Guidelines Review

Proposed Addendum to 2012 Recommendations for Standardised Reporting of Protein Electrophoresis in Australia and New Zealand

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Abstract

It is apparent that there is a need for greater harmonisation of the reporting and quantification of paraproteins on protein electrophoresis with the introduction of the electronic health record and recent survey findings indicating ongoing areas of heterogeneity on serum protein electrophoresis. The proposed addendum aims to update the 2012 recommendations for standardised reporting of protein electrophoresis in Australia and New Zealand. The sections which need to be updated include those on the quantification of gamma- and non-gamma-migrating paraproteins; interpretive commenting in specimens with a paraprotein and/or small abnormal bands; the utility of serum free light chains compared with Bence Jones protein measurement; and a new table with interpretive commenting for serum free light chains. It is expected that such standardised reporting will reduce both variation between laboratories and the risk of misinterpretation of results.

Introduction

The aim of this proposed addendum is to update the 2012 recommendations for standardised reporting of protein electrophoresis in Australia and New Zealand. A recent paraprotein sample exchange and survey of current protein electrophoresis practices by the Royal College of Pathologists of Australasia Quality Assurance Programs (RCPAQAP), both conducted in early 2018, have highlighted ongoing areas of heterogeneity in both the quantification and reporting of serum protein electrophoresis (SPEP). In addition, at the Australasian Association of Clinical Biochemists (AACB) and RCPAQAP Proteins Workshop held in Melbourne in September 2017, participants discussed ways to best quantify and report beta-migrating paraproteins that would result in greater consistency of results between laboratories. Currently there is no accurate method of quantifying beta-migrating paraproteins either by SPEP, total immunoglobulin assays or using heavy/light chain assays. Paraprotein concentrations may include polyclonal immunoglobulin or other normal co-migrating proteins in the gamma or beta/alpha-2 fractions.

The ultimate aim of the addendum is to better harmonise the quantification and reporting of paraproteins by laboratories when monitoring disease response for monoclonal gammopathies. The need for greater harmonisation of results has largely come about with the introduction of the electronic health record (eHR) and Australians having the right to have their blood analysed at any laboratory, not necessarily the one indicated on the test request slip. According to the 2016 RCPAQAP program for paraproteins, the between-laboratory variation for all samples ranges from 14% CV at 33.5 g/L mean paraprotein concentration to 50% CV at 1.6 g/L. However, the current between-laboratory variation for the quantification of low concentration, beta-migrating bands on SPEP can be quite large as shown for the IgA lambda paraprotein in Table 1 with values ranging from 2.0 to 15.6 g/L. This between-laboratory variation may impact patient care if the patient uses different pathology services with different laboratory SPEP methods for monitoring their disease response.

In 2014, Australian and New Zealand recommendations for measurement of serum free light chains (FLC) were circulated to protein laboratories via the RCPAQAP and presented at the...
Addendum to 2012 Recommendations

Table 1. Variation in quantification of serum IgAλ monoclonal protein by 66 laboratories participating in RCPAQAP 2016 paraprotein program.

<table>
<thead>
<tr>
<th>Electrophoresis method, manufacturer (n)</th>
<th>Monoclonal IgAλ protein reported as ‘Monoclonal IgAλ’ Median [range] g/L (n)</th>
<th>Monoclonal IgAλ protein reported as ‘Beta globulins + IgAλ’ Median [range] g/L (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gel, Helena* (9)</td>
<td>6.0 [4.3–6.7] (8)</td>
<td>17.5 (1)</td>
</tr>
<tr>
<td>Gel, Sebia†(35)</td>
<td>5.0 [2.0–15.6] (29)</td>
<td>6.8 [5.0–12.4] (6)</td>
</tr>
<tr>
<td>Gel, Interlab‡(2)</td>
<td>5.5 (2)</td>
<td>-</td>
</tr>
<tr>
<td>Gel, lab-prepared (2)</td>
<td>7.5–9.0 (2)</td>
<td>-</td>
</tr>
<tr>
<td>CZE, Helena (1)</td>
<td>-</td>
<td>15.0 (1)</td>
</tr>
<tr>
<td>CZE, Sebia (17)</td>
<td>5.0 [4.9–10.0] (12)</td>
<td>6.8 [6.0–17.0] (5)</td>
</tr>
<tr>
<td>All laboratories (66)</td>
<td>6.0 [2.0–15.6] (53)</td>
<td>8.0 [5.0–17.5] (13)</td>
</tr>
</tbody>
</table>

