

# Laboratory Advisor

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## FREELITE: IMMUNOGLOBULIN FREE LIGHT CHAIN ASSAYS IMPROVE THE DIAGNOSIS OF PLASMA CELL DYSCRASIAS

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### ABSTRACT

Conditions characterized by the abnormal synthesis of intact monoclonal immunoglobulins or their components are collectively called plasma cell dyscrasias or monoclonal gammopathies. These conditions include multiple myeloma, Waldenström's macroglobulinemia, and several other abnormalities of immunoglobulin production. The standard laboratory tests to diagnose these conditions are serum protein electrophoresis and immunofixation electrophoresis. Immunoassays for the free kappa and free lambda light chain components of immunoglobulins were introduced in 2001. These two assays and their ratio, collectively known as free light chains or Freelite, measure the concentration of light chains that are not associated with immunoglobulin heavy chains. The excess synthesis of light chains during the production of immunoglobulins makes these assays very sensitive for detecting related abnormalities. Many laboratories have added these assays to their traditional testing. This article reviews these tests and the added advantages of the free light chain assay for the detection of monoclonal gammopathies.

Abbreviations: AL, primary amyloidosis; BJP, Bence Jones Protein; FLC, free light chain; IFE, immunofixation electrophoresis; IIMM, intact immunoglobulin multiple myeloma;  $\kappa$ , kappa immunoglobulin light chain;  $\lambda$ , lambda immunoglobulin light chain; LCMM, light chain multiple myeloma; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; M-protein, monoclonal immunoglobulin; NSMM, non-secretory multiple myeloma; SPEP, serum protein electrophoresis.

### INTRODUCTION

Plasma cell dyscrasias are monoclonal neoplasms of terminally differentiated B lymphocytes (plasma cells). These conditions are sometimes called monoclonal gammopathies or paraproteinemias and include multiple myeloma (MM), Waldenström's macroglobulinemia, primary amyloidosis (AL), and pre-malignant conditions called asymptomatic "smoldering" MM and monoclonal gammopathy of undetermined significance (MGUS). The monoclonal immunoglobulin (M-protein) may be a member of any one of the five heavy chain isotypes (G, A, M, D, or E) and either of the two light chain isotypes, kappa ( $\kappa$ ) or lambda ( $\lambda$ ).

The most common plasma cell dyscrasia is MM. It accounts for 1% of all malignancies; 10% of all hematological malignancies in Caucasians and 20% in African Americans. After non-Hodgkin lymphoma, it is the second most common hematologic

malignancy in the United States. The American Cancer Society (ACS) reports that about 20,000 new cases are diagnosed in the United States per year and about half of these are expected to die of the disease (1). Clinical manifestations vary widely depending on the type of immunoglobulin, the degree of expansion of the clone of neoplastic cells, and the magnitude of secretion of other plasma cell products such as lymphokines. Symptoms often include bone pain or fracture, renal failure, susceptibility to infection, anemia, hypercalcemia, clotting abnormalities, neurologic symptoms, and manifestations of hyperviscosity. A diagnosis of MM requires finding a bone marrow plasma cell count greater than 10% (2). In most cases of MM, an M-protein can be found in serum. These are called Intact Immunoglobulin MM (IIMM). However, 15% of MM cases produce only monoclonal light chains (LCMM), 3% of cases do not secrete the immunoglobulin into the serum (NSMM), and, rarely, only monoclonal heavy chains are produced. AL, the deposition of excess free light chains in various tissues, may occur as a component of MM or independent of MM. The current 5-year survival for a patient newly diagnosed with MM in the United States is 34% (data from 1996-2003) (1), up from 26.5%, thirty years ago. These improvements are not only due to new treatments, but also due to the great improvements in diagnosis and monitoring provided by the new free light chain assays.

The standard laboratory tests to diagnose these conditions are serum protein electrophoresis (SPEP) and immunofixation electrophoresis (IFE). Immunoassays for the free  $\kappa$  and  $\lambda$  light chain components of immunoglobulins were introduced in 2001 by The Binding Site Ltd.. These two assays and their ratio (free  $\kappa/\lambda$ ), collectively known as free light chains (FLC) or Freelite, measure the concentration of light chains that are not bound to an immunoglobulin heavy chains (e.g., G, A, M). The excess synthesis of light chains during the synthesis of normal and abnormal immunoglobulins makes these assays very sensitive for detecting plasma cell dyscrasias.

