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UHL GP NEWS

Referrals to Myeloma Service

Summary

Myeloma service has seen an influx of inappropriate referrals from primary and secondary care due to inadequate understanding of the results of Immunoglobulins and the serum free light assay.

Serum free light assay measures Free serum kappa and lambda light chains (i.e. not attached to heavy chain to form an intact immunoglobulin).

This assay has become mandatory for the immunology lab to perform whenever you ask for serum Immunoglobulins or ask for a myeloma screen and has created an influx of work for Haematology mostly rejecting referrals.

Below is an explanation that is being circulated to all Primary and Secondary colleagues. Any feedback will be gratefully received - please feel free to write an email if you need any advice related to these reports.

Who to contact for more information?

Dr Mamta Garg, mamta.garg@uhl-tr.nhs.uk.



UNDERSTANDING SERUM IMMUNOGLOBULINS and SERUM FREELITE RATIO – EXECUTIVE SUMMARY

General rules:

Serum free light assay measures circulating free or unbound serum light chains i.e. kappa and lambda (when not part of intact immunoglobulin). It is reported in mg/L and not g/L and needs to be taken into account and taken in perspective when looking at a report. Minimal elevation of these light chains up to 100 mg/L (0.1 g/L) can occur when immunoglobulin synthesis is elevated or when light chain excretion is reduced (renal impairment).

Following situations are not MGUS or Myeloma and do not require referral to haematology and monitoring:

1. Polyclonal rise in Immunoglobulins that may also be associated with polyclonal rise of both kappa and lambda light chains.
 - Polyclonal rise of IgG is seen in inflammatory/autoimmune conditions/chronic infections like TB
 - Polyclonal rise in IgA is often seen in alcoholic liver disease and NAFLD/NASH
 - Polyclonal rise in IgM is seen in primary biliary cirrhosis.
2. Isolated low IgM - often insignificant and needs no further action
3. Raised Kappa as well as Lambda chains due to renal impairment. Note wider normal range of kappa lambda ratio of **0.37 to 3.1** in patients with low GFR.
4. **Please note light chain excess is usually not relevant unless >100 mg/L and needs no further action.**

Exception: Oligo-secretory myeloma and amyloidosis when there is organ damage such as nephrotic range proteinuria, Congestive cardiac failure, Peripheral Neuropathy, significant bone disease where presentation to relevant specialty is due to organ damage and checking Immunoglobulins is part of their workup.

Differential Diagnosis of a *monoclonal* presence of a paraprotein (plasma cell dyscrasia):

1. Myeloma
2. MGUS
3. Lymphoma
4. Amyloidosis POEMS syndrome.

When to refer a paraprotein to Myeloma or Haematology team? Also see PRISM guidelines:

1. IgG paraprotein of >15 g/L,
2. Non IgG paraprotein at any level – IgA or IgD
3. Free kappa or lambda light chain >100 mg/L with an abnormal ratio
4. Kappa Lambda Ratio >10 or <0.1



When to do a myeloma screen or check serum Immunoglobulins?

1. Suspected myeloma
 - a. Unexplained anaemia
 - b. Unexplained macrocytosis
 - c. Significantly raised **serum** total protein with low or normal albumin
 - d. Disproportionate **urine** PCR and ACR (PCR >5 times ACR)
 - e. Pathological Fracture
 - f. Unexplained renal impairment
 - g. Hypercalcaemia
 - h. Unexplained Hyponatraemia
 - i. Unexplained Hyperphosphatemia

2. Recurrent bacterial infections

Note:

Serum total protein is done routinely in 50% of the labs as part of LFT. The lab at UHL does not provide it, but nevertheless it is an important way of suspecting presence of a paraprotein for many labs.

Urine PCR and ACR is not routinely done in all patients but is routine practice in patients with diabetes, hypertension and unexplained renal impairment.

If Urine PCR is >100 and 5 times of ACR, suspect presence of bence jones protein in the urine and send serum for myeloma screen.

Spurious Hyponatraemia and Hyperphosphatemia is seen when there is a very high paraprotein as that interferes with the assays in the lab. Often serum sample from such a patient is NOT analysable.