CZE, capillary zone electrophoresis; Gel, agarose gel electrophoresis; * Helena Laboratories (Beaumont, TX); † Sebia (Lisses, Evry, France); ‡ Interlab SRL (Rome, Italy)

Methodology
Suggestions about ways to achieve greater harmonisation of the quantification and reporting of small bands on SPEP and co-migrating paraprotein reporting were discussed at the September 2017 AACB/RCPAQAP Protein Harmonisation Workshop by international and local speakers, with discussion sessions involving scientists, pathologists and immunologists performing SPEP. In addition, paraprotein sample exchanges were conducted in early 2018 in five Australian states by local laboratories and across New Zealand, and a 2018 survey on current SPEP and reporting practices was conducted through the RCPAQAP. Results were presented to pathologists and scientists at the May 2018 AACB Harmonisation Workshop. In June 2018, the AACB met with haematologists from the Myeloma Scientific Advisory Group (MSAG) to present results from the surveys and to discuss the way forward. Further to this meeting, MSAG and the RCPA Chemical Pathology and Immunopathology Advisory Committees endorsed the proposed amendments.

The sections in the 2012 recommendations paper that remain unchanged include: nomenclature; analytical requirements of a protein electrophoresis including detection system for protein electrophoresis; serum protein and albumin quantification; quantitative reporting of SPEP fractions; urine paraprotein separation and quantification; paraprotein characterisation; laboratory performance of SPEP, urine protein electrophoresis (UPEP) and immunofixation (IFE); laboratory expertise and staffing; and interpretive commenting in protein electrophoresis reports including general interpretive commenting for all specimens (Table 3 in 2012 paper).

The sections that need to be updated include: serum paraprotein quantification including paraproteins migrating in the gamma-region; paraproteins co-migrating with other normal proteins in alpha- and beta-regions; and quantification of small bands. In order to achieve greater harmonisation of results for quantification of gamma-migrating paraproteins, one gating method is recommended. A section on serum FLC has been added and provides information for clinicians and technical recommendations for laboratories. The utility of serum FLC compared with Bence Jones protein (BJP) measurement is described with clinical studies now showing that serum FLC provide better prediction of overall survival (OS) and progression free survival (PFS) compared with UPEP/IFE in light chain myeloma (LCMM).

Harmonised Reporting and Quantification of Paraproteins

Paraproteins Migrating in the Gamma-Region
According to the 2018 RCPAQAP survey, 51% (21/41) of laboratories currently use the perpendicular drop (PD, orthogonal, top to bottom) method of gating paraproteins in the gamma-region. The corrected PD (cPD) method where normal gamma globulins are decreased is used by 7% of laboratories and the tangent skimming (TS, valley to valley) method by 17% of laboratories. In the absence of a reference method to know the exact peak concentration, it is not possible to determine the accuracy of these gating methods.

The French myeloma group, Intergroupe Francophone du Myélome (IFM), recommends PD to gate paraproteins. As stated in the French recommendations, the value of the peak concentration does not have a prognostic value itself, but is...
immunoglobulin (Ig). In their usual way) and also quantify total involved and densitometry (reporting the paraprotein concentration paraprotein quantification by serum protein electrophoresis paraproteins and laboratories were asked to perform in early 2018. Samples generally contained beta-migrating in five Australian states and in New Zealand Australia and New Zealand, paraprotein sample exchanges identify the practical problems and lack of agreement in determining and reporting the concentration of paraproteins migrating in the beta-region as shown in Table 1. To better “small band cannot be quantified reliably”. Paraproteins visible only by immunofixation should be described in the comment section (e.g. IgG kappa paraprotein only visible by immunofixation) rather than being given a quantified value. The perpendicular drop method for quantification is proposed for gating of gamma-region paraproteins as opposed to tangent skimming or corrected perpendicular drop.

Box 1. Proposed recommendations for quantification of gamma-migrating serum paraproteins.

