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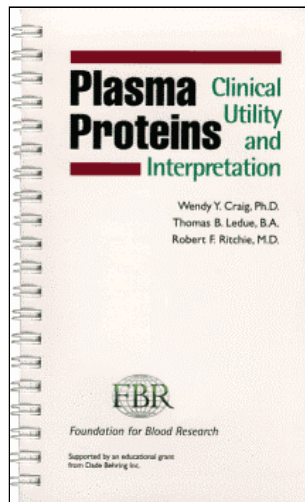
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PLASMA PROTEIN BOOK

Serum protein testing has been an integral, although underutilized, part of clinical laboratory science for many years. As our appreciation for the power of these measurements in clinical practice grows, so does the need for continued education. At the RDL, where serum proteins are our major research focus, work has centered on state-of-the-art methodology with relevant reference ranges and clinical data, to improve the interpretations of serum protein data in clinical practice.

As a result of our long experience in this field, we were asked by Dade-Behring, Inc. to develop a guidebook to serum protein analysis for practitioners and laboratorians in clinical practice. “*Plasma Proteins: Clinical Utility and Interpretation*” is a

distillation of the current world literature on the subject. The information contained in the book is fully indexed, and is presented both from the perspective of a given disease state (Section I), as well as from the perspective of individual proteins (Section II). The book may be ordered by calling (207-883-4131). Only limited quantities are available.



TWO NEW LABORATORY TESTS AVAILABLE

hsCRP: A NEW MARKER FOR CHD RISK

Both basic and clinical research studies have demonstrated that inflammation is a central process in the development of atherosclerosis.¹ Injured epithelial cells and activated macrophages at the arterial endothelium elaborate chemotactic factors, adhesion molecules, and growth factors, resulting in a cycle of damage and inflammation, and the development of a typical atherosclerotic lesion.

Levels of C-reactive protein (CRP), an acute phase protein, rise during infection, inflammation, and tissue trauma. Traditionally, CRP has been measured using methods with sensitivity to ~0.5 mg/dL. In 1998, we published the first laboratory evaluation of a new, high sensitivity CRP (hsCRP) test in which levels down to 0.0175 mg/dL were obtained with excellent precision.²

Since that time, data from at least 10 studies involving tens of thousands of patients³ have revealed that low levels of CRP – levels within the range presently considered normal – may indicate a silent atherosclerosis six or more years prior to clinical expression of coronary heart disease (CHD).⁴ New research indicates that hsCRP may be a good indicator for propensity for plaque instability, that is the process by which plaque may rupture.⁵ When combined with blood lipid measures (see Table 1), hsCRP has been reported to add to the prediction of first myocardial infarction.⁶

Note: Although the evidence convincingly suggests an association between CRP and cardiovascular disease risk one must be aware that there are many medical and nonmedical events that may have increased CRP

levels. Thus, the patient should be metabolically stable before being tested for cardiovascular risk.

Table 1: CHD risk evaluation using hsCRP

		hs-CRP level (mg/dL)		
		<0.072	0.072 to 0.169	>0.169
		Relative Risk of First MI		
TC (mg/dL)	>223	2.3	4.3	5.3
	191 - 223	1.4	1.5	2.3
	<191	1.0	1.2	1.1
TC:HDLC ratio	>5.01	2.8	3.4	4.4
	3.78 - 5.01	1.2	2.5	2.8
	<3.78	1.0	1.1	1.3

Abbreviations: TC, total cholesterol; HDLC, high density lipoprotein cholesterol.

References on p. 4

CELIAC DISEASE TESTING: ANTI- tTG ANTIBODY

Celiac disease (CD), which is classically associated with gastrointestinal symptoms, may also present with more nonspecific complaints, such as fatigue and arthralgia (see RDL Newsletter Vol 11 No. 1).⁷ Clinically overt CD is seen in 0.4-0.5% of the general population, with a higher frequency (1-4%) in certain subgroups such as type I diabetics.^{7,8} Identification of patients with CD is important, as treatment may help prevent growth retardation in pediatric cases, as well as some of the late consequences of the disease such as intestinal lymphoma. Although intestinal biopsy remains the gold standard for the diagnosis of CD, advances in serologic testing have allowed this approach to play an increasing role as a diagnostic aid.

The combination of testing for IgG and IgA anti-gliadin antibodies (AGA: high sensitivity) and IgA anti-endomysial antibodies (EmA: high specificity) has become a frequent approach in serologic testing for CD (Table 2). Despite excellent diagnostic performance, however, the IgA EmA test is not offered widely, due to the technical and semi-quantitative nature of the indirect immunofluorescence assay method.

