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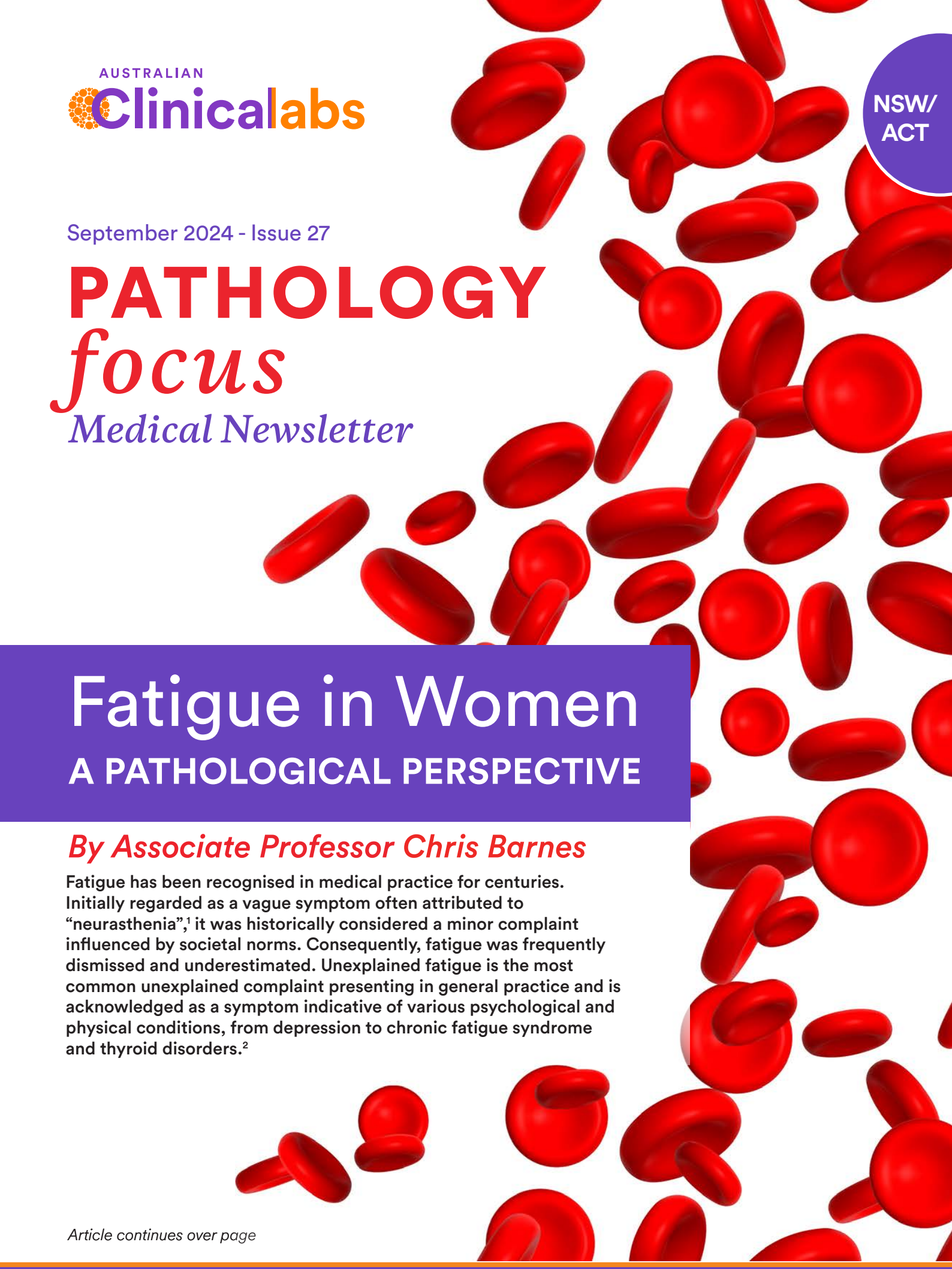

Fatigue in Women

A PATHOLOGICAL PERSPECTIVE

By Associate Professor Chris Barnes

Fatigue has been recognised in medical practice for centuries. Initially regarded as a vague symptom often attributed to "neurasthenia",[1] it was historically considered a minor complaint influenced by societal norms. Consequently, fatigue was frequently dismissed and underestimated. Unexplained fatigue is the most common unexplained complaint presenting in general practice and is acknowledged as a symptom indicative of various psychological and physical conditions, from depression to chronic fatigue syndrome and thyroid disorders.[2]

Article continues over page

Despite its prevalence—reported more commonly in women due to factors like menstrual cycles, pregnancy, and iron deficiency anaemia—fatigue often suffers from a lack of serious consideration in both the community and healthcare settings. This is compounded by a gender bias that sometimes leads to women's symptoms being taken less seriously, potentially delaying crucial diagnosis and treatment.