- Paraproteins in the gamma-region should be quantified by densitometric or CZE measurement in g/L rounded to the nearest whole number.
- Paraproteins of <1 g/L visible on SPEP or CZE cannot be quantified reliably, especially if there is a polyclonal gammaglobulin background, and should be referred to as ‘<1 g/L’ or ‘trace’ with comments such as ‘small band cannot be quantified reliably’.
- Paraproteins visible only by immunofixation should be described in the comment section (e.g. IgG kappa paraprotein only visible by immunofixation) rather than being given a quantified value.
- The perpendicular drop method for quantification is proposed for gating of gamma-region paraproteins as opposed to tangent skimming or corrected perpendicular drop.

Paraproteins Co-Migrating with Other Normal Proteins in Alpha-2 and Beta-Regions

Quantification of paraproteins migrating in a non-gamma-region presents an ongoing challenge for laboratories performing SPEP. Paraproteins migrating in the beta-region may co-migrate and be obscured by varying concentrations of C3 complement or transferrin making their quantification by densitometry unreliable. This is known to particularly affect IgA paraproteins, greater than 40% of which migrate in the beta-region, but up to 25% of all paraproteins may migrate in the beta-region or beta-gamma junction.

There is significant variation in laboratory practice when determining and reporting the concentration of paraproteins migrating in the beta-region as shown in Table 1. To better identify the practical problems and lack of agreement in Australia and New Zealand, paraprotein sample exchanges were conducted in five Australian states and in New Zealand in early 2018. Samples generally contained beta-migrating paraproteins and laboratories were asked to perform paraprotein quantification by serum protein electrophoresis and densitometry (reporting the paraprotein concentration in their usual way) and also quantify total involved immunoglobulin (Ig).

The sample exchange study confirmed that the value reported in the paraprotein field has a large between-laboratory variation, with CVs up to 71%, similar to the variation observed in the RCPAQAP paraprotein program. The main contributor to the variation is gating methods used to quantify beta-migrating paraproteins and reporting procedures rather than the protein electrophoresis methods. A recent RCPAQAP survey found that the value reported in the paraprotein field for beta-migrating paraproteins is derived from ‘total beta + paraprotein’ for 40% of laboratories, ‘total beta-1 + paraprotein’ or ‘total beta-2 + paraprotein’ for 21% of laboratories and total beta minus a predetermined value for 6% of laboratories. Also, 15% of laboratories report total involved Igs additionally or exclusively in the paraprotein field for a beta-migrating paraprotein.

Possibilities for harmonised gating and reporting procedures were also assessed in the sample exchanges. ‘Total beta + paraprotein’ from SPEP was assessed in the Victorian sample exchange and performed reasonably well with inter-laboratory CVs of 4–18%.

We did not directly assess whether using ‘total beta-1 + paraprotein’ or ‘total beta-2 + paraprotein’ for quantification would also improve inter-laboratory CVs. This may provide a possibility for improved harmonisation but may also be hampered by the differences in the ability of laboratories’ SPEP systems to resolve the beta-1 and beta-2 regions independently. Further studies would need to be performed to determine whether this approach would improve inter-laboratory variation over the reporting of ‘total beta + paraprotein’.

The use of a total involved Ig level using immunonephelometric or immunoturbidimetric assay (INA/ITA) performed best with most between-laboratory CVs <10%. Despite the good inter-laboratory agreement of total Igs between methods, it should be noted that some laboratories do not report total Igs routinely on their SPEP reports. Some do not report a value over certain absolute concentrations as results may be overestimated due to non-linearity at higher sample dilutions. The recent RCPAQAP survey showed that there was a large variation in acceptable upper reportable values for total involved Ig. This problem would have to be overcome and more work is required to determine harmonised upper limits of reporting for use by all laboratories.

