GIG CYMRU NHS WALES
Bwrdd Iechyd Prifysgol Caerdydd a'r Fro
Cardiff and Vale University Health Board

Issue 3
December 2018

Laboratory Medicine Directorate

Newsletter for Primary Care

Inside this issue:

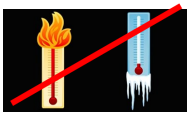
Best Practice in the Pre-Analytical Stage

The Pathologist March 2018

The pre-analytical stage includes any actions or factors involved in acquiring, handling, transporting and processing a patient sample prior to the actual analysis. Extraordinary efforts have been made in pathology to rigorously assure the quality of tests, the standard operating procedures (SOPs) used to perform tests and the proficiency of the people performing the tests. However little rigor has been applied to the control of factors that adversely affect specimen quality before testing is performed. No matter how advanced our analytical platforms, the quality of the results produced can never be higher than the quality of the starting material – the patient sample.

What is Best Practice?

Following venesection all primary care pathology samples should be stored at room temperature (18-25°C) and transported to the blood science or microbiology department within 4-6 hours of collection. Storage of specimens below 18-25°C and delayed transport will affect some tests e.g. potassium, phosphate and coagulation samples (particularly APTT) such that the samples will not be suitable for analysis.



Specimen collection tubes in use and in storage should not be exposed to extremes of temperature e.g. placed in direct sunlight, near a heat source (e.g. radiator) or allowed to freeze.

Phlebotomy should take place at 18-25°C. Once blood has been collected specimens should not be exposed to extremes of temperature. They should be kept between 18-25°C.

Ideally samples should be transported to the laboratory for processing within 4 - 6 hours of venesection.

It is important to record the time of sample collection on the request form so that delays in transport to the laboratory for processing can be identified. This helps the laboratory identify samples that may have deteriorated. Failure to identify them can result in the release of spurious or incorrect patient results.

These guidelines apply to the common laboratory test repertoire. For advice on specific tests please consult the laboratory test knowledge base.

Author: Dr Carol Evans For further advice please contact Mrs jane James: jane.james5@wales.nhs.uk

Faecal calprotectin use in primary care

Abdominal pain and bloating with changes in bowel habit are gastrointestinal (GI) symptoms which occur in both Irritable Bowel Syndrome (IBS) and Inflammatory Bowel Disease (IBD). IBS a functional disorder of unknown cause is not associated with serious morbidity. The varied presentation as well as phenotypic overlap with more serious pathology makes clinical diagnosis challenging however.

IBD occurs more commonly in females, typically presents during the 20's and 30's and is associated with significant long term morbidity with many patients requiring surgical intervention as well as an increased risk of GI malignancy. IBD is thought to develop in individuals with a genetic predisposition exposed to various environmental triggers resulting in a range of immune responses including neutrophil activation.

Calprotectin is a bacteriostatic protein that constitutes 60% of neutrophil cytosol proteins. Any process that affects mucosa integrity allows neutrophils present at sites of active inflammation in the gut to be released into the GI lumen. As a result faecal calprotectin is a measure of GI inflammation and the faecal concentration correlates well with the degree of inflammation. The higher the concentration, the more likely organic pathology.

Although not specific to inflammation of IBD, it has established clinical utility as a rule out test in the primary care setting in the differential diagnosis of IBS and IBD without endoscopy. In secondary care it is used additionally in IBD to monitor activity and assess response. Other causes of a raised faecal calprotectin concentration include GI infections such as gastro-enteritis, GI neoplasia, untreated coeliac disease, non-steroidal anti-inflammatory drugs and diverticular disease.

Locally the following approach is recommended: in the above clinical setting first line investigations to exclude pathology include a full blood count, C-reactive protein, thyroid function tests, anti-TTG antibodies and total IgA, stool microscopy and culture.

In view of the limitations described, faecal calprotectin testing is recommended as a second line test only in patients aged 16- 50 years with chronic diarrhoea >4 weeks or where symptoms are suggestive of IBD, not already known with IBD and who do not have typical IBS symptoms. In patients needing a colonoscopy based on the Colorectal Symptom Pathway, please do not request a calprotectin but refer as appropriate.

A calprotectin specific referral form indicating the above criteria is required before samples can be processed. Samples received without the referral forms are stored for two weeks to offer practices time to provide the referral form after which time samples are discarded. The referral form can be found in the Lab Test Handbook under Calprotectin and the Gastroenterology CAV intranet pages. Biochemistry accepts samples on children only if the case has been discussed with a named gastroenterologist and this is indicated on the request form.

Level		Interpretation
<50ug/g	Normal	No evidence of gut inflammation.
50-150ug/g	No evidence of gut inflammation	Gut inflammation is very unlikely. Consistent with IBS if symptoms are suggestive.
>150ug/g	Raised	Refer to Gastroenterology. IBD quite likely.

Faecal calprotectin use in primary care (cont.)

