# Q & A, 08/13

***Editor: Frederick L. Kiechle, MD, PhD***

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Submit a Question

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[pulledquote]Q. What are considered best practices for tracking re-sult trending in the lab? We use hemoglobin running mean in our hematology department because it is built into the analyzer software. The chemistry department will have a difficult time applying moving averages without purchasing middleware.[/pulledquote]

A. Applications of averages of patient data (AOP) have been used for almost 50 years.[1] An error condition is signaled when the average of consecutive centrally distributed patient data is beyond the control limits established for the average of the patient data. The assumption underlying AOP is that the patient population is stable and a significant change in the AOP would arise from an analytical shift. Perhaps the greatest value of AOP is that it permits assessment of an analyzer during the intervals when control materials are not being run. Control materials can be analyzed at any time without the requirement to accumulate patient specimen results, and thus are especially useful at instrument startup and after maintenance and recalibration.

AOP can be used retrospectively for quality assurance (for example, comparing the means of patient data from similar analytic systems housed in the same laboratory). The use of AOP for prospective quality control is complex and has significant limitations in the acute care (hospital) environment. The error-detection capabilities of AOP depend on several factors, with the most important being the number of patient results averaged and the variances of the patient population and analytical method.[2] Variations of AOP have been used extensively in hematology to monitor patient red blood cell indices and, indirectly, their constituent measurements, hemoglobin and red blood cell count as well as hematocrit.3-5 In a large Pennsylvania robotic reference laboratory, the exponential smoothing of truncated groups of 60 WBC, RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, RDW, platelets, neutrophils, and lymphocytes replaced the periodic analysis (once for every 60 patient specimens) of a commercial control.6 In addition to the patient moving averages, three levels of commercial controls were run at startup and then at eight-hour intervals. After implementing patient average quality control for one year, the hematology laboratory had saved $19,000 and $14,000—costs of quality control material and labor, respectively.

AOP is more suited to large reference laboratories that evaluate largely normal patients. In hospital laboratories, AOP can be shifted by changes in the proportion of patient samples originating from specific patient units or by changes in the proportions of patients with more severe illness. In hematology, for example, the averaging of a large number of specimens from a neonatal unit or hematology unit can cause the red blood cell indices to inappropriately indicate an out-of-control situation. In clinical chemistry, analysis of specimens from renal units will cause large shifts in the AOP of creatinine, glucose, and urea nitrogen. Hospital patient AOP is significantly influenced by longer-term, within-day, and within-week trends. During evenings and weekends, test volumes are reduced; this weekend and nightly testing is generally performed on more acutely ill patients. As a result, evening and weekend AOP will demonstrate higher proportions of out-of-control averages, including elevated glucose, low sodium, low protein, and low calcium averages.7 In reference laboratory testing, the patient data tend to be more centrally distributed and there is “natural randomization” of patient specimens, rendering AOP a powerful tool to

guarantee acceptable analytical performance. As hematology and chemistry analyzers become more precise and accurate, investigation of outlying AOP in hospital environments will more often demonstrate changes in patient mix rather than analytic shift. Over time, the applications of traditional prospective AOP, especially in hospital environments, will wane.


1. Hoffmann RG, Waid ME. The "average of normals" method of quality control. *Am J Clin Pathol.* 1965;43:134–141.
2. Cembrowski GS, Chandler EP, Westgard JO. Assessment of "average of normals" quality control procedures and guidelines for implementation. *Am J Clin Pathol.* 1984;81(4):492–499.
3. Bull BS, Elashoff RM, Heilbron DC, et al. A study of various estimators for the derivation of quality control procedures from patient erythrocyte indices. *Am J Clin Pathol.* 1974;61(4):473–481.
4. Cembrowski GS, Westgard JO. Quality control of multichannel hematology analyzers: evaluation of Bull's algorithm. *Am J Clin Pathol.* 1985;83(3):337–345.
5. Lunetzky ES, Cembrowski GS. Performance characteristics of Bull's multirule algorithm for the quality control of multichannel hematology analyzers. *Am J Clin Pathol.* 1987;88(5):634–638.
6. Cembrowski GS, Parlapiano E, O'Bryan D, et al. Successful use of patient moving averages (PMA) as an accuracy control for multichannel hematology analyzers in a high-volume robotic clinical laboratory (abstract). *Lab Hematol.* 2001;7:35. Abstract 3.
7. Cembrowski GS. Thoughts on quality-control systems: a laboratorian's perspective. *Clin Chem.* 1997;43(5):886–892.