Recommendations for Laboratories

Laboratories should measure and report the total involved Ig by INA/ITA as the preferred option for monitoring beta-region migrating paraproteins. This is in agreement with the 2016 International Myeloma Working Group (IMWG) consensus.
criteria for response and minimal residual disease in multiple myeloma which states quantitative immunoglobulins are preferred for disease assessments for IgA myelomas, which constitute a large percentage of paraproteins migrating in the beta-region.\textsuperscript{12}

A consistent approach to reporting beta-migrating paraproteins on SPEP is also required. Given the findings noted above and the need for harmonisation, we propose to report ‘total beta + paraprotein’ measured by densitometry in the paraprotein field. This should include a clear comment identifying the paraprotein as migrating in the beta-region and stating that the concentration includes normal beta proteins. This is suggested in preference to ‘total beta-1+ paraprotein’ or ‘total beta-2 + paraprotein’ even if a laboratory has good separation as it is consistency of reporting that is required across methods in different laboratories in order to monitor patient response. In general, the majority of beta/alpha-2-migrating bands will run on SPEP in the same fractions across methods, although there will be exceptions. The clinical importance of having both densitometric and immunochemical quantification of paraproteins in the alpha- and beta-regions was also noted in the 2012 guidelines, providing clinicians flexibility in health systems where drug funding and availability is linked to paraprotein response.\textsuperscript{1}

We noted that a minority of laboratories continue the practice of subtracting a predetermined value for the beta-region to provide an estimation of paraprotein concentration. As noted in the 2012 recommendations, attempts to provide an estimate of the ‘true’ paraprotein concentration by subtracting other beta globulins are inherently unreliable due to the non-constant levels of the co-migrating proteins. In addition, this method may result in calculated paraprotein levels in the negative range on some occasions. We therefore recommend against this process.

Overall, as summarised in Box 2, both SPEP and total involved Ig are required to be quantified and reported for beta/alpha-2-migrating paraproteins. The use of the involved Ig for monitoring response provides clinicians with an alternative option for monitoring disease response and SPEP is required for determining complete response (CR) or very good partial response (VGPR). The proposed use of the ‘total beta + paraprotein’ concentration rather than different gating methods will reduce the inter-laboratory variation.

Serum Free Light Chains and Urine Protein Electrophoresis

The serum FLC assay is now well established as a key laboratory test in the diagnosis and monitoring of plasma cell dyscrasias. The use of serum FLC for diagnosis, monitoring and prognostication in myeloma and AL amyloidosis is included in clinical guidelines,\textsuperscript{12-14} and is discussed in the accompanying review in this issue of The Clinical Biochemist Reviews.\textsuperscript{15} Serum FLC testing can provide sensitive monitoring for patients and should be further integrated into routine clinical practice. The current IMWG recommendation for monitoring of LCMM is to measure 24-hour excretion of BJP.\textsuperscript{16} However, in the IFM 2009 study of LCMM patients by Dejoie et al., all diagnostic samples had an abnormal κ/λ FLC ratio and all involved FLC were measurable for monitoring whereas only 64% of 113 patients had measurable BJP on UPEP.\textsuperscript{3} In addition, normalisation of FLC ratio during disease monitoring better predicted OS and PFS than if negative by urine IFE. Another study by Heaney et al. compared serum FLC and a random urine BJP/creatinine ratio at diagnosis in LCMM. Whereas 116 of 576 patients did not have measurable BJP, only 3 could not be monitored by serum FLC. Serum FLC response predicted outcome.\textsuperscript{6}

Box 2. Proposed recommendations for quantification of beta/alpha-2-migrating serum paraproteins.

- For patients with known plasma cell dyscrasias and paraproteins in the non-gamma-regions, laboratories should report both the densitometric paraprotein (see 3\textsuperscript{rd} dot point) AND INA/ITA immunoglobulin measurement to facilitate disease monitoring.
- Quantification of total IgG, IgA and IgM by INA/ITA provides an approximate concentration of the paraprotein, which may be overestimated due to non-linearity at higher sample dilution. However, they are particularly useful in situations where densitometry cannot reliably quantify a paraprotein (e.g. low-level paraproteins in the beta-region) and is preferred by the IMWG for the monitoring of IgA myeloma. A comment about the effect of overestimation may be required at higher concentrations.
- For a paraprotein in the non-gamma-regions, the beta-region being the most common region for IgA paraproteins, report as total protein in the beta-region (‘total beta + paraprotein’) quantification at presentation and during monitoring.
- The report should include a comment identifying the paraprotein as migrating in the beta-region and stating that the concentration includes normal beta proteins.
- Attempts to provide an estimate of the ‘true’ paraprotein concentration by subtracting a predetermined level for other beta proteins are inherently unreliable due to the non-constant levels of the co-migrating proteins and are not recommended.
Serum FLC assay properties also have been widely reported, including in the 2014 Australian and New Zealand recommendations for their measurement which were circulated to protein laboratories via the RCPAQAP.17 The following information is intended for laboratories measuring serum FLC and requesting clinicians.