Recently, tissue transglutaminase (tTG) was identified as the predominant autoantigen responsible for EmA activity in CD;⁹ tTG is expressed in many cell types both intra- and extracellularly and has been shown to play a role in cell adhesion and wound healing after

tissue injury.¹⁰ The physiologic mechanism that links tTG to CD is not fully understood, although gliadin is a major substrate for this enzyme. These findings have allowed the development of a high-throughput, quantitative ELISA assay with similar diagnostic characteristics to the EmA assay; there is 95% concordance between the two assays.¹¹ As a diagnostic tool for untreated CD, the direct IgA anti-tTG assay improves on the sensitivity of other serologic testing options (Table 2),¹² although it remains slightly less specific a test than IgA EmA, most likely because the latter indirect immunofluorescence test detects additional, though minor, autoantibody reactivities.¹³ Its major advantage is perhaps in the quantitative nature of the data, which may prove more useful for monitoring celiac disease patients than the semi-quantitative approach.

Table 2: Clinical performance of serologic tests for celiac disease

Test	Sensitivity	Specificity	Monitor ^{11,14,15} dietary compliance	Detected in IgA deficiency
IgA EmA	85-95%	97-100%	yes	no
IgA AGA	80-90%	85-95%	yes	no
IgG AGA	75-85%	75-90%	less useful	yes
IgA + IgG AGA	95%	75-95%	-	-
IgA tTG	95-98%	95%	yes	no

** False negative results may occur among the 3% of CD patients who are IgA deficient. Thus, IgA deficiency should be evaluated among patients with clinical symptoms strongly suggestive of CD, but negative serology.*

In conclusion, the three categories of serologic tests now available – anti-gliadin antibodies (AGA), anti-endomysial antibodies (EmA) and, most recently, anti-transglutaminase antibodies (tTG) – have different and often complementary functions in the detection and monitoring of CD. Using combinations of these tests may maximize the utility of serologic testing in the diagnosis of celiac disease

References on p. 4

MEDICARE PART B: APOLIPOPROTEIN TESTING

Effective January 31, 2001, Medicare has established a local medical review policy for Apolipoproteins (A1, B and Lp(a)). The following ICD-9 CM codes support medical necessity for these tests:

- 272.0 Pure hypercholesterolemia
- 272.1 Pure hyperglyceridemia
- 272.2 Mixed hyperlipidemia
- 272.3 Hyperchylomicronemia
- 272.4 Hyperlipidemia, other and unspecified
- 272.5 Lipoprotein deficiencies
- 272.9 Lipoid metabolism, unspecified disorder
- 410 Acute myocardial infarction
- 411 Ischemic heart disease, other acute and subacute forms
- 412 Myocardial infarction, old
- 413 Angina pectoris
- 414 Ischemic heart disease, other chronic forms
- 429.2 Cardiovascular disease, unspecified
- 429.9 Heart disease, unspecified
- 436 Cerebrovascular disease, acute but ill-defined
- 437 Cerebrovascular disease, other and ill-defined
- 440 Atherosclerosis
- 443.9 Peripheral vascular disease, unspecified

In response to these changes we have redesigned the General Requisition form to include space for insertion of ICD-9 codes. In addition, the back of the requisition includes an updated Advance Beneficiary Notice in the event that the physician in conjunction with the patient have decided to order this service for non-covered medical reasons. If you have not received these new forms please call Lynda Leavitt at (207) 883-4131. For additional policy information on apolipoproteins, please consult your local Medicare bulletin.

MODEL COMPLIANCE PLAN

Information regarding FBR's Model Compliance Plan is now posted on our website. The site (www.fbr.org) includes information related to medical necessity and laboratory testing, completing an Advance Beneficiary Notice, and other relevant information.

FBR's LABORATORY RESOURCE GUIDE ***AVAILABLE ON FBR WEB SITE***

FBR's web site (www.fbr.org) now includes the most recent version of the FBR *Resource Guide*. The *Guide* contains extensive details on all of FBR's laboratory

services and programs and is a convenient tool for seeking detailed information regarding laboratory licenses, business hours, specimen collection techniques, CPT codes, instructions for completing a requisition, and physician and patient educational resources, etc. Highlighted keywords simplify searches. You may wish to place a bookmark for this site on your Internet browser for quick reference

Q&A FBR GENERAL REQUISITION

Our requisition is designed to allow flexibility in test ordering. If you have any questions about using the requisition, please let us know; we will publish frequently asked questions in this space.

Q. How do I order hsCRP testing?

A. This test is listed under "individual Studies", as C-reactive protein, high sensitivity. The test requires 2 mL of serum.

Q. How do I order tTG testing?

A. This test may be ordered by checking the box for tissue transglutaminase under "Celiac Disease" on the general requisition form. The test requires 2 mL of serum.

Q. What is the best way to provide specific ICD-9 codes when I request apolipoprotein testing?

A. The latest version of the FBR general requisition includes a space (marked in RED) next to each apolipoprotein check-off box, where the appropriate ICD-9 code may be inserted. Please remember to provide this information whether tests are ordered individually or as part of a profile.

RDL RESEARCH NEWS

Population Study of Hemochromatosis. FBR scientists are working collaboratively with investigators from the Wolfson Institute for Preventive Medicine (London University) to study a cohort of 10,000 healthy adults to learn more about the prevalence of genetic variants that are responsible for hemochromatosis and the extent to which those variants lead to iron overload and health problems.

Recent publications

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