

Case Study: Laboratory investigation of tiredness

1. A 28 year-old woman presents complaining of tiredness. Lately she has noticed an increase in her menstrual bleeding, you suspect iron deficiency. Which of these tests would you request?	CBC	
	ESR	
	Ferritin	
	Iron studies	
2. A 19 year-old man presents with two weeks of tiredness. He changed to a vegan diet 3 months ago. Would you test for vitamin B12 and folic acid?	Yes	
	No	
3. A 41 year-old woman has been feeling more tired than usual for almost a month. She has a busy life and is now working part time, as well as looking after her 3 children. A review of her notes reveals she had an episode of post partum thyroiditis following the birth of her youngest son 4 years ago. Which of these blood tests would you order	CBC	
	Iron studies	
	Ferritin	
	Thyroid function tests	
	TSH	
4. A 20 year-old woman attends for a repeat of her oral contraceptives. In the course of the consultation she mentions a few of her friends have had glandular fever in the last few months. She thinks she is feeling a bit more tired than usual and wonders if she could have glandular fever too. Would you request any of these tests?	CBC	
	ESR	
	Iron studies	
	Ferritin	
	Paul Bunnell	
	EBV antibodies	
5. A 58 year-old woman has tiredness and generally feels "off colour". She is urinating more frequently, but dismissed this symptom as part of aging. A dipstick urine test is positive for leukocytes and nitrites. Do you send the urine to the laboratory for culture and sensitivities?	Yes	
	No	
6. A 20 year-old woman complains of recent tiredness. The main reason for her tiredness appears to be the stress of upcoming exams, and poor sleep. Would you perform any laboratory tests?	Yes	
	No	
If yes, what tests would you request?		
7. A 58 year-old man complains of tiredness over the previous month and you decide to perform laboratory tests. Would you request tests for haemochromatosis?	Yes	
	No	
If Yes, what tests would you request?		

Case Study Feedback

For each scenario decide which (if any) of the provided blood tests would be part of your investigation.

1. A 28 year-old woman presents complaining of tiredness. Lately she has noticed an increase in her menstrual bleeding, you suspect iron deficiency. Which of these tests would you request?

	CBC	ESR	Ferritin	Iron Studies
You				
Your Peers	95%	2%	95%	17%
GP Panel	✓		✓	

The GP panel and most respondents would request CBC and ferritin in this scenario. One in five respondents opted to do iron studies which are usually made up of iron, ferritin, transferrin and transferrin saturation.

Ferritin is the best test of depleted iron stores and usually demonstrates iron deficiency before anaemia occurs. When iron deficiency is suspected in the absence of concurrent inflammation, iron studies are unlikely to give any additional information than ferritin alone. Inflammation and acute phase response can make all iron tests difficult to interpret.

A ferritin below the lower limit of the reference range has a high probability of iron deficiency. In addition, there is some evidence that non-anaemic woman with unexplained fatigue and a ferritin toward the lower end of the reference range may benefit from iron supplementation (Verdon, 2003). This does not mean that every woman with a ferritin at this level will benefit from iron therapy.

The panel all commented that they had used iron in this situation and found it beneficial.

Verdon, F. et al. (2003). Iron supplementation for unexplained fatigue in non-anaemic women: double blind randomised placebo controlled trial. *BMJ*, 326, 1124.

Specialist comment

No further comments

2. A 19 year-old man presents with two weeks of tiredness. He changed to a vegan diet 3 months ago. Would you test for vitamin B12 and folic acid?

	Yes	No
You		
Your Peers	21%	79%
GP Panel		✓

This man has only been on a vegan diet for three months and is very unlikely to have developed deficiencies in this time. Vitamin B12 can take two years or more to become depleted following inadequate intake. However the panel pointed out that in their experience people usually work their way into vegan diets and graduate to it through a period of intermediate diets. So they would question directly regarding this and may perform blood tests if there was the possibility of a poor diet for an extended period of time.