**Serum Free Light Chain Assays**

Three relatively new serum FLC assays separate to the Freelite® assay have recently been introduced into the marketplace. Clinicians should recognise that clinical guidelines recommending cut-off values for serum FLC are based on the Freelite® assay and that there remains an urgent need to determine uniform response criteria for serum FLC that are applicable to all assays. Results of the various FLC assays cannot be used interchangeably as concentrations for monoclonal proteins can differ widely; hence an individual patient may or may not meet certain diagnostic, prognostic or response criteria, depending on the FLC assay and platform used. It is recommended patients be tested at the same laboratory for FLC measurement when monitoring disease response. Assay validation in one clinical group of patients using the newer FLC methods does not necessarily imply validity in all groups of patients, unlike the Freelite® assay where many clinical validations are cited in the literature. Different diagnostic ranges for κ/λ ratio are required for chronic kidney disease (CKD) patients depending on the assay.18–20

**Recommendations for Laboratories**

Imprecision

Laboratories should use a serum-based control, either within the reference interval or close to the FLC upper reference limit values, to monitor assay imprecision and any reagent lot-to-lot variation. Alternately, several samples assayed with the previous reagent lot should be re-assayed and values compared with the current lot. Manufacturers quote values with a ±20% CV for their quality controls.

Sample Dilutions

In general, manufacturers recommend the use of specific sample dilution protocols to detect antigen excess and nonlinearity of FLC methods for some samples. Further sample dilutions may be helpful for interpreting results in problematic samples. ‘Unusual’ serum FLC results will still occur and it is important that results are interpreted in combination with SPEP and UPEP. It is recommended that laboratories continue to use urinary BJP for screening in difficult cases.

Reference Intervals and Diagnostic Ranges

It is recommended that the manufacturers’ κ and λ reference intervals and κ/λ FLC ratio diagnostic ranges are used and that laboratories validate manufacturers’ values according to the CLSI document C28-A3.21 In CKD, a different κ/λ FLC ratio range may need to be applied depending on the assay (e.g. Freelite® 0.37–3.1).

Reporting of FLC Results

The assay type (Freelite®, N-Latex, Seralite® or Sebia) should be mentioned in the report to avoid confusion by clinicians when patients are tested by different pathology providers. As there can be gross differences in absolute concentrations and ratios between the assays, patients should have their disease response monitored using the same manufacturer’s assay and same platform. According to the RCPAQAP survey, most laboratories in Australia and New Zealand perform serum

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**Table 2. Interpretive commenting for serum free light chains (FLC).**

<table>
<thead>
<tr>
<th>FLC result</th>
<th>Minimal information to be provided in the interpretive comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both κ and λ FLC levels elevated but normal κ/λ ratio</td>
<td>Increased serum free light chains concentrations with a normal κ/λ FLC ratio can occur when immunoglobulin synthesis is elevated (e.g. autoimmune, liver and inflammatory diseases, infection), or light chains excretion is reduced (e.g. renal impairment).</td>
</tr>
<tr>
<td>κ/λ FLC ratio in CKD (required if the range for κ/λ FLC ratio is different in CKD e.g. Freelite® assay)</td>
<td>A κ/λ FLC ratio in the range 0.37–3.10 may be seen in CKD by Freelite® assay in the absence of a monoclonal gammopathy.</td>
</tr>
<tr>
<td>Borderline high κ/λ FLC ratio (up to 3.0)*</td>
<td>A borderline high κ/λ FLC ratio is not always indicative of a plasma cell disorder but may occur when immunoglobulin synthesis is elevated (e.g. autoimmune, liver and inflammatory diseases, infection), or light chains excretion is reduced (e.g. renal impairment). Recommend serum protein immunofixation electrophoresis and repeat FLC in 2–3 months if clinically indicated.</td>
</tr>
<tr>
<td>Abnormal κ/λ FLC ratio where both κ and λ FLC levels are normal/low</td>
<td>At very low levels of serum free light chains an abnormal κ/λ ratio is of uncertain significance.</td>
</tr>
</tbody>
</table>

* This finding has only been demonstrated for the Freelite® assay. CKD, chronic kidney disease.
FLC assays or send the sample out to a laboratory that does. However, only 48% of laboratories state the FLC method on the report.