This article will briefly review the traditional laboratory testing (SPE and IFE) for monoclonal gammopathies; explain the rationale and principle for measurement of FLCs; demonstrate the improved sensitivity of FLCs; and explain how these assays are especially useful in some types of monoclonal gammopathies.

## TRADITIONAL LABORATORY TESTS FOR MONOCLONAL GAMMOPATHIES

### SERUM PROTEIN ELECTROPHORESIS (SPEP)

In SPEP, serum is separated by an electric current on an agarose gel at alkaline pH. Under these conditions, the serum proteins are resolved into five major fractions. Fig. 1A shows a normal SPEP pattern. The largest and fastest fraction (to the left) is albumin followed by the  $\alpha_1$ -globulin fraction (primarily  $\alpha_1$ -antitrypsin); the  $\alpha_2$ -globulin fraction (primarily  $\alpha_2$ -macroglobulin and haptoglobin); the  $\beta$ -globulin fraction (primarily transferrin and complement); and, the  $\gamma$ -globulin fraction (primarily immunoglobulins). Fig. 1B shows an abnormal SPEP pattern with a large, narrow band of restricted mobility in the  $\gamma$ -globulin fraction. A narrow band of restricted mobility implies that the protein is homogeneous and the position of the band in the  $\gamma$ -fraction suggests that the protein is an immunoglobulin. Thus, this abnormal protein is most likely a monoclonal immunoglobulin frequently referred to as an M-protein. IFE is required to prove it is a monoclonal immunoglobulin. M-proteins are most commonly found in the gamma fraction, but may be found anywhere in the globulin region. The M-protein shown in Fig. 1A is very large; in fact the estimated concentration of this M-protein is greater than the concentration of albumin.

SPEP can detect M-proteins when present above about 500-2000 mg/L, depending on possible co-migration with normal globulin components. It therefore cannot detect mildly elevated levels of M-protein; the tumor burden is usually greater than  $10^9$  cells before

positive results occur (2). Furthermore, it fails to detect 10% of IIMM, 50% of LCMM, > 50% of AL, and 100% of NSMM. If the M-protein concentration is greater than 5.0 g/L, SPEP is the preferred method for monitoring

increases in tumor burden or success of treatment. Urine protein electrophoresis for the detection of Bence Jones Protein (BJP), which are urinary FLC, is fraught with disadvantages and is being supplanted by serum FLC assays, which become elevated long before they appear in the urine.

### IMMUNOFIXATION ELECTROPHORESIS (IFE)

IFE is a procedure that combines principles of protein electrophoresis and immunoelectrophoresis. The gel and buffer are

similar to those used for standard SPEP. A sample of serum is applied to each of six lanes and electrophoresed. After electrophoresis one lane is stained for protein and is essentially the same as the SPEP; each of the other lanes are treated with antiserum to IgG, IgA, IgM,  $\kappa$  and  $\lambda$ . Immune complexes form and precipitate. After washing soluble proteins away the precipitated immune complexes are counter stained for protein. Normal concentrations of immunoglobulins are visible and their staining is diffuse, indicating polyclonal immunoglobulins. If a monoclonal immunoglobulin is present, a band of restricted mobility will again be seen and the specific antiserum lanes allow typing of this M-protein. Figure 2 shows the IFE patterns for the same two patients whose SPEP patterns are shown in Figure 1. The IFE shows no bands for the normal patient (panel A) and the M-protein is an IgG  $\kappa$  immunoglobulin for the patient with a band (panel B).

The frequency of M-protein classes is proportional to the normal concentration of the immunoglobulins themselves: IgG > IgA > IgM > IgD > IgE. Standard IFE does not include antisera for the rare IgD or IgE. If one of these monoclonal immunoglobulins is present, there would be a band of restricted mobility for one of the light chains,  $\kappa$  or  $\lambda$ , but no corresponding heavy chain (G, A or M). In a case like this, further testing for monoclonal IgD or IgE is indicated. A light chain M-protein without a corresponding heavy chain protein is also possible in LCMM, where only monoclonal light chains are produced. Usually, this pattern would not be seen in the serum until renal function had greatly diminished because FLCs are filtered by the glomerulus and degraded in the kidney.