This introduction sets the stage for a discussion on the modern investigation of fatigue in women, highlighting the need for greater recognition and a systematic approach in medical diagnostics to improve outcomes for those affected.

Diagnostic approach to fatigue in women:

Thyroid function tests

Thyroid dysfunction, particularly hypothyroidism and less commonly hyperthyroidism, can significantly impact energy levels. These conditions can lead to fatigue when the thyroid gland either produces too little or too much thyroid hormone. Testing TSH and free T4 helps to diagnose these conditions, which are manageable through hormonal therapies.

Glucose levels

Fatigue can be a symptom of both diabetes and pre-diabetes, where the body struggles with insulin regulation leading to abnormal glucose levels. Early detection through fasting glucose tests or HbA1c measurements can guide interventions that may alleviate fatigue and manage the underlying metabolic dysfunction.

Full Blood Examination (FBE)

This test can detect a variety of conditions that may cause fatigue. Iron-deficiency anaemia is a common finding, particularly where there is chronic blood loss such as in heavy menstrual periods or gastrointestinal bleeding. FBE can also identify other forms of anaemia caused by vitamin deficiencies or chronic diseases, and less commonly, haematologic malignancies.

Iron studies

Besides iron-deficiency anaemia, iron overload disorders like haemochromatosis can also cause fatigue. This test measures ferritin and transferrin saturation, which can guide appropriate treatment strategies, such as dietary adjustments, iron supplementation, or investigation for causes of increased iron stores.

Vitamin B12 and folate levels

Deficiency in either of these vitamins can lead to megaloblastic anaemia, characterised by the production of abnormally large red blood cells that are inefficient at oxygen transport, resulting in fatigue. Causes include poor dietary intake, malabsorption conditions like coeliac disease, or intrinsic factor deficiency leading to pernicious anaemia.

Vitamin D levels

Deficiency in vitamin D is linked not only to musculoskeletal pain and weakness but also to chronic fatigue. This nutrient is pivotal for bone health and immune function, and deficiency can be due to inadequate sunlight exposure, poor dietary intake, or malabsorption disorders.

References

1. Beard, G., Neurasthenia, or nervous exhaustion. *The Boston Medical and Surgical Journal*, 1869. *80*(13): p. 217-221.
2. Koch, H., *et al.*, Demographic characteristics and quality of life of patients with unexplained complaints: a descriptive study in general practice. *Quality of Life Research*, 2007. 16: p. 1483-1489.

Order our *'Fatigue in Women'* test profile — only with Clinical Labs' eOrders.

For clinicians using eOrders in Best Practice, MedicalDirector Clinical, or Clinical Labs eResults, we have developed a 'Fatigue in Women' test profile that follows the clinical recommendations provided by A/Prof Barnes in this article.

How to order:

1. Ensure you have eOrders with Clinical Labs activated in your practice management software.

2. Navigate to 'Clinical Recommendations' (MD) or 'Clinical Details' (BP).

3. Choose our pre-configured 'Fatigue in Women' test profile that can be ordered with the click of a button.

Cost: Bulk-billed, subject to Medicare eligibility criteria.

For vitamin D testing, note the reason the patient meets the eligibility criteria for bulk-billing in the 'Clinical Notes' section when ordering.

eOrders

Fatigue in Women

- B12
- Folate - Serum
- Full Blood Examination
- Glucose - Serum (BSL)
- Iron Studies
- Thyroid Function Tests
- Vitamin D (25 Hydroxy)

For further information on MBS guidelines for B12 testing, view Assoc. Prof. Chris Barnes' article "Choosing between vitamin B12 and active B12 testing" by scanning the QR code.

