

Antiquated Tests Within the Clinical Pathology Laboratory

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Objective: To provide evidence supporting the discontinuation of laboratory tests that do not have clinical utility today.

Study Design: We selected 10 representative tests considered antiquated by most experts in the clinical laboratory medicine field: creatine kinase-MB, myoglobin, serum folate and red blood cell folate, amylase, lecithin/sphingomyelin ratio, qualitative serum human chorionic gonadotropin, prostatic acid phosphatase, bleeding time, and erythrocyte sedimentation rate.

Methods: Published literature was reviewed to provide evidence of the poor performance and/or limited clinical utility of these tests. When available, subscriptions to the Proficiency Testing Program of the College of American Pathologists were tracked from 1993 to 2008 as supporting evidence. Finally, when appropriate, alternative testing was suggested.

Results: The data show clearly that there is a national trend toward reduction or elimination of these 10 tests.

Conclusion: Together with their clinical colleagues, clinical laboratorians should review their menu of tests and consider removing tests that do not provide clinical benefit. In most cases, alternative tests are already in clinical use.

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Given the current economic climate for medical practices, it is the responsibility of clinical laboratory directors in hospitals and medical centers to review their test menu and, in collaboration with their clinical staff leaders, remove tests that do not provide clinical value to a particular medical practice, whether such testing is conducted in-house or sent to a reference laboratory. However, many physicians who are experienced with the use of older tests may resist adoption of newer technologies even if the tests have been shown to have superior clinical value or are recommended in contemporary clinical guidelines. Changing the testing menu can be a difficult process and should involve laboratorians and the medical staff, especially the staff who frequently order the tests that are to be eliminated. This article provides documentation for laboratorians who are considering the removal of tests from their menu and can serve as an educational platform for discussions with clinical colleagues.

Here we have selected 10 tests that most experts consider antiquated in clinical laboratory medicine: creatine kinase-MB (CK-MB), myoglobin, serum folate and red blood cell folate, amylase, lecithin/sphingomyelin (L/S) ratio, qualitative serum human chorionic gonadotropin (hCG), prostatic acid phosphatase, bleeding time, and erythrocyte sedimentation rate (ESR). There may be many other tests that can be eliminated after a systematic review. After examination of the literature, we have provided published evidence for these tests' limited diagnostic and clinical utility. As supporting evidence, when possible, we have provided subscription trends from the College of American Pathologists (CAP) Proficiency Testing Program to examine trends in the subscription as a surrogate for the clinical utilization of these tests among participants. Finally, when appropriate, we have suggested alternate testing that should replace the antiquated methods.

CREATINE KINASE-MB AND MYOGLOBIN

The use of CK-MB isoenzymes as markers for acute myocardial infarction (AMI) dates back to the early 1970s with enzymatic measurement by electrophoresis.¹

Currently, most laboratories use the automated mass assays for CK-MB described in the mid-1980s.² Release of CK-MB into

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the blood occurs in patients with heart or skeletal muscle injury or disease. A calculation of the CK-MB amount relative to total CK measurements (relative index) has been useful to differentiate the source of CK-MB release. Following AMI, there is a delay in the appearance of CK-MB due to its relatively large size (84 kDa). The clinical interest in myoglobin dates to the early 1990s with the development of automated immunoassays.³ Myoglobin is a smaller protein than CK-MB (17 kDa) and is released into the blood sooner than CK-MB after the onset of AMI. Myoglobin also is released into the blood of patients with skeletal muscle injury, and the clearance of myoglobin is retarded in cases of renal damage. Each condition leads to increased blood concentrations. The isoenzymes of lactate dehydrogenase can differentiate between release of this enzyme because of cardiac damage and release from other organs such as the liver or lungs.