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[pulledquote]Q. We are using the Advia Centaur assay to measure testosterone, which has a level of detection of 10 ng/dL. Will reporting <10 ng/dL be sufficient for clinicians to diagnose a child? [/pulledquote]

A. There are three aspects to this question: **1)** What is the lowest value one can reliably report with any given assay? **2)** How are testosterone measurements used in the care of children? **3)** Are testosterone immunoassays in general (and Advia Centaur in particular) reliable enough to use in pediatric patients?

With respect to the first question, two terms are commonly used (and confused) in determining the lowest values one can report: limit of detection and limit of quantitation.[1] The first, limit of detection, is typically determined by performing the assay on the zero standard 20 times, and then determining from the standard curve the concentration corresponding to the mean plus two standard deviations of those measurements. The latter, limit of quantitation, is comparable to "functional sensitivity"; it is always a higher concentration than the limit of detection. The limit of quantitation is determined by finding the imprecision of pools of patient samples at various (low) concentrations and finding the lowest concentration at which the coefficient of variation does not exceed some arbitrary limit (usually 10 percent or 20 percent).

The package insert for the Advia Centaur testosterone assay2 cites the limit of detection as 10 ng/dL but provides no value for the limit of quantitation. For comparison, another manufacturer's package insert for its testosterone immunoassay cites a limit of detection of 2.50 ng/dL and a limit of quantitation, using a 20 percent threshold for imprecision, of 12.0 ng/dL.

To answer the second question, testosterone measurements in children are generally made for the classification and monitoring of congenital adrenal hyperplasia and adrenal insufficiency, in the diagnosis of polycystic ovarian syndrome in girls, and in evaluating precocious or delayed puberty in boys. It is only in evaluating delayed puberty that precise determination of results <10 ng/dL is likely to be important.

Perhaps more important, though, is the third question: Should immunoassays for testosterone be used at all for pediatric samples? Although the assays may be "FDA approved," many experts believe that most immunoassays are not reliable enough to be used in pediatric (or even adult female) patients, because values in these populations are typically in the low range (1–50 ng/dL), where imprecision and cross-reacting substances may cause clinically significant problems.3-7

In other words, for Advia Centaur in particular, for which the manufacturer provides no limit of quantitation, the reproducibility of all results in the low range (even those with numbers above 10 ng/dL) may be poor, and there are published data to suggest that numerical values obtained may not represent testosterone at all.
More generally, testosterone immunoassays, regardless of manufacturer, should be used with caution, if at all, in children and in adult females.


1. Clinical and Laboratory Standards Institute. Protocols for determination of limits of detection and limits of quantitation; approved guideline. CLSI document EP17-A. Wayne, Pa.: CLSI;2004.
2. Siemens [package insert]. Testosterone *111751 Rev. N,* 2009-07.
3. Rosner W, Auchus RJ, Azziz R, Sluss PM, Raff H. Position statement: Utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement. *J Clin Endocrinol Metab.* 2007;92(2):405–413.
4. Taieb J, Mathian B, Millot F, et al. Testosterone measured by 10 immunoassays and by isotope-dilution gas chromatography-mass spectrometry in sera from 116 men, women, and children. *Clin Chem.* 2003;49(8):1381–1395.
5. Herold DA, Fitzgerald RL. Immunoassays for testosterone in women: better than a guess? Clin Chem. 2003;49(8):1250–1251.
6. . Accessed Nov. 2, 2012.
7. Kushnir MM, Blamires T, Rockwood A, et al. Liquid chromatography-

tandem mass spectrometry assay for androstenedione, dehydroepiandrosterone, and testosterone with pediatric and adult reference intervals. *Clin Chem.* 2010;56(7):1138–1147.

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[pulledquote]Q. An age-old problem exists regarding the differentiation of allergic rhinitis/sinusitis from an infectious etiology (bacterial or viral). The distinction has been based primarily on clinical signs and symptoms. Would a simple nasal swab stained for eosinophils help differentiate an allergic from an infectious etiology?[/pulledquote]

A. Unfortunately, the presence of eosinophils or Charcot-Leyden crystals, or both, is not completely specific for allergic rhinitis/sinusitis. This is because allergic fungal sinusitis is an entity that includes the presence of viable fungal elements in an allergic mucous. Apart from this entity, the presence of eosinophils and evidence of their products is definitely useful, in conjunction with other studies, for the diagnosis of allergic rhinitis/sinusitis.

Chang C, Gershwin ME, Thompson GR 3rd. Fungal disease of the nose and sinuses: an updated overview. *Curr Allergy Asthma Rep.* 2013;13(2):152–161.

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