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Associate Professor Chris Barnes is the National Director of Haematology and provides strategic direction for haematology at Clinical Labs on a national level. He is a clinical and laboratory-trained haematologist who has been part of Melbourne Haematology and has worked with Clinical Labs (and previously Healthscope) for several years. A/Prof Barnes is also the director of the Haemophilia Treatment Centre at the Royal Children's Hospital, and has experience in management and leadership positions. He has an active clinical research interest and serves as the director of both Melbourne Haematology (Clinical) and Melbourne Paediatric Specialists.

Diagnosing *Helicobacter pylori*: The Urea Breath Test and Alternative Methods

By Dr Phoebe Stanford and Dr Stella Pendle

Helicobacter pylori (*H. pylori*)

H. pylori is a Gram-negative bacillus that is found as a natural coloniser of the human gastric mucosa in about 50% of adults worldwide. *H pylori* was first identified in Australia by Marshall and Warren in 1983, who established the association with gastric and duodenal ulcers.[1] More than 80% of duodenal ulcers and more than 60% of gastric ulcers (see Figure 1) are associated with *H. pylori*, as well as some cancers of the stomach.

> ***"More than 80% of duodenal ulcers and more than 60% of gastric ulcers are associated with H. pylori."***

Most infections are acquired during early childhood, postulated to be due to transmission from close family members by oral-oral or faecal-oral routes.[2] In Australia, 25 to 30% of the population is infected, with the prevalence increasing with age. Acute infection may be asymptomatic or associated with mild dyspeptic symptoms. Acquisition of infection in adulthood is uncommon. Once acquired, the infection usually persists, resulting in chronic gastritis with the potential to cause gastroduodenal complications, including peptic ulcer disease, gastric atrophy, and intestinal metaplasia, as well as increasing the risk of gastric cancer and gastric mucosa-associated lymphoid tissue (MALT) lymphoma.

H. pylori may also be associated with iron and/or vitamin B12 deficiency due to reduced absorption caused by gastric atrophy and hypochlorhydria induced by chronic infection.

In adults, once *H. pylori* is diagnosed, eradication treatment is recommended.

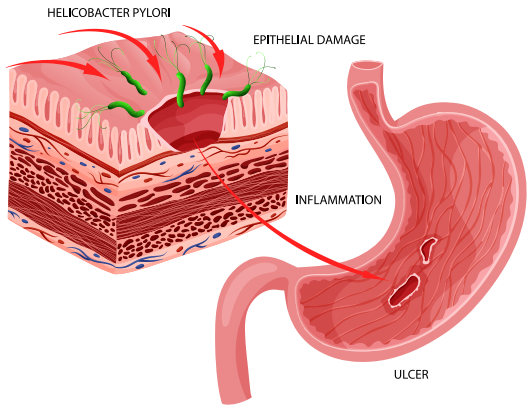

Figure 1. Gastric ulcer caused by H.pylori infection.

Diagnosis of *H. pylori*

The choice of test used to diagnose *H. pylori* is dependent on whether the patient requires an endoscopy to evaluate their symptoms. If an endoscopy is not required on the basis of clinical presentation, non-invasive tests for *H. pylori* are recommended.

Non-invasive tests are also useful where there is a potential false negative test during endoscopy (due to use of certain medications or active peptic ulcer bleeding) and for follow-up to confirm successful eradication after treatment.

Indications for testing (adults)[3,4]

- Established peptic ulcer disease
- Non-ulcer dyspepsia
- Monitoring the success of eradication of *H. pylori* after treatment
- Prior to chronic treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) or low-dose aspirin
- Unexplained iron deficiency anaemia (after investigation for other causes)

In children, testing is generally only recommended where there is established peptic ulcer disease or during endoscopy if treatment is intended. Such patients should be under specialist care.

Urea breath testing for *H. pylori*

The urea breath test is an accurate, non-invasive way to diagnose active *H. pylori* infection.

The test relies on the fact that *H. pylori* produces bacterial urease, which hydrolyses urea to produce CO_2 and ammonia. This helps to neutralise gastric acid and allows *H. pylori* to survive in the gastric environment.

In the ^{14}C Urea Breath Test, a capsule containing ^{14}C-labelled urea is given by mouth, and 10 minutes later, exhaled breath is collected into a balloon. If *H. pylori* is present, $^{14}CO_2$ will be produced, and this can be detected in the breath sample. If *H. pylori* is not present, the labelled urea will not be broken down, and the breath will not contain $^{14}CO_2$.

Is the test safe?