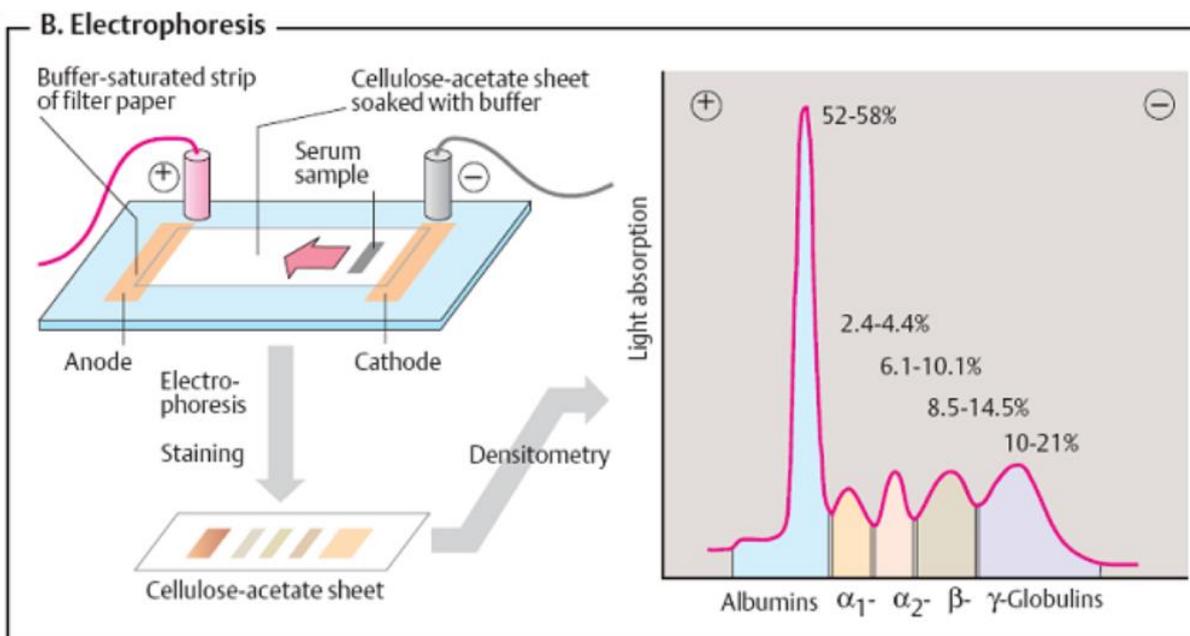
SCIENCE BASED EXPLANATION WITH EXAMPLES

B lymphocytes mature to become plasma cells and their main function is to produce protective antibodies also called Immunoglobulins (Igs). These Igs have heavy and light chains. There are five type of Igs based on the type of heavy chain, namely, IgG IgA, IgM, IgD and IgE. The light chains are of two types, namely, kappa and lambda and are also called Bence Jones proteins when present in urine.

Serum protein electrophoresis (SPEP) measures albumin (alb) and globulins (glb) and separates different globulins. Globulins run at different speeds and are in three regions - alpha beta and gamma.

Total protein (TP) is simply an addition of alb and glb reported by ~50% of the chemistry laboratories in the country when you ask for LFT.

Total protein	60-80	g/L
Albumin	35-50	g/L
Globulins by inference	25-30	g/L



Alpha(α) and Beta(β) globulins are often raised in acute inflammatory conditions as many of the proteins are acute phase reactants (APRs). CRP though lies in gamma region
Glycoproteins, complement protein, metal binding proteins, transfer proteins, clotting factors, proteinase inhibitors etc are present in the α and β regions of globulins on SPEP.

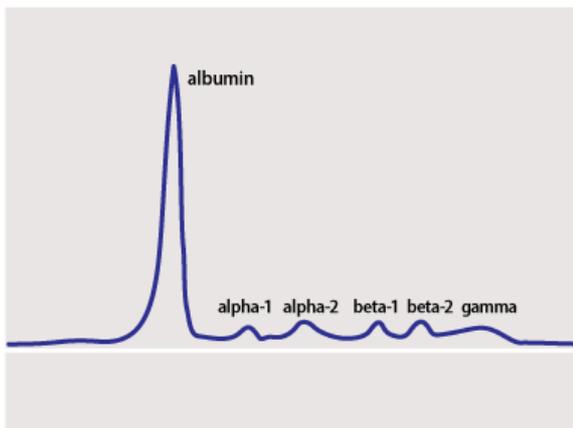


Igs are in the gamma (γ) region of Globulins. Igs are reported in g/L and light chains in mg/L