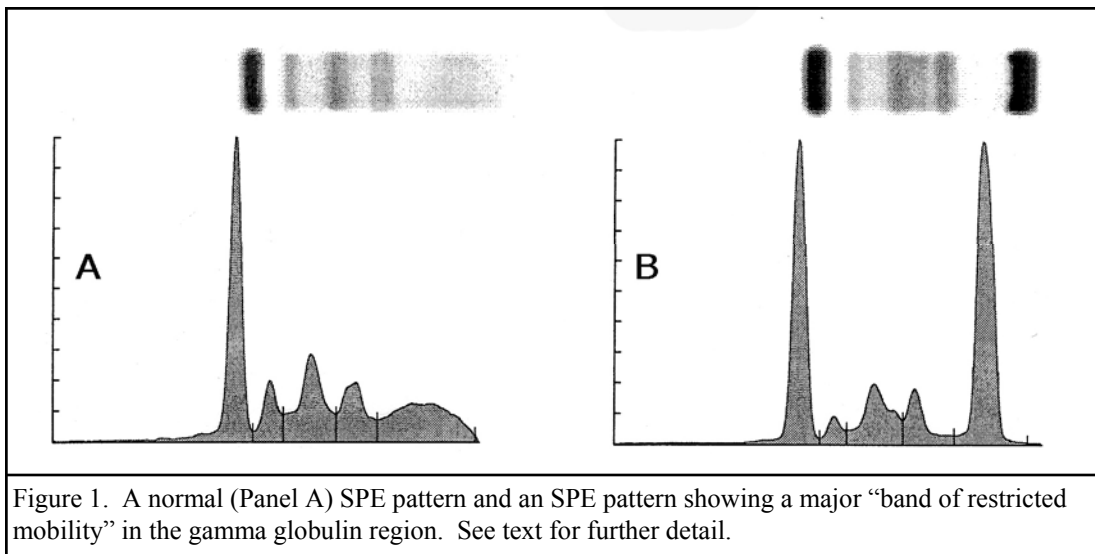


Figure 1. A normal (Panel A) SPE pattern and an SPE pattern showing a major “band of restricted mobility” in the gamma globulin region. See text for further detail.

As mentioned above, SPEP can detect M-proteins above 500-2000 mg/L. IFE is about 4-13 times more sensitive, detecting M-proteins above 150 mg/L. Despite its superior sensitivity, IFE is expensive and labor intensive making it

unattractive as a screening procedure.

### THE FREE LIGHT CHAIN ASSAY

BJP are monoclonal FLCs, either  $\kappa$  or  $\lambda$ , found in the urine of patients with plasma cell dyscrasias when the amount of FLCs exceeds the resorptive capacity of the kidney. With the advent of sensitive assays capable of detecting normal concentrations of free  $\kappa$  and free  $\lambda$  in the serum, elevation of free  $\kappa$  and free  $\lambda$  with

an abnormal  $\kappa/\lambda$  ratio can detect most plasma cell dyscrasias before they are detectable by SPEP or IFE.

In the 1980s, it was first recognized that elevated serum FLC concentrations could be demonstrated whenever BJPs were present in the urine (3, 4). These early research assays for FLCs required initial separation of intact immunoglobulins from the FLC by gel filtration. This separation step greatly decreased the feasibility of routine measurements of FLCs. Measurement of FLCs directly in a serum sample containing intact immunoglobulins with their bound light chains required detection of neoepitopes, that is epitopes on FLCs that are hidden when bound to heavy chains. Antibodies specific for these neoepitopes in free  $\kappa$  chains and free  $\lambda$  chains were developed in the 1990s and released as the commercially available Freelite assay by The Binding Site Ltd in 2001.

Several characteristics of serum FLCs make them useful in the evaluation of plasma cell dyscrasias. First, light chains are synthesized in 40% excess of the amount incorporated into intact immunoglobulins. In normal individuals, B-lymphocytes and plasma cells produce about 500 mg of excess FLC per day (5, 6). FLCs in the blood are rapidly (within hours) cleared and metabolized by the kidneys. Only small concentrations of FLC appear in the urine unless the production rate is greatly increased, as in MM, or kidney function is markedly impaired (7).