In 2014, the RCPAQAP Immunology Working Party recommended that the reporting of FLC concentrations be in whole numbers from 0 to 100 mg/L. Values >100 mg/L can be reported to two significant figures after rounding. For calculation of κ/λ ratio, individual κ or λ FLC raw values from the analyser to one decimal place are initially retained and, depending on a laboratory’s LIS, κ/λ FLC ratio at 0 to <10 should be reported to two decimal places and when ≥10, to one decimal place or as a whole number. Note that if either κ or λ FLC concentration is within or below the reference interval and the other FLC value is below the reference interval, calculation of the κ/λ FLC ratio is problematic. It is preferable to not report the calculated κ/λ ratio but rather to indicate that the ratio is of uncertain clinical significance. Serum FLC comments are shown in Table 2.

### Urine Protein Electrophoresis and Total Urine Protein

UPEP and urine total protein should continue to be available in laboratories when screening for PCD as all serum FLC assays will have limitations and may occasionally fail to react with an individual’s monoclonal FLC. UPEP is useful for screening for BJP in difficult cases. According to the RCPAQAP survey, laboratories are still performing UPEP for screening for BJP in difficult cases. According to the RCPAQAP survey, laboratories are still performing UPEP to screen for BJP. Units of reporting of urine total protein and BJP (concentration, excretion, creatinine ratio) remain diverse despite recommendations by the RCPA Pathology Information Terminology Units Standardisation (PITUS) and other harmonisation initiatives intended to deliver uniform terminology, units of reporting and report formatting.

### Reporting of Small Bands and Interpretive Commenting

High-resolution SPEP detects 0.5–1 g/L size bands, the clinical significance of which is often uncertain. They could represent lymphoma, AL amyloidosis, oligosecretory myeloma or monoclonal gammopathy of renal significance (MGRS). It is important not to miss these diagnoses. However, small bands, usually <1 g/L, are a more common occurrence on SPEP due to inflammatory, infectious and autoimmune diseases in which case they are often transient.

The reporting of these small bands is a source of confusion for clinicians and is difficult for some laboratories if there are incomplete notes and lack of access to patient clinical history. They may be mistakenly reported to suggest relapsed myeloma in patients following stem cell transplantation or post-novel agent therapy, whereas in the majority of cases they are associated with improved remission depth and outcome and do not reflect relapse with isotype switch. Overall, these small bands are more likely to be of a reactive nature than to represent underlying monoclonal plasma cell disease. It is therefore important that reports indicate the uncertainty of these small bands. Laboratory reporting should recognise these small bands but not report them as new paraproteins to reduce patient and clinician anxiety and unnecessary investigations.

Small, abnormal protein bands are frequently seen on SPEP in patients with a known paraprotein following transplantation. They are typically IgG kappa isotype and ≤1 g/L but may occasionally be larger and may persist for 1–18 months. They

### Box 3. Proposed recommendations for measurement of serum free light chains.

- Some form of quality control, either serum-based or a manufacturer’s control or a small set of previously assayed patient samples, is required to detect any serum FLC reagent lot-to-lot variation.
- Specific sample dilution protocols are recommended by manufacturers for specific analysers and should be followed to detect antigen excess and nonlinearity of FLC methods.
- Use the manufacturer’s κ and λ reference intervals and κ/λ FLC ratio diagnostic range, applying the CLSI procedure to verify them.
- In CKD, a different κ/λ FLC ratio range may need to be applied depending on the assay.
- The specific FLC assay (e.g. Freelite®, N Latex) should be clearly stated on the patient report.
- Report FLC concentrations in whole numbers from 0 to 100 mg/L. Values >100 mg/L can be reported to two significant figures after rounding. For calculation of κ/λ ratio, retain individual κ or λ FLC raw values from the analyser to one decimal place, depending on a laboratory’s LIS, and report ratios at 0 to <10 to two decimal places and when ≥10, to one decimal place or as a whole number.
- If either κ or λ FLC concentration is within or below the reference interval and the other FLC value is below the reference interval, calculation of the κ/λ FLC ratio is problematic. It is preferable to not report the calculated κ/λ ratio but rather to comment that the ratio is of uncertain clinical significance.
- UPEP and urine total protein should continue to be available in laboratories when screening for plasma cell dyscrasias as all serum FLC assays will have limitations and may not detect occasional patients.
- Units of reporting of UPEP and urine total protein require greater harmonisation as recommended by the PITUS project.
are also, somewhat confusingly, called secondary monoclonal gammopathy of undetermined significance (MGUS) and occur in 10–73% of myeloma patients after autologous transplant.25