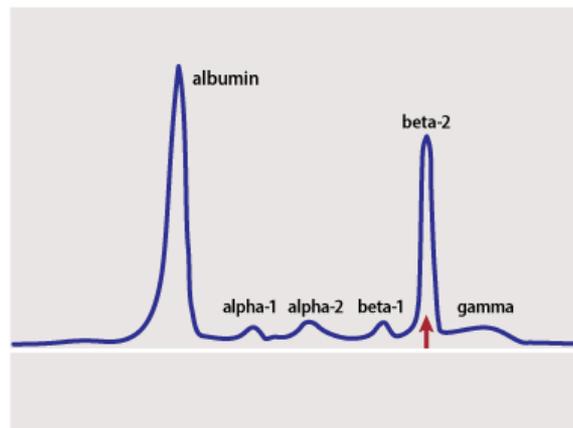
Serum IgG	6.0 -16.0	g/L
Serum IgA	0.8 - 4.0	g/L
Serum IgM	0.5 - 2.0	g/L
Serum free kappa light chains	3.3 to 19.4	mg/L
Serum free lambda light chains	5.7 to 26.3	mg/L

Serum kappa/lambda ratio	0.26 to 1.65
Serum kappa/lambda ratio (GFR <30 ml/min)	0.37 to 3.1

SPEP Test Results



Normal SPEP result



Abnormal result with myeloma cells producing the M-protein, creating an M-spike in the beta-2 zone

Myeloma being a cancer is monoclonal and as the cell originates from a single plasma cell and produce only one type of antibody or immunoglobulin which is seen as a single band on SPEP and hence called a paraprotein and could be of any type such as IgG, IgA or IgD. The paraprotein usually is seen in the gamma and sometimes in beta2 region of SPEP.

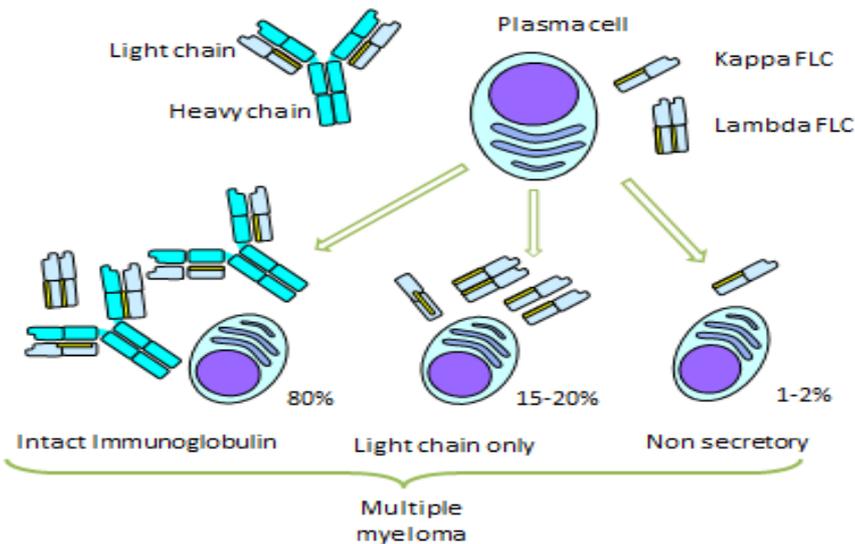
Myeloma is also light chain restricted in being either kappa or lambda.



Majority of myeloma patients produce an intact paraprotein comprising of 2 heavy and 2 light chains but some can produce an *excess of light chains* or produce *just the light chains*.

As these light chains are small in size they traverse through glomerulus and are a threat to glomerular function by creating casts in the tubules if excreted in excess of 500 mg/L.