Table 1 gives the reference intervals for FLC and for comparison total immunoglobulin heavy chain and light chain isotypes. Note that IgG, IgA, IgM and the total light chain fractions are typically reported in mg/dL, whereas the FLC fractions are reported in mg/L. The total  $\kappa$  and total  $\lambda$  assays include the free fractions, but one can see from these reference ranges that the free  $\kappa$  concentration is only about 0.1% of the total  $\kappa$  concentration and the free  $\lambda$  concentration is only about 0.3% of the total  $\lambda$  fraction. Also note that the free  $\kappa/\lambda$  ratio is somewhat lower than the total  $\kappa/\lambda$  ratio. Free  $\lambda$  chains tend to dimerize, thus free  $\kappa$  chains are cleared by the kidney a bit faster leading to the lower free  $\kappa/\lambda$  ratio.

Figure 3 shows a graph of the free  $\lambda$  concentration plotted against the free  $\kappa$  concentration in normal individuals and patients with a variety of diseases that affect immunoglobulin production and therefore FLC production. Focus first on the normal serum (red +), the patients with renal impairment unrelated to a plasma cell dyscrasia (blue +), and the patients with high polyclonal immunoglobulins (green triangles) due to a normal immune response. These results are on the same diagonal, which represents a normal  $\kappa/\lambda$  ratio. The patients with unrelated renal impairment and increased polyclonal immunoglobulins have elevated  $\kappa$  and  $\lambda$ , but they have a normal  $\kappa/\lambda$  ratio. The figure also indicates the sensitivity limits for SPEP and for IFE. Note that many patients with AL (yellow circles), IIMM (blue diamonds), and NSMM (white circles) have abnormal  $\kappa/\lambda$  ratios but would not have been diagnosed by SPEP or IFE. Also note that there are a few patients with AL, IIMM, and NSMM with normal free  $\kappa$ , free  $\lambda$ , and free  $\kappa/\lambda$  ratio. These patients were not diagnosed as abnormal by the FLC assays.

The  $\kappa/\lambda$  ratio is of significant value both for diagnosis and monitoring of patients with plasma cell disorders. An abnormal  $\kappa/\lambda$  ratio suggests a clonal expansion of plasma cells. On the other hand, a normal  $\kappa/\lambda$  ratio, in the presence of elevated levels of FLCs, suggest either renal impairment or polyclonal expansion of plasma cells.

### CLINICAL UTILITY OF SERUM FCL ESTIMATIONS

FLCs are markers for B lymphocyte/plasma cell tumors. Chan and Schwartz (9) listed a number of potential clinical uses for tumor markers in general. These include differential diagnosis in symptomatic patients; clinical disease staging; estimating tumor burden; prognostic indicator of disease progression; monitoring therapy; monitoring for tumor recurrence; screening symptomatic patients; and screening the general (asymptomatic) population. FLCs have been shown to have clinical utility in all but the last of these uses (10). A few examples are given below.