The development and implementation of, and continued improvements in, cardiac troponin have put in question the need for clinical laboratories to offer CK-MB, myoglobin, and lactate dehydrogenase isoenzymes. Unlike those biomarkers, release of troponin T or I is specific to cardiac injury. When the myocyte is irreversibly damaged, there is an initial rise in troponin due to its release from the free cytosolic pools, followed by a prolonged increase due to degradation of the myofibrils. Using first-generation assays, troponin becomes detectable in blood at the same time as CK-MB and remains elevated longer than CK-MB or lactate dehydrogenase.⁴ With improvements in analytical sensitivity and use of the 99th percentile as a cutoff limit for AMI, as recommended by the Task Force for the Redefinition of Myocardial Infarction,⁵ troponin is released before CK-MB and appears in the blood as early as if not earlier than myoglobin after AMI onset.⁶

Based on the CAP Cardiac Markers Survey (**Table**), utilization of CK-MB and myoglobin has undergone a gradual decline in subscriptions in recent years. In contrast, the corresponding proficiency survey subscription rate for cardiac troponin has remained steady or slightly increased (data not shown). Critics opposed to the removal of CK-MB and/or myoglobin argue that because troponin remains increased for 5 to 7 days, the test cannot determine the presence of a reinfarction. However, in a case series, Apple and Murakami showed that troponin tracks closely with CK-MB.⁷ Moreover, in a controlled coronary care unit environment, measurement of total CK, a test that is not considered obsolescent, can be used to detect a reinfarction. Total CK also can be important in the evaluation of patients with skeletal muscle

Take-Away Points

Although the clinical laboratory plays a critical role in management of patients in both disease and health, some tests have been replaced by others and no longer provide value.

- Newer analytes such as troponin, prostate-specific antigen, and C-reactive protein have replaced creatine kinase-MB, myoglobin, and lactate dehydrogenase; prostatic acid phosphatase; and the erythrocyte sedimentation rate, respectively.
- The need for folate testing has been dramatically reduced with the supplementation of dietary folic acid.
- Testing technologies have improved, making bleeding time, the lecithin/sphingomyelin ratio, and amylase redundant or unnecessary.

injury and/or diseases such as Duchenne muscular dystrophy or rhabdomyolysis.

Others have advocated retention of the CK-MB test to make estimates of infarct size. Such assessments require measurement of the area under the enzyme versus time curve, and are inaccurate when there is reperfusion of the target vessel. Cardiologists should not delay in treating patients to obtain peak CK-MB levels to document infarct size, as the objective of early intervention is to minimize the extent of myocardial damage. If determination of the severity of AMI is desired, some investigators have shown that single-point troponin measurements equate to infarct size.⁸ Today, myoglobin testing has largely been discontinued by clinical laboratories. It is likely that more laboratories will abandon CK-MB testing in the near future as well.

SERUM FOLATE AND RED BLOOD CELL FOLATE

A deficiency in folic acid and vitamin B₁₂ is one cause of macrocytic anemia. The detection of low folate concentrations in serum or red blood cells is useful for finding folic acid deficiencies. Red blood cell folate is thought to be more reflective of tissue stores, but requires an extraction step prior to analysis.⁹ In January and November 1998, the United States and Canada, respectively, mandated that foods with processed grains be fortified with folic acid. Dietary folate supplementation has resulted in a significant decline in the incidence of folate deficiency.¹⁰⁻¹³ The incidence of folic acid deficiency was even low in indigent patients, in whom dietary deficiency would be expected to be more prevalent.⁹ Therefore, routine screening of serum and/or red blood cell folate as a means to evaluate patients with anemia is difficult to justify. Shojania has shown that folate deficiency is also a rare cause of untreated celiac disease.¹⁴ For the rare patients suspected of such a deficiency, many clinicians now suggest that simply treating with folic acid is a more cost-effective approach than blood testing.¹⁵ For laboratories testing international populations in which there is no folate supplementa-

■ **Table.** Enrollments in the College of American Pathologists Proficiency Surveys for Selected Laboratory Analytes

CK-MB ^a		L/S Ratio ^b		Acid Phosphatase ^c		RBC Folate ^d		ESR ^e	
Year	No.	Year	No.	Year	No.	Year	No.	Year	No.
1993	3046	1994	218	—	—	—	—	—	—
1996	3234	1996	262	1996	372	1997	244	—	—
1999	3531	1999	189	1999	274	1999	355	1999	4114
2002	3411	2002	138	2002	142	2002	258	2002	3484
2005	2706	—	—	2005	95	2005	273	2005	2825
2008	2723	2007	71	2008	46	2008	230	2008	3138
2010	2741	2010	49	2010	35	2010	236	2010	3513

CK-MB indicates creatine kinase-MB; ESR, erythrocyte sedimentation rate; L/S, lecithin/sphingomyelin; RBC, red blood cell.