^{14}C is a naturally occurring radioactive form of carbon, present in very small amounts in all living things, with the more common form being ^{12}C. The dose of radiation in the ^{14}C Urea Breath Test is approximately equivalent to one day of background radiation exposure, far less than a standard X-ray.[5]

However, as studies have not been performed to determine safety in pregnancy, breastfeeding, and for children under 12 years, testing is not routinely performed in these groups. A stool antigen test is available as an alternative when testing for *H. pylori* is indicated.

Patient preparation

The patient will need to fast for a minimum of 6 hours before the test.
The following medications should be discontinued before the test to prevent false negative results.

Medication	Exclusion period
Antibiotics and bismuth containing products	4 weeks
Sucralfate	2 weeks
Proton Pump Inhibitors	7 days
Antacids and H2 Antagonists	No exclusion period, other than during fasting and during the test

Testing to confirm eradication following treatment should be performed at least 4 weeks following completion of treatment.

Alternative tests

Invasive tests

Invasive tests require upper endoscopy to obtain gastric tissue biopsies, which can be used for bacterial culture, susceptibility testing, and histopathology. The main limitation of these methods is their invasiveness and the ability to analyse only a small part of the gastric mucosa.[6] These tests are of value in the management of recurrent infection and in patients who are failing therapy, where specialist consultation is required.

Non-invasive tests

In addition to the urea breath test, non-invasive tests include serology and stool antigen tests. These tests provide high reliability in the detection of *H. pylori* due to their high sensitivity and specificity (Table 1). However, all of these methods have limitations, and the selection of test will depend on the clinical circumstances. Only the urea breath test and stool antigen test identify active infection.

The Stool Antigen Test (SAT) is based on the direct identification of *H. pylori* in stool samples. SAT is recommended for both the primary diagnosis of *H. pylori* infection and for the monitoring of therapy effectiveness. The test is non-invasive, quick, and easy to use, with a sensitivity of 95% and specificity of 97%. It is suitable for the diagnosis of *H. pylori* in children.

Serology: Antibodies to *H. pylori* appear in the blood 3 to 4 weeks after infection and may be present for life. Serologic tests are widely available to diagnose *H. pylori*. They are non-invasive, rapid, and can be used in screening populations. However, there are a number of limitations. Serology may be positive due to the presence of an active infection at the time of the test, a previous infection, or non-specific cross-reactive antibodies. The results must therefore be interpreted within the context of the clinical illness. Antibodies do not decline following treatment, so the test is of no value in monitoring therapy.

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Table 1: Accuracy of *H. pylori* diagnostic methods[6]

Specimen type	Sensitivity (%)	Specificity (%)
Non-invasive tests		
Urea Breath Test	96-100	93-100
Stool Antigen Test	95	97
Serology	76-84	79-80
Invasive (requires Endoscopy)		
Rapid Urease Test	85-95	95-100
Histology	91-93	100
Culture	76-90	100

Requesting the ^{14}C Urea Breath Test with Clinical Labs

How to order: Request 'Urea Breath Test' on a Clinical Labs General Pathology Request Form.

Follow-up testing: Testing to confirm eradication following treatment should be performed at least 4 weeks following completion of treatment.

Cost: The Urea Breath Test is bulk-billed subject to Medicare criteria, which includes both confirmation of *H. pylori* colonisation and monitoring of successful eradication.

Alternative non-invasive tests (for pregnancy, breastfeeding and children):

- The Stool Antigen Test (SAT) – Specify 'Stool Antigen Test (SAT)' on the request form.
- Serology – Specify 'Serology for H. pylori' on the request form.

References

1. Warren J, Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet* 1983; 1:1273–75.
2. Kusters J, van Vliet A, Kuipers E. Pathogenesis of Helicobacter pylori Infection. *Clinical Microbiology Reviews* 2006; *19*(3): 449-490.
3. Crowe S. Helicobacter pylori Infection. N *Engl J Med* 2019; 380:1158.
4. Chey W, Leontiadis G, Howden C, Moss S. ACG Clinical Guideline: Treatment of Helicobacter pylori Infection. *Am J Gastroenterol* 2017; 112:212.
5. Lamont T. Indications and diagnostic tests for Helicobacter pylori infection in adults (2023). UpToDate. Retrieved May 28 2024 from https://www.uptodate.com/contents/indications-and-diagnostic-tests-for-helicobacter-pylori-infection-in-adults
6. Bordin, D.S.; Voynovan,I.N.; Andreev, D.N.; Maev, I.V .Current Helicobacter pylori Diagnostics. *Diagnostics* 2021, 11,1458. https://doi.org/10.3390/diagnostics11081458