The panel would do few tests for this man as he only has a two week history of tiredness and is likely to have other issues which need further exploration. Four out of every five respondents would not test for B12 or folic acid.

The panel commented on the difficulty at times in interpreting vitamin B12 levels that fall within the 'indeterminate' range. Falsely low B12 levels may occur in folate deficiency, pregnant women and women using oral contraceptives. Management should be guided by the presence of haematological abnormalities or clinical symptoms. A follow up in 6 months may be a prudent approach.

Specialist comment

“The irreversible neurological complications of vitamin B12 deficiency highlight the importance of detecting this deficiency, but diagnosis can be difficult. Since therapy is, in general, life-long the diagnosis should be as solid as possible. Unfortunately, there is considerable overlap between the serum B12 levels of healthy persons and those with deficiency. In patients with low or indeterminate serum B12 levels, the haemoglobin, MCV and neurological status should be reviewed. Antibody tests for pernicious anaemia may help but are of limited value since there are many other causes of B12 deficiency, and they have poor sensitivity (intrinsic factor antibodies) or specificity (parietal cell antibodies). In difficult cases, serum methylmalonic acid can be very useful, since elevated levels have high sensitivity and specificity for B12 deficiency. While it is clear that vegans often have B12 deficiency, lacto- and lacto-ovo-vegetarians also appear to have an increased risk of deficiency. Note, that in vegetarians the MCV can be normal due to concomitant iron deficiency. As noted above, the B12 stores of a normal person are approximately 1000 fold greater than daily requirements and thus a B12 deficiency state can take years to develop.” Dr Ian Morison.

3. A 41 year-old woman has been feeling more tired than usual for almost a month. She has a busy life and is now working part time, as well as looking after her 3 children. A review of her notes reveals she had an episode of post partum thyroiditis following the birth of her youngest son 4 years ago. Which of these blood tests would you order?

	CBC	Iron Studies	Ferritin	Thyroid Function tests	TSH
You					
Your Peers	84%	10%	77%	9%	93%
GP Panel	✓		✓		✓

The panel and most respondents would do a CBC and ferritin with the addition of a TSH because of the woman's past history of post-partum thyroiditis. It is also important to consider lifestyle causes of her tiredness as she has plenty going on in her life to account for her tiredness and it is quite possible the test results will be normal.

Approximately one in ten doctors would add full iron studies and thyroid function tests. These would be better utilised in response to either a high ferritin or abnormal TSH. In some cases the laboratory may decide to perform these tests (reflex testing) or the GP can request them by phone within a day or two of the original specimen collection and have the extra tests added to the initial request form.

This led the panel into a discussion of when and how to notify patients of the results of blood tests. Each practice will have their own procedure for managing test results, and protocols for which results are communicated directly to the patient. Potentially this is a tricky medico-legal area, for which we need well thought out procedures in place.

Specialist comment

“In the context of targeted screening for hypothyroidism, I think the request for TSH in this scenario is justified - so long as practitioners remain alert to the potential trap of pituitary hypothyroidism. Patients can be quite markedly hypothyroid with a normal or even low TSH. If the clinical findings suggest hypothyroidism and the TSH is normal or low, FT4 should also be requested. It is important to remember that the lab may not reflex a FT4 on the basis of a normal TSH if there is no information to alert them to a high risk of hypothyroidism.

Post-partum thyroid dysfunction is common (approximately 5-9% of all pregnancies) and is especially common in women with type I diabetes mellitus. It is not clear from the scenario whether the post partum thyroiditis presented as hyper- or hypothyroidism but in those who develop post-partum thyroiditis characterised by hypothyroidism, hypothyroidism becomes permanent in 25-30%.

Again, I agree that it is reasonable to start the cascade of iron testing with a ferritin and that normally, in a situation of suspected iron deficiency, full iron studies add little useful additional information.” Dr Geoff Smith.