^a22% decline from peak of 1999 for CK-MB.

^b81% decline from peak of 1996 for the L/S ratio.

^c91% decline from peak of 1996 for acid phosphatase.

^d34% decline from peak of 1999 for RBC folate.

^e19% decline from peak of 1999 for ESR.

tion, this testing may be warranted. If deficiencies are found, follow-up testing may be important to determine therapeutic efficacy of folate fortification.

AMYLASE

Amylase and lipase are digestive enzymes normally released from the acinar cells of the exocrine pancreas into the duodenum. Following injury to the pancreas, these enzymes are released into the circulation and cause a subsequent increase in their measured activity. Both amylase and lipase are low-molecular-weight enzymes (40-50 kDa) and are filtered through the glomerulus. Amylase is cleared in the urine, whereas lipase is reabsorbed back into the circulation. In patients with acute pancreatitis, the activities are greatly increased in serum above the reference range. There is historic confusion regarding the clinical utility and enzyme profiles of amylase and lipase in acute pancreatitis.¹⁶ This confusion stems from the discovery that lipase assays devoid of colipase and bile salts were an insensitive and imprecise measure.¹⁷ As these constituents are now incorporated into all commercial reagents, lipase has clinical sensitivity equivalent to that of amylase and superior clinical specificity.¹⁸ For example, amylase is increased in patients with salivary gland inflammation.¹⁹ The salivary isoenzyme also can bind with immunoglobulin to form a macromolecular complex that is not cleared from the circulation, and persistent elevations are observed in the absence of pancreatic diseases.²⁰ Werner et al showed that there was no diagnostic advantage to combining results of lipase and amylase tests compared with the clinical performance of the individual tests.²¹ The development of assays for the pancreatic amylase isoenzyme has improved the specificity of the test.²² However, if the objective of amylase and lipase testing is to detect pan-

creatic diseases, amylase provides redundant information and elimination of this test can be considered.

It should be noted that lipase and amylase testing is performed on routine clinical chemistry analyzers at minimal incremental reagent costs, and the cost savings to the laboratory in eliminating amylase will be marginal. Nevertheless, elimination of a nonspecific test may mean less diagnostic confusion and fewer unnecessary workups for a patient with a nonspecific increase in amylase activity. It also opens up a “reagent channel” on the chemistry analyzer that can be used for another test.

LECITHIN/SPHINGOMYELIN RATIO FOR FETAL LUNG MATURITY

First reported in 1971, the L/S ratio, determined by thin-layer chromatography, was the first biochemical test for assessing the maturity of fetal lungs. Many outcome studies have demonstrated that the L/S ratio has good sensitivity (80%-100%) and specificity (70%-97%).²³ Because it was the first test developed, it was long considered to be the gold standard for assessing fetal lung maturity. However, today, use of L/S testing has become largely obsolete and has mostly been replaced by fluorescent polarization and lamellar body counts.

Reports have suggested that the volume of *all* fetal lung maturity testing is decreasing nationally, with one laboratory demonstrating a 64% decrease in test volumes from 1994 to 2004.²⁴ Among tests of fetal lung maturity, the frequency of L/S ratio testing in the United States has declined the most dramatically (Table). Results of a survey of 417 physicians indicated that their use of the L/S ratio had decreased by 70%, in contrast to a 35% decrease for fluorescence polarization.²⁴ The reason for this dramatic decrease in the use of the L/S ratio is likely multifactorial.

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A commercial assay for assessing the L/S ratio exists (Fetal-Tek 200, Helena Laboratories, Beaumont, TX), but it is used by only just over half of all laboratories that perform L/S ratio testing.²⁵ Still, there is poor interlaboratory precision even among those using the commercial method. In addition, there is great variability in the cutoff used for identifying lung maturity between laboratories. This poor precision, variability in cutoffs, and declining testing volume led CAP to issue a statement indicating that it is likely that consensus in proficiency testing results will only be seen in extremely mature or extremely immature results.²⁵ In contrast, among the laboratories that use fluorescent polarization, 98% use the commercially available Abbott TDx FLM II method, and the coefficient of variation between laboratories was less than 7.2% for all 3 materials tested.²⁶

Multiple studies have compared the utility of the L/S ratio and fluorescent polarization in predicting fetal lung maturity.^{23,26-28} These studies have shown that fluorescent polarization performs like the L/S ratio, with ~100% sensitivity and ~70% specificity.²³ In addition, the TDx FLM II test can be performed rapidly, requires no sample extraction, and is considerably simpler to perform than the L/S ratio test. Unfortunately, the manufacturer (Abbott Laboratories) may be removing this test from the market.