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Dr Stanford graduated from the University of New South Wales in 2005. She completed Basic Physician Training, followed by Advanced Training in Chemical Pathology and Endocrinology. This included undertaking a year with a focus on bone disease at St Vincent's hospital (Sydney), followed by a year of general clinical endocrine training at Prince of Wales Hospital. Dr Stanford then completed her joint training based at the Prince of Wales and Royal North Shore Hospital Laboratories. In 2019, she was awarded fellowship of both the Royal Australasian College of Physicians and The Royal College of Pathologists of Australasia. Dr Stanford then worked at Tan Tock Seng hospital laboratory in Singapore before returning to Australia to take up a Chemical Pathologist position at Australian Clinical Labs.

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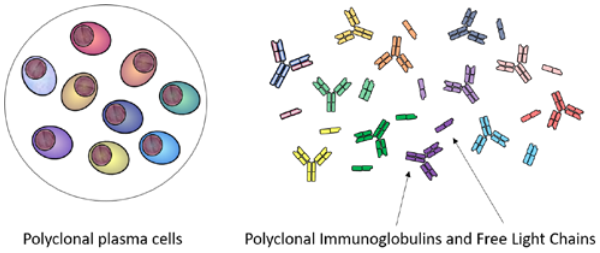
Dr Pendle has been working as a Clinical Microbiologist in Australia since 2005, when she obtained her fellowship of the Royal College of Pathologists of Australasia (FRCPA). In 2012, she joined Australian Clinical Labs (formerly Healthscope Pathology) as Supervising Pathologist in charge of the microbiology, infectious serology, and molecular diagnostics departments. Dr Pendle has special interests in general bacteriology, infectious serology, syphilis, and hepatitis. She has published several papers in her fields of interest, including VRE, chlamydial infections, and HIV. She actively participates in hospital infection control and promotes rational antibiotic prescribing. She is a member of the Australasian Society for Infectious Diseases and the Antimicrobial Society of Australia.

Free light chains and Multiple Myeloma – What, When and Why

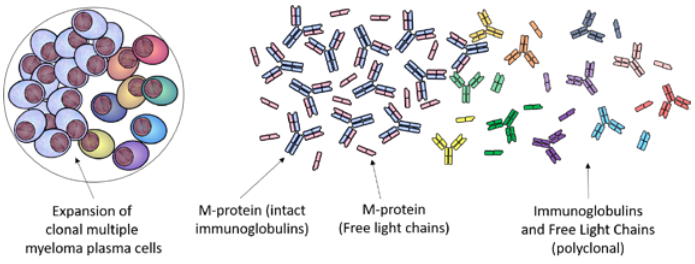
What are free light chains?

Light chains are small proteins produced in two isoforms (kappa, κ; and lambda, λ) by plasma cells which are responsible for producing antibodies. Light chains are bound to heavy chains to form an antibody, also called immunoglobulin. Heavy and light chains are produced independently and assembled together within the plasma cell; however, light chains are produced in excess and secreted as free κ and free λ light chains (κFLC, λFLC) in the blood (i.e., not bound to a heavy chain as it happens in an intact immunoglobulin).



When do free light chains matter?

When a monoclonal gammopathy (or plasma cell dyscrasia) develops, the majority of plasma cells retain the capability of producing intact immunoglobulins and free light chains. These can be used as biomarkers in multiple myeloma. As the plasma cells grow uncontrollably from one single plasma cell clone, the blood of the patient may have increased levels of a monoclonal protein (M-protein). In the majority of myeloma patients, the M-proteins can be both intact immunoglobulins and free light chains (FLC); however, around 20% of multiple myeloma patients only secrete FLCs or secrete low levels of intact immunoglobulin.