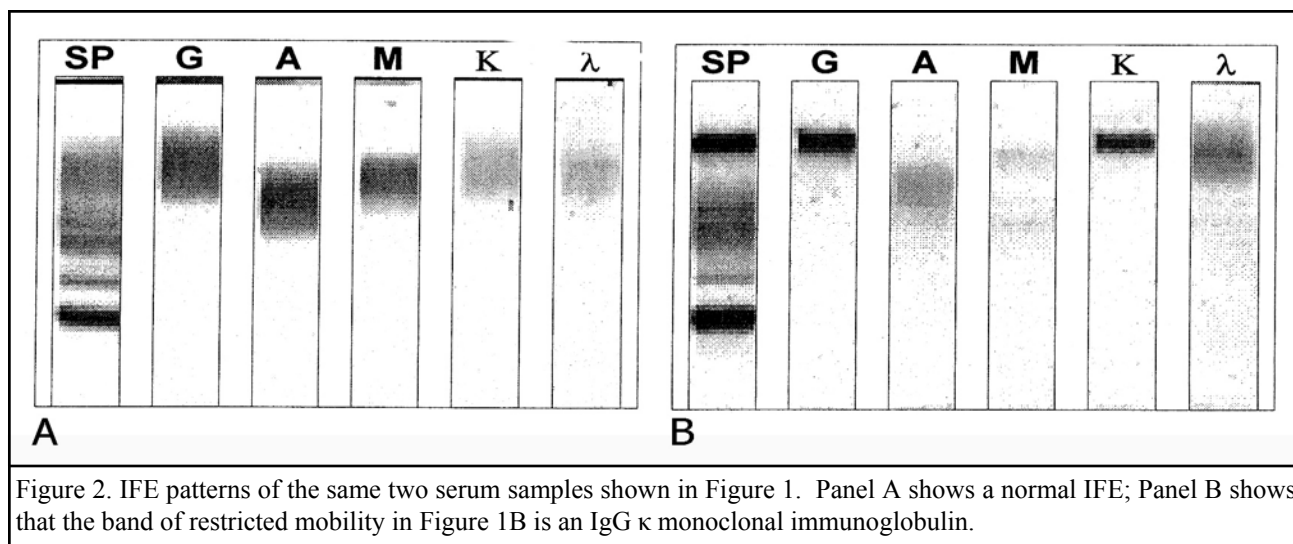


Figure 2. IFE patterns of the same two serum samples shown in Figure 1. Panel A shows a normal IFE; Panel B shows that the band of restricted mobility in Figure 1B is an IgG  $\kappa$  monoclonal immunoglobulin.

Table 1. Reference intervals used at University of Louisville Hospital Laboratory.	
IgG	750-1560 mg/dL
IgA	80-450 mg/dL
IgM	46-304 mg/dL
Total $\kappa$	629-1350 mg/dL
Total $\lambda$	131-723 mg/dL
Total $\kappa/\lambda$ ratio	1.31-3.18
Free $\kappa$	3.3-19.4 mg/L
Free $\lambda$	5.7-26.3 mg/L
Free $\kappa/\lambda$ ratio	0.26-1.65
Reference intervals for IgG, IgA, IgM and total $\kappa$ and $\lambda$ are for the Beckman Coulter Immage nephelometric assays; reference intervals for the free light chains and their ratio are from ref. 8.	

Approximately 15% of MM patients have no detectable intact M-protein in serum but only free light chains in serum and urine. Furthermore, only 50% of these patients with LCMM will have an abnormal SPEP. One might expect assays for FLC to be most useful in patients with LCMM. Indeed, in a recent study, of 224 cases of LCMM, confirmed by bone marrow plasma cell count and presence of osteolytic lesions, FLC assays were abnormal with an abnormal FLC k/l ratio (11). This study also showed that the short half life of FLCs (2-4h)

made it more suitable to monitor therapy than measuring intact IgG with a half-life of 21-25 days. Monitoring urine FLC for response is not recommended because urine FLC may be undetectable before serum FLC concentrations have completely normalized.

As seen in Fig. 3, a large number of patients with IIMM, who would have been missed by SPEP and IFE, may be diagnosed with the FLC assay. In addition, as with LCMM, the FLC assay

allows a more rapid and sensitive method of monitored treatment. NSMM accounts for 3% of all patients with MM. In spite of the non-secretory nature of this type of MM, many patients can be detected by abnormal serum FLC and  $\kappa/\lambda$  ratios (11, 12).

MGUS is an asymptomatic condition which occurs in approximately 3% of the population >70 years of age. It is associated with the presence of a monoclonal band (<30g/L) in serum, no BJP in the urine and <10% plasma cells in the bone marrow. Although MGUS patients should not be treated, it is essential that they be monitored on regular basis, since 1% per year develop MM or a related