Other small IgG kappa bands that can interfere with assessment of CR in a patient with IgG kappa myeloma include the therapeutic monoclonal antibodies (mAbs) such as daratumumab. Daratumumab is a mAb against CD38 which is highly expressed on myeloma cells. It is highly active as a single agent and as part of combination therapies in myeloma. Daratumumab typically presents in trace or up to 1 g/L on SPEP/IFE. Laboratories should know the position of mAbs on their SPEP system. The IMWG response criteria 2015 footnote states: “Also, appearance of monoclonal IgG kappa in patients receiving monoclonal antibodies should be differentiated from the therapeutic antibody.”26 Methods such as the Daratumumab IFE reflex assay (DIRA) or the Hydrasys™ Shift (Sebia) can be used to identify the presence or absence of daratumumab.27 According to a recent international survey, only 4% of laboratories test for the presence of daratumumab or other mAbs, 60% intend to outsource the testing, and currently there is not yet a clear consensus of the preferred method to detect mAb interference.28

The comments in Table 3 (Table 4 of the 2012 recommendations) have been changed to emphasise the utility of serum FLC measurement as an alternative to urine BJP measurement. Serum FLC may help identify the clonality of small bands detected on SPEP.

Table 3. General interpretive commenting recommendations: specimens with a paraprotein and/or small abnormal band (an update to Table 4 in the 2012 paper).

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Minimal information to be provided in the interpretive comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>New, small abnormal band with different electrophoretic mobility from</td>
<td>There is a small (type: e.g. IgG kappa) band approximately (amount: e.g. 1 g/L) on a background of a polyclonal and/or oligoclonal pattern. This band is different from the original paraprotein. Its clinical significance is uncertain.</td>
</tr>
<tr>
<td>the original paraprotein in a patient with a known paraprotein</td>
<td></td>
</tr>
<tr>
<td>First presentation of small abnormal band (and no known paraprotein)</td>
<td>There is a small (type: e.g. IgG kappa) band approximately (amount: e.g. 1 g/L). Its clinical significance is uncertain. Suggest serum free light chains or urine protein electrophoresis and immunofixation and repeat serum protein electrophoresis in 3–6 months if clinically indicated.</td>
</tr>
<tr>
<td>First presentation of small abnormal band in polyclonal/oligoclonal</td>
<td>There is a small (type: e.g. IgG kappa) band approximately (amount: e.g. 1 g/L) on a background of a polyclonal and/or oligoclonal pattern. Its clinical significance is uncertain but may reflect an inflammatory/reactive process. Suggest serum free light chains or urine protein electrophoresis and immunofixation and repeat serum protein electrophoresis in 3–6 months if clinically indicated.</td>
</tr>
<tr>
<td>background (and no known paraprotein)</td>
<td></td>
</tr>
<tr>
<td>An IgG kappa band of similar electrophoretic mobility to that of</td>
<td>A monoclonal IgG kappa band approximately (amount: e.g. 1g/L) has been found in the gamma fraction on immunofixation. The band has similar mobility to that of Daratumumab. This could represent the presence of a therapeutic monoclonal antibody. Clinical correlation is required.</td>
</tr>
<tr>
<td>Daratumumab in a patient known to have IgG kappa myeloma</td>
<td></td>
</tr>
</tbody>
</table>

The comments in Table 3 (Table 4 of the 2012 recommendations) have been changed to emphasise the utility of serum FLC measurement as an alternative to urine BJP measurement. Serum FLC may help identify the clonality of small bands detected on SPEP.

Competing Interests: None declared.

References