A pictorial presentation is as below:



EXAMPLES

Immunoglobulin report looks like this on ICE or iLab:

Example 1:

IgG	11.1	g/L	(6.0 to 16.0)
IgA	1.90	g/L	(0.80 to 4.0)
IgM	1.54	g/L	(0.5 to 2.0)
Serum Electrophoresis	No monoclonal band detected		

As the test is totally normal and myeloma is not suspected by the requester, serum free light chains is not performed by the lab automatically

Example 2:

IgG	10.2	g/L	(6.0 to 16.0)
IgA	2.48	g/L	(0.80 to 4.0)
IgM	0.76	g/L	(0.5 to 2.0)
Serum Electrophoresis	No monoclonal band detected		
Serum free kappa light chains	33.4*	mg/L	(3.3 to 19.4)
Serum free lambda light chains	36.4*	mg/L	(5.71 to 26.3)
Serum kappa/lambda ratio	0.92		(0.26 to 1.65)

Note:

- 1. As myeloma is raised as a possibility in the request, even though serum Igs are normal, lab has organised serum free light chains automatically (NICE guidance)*
- 2. Both kappa and Lambda light chains are raised but the ratio is normal*
- 3. No evidence of myeloma and hence does not need monitoring, referral or repeat*

Example 3: Low Risk MGUS

IgG	12.7	g/L	(6.0 to 16.0)
IgA	2.55	g/L	(0.80 to 4.0)
IgM	0.72	g/L	(0.5 to 2.0)
Serum Electrophoresis	1.4*	g/L	
Serum Immunofixation: Monoclonal band typed as IgG kappa			
Serum free kappa light chains	78.2*	mg/L	(3.3 to 19.4)
Serum free lambda light chains	56.9*	mg/L	(5.71 to 26.3)
Serum kappa/lambda ratio (sFLR)	1.38		(0.26 to 1.65)



Note:

1. This is low risk MGUS with a small paraprotein <15 g/L with a normal sFLR (0.26 to 1.65) – no intervention is needed in this patient especially if above 70 years of age
2. Monitoring of such cases in primary care is entirely appropriate with FBC U&E Bone Igs and sFLR every 3m in year 1, 6m in year 2 and annually thereafter.
3. A routine referral to myeloma clinic is indicated if there is rising paraprotein above 10 g/L from baseline or light chain rises above 100 mg/L – discuss on advice and guidance example
4. A **routine** (not 2WW) referral to myeloma clinic is indicated if patient has unexplained Congestive cardiac failure, proteinuria or is <60 years of age.
5. In patients who are NOT fit for steroids or chemotherapy due to co-morbid conditions such as dementia or poor performance status – monitoring is not indicated or appropriate.

Example 4: Isolated low IgM without a paraprotein

IgG	10.2 g/L	(6.0 to 16.0)
IgA	2.48 g/L	(0.80 to 4.0)
IgM	0.21* g/L	(0.5 to 2.0)
Serum Electrophoresis	No monoclonal band detected	
Serum free kappa light chains	18.3 mg/L	(3.3 to 19.4)
Serum free lambda light chains	14.1 mg/L	(5.71 to 26.3)
Serum kappa/lambda ratio	1.29	(0.26 to 1.65)

This is **insignificant** esp in the elderly and does not need referral, repeat or monitoring.

Example 5: Polyclonal rise in Immunoglobulins without a paraprotein associated with a polyclonal rise in light chains as well with normal ratio

IgG	20.9* g/L	(6.0 to 16.0)
IgA	9.26* g/L	(0.80 to 4.0)
IgM	0.31* g/L	(0.5 to 2.0)
Serum Electrophoresis	No monoclonal band detected	
Serum free kappa light chains	62.0* mg/L	(3.3 to 19.4)
Serum free lambda light chains	43.4* mg/L	(5.71 to 26.3)
Serum kappa/lambda ratio	1.43	(0.26 to 1.65)

Note: Polyclonal rise in IgG is noted in autoimmune conditions like SLE, RA or Sjogren’s disease
 Polyclonal rise in IgA is often noted in liver disease due to fatty liver and or alcoholic liver disease or NASH
 Non-alcoholic steatohepatitis
 Polyclonal rise in IgM is often seen in primary biliary cirrhosis.



