food and Drug Administration. FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use. FDA Drug Safety Communication. https://www.fda.gov/Drugs/DrugSafety/ucm436259.htm. Accessed November 18, 2019.
15. Handelsman DJ. Testosterone and male aging: faltering hope for rejuvenation. *JAMA*. 2017;317:699-701.
16. Morden NE, Woloshin A, Brooks CG. et al. Trends in testosterone prescribing for age-related hypogonadism in men with and without heart disease. *JAMA Internal Medicine*. 2019;179:446-448.
17. Bassil N, Alkaade S, Morley JE. The benefits and risks of testosterone replacement therapy: a review. *Ther Clin Risk Manag*. 2009;5:427-448.
18. Coviello AD, Kaplan B, Lakshman KM, et al. Effects of graded doses of testosterone on erythropoiesis in healthy young and older men. *J Clin Endocrinol Metab*. 2008;93:914-919.
19. Jones SD Jr, Dukovac T, Sangkum P, et al. Erythrocytosis and polycythemia secondary to testosterone replacement therapy in the aging male. *Sex Med Rev*. 2015;3:101-112.
20. US Food and Drug Administration. Guidance for Industry: Variances for blood collection from individuals with hereditary hemochromatosis. http://www.fda.gov/cber/guidelines.htm. Accessed November 22, 2019.
21. Patel AJ, Wesley R, Leitman SF, et al. Capillary versus venous haemoglobin determination in the assessment of healthy blood donors. *Vox Sang*. 2013;104:317-323.
22. Choosing Wisely. Our mission. https://www.choosingwisely.org/our-mission/. Accessed November 22, 2019.
23. Choosing Wisely. Thirty things physicians and patients should question. https://www.choosingwisely.org/societies/american-society-of-clinical-pathology/. Accessed November 22, 2019.

DOI: 10.1093/AJCP/AQAA019