Q&A column, 9/15

Editor: Frederick L. Kiechle, MD, PhD

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Submit a Question

Q. In the article on novel oral anticoagulants in the May 2015 issue of Archives of Pathology & Laboratory Medicine (139:687–692), a few blood products that are mentioned are not described. What is the composition of 3-factor PCC, 4-factor PCC, and FEIBA, and how are they prepared commercially?

A. Three-factor prothrombin complex concentrates (PCCs), 4-factor PCCs, and factor eight inhibitor bypass activity (FEIBA) are all factor concentrates that are created from large pools of allogeneic donor human plasma. As such, they are not recombinant and are typically derived through extraction methods (for example, affinity chromatography).[1] In addition, they are subjected to pathogen inactivation/removal treatments (such as nanofiltration and heat treatment), making them quite safe from the standpoint of transfusion-transmitted diseases.[1]

FEIBA and 3- and 4-factor PCCs all contain, to varying degrees, the vitamin K-dependent procoagulant factors II, VII, IX, and X.[1,2] However, the indications for the usage of these concentrates are quite different. Three-factor PCCs contain factors II, IX, and X, but they often harbor low levels of factor VII and thus may not be effective as solo agents in reversing vitamin K antagonists. Instead, 3-factor PCCs are primarily indicated as therapy for hemophilia B.[1,2] In contrast, 4-factor PCCs contain therapeutic levels of factor VII (in addition to the other vitamin K-dependent factors) and are primarily used for vitamin K antagonist reversal.[1,2] Finally, FEIBA also contains factors II, VII, IX, and X, but is specifically formulated to have most of its factor VII in the activated form (fVIIa). As such, FEIBA is primarily used as a bypass agent to induce clotting in hemophilia A and B patients who have developed inhibitors to factors VIII and IX, respectively, and who are bleeding.[1,2]

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Q. What is the current state of serum testosterone testing in the adult male population?

A. As a result of widespread direct-to-consumer marketing to middle-aged and elderly males of the availability of convenient androgen supplements,[1] there has been a dramatic increase in requests for testosterone testing, as these levels are necessary to establish the existence of androgen deficiency prior to treatment. A guideline from the Endocrine Society[2] deals with this topic in great detail, including recommendations for laboratory testing as well as recommendations regarding whom to test and therapeutic options. The Endocrine Society guideline is an excellent discussion; pathologists and other laboratory professionals who would like more detail on this topic are encouraged to read the document in its entirety. The critical point, however, is that in order for treating physicians to use the concentration thresholds cited in the document, laboratory directors must ensure that their laboratories' testosterone measurements are accurate.

One way to ascertain the accuracy of one's testosterone assay (whether immunoassay or liquid chromatography/mass spectrometry) is to participate in a proficiency test using commutable samples with reference method target values.[3] One such survey is the CAP Accuracy-Based Testosterone and Estradiol (ABS) Survey. Such Surveys indicate that many commercially available immunoassays are sufficiently accurate to be used for screening of adult males.[4] (There has been considerable controversy related to the use of automated testosterone immunoassays in children and women. In these populations, where much lower testosterone concentrations are encountered, the use of liquid chromatography/mass spectrometry is recommended because it typically exhibits increased analytical sensitivity and specificity.[5,6])

In adult men with signs and symptoms suggestive of androgen deficiency, a morning total testosterone level is an excellent screening test. Consistent with other endocrinopathies, the recommendation for testing in the morning relates to diurnal variation. Testosterone levels are typically highest in the morning; therefore, testing for deficiency is best performed at this time.

If the testosterone level, by a reliable assay, is greater than 280 ng/dL (10.4 nmol/L), androgen deficiency is essentially ruled out. Lower levels should be confirmed by measurement on a second (morning) sample. Testosterone levels well below 280 ng/dL (for example, less than 200 ng/dL) on two morning samples are consistent with a diagnosis of androgen deficiency.

For testosterone levels between 200 ng/dL and the 280 ng/dL threshold, additional testing for free testosterone may provide clarification. Such testing should be performed using equilibrium dialysis or by calculation from total testosterone, albumin, and sex hormone binding globulin (SHBG).[7] These additional tests may be beyond the scope of most clinical laboratories but can be obtained from reference laboratories. Assessment of free testosterone concentrations is typically needed only when total testosterone levels are reproducibly close to the 280 ng/dL threshold. In addition, it should be noted that one should probably avoid using analog free testosterone immunoassays.[2,8]

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2. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin*

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