Example 6: Minimally abnormal sFLR, note the normal limit is wider in patients with renal failure:

IgG	9.1 g/L	(6.0 to 16.0)
IgA	3.31 g/L	(0.80 to 4.0)
IgM	0.87 g/L	(0.5 to 2.0)
Serum Electrophoresis	No monoclonal band detected	
Serum free kappa light chains	32.5* mg/L	(3.3 to 19.4)
Serum free lambda light chains	16.5* mg/L	(5.71 to 26.3)
Serum kappa/lambda ratio	1.97	(0.26 to 1.65)

LTG comment: *Minimally increased serum free light chain concentrations or minor abnormality in kappa lambda ratio (up to 10) can occur when immunoglobulin synthesis is elevated (e.g. autoimmune, liver and inflammatory diseases, infection), or when light chain excretion is reduced (e.g. renal impairment). Minor abnormalities are unlikely to be clinically significant especially in patients with eGFR<60 mL/min. This is not MGUS and is not related to patient symptoms and does not require referral*

Example7: Pan-hypo-gamma-globulinaemia and normal serum freelite ratio

IgG	2.1 g/L	(6.0 to 16.0)
IgA	<0.25 g/L	(0.80 to 4.0)
IgM	<0.17 g/L	(0.5 to 2.0)
Serum free kappa light chains	33.4* mg/L	(3.3 to 19.4)
Serum free lambda light chains	36.4* mg/L	(5.71 to 26.3)
Serum kappa/lambda ratio	0.92	(0.26 to 1.65)

Differential Diagnosis: Immunological diseases like CVID, Lymphoproliferative diseases such as CLL and Non secretory Myeloma – needs referral to immunology

This is severe hypo gamma glb and hence needs a referral to immunology Services



Example 8: Pan-hypo-gamma-globulinaemia with an abnormal serum free light ratio

IgG	2.1 g/L	(6.0 to 16.0)
IgA	<0.25 g/L	(0.80 to 4.0)
IgM	<0.17 g/L	(0.5 to 2.0)
Serum Electrophoresis	No monoclonal band detected	
Comments :	Reduced gamma region on electrophoresis	
Serum free kappa light chains	72.2 mg/L	(3.3 to 19.4)
Serum free lambda light chains	10.7 mg/L	(5.71 to 26.3)
Serum kappa/lambda ratio	6.75	(0.26 to 1.65)

This could be a patient with myeloma who is profoundly immunosuppressed and should be referred to myeloma service.

Example 9: Light Chain only Myeloma with low IgA , IgM and Lambda

IgG	7.8 g/L	(6.0 to 16.0)
IgA	0.58* g/L	(0.80 to 4.0)
IgM	0.38* g/L	(0.5 to 2.0)
Serum Electrophoresis	4.1* g/L	
Serum Immunofixation:	Monoclonal band typed as Free kappa	
Serum free kappa light chains	10394* mg/L	(3.3 to 19.4)
Serum free lambda light chains	8.5* mg/L	(5.71 to 26.3)
Serum kappa/lambda ratio (sFLR)	1222*	(0.26 to 1.65)

LTG Comments amended and sent once sFLR was ready :

Marked free kappa chain excess with abnormal ratio, amended report will be issues for total Immunoglobulins as this is a free kappa paraprotein NOT an IgG kappa paraprotein. Duty GP telephoned at 1555hrs 14/6/18 and urgent 2WW referral to haematology advised and to ensure recent U&E< FBC and Ca2+ checked. Myeloma team emailed with result. AP



Example 10: Intact paraprotein Myeloma with minimal light chain excess

CP838725E Request Reason: normochromic normocytic anaemia

IgG	75.1*	g/L	(6.0 to 16.0)
IgA	0.23*	g/L	(0.80 to 4.0)
IgM	0.28*	g/L	(0.5 to 2.0)
Serum Electrophoresis	50.6*	g/L	
Serum Immunofixation: Monoclonal band typed as IgG kappa			

Serum free kappa light chains	6.4	mg/L	(3.3 to 19.4)
Serum free lambda light chains	153.8*	mg/L	(5.71 to 26.3)
Serum kappa/lambda ratio (sFLR)	0.04		(0.26 to 1.65)

LTG Comments:

Large IgG lambda paraprotein, result telephoned to GP surgery and message left with reception at 1120hrs 11/9/18, no call back by 13:10 hrs 11/9/18. Recommend urgent referral to haematology for further assessment, result emailed to myeloma team 11:44hrs 11/9/18. AP