Likewise, multiple studies have compared the utility of L/S ratio and lamellar body counts in predicting fetal lung maturity.^{29,30} A meta-analysis that examined these data demonstrated that the lamellar body counts performed slightly better than the L/S ratio in the prediction of respiratory distress syndrome.²⁹ The lamellar body count test also can be performed rapidly, requires no sample extraction, and is considerably simpler to perform than the L/S ratio test. In consideration of all these factors, it is clear that fluorescent polarization and lamellar body counts are the preferred methods of testing for fetal lung maturity.

QUALITATIVE SERUM HUMAN CHORIONIC GONADOTROPIN

The qualitative detection of hCG in urine through the use of rapid, point-of-care test devices is a well-established practice in healthcare for identifying pregnancy. The analytical performance of these tests has been extensively studied, although contemporary reports of their clinical performance are scarce.^{31,32} This latter point is important, as the analytical technology for detecting hCG has changed dramatically since it was first introduced in the 1970s. The National Academy of Clinical Biochemistry concluded that, despite their widespread use, there are no data to demonstrate that the use of qualitative urine hCG tests improved patient outcomes, and noted that clinical outcome studies using current analytical technologies were needed.³²

The qualitative detection of hCG in urine is a test granted waived status under the Clinical Laboratory Improvement Amendments. In contrast, use of serum as a sample matrix is considered a moderately complex test, even when the test device itself is approved for use with either urine or serum. The difference in test complexity status is because serum, not whole blood, must be analyzed and centrifugation of the specimen is necessary. As such, the majority of qualitative serum hCG tests are performed in laboratories and not at the point of care, leading one to question the clinical need for this type of testing in any circumstance. The following arguments can be made in favor of discontinuing the use of qualitative serum hCG tests.

First, the inability to perform serum testing at the point of care necessitates sending the collected specimen to the laboratory for processing and testing. A primary contributor to the turnaround time of laboratory tests that are performed rapidly is the time required for specimen transport to the laboratory. Many clinical laboratories have the ability to perform quantitative serum hCG analyses, and the analytical time for these immunoassays is brief (~10-20 minutes). That is only slightly longer than the time required to perform qualitative testing, but produces more accurate results (see below).

Second, qualitative hCG tests are less analytically sensitive than quantitative tests. Although analytical thresholds vary by device, these tests are designed to produce a positive result when the hCG concentration is 10 to 25 IU/L. In contrast, quantitative hCG tests are more exquisitely sensitive, with limits of detection as low as 1.0 IU/L. Given that the only clinical use of a qualitative serum hCG test is to detect (or rule out) a possible pregnancy, then the most sensitive test available should be utilized. This is particularly true in the healthcare setting (the *only* setting in which serum hCG testing could be performed), where pregnancy status must be determined prior to an intervention that is potentially harmful to a fetus. In short, serum is a technically demanding specimen to obtain, and qualitative serum hCG analyses cannot currently be performed bedside. Therefore, in cases where a serum specimen has been collected and transported to the laboratory, there is no reason to perform a clinically and analytically less sensitive qualitative test when a quantitative test is readily available.