Serum protein electrophoresis (EPG) and capillary zone electrophoresis (CZE) lack the sensitivity to detect low levels of serum FLC (sFLC); in line with this, 1 in 8 patients may be missed if sFLCs are not investigated alongside EPG when ruling out multiple myeloma.[1]

For this reason, international[2] and national[3] guidelines recommend including sFLC testing when querying multiple myeloma to maximise the detection of signs indicative of myeloma. Multiple myeloma can be very difficult to diagnose due to the vague nature of its symptoms, and this is reflected in a longer time to diagnosis compared to other blood cancers.[4] This is why it is pivotal that the correct tests are requested if myeloma is suspected. Through the calculation of serum κFLC / λFLC ratio, it is possible to identify plasma cell clonality and by combining EPG (and immunofixation) and sFLC analysis, >99% of myeloma patients can be correctly diagnosed.[1]

EPG and sFLC measurements are also used when monitoring patients with multiple myeloma and they aid clinicians in the assessment of response to therapy.[5]

With just one blood sample, it is possible to test both EPG and sFLC, enabling correct diagnosis in over 99% of myeloma patients.[1]

Why is serum free light chain testing recommended over urine testing?

Free light chains are sometimes referred to as Bence-Jones Protein (BJP) when they are identified in urine by the presence of a band in urine protein electrophoresis or immunofixation. However, looking for FLCs in urine can be complicated.

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Normal plasma cells produce 0.5-1 g of FLC per day; however, 10-30 g/day can be metabolised by healthy kidneys.[6] This means that for FLCs to be detected in the urine, the production needs to be higher than the metabolic capacity of the kidney, or the kidney needs to be damaged. Not all myeloma patients will produce high levels of FLC or have impaired kidney function at diagnosis, and FLC might not be present in the urine, potentially leading to delays in diagnosis.

It has been demonstrated that sFLC measurement provides equivalent or better diagnostic sensitivity to urine analysis[1, 8-11] in myeloma diagnosis.

If FLCs are present in the urine, they were in serum first: with just one blood sample it is possible to test both EPG and sFLC, and complying with the guideline recommendations for ruling out multiple myeloma.

References

1. Katzmann JA, *et al*. Screening panels for detection of monoclonal gammopathies. *Clin Chem* 2009; 55:1517-1522
2. Rajkumar SV, *et al*. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol*. 2014; 15:e538-e548
3. Quach H & Prince H. Clinical practice guideline: multiple myeloma. *Australia: Myeloma Australia* 2022
4. Howell DA, *et al*. Time-to-diagnosis and symptoms of myeloma, lymphomas and leukaemias: a report from the Haematological Malignancy Research Network. *BMC Hematol* 2013; 13:9
5. Kumar S, *et al*. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol* 2016; 17:e328-46
6. Dispenzieri A, *et al*. International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders. *Leukemia* 2009; 23:215-224
7. Robson EJD, *et al*. Utility of serum free light chain analysis when screening for lymphoproliferative disorders. *Lab Med* 2009; 40:325-329
8. Hill PG, *et al*. Serum free light chains: an alternative to the urine Bence Jones proteins screening test for monoclonal gammopathies. *Clin Chem* 2006; 52:1743-1748
9. Holding S, *et al*. Use of serum free light chain analysis and urine protein electrophoresis for detection of monoclonal gammopathies. *Clin Chem Lab Med* 2011; 49:83-88
10. McTaggart MP & Kearney EM. Evidence-based use of serum protein electrophoresis in laboratory medicine. *Clin Chem Lab Med* 2013; 51:e113-e115
11. Baulch DA, *et al*. Optimising the Laboratory Detection of Plasma Cell Proliferative Disorders. Presented at IBMS 2015 2015

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UPDATE: Global Blood Culture Bottle Shortage

Referrers may be aware that there is currently a global shortage of BD Bactec blood culture media bottles due to weather conditions affecting the production of the plastic bottles. This shortage is expected to continue until September 2024. As this is a global issue, it has impacted various laboratory networks, including Clinical Labs, which utilise this blood culture bottle system. In light of the supply issue, we have actively managed and reconciled our supply while reducing wastage, ensuring there is no expected impact within our laboratory network. Additionally, we have contingency plans in place for an alternative culture bottle supply should the shortage continue beyond September.

For referrers, please note that there has been a change in the availability of blood culture collection at some of our outpatient collection centres. When using our location finder at clinicallabs.com.au/location, please select 'Blood Culture Collection' from the drop-down menu to identify the specific collection centres where blood cultures can be performed. We appreciate your understanding and cooperation during this period and are committed to ensuring minimal disruption to our services.

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