4. A 20 year-old woman attends for a repeat of her oral contraceptives. In the course of the consultation she mentions a few of her friends have had glandular fever in the last few months. She thinks she is feeling a bit more tired than usual and wonders if she could have glandular fever too. Would you request any of these tests?

	CBC	ESR	Iron Studies	Ferritin	Paul Bunnell	EBV antibodies
You						
Your Peers	63%	2%	5%	50%	17%	27%
GP Panel						

The panel would not perform any tests in this situation; although most respondents would do some blood tests.

Over half of respondents would test for CBC and ferritin and this seems a reasonable compromise. Glandular fever would be unlikely in this situation in the absence of other classical symptoms (fever, sore throat and generalised lymphadenopathy). The split between Paul Bunnell and EBV antibodies for testing for glandular fever is interesting. The Paul Bunnell test is significantly cheaper.

The panel then went on to discuss the many factors that influence the decisions to request tests. While there are obvious clinical indications to request tests, a number of other factors influence the doctor to request tests. These may include the relationship between the doctor and patient, expectations of the patient, practical issues around blood taking and result provision.

Specialist comment

“Two opposite approaches to suspected EBV infection can be considered. On one hand, it could be argued that acute EBV is a benign condition for which no specific therapy is needed, and in a characteristic clinical setting the demonstration of atypical lymphocytes and a positive EBV screening test (e.g. Paul-Bunnell) may be sufficient. The Paul-Bunnell and related screening tests should be used carefully since their sensitivity is poor (80-90% in adults; 50% in children) as is their specificity (85-95%).

On the other hand, it could be argued that clear documentation of EBV infection is important for current and future management. Other infections (CMV, HIV and toxoplasmosis) can mimic acute EBV infection. If specific EBV serologic tests are used, a diagnosis of current infection can usually be definitively established, or alternatively, a diagnosis of past infection can be used exclude current EBV. Once a diagnosis of acute or past EBV infection is established there is no indication for repeat testing in the future. I prefer this latter approach and always recommend it for atypical cases and suspected infections outside of the characteristic glandular fever age-group.” Dr Ian Morison

- 5. A 58 year-old woman has tiredness and generally feels “off-colour”. She is urinating more frequently, but dismissed this symptom as part of aging. A dipstick urine test is positive for leukocytes and nitrites. Do you send the urine to the laboratory for culture and sensitivities?

	Yes	No
You		
Your Peers	62%	38%
GP Panel		+/-

Positive nitrites and leukocytes on dipstick usually provides sufficient indication of urinary tract infection unless there are complicating factors present. There is no indication to send the urine to the laboratory in this situation or to test a post treatment specimen as long as symptoms settle. However, in this scenario over half of respondents would send a urine sample to the laboratory. This may be because respondents were concerned that she felt “off colour” and were not sure what this meant. The panel would certainly want to explore this further. They would also, as a minimum, ask about past or current genitourinary symptoms, check her temperature and examine her abdomen for renal tenderness. A urine test for Chlamydia may be appropriate after discussion with the patient.

Specialist comment

Our specialist commentary on this scenario offers a microbiologist’s perspective.

“The positive leukocyte esterase and nitrite tests are indeed strongly indicative of a urinary tract infection, but culture, bacterial identification and susceptibility testing will give valuable additional information.

The most important reason for culture and susceptibility testing is to avoid inappropriate use of antimicrobials. It is good practice to prescribe an empirical course of antimicrobials, but only if a culture is taken can antimicrobials be discontinued (if culture does not confirm infection) or changed (if bacterial identification and susceptibility testing indicates that the empirical choice was less than optimal).