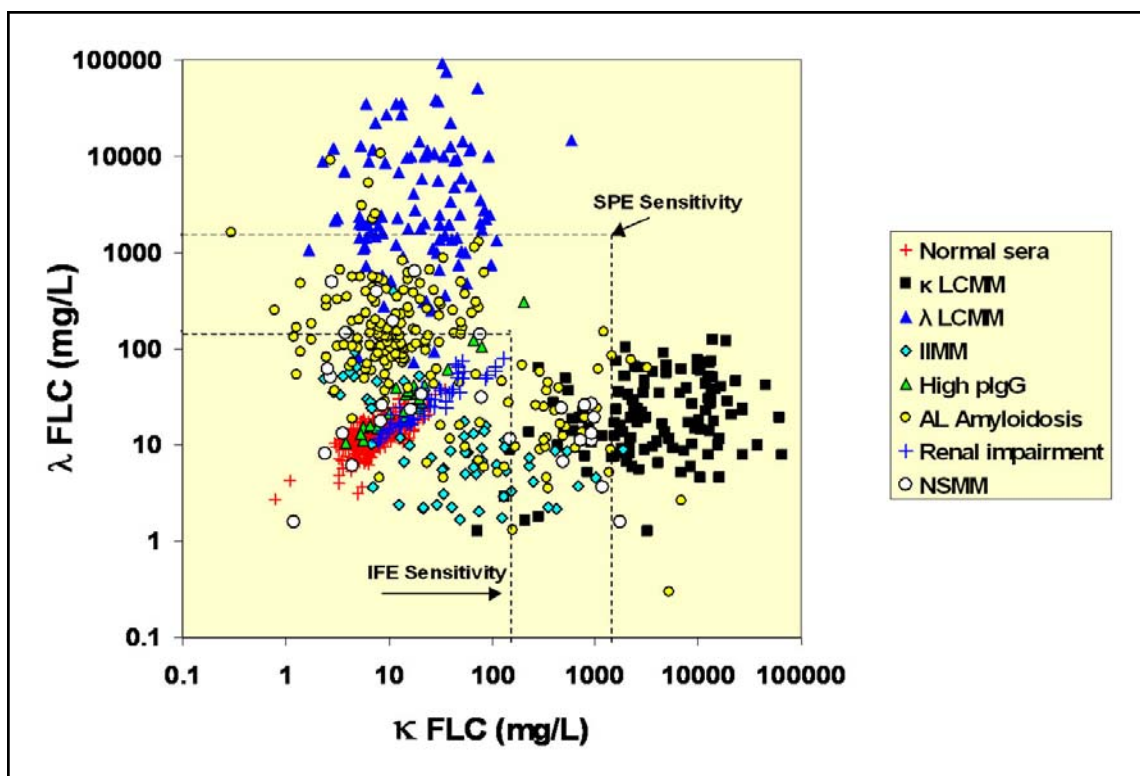


Figure 3. Free  $\lambda$  concentration vs free  $\kappa$  concentration plot in various disease. Figure 1.1 in Ref. 8 used with permission of The Binding Site Ltd.

malignant condition (13). The finding of BJP in the urine of MGUS patients is associated with an increased risk of malignant evolution to MM and serum FLC levels in these patients also provide useful prognostic information (10, 14).

AL is the most common and severe form of systemic amyloidosis. It is characterized by the deposition of monoclonal FLCs, or their fragments, as amyloid in tissues, and is difficult to monitor quantitatively using conventional electrophoresis methods. SPEP fails to detect a monoclonal protein at the time of diagnosis in about half of AL patients, and the concentration of monoclonal protein is so low in many other patients that quantitation by SPEP is either imprecise or impossible. Although urine IFE can detect approximately 80-90% of patients, the results are not quantitative and are dependent on renal function. In AL, the serum FLC assay is more sensitive for detection and diagnosis, allows a greater number of patients to be followed during treatment, can reveal responses earlier than

other assays, and can be used to effectively guide treatment (15, 16).

## CONCLUSIONS

Serum FLC assays are likely to become a standard component of the routine clinical diagnosis and monitoring of patients with monoclonal gammopathies. It is clear from the information presented above that FLC assays are more sensitive than SPEP and IFE. However, most of the citations above and others (17-19) include a few patients with known plasma cell dyscrasias recurrence, who did not have abnormal FLC results. Thus, we conclude that FLC should be considered to be a valuable addition to the diagnostic armamentarium for plasma cell dyscrasias, but should not be used alone for diagnosis. FLC assays alone may be useful for monitoring therapy and monitoring for disease

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