PROSTATIC ACID PHOSPHATASE

Until the introduction of prostate-specific antigen (PSA) in the 1980s, serum prostatic acid phosphate was the only tumor marker used for prostate cancer in the preceding 50 years. In the 1930s, a phosphatase with activity at acidic pH was discovered to be increased in prostate cancer tissue and sera, and was subsequently introduced as a tumor marker.³³ Acid phosphatases are lysosomal isoenzymes found in secretory

epithelial cells that hydrolyze phosphate monoesters with an optimal activity below pH 7.0. Acid phosphatase is found in the prostate epithelium as well as in erythrocytes, leukocytes, bone, liver, and other cells and tissues.^{34,35} The prostate form is inhibited by tartrate, which can aid in distinguishing it from the other forms. Substrates more specific for prostatic acid phosphate (eg, thymolphthalein monophosphate, α -naphthyl phosphate) have been used for the measurement of enzymatic activity. Immunoassays also have been developed, although enzymatic activity methods are preferred.³⁴

Similar to PSA, prostatic acid phosphate can be elevated in benign prostate conditions and can be affected by prostate manipulations. Unlike PSA, prostatic acid phosphate is not prostate-specific and can be increased in other benign and malignant diseases. Prostate-specific antigen is more sensitive for the early detection of prostate cancer because prostatic acid phosphate is more likely to be elevated only in men with advanced-stage disease; prostatic acid phosphate also has been replaced by PSA for monitoring therapy.^{34,35} The National Academy of Clinical Biochemistry, the European Group on Tumor Markers, and the Canadian Society of Clinical Chemists all have declined to recommend the use of prostatic acid phosphate, stating that the marker provides no clinical benefit in addition to that of PSA.³⁶⁻³⁸ As an individual marker, prostatic acid phosphate may be useful for disease management in the rare patient whose tumor does not secrete PSA³⁸ and may have utility when combined with other markers for improving prostate cancer detection³⁹ or predicting recurrence after radical prostatectomy.⁴⁰ The demise of the prostatic acid phosphate test can be ascertained from recent CAP proficiency survey participation data (Table). In 2010, more than 2200 laboratories (16 methods/instruments) reported PSA results, whereas 35 laboratories reported prostatic acid phosphate results.

BLEEDING TIME

The bleeding time test was initially developed as an *in vivo* test of primary hemostasis to assess formation of a platelet plug.⁴¹ Abnormal results may be observed in a variety of conditions including use of various drugs (eg, aspirin, alcohol, nonsteroidal anti-inflammatory drugs), platelet disorders including thrombocytopenia and inherited disorders, low hematocrit, and various medical conditions such as uremia, liver disease, and diabetes.^{42,43} The original bleeding time test was called the Duke bleeding time. In this test the earlobe or fingertip was pierced with a lancet. Subsequently, the Ivy bleeding time was introduced. This version used a blood pressure cuff on the arm inflated to 40 mm Hg and a lancet to make a cut on the forearm. The most recent modification is known as the Mielke bleeding time. This version uses a

template to standardize the length and depth of the cut on the forearm. Despite these modifications, the test continues to be affected by many technical issues such as skin thickness, temperature, and variations in operator performance of the test.^{41,42}

Historically, the most common indication for performing a bleeding time test was as a screening test to assess the risk of bleeding during planned surgery or procedures.⁴² However, the test lacks sensitivity and specificity and does not predict bleeding risk in patients with a negative bleeding history.⁴³ Other proposed uses of the bleeding time include screening for platelet disorders and evaluating the effect of treatment in conditions such as uremia.^{42,44} In a meta-analysis, 862 articles concerning the utility of the bleeding time were reviewed.⁴⁴ This analysis included the ability of the test to detect aspirin intake (highly variable results), to predict surgical bleeding (no statistical significance), to evaluate bleeding in uremia (no better than platelet count and hematocrit), and to predict bleeding following procedures (for renal biopsy, the test did not change *a priori* estimates of bleeding risk). In 1998, a position statement by CAP and the American Society of Clinical Pathologists concluded that “the bleeding time fails as a screening test and is, therefore, not indicated as a routine preoperative test.”⁴¹

There continue to be occasional reports in the literature concerning applications of the bleeding time in selected clinical settings. For example, Posan et al reported a comparison of the bleeding time with the platelet function analyzer (PFA-100) when screening for von Willebrand disease and intrinsic platelet hypofunction, and found that the PFA-100 could replace the bleeding time for this application.⁴⁵ However, the accumulated literature on the bleeding time test has consistently shown that the test does not predict bleeding prior to planned surgery or procedures, cannot accurately predict aspirin exposure, and can be replaced by other tests to evaluate platelet function in specialized applications such as platelet aggregometry and testing for aspirin⁴⁶ and clopidogrel resistance.⁴⁷