The initial empirical treatment can only be rationally chosen if the practitioner is aware of the susceptibility trends in the population(s) he or she serves. If the decision to culture is biased towards complicated and recurrent UTIs, more likely to involve organisms other than E. coli, and more likely to involve resistant organisms, an impression may be gained of a higher prevalence of resistance than is in fact the case. Such an impression may lead the practitioner to be less likely to prescribe trimethoprim, and more likely to prescribe more problematic antimicrobials.

Trimethoprim is widely regarded as the ideal empirical treatment for uncomplicated urinary tract infection. This is for good reason. It is cheap, safe, and, because little used for serious systemic infections, increasing resistance to trimethoprim is less of a public health disaster than is resistance to B-lactams or fluoroquinolones.

Resistance to antimicrobials is driven by use. As elsewhere in the world, resistance rates of uropathogens to trimethoprim are rising in New Zealand. It nonetheless remains a good choice of empirical therapy provided that there is culture confirmation and susceptibility testing of urinary isolates.

It will be a tragedy, and an easily preventable tragedy, if short-term cost saving on urine cultures contributes to the overuse of B-lactams and fluoroquinolones, resulting in the loss to Medicine of the utility of these very important classes of drugs.

I note the comment by the panel that it feels testing for Chlamydia might be appropriate. While I do not disagree - given the increasing prevalence of Chlamydia, it is always something to consider - I do not believe that there are specific indications in this patient. Whereas the positive leukocyte esterase is consistent with chlamydial infection, the positive nitrite test points towards growth of a nitrate reducing bacterium in the bladder.” Dr Richard Doerhing.

6. A 20 year-old woman complains of recent tiredness. The main reason for her tiredness appears to be the stress of upcoming exams, and poor sleep. Would you perform any laboratory tests?

	Yes	No
You		
Your Peers	28%	72%
GP Panel		✓

The panel and three quarters of respondents would not perform any laboratory tests. The panel felt that students often present in this situation because they are away from home and need support. They may want an impaired performance certificate in case the exams do not go well. Sometimes laboratory tests may be performed to show that you are taking the student’s concerns seriously but in this situation this reassurance is probably better demonstrated by the use of sound empathic consultation skills.

In the respondents who would request tests, CBC and ferritin were tested in the majority of occasions. Less frequently, liver function, renal function and thyroid function tests were indicated by this group.

Specialist comment

No further comment

7. A 58 year-old man complains of tiredness over the previous month and you decide to perform laboratory tests. Would you request tests for haemochromatosis.

	Yes	No
You		
Your Peers	39%	61%
GP Panel		✓

The panel would not normally consider haemochromatosis in the workup of this patient, and they would not request tests to specifically look for the condition. This was echoed in 60% of the respondents who would also not specifically test for haemochromatosis.

The panel commented that haemochromatosis was normally identified following an elevated ferritin or abnormal liver function tests. The panel were reasonably comfortable that a ferritin elevated above 500 µg/L would alert them to consider haemochromatosis as a diagnosis.

In the respondents who would request blood tests in this situation, the vast majority of doctors included a test of iron status (iron, transferrin, transferrin saturation, and ferritin). Of these, elevation of the transferrin saturation provides the most sensitive marker of hereditary haemochromatosis.

A number of respondents requested a range of tests because the man reported he had been tired for one month. The tests chosen were generally selections made from the bpac^{nz} “Investigating tiredness” guide.

Specialist comment

“Although the need for population screening for hereditary haemochromatosis remains controversial, I strongly encourage opportunistic investigation for this common condition (1 in 200 New Zealanders), especially in patients with fatigue, arthropathy, abnormal LFTs or macrocytosis. Although the life-threatening complications (e.g. liver cancer) of haemochromatosis occur only at ferritin levels > 1000 ug/L, fatigue and arthropathy symptoms occur at any ferritin level. Treatment is simple and the benefits often extend beyond the patient (e.g. donated blood). In a patient with chronic fatigue, the use of full iron studies will not only detect haemochromatosis and iron deficiency, but can also provide evidence for alcoholism and inflammation.” Dr Ian Morison.