ERYTHROCYTE SEDIMENTATION RATE

The clinical utility of the ESR, a nonspecific test used to evaluate inflammation, depends on the clinical setting, the availability of other more specific tests, and the patient population. An elevated ESR indicates the presence of acute-phase reactants that rise in concentration during the initial inflammatory stage. Several acute-phase reactants such as fibrinogen, alpha-1 antitrypsin, and C-reactive protein are regulated by cytokines released by monocytes and macrophages.⁴⁸ Although many of the acute-phase reactants can be measured

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individually, some clinicians still find it useful to use the ESR as a nonspecific indicator of inflammation.

Several methods are used currently to measure the ESR; however, the most well known is the Westergren method. In the original Westergren method, a 30-cm glass tube is filled with blood and allowed to stand vertically for 60 minutes while the blood cells sediment. The interface between the cleared plasma and the sedimenting red cells is measured to the nearest millimeter, and the result is reported as millimeters per hour. Newer methods have been devised to avoid biohazard exposure due to handling of blood and to provide a semiautomated/automated procedure to reduce variability. For example, in one method, enclosed ESR vacuum tubes filled with blood are scanned with infrared light to measure the red cell sedimentation.⁴⁹ Another technology, the TEST 1 (Alifax, Padova, Italy), is an automated instrument reported to reflect inflammation better than the traditional Westergren method in those patients with malignancy, autoimmune disease, or infection.⁵⁰

Historically, the ESR has been used to follow rheumatic diseases, particularly rheumatoid arthritis, systemic lupus erythematosus, vasculitis associated with antineutrophil cytoplasmic antibody,⁵¹ and temporal arteritis and polymyalgia rheumatica.⁵² However, positive predictive values of ESR for the diagnosis of connective tissue disease and rheumatoid arthritis have been low in one study (35% and 17%, respectively),⁵³ and other studies⁵⁴ have shown that both the ESR and C-reactive protein are weakly correlated with disease activity measures in patients with rheumatoid arthritis, systemic lupus erythematosus, and osteoarthritis. In a review of the pediatric literature, Breda et al concluded that the ESR, as well as other laboratory markers, were useful in monitoring disease activity and treatment response in pediatric rheumatic diseases.⁵⁵ The ESR has been used as 1 criterion for evaluation of treatment response in patients with juvenile idiopathic arthritis during a clinical trial.⁵⁶ Although anticyclic citrullinated peptide antibodies have been shown to be highly specific and sensitive for rheumatoid arthritis, the test is not recommended for children with juvenile idiopathic arthritis because only children with rheumatoid factor–positive juvenile idiopathic arthritis have circulating antibodies against citrullinated peptide antibodies.⁵⁷

The ESR has also been used as a general marker for infections such as septic arthritis⁵⁸ and as an independent predictor for the development of heart failure.⁵⁹ C-reactive protein, another marker used to measure the acute-phase response, has been used similarly to ESR to identify and monitor inflammatory conditions, but more recently, high-sensitivity C-reactive protein has found a specific role as a major risk marker for cardiovascular disease.^{60,61}

The CAP proficiency surveys have shown a 19% decline in ESR enrollment from 1999 (Table). Compared with other assays included in the table (eg, acid phosphatase at 91% and the L/S ratio at 81%), the ESR has not declined as much. This may be because the assay is still utilized for patients with rheumatologic diseases. Because it is relatively inexpensive to perform, some smaller laboratories may keep the ESR on their test menu if newer technology is too expensive or not available. In addition, laboratories with more sophisticated testing may keep the ESR to use in conjunction with newer testing if this test is requested by the clinicians.

COMMENTARY

Laboratory directors should engage in a dialogue with the physician leaders of the various medical and surgical specialties to determine whether these tests should be eliminated from the test menu. In addition, laboratory directors, in association with their clinical colleagues, should create testing pathways based on evidence-based medicine that will streamline testing and incorporate the most appropriate tests for the diagnosis or management of the specific disease state. Although not every physician on the medical staff is likely to agree, this collaboration will allow the field of laboratory medicine to grow, and not provide unnecessary services simply because of tradition.

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