All patients with a calprotectin concentration >150ug/g need referral to gastroenterology for urgent colonoscopy.

The availability of the test to primary care now means that testing of patients where there is diagnostic uncertainty can be undertaken at an earlier stage to guide treatment.

References:

Manceau H et al. Fecal calprotectin in inflammatory bowel disease. Clin Chem Lab Med 2017;55(4):474-83.

Ayling RM. New faecal tests in gastroenterology. Ann Clin Biochem. 2012;49:44-54

Tietz Textbook of Clinical Chemistry and Molecular diagnostics. 6th edition. 2018. Elsevier. Ed Rifai, Horvath and Wittwer. Chapter 62, Gastric, Pancreatic and Intestinal function.

NICE clinical guideline 61: Irritable bowel syndrome in adults: diagnosis and management. 2017.

Author: Dr Danja Schulenburg-Brand (*Consultant Chemical Pathologist)*

To discuss laboratory investigations please contact: Danja.Schulenburg-brand@wales.nhs.uk

Thyroid Reference Ranges in the Elderly

Thyroid function has an integral effect on cardiovascular, metabolic and bone health and even modest variation is associated with adverse outcomes[1,2]. Levothyroxine is one of the commonest drugs prescribed in the UK and its use is steadily increasing[3]. There is good evidence of widespread prescribing of levothyroxine at TSH levels less than 6.0 mU/l and up to 20% of patients end up with a low or suppressed TSH[3]. On the basis of first principles treating low thyroid function such as subclinical hypothyroidism (TSH > reference-range with normal FT4) is seductive.

Many prescriptions are likely initiated with a view to improving energy, fatigue or even reducing cholesterol and improving cardiac function. These symptoms are common in the elderly and screening for dementia also encourages widespread thyroid function testing. Many elderly people may thus be started on levothyroxine at marginally high TSH levels although this practice could be questioned as there is growing evidence that a low activity of thyroid hormone might be beneficial in the elderly[4].

It is increasingly accepted that serum TSH levels increase with age, independent of the presence of antithyroid antibodies. This suggests that thyroid function decreases with age[4]. The 97.5th percentile of the TSH distribution is higher than in younger adults at around 7.5 mU/liter in subjects age 80 yr and older[4]. Therefore it is likely that an age specific reference range will result in TSH levels above the reference range for the young will still be in the “normal range” in elderly individuals. In other words, the prevalence of subclinical hypothyroidism is clearly overestimated in this group, unless an age-specific reference range is used. However more precise reference ranges in the elderly still need to be defined.

It should also be highlighted that increased levels of TSH[5] have been associated with longer survival in elderly subjects. Furthermore studies in the oldest old centenarians have indicated that those with a genetically higher TSH appear to have enhanced longevity[6].

What about the potential benefits of treating subclinical hypothyroidism in the elderly? Reducing cardiovascular mortality is clearly attractive. Therefore could it be argued that correction of subclinical hypothyroidism may have a beneficial impact. It is important not to extrapolate data from younger individuals to the elderly as there appears to be interaction with age[7]. Data for the beneficial effects of treatment of subclinical hypothyroidism on cardiovascular outcomes suggest any treatment benefit appears to be in younger (<65 years) rather than older individuals[8].

There is also lack of clear benefit in other aspects of health in the elderly. The recent trial of Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism[9] found no benefit from levothyroxine in subclinical hypothyroidism on hypothyroid symptoms. Given that subclinical hyperthyroidism is a risk factor for increased mortality[10] and TSH suppression is a very common complication of levothyroxine therapy even in the eldery[3] the adage “primum non nocere” might be the best answer.

Overall one should be comfortable monitoring a TSH level of up to 7.5 mU/l in the elderly and initiating treatment at levels higher. If a trial of levothyroxine is given between 4.0-7.5 mU/l care should be taken not to over-replace with a TSH target of 2.5-4.0mU/l being a practical target.

Thyroid Reference Ranges in the Elderly - References

1 Taylor, P. N., Razvi, S., Pearce, S. H. & Dayan, C. M. A review of the clinical consequences of variation in thyroid function within the reference range. *J Clin Endocrinol Metab* **98**, 3562-3571, doi:10.1210/jc.2013-1315 (2013).

2 Taylor, P. N. *et al.* Global epidemiology of hyperthyroidism and hypothyroidism. *Nature reviews. Endocrinology*, doi:10.1038/nrendo.2018.18 (2018).

3 Taylor, P. N. *et al.* Falling threshold for treatment of borderline elevated thyrotropin levels-balancing benefits and risks: evidence from a large community-based study. *JAMA Intern Med* **174**, 32-39, doi:10.1001/jamainternmed.2013.11312 (2014).

4 Peeters, R. P. Thyroid Function and Longevity: New Insights into an Old Dilemma. *The Journal of Clinical Endocrinology & Metabolism* **94**, 4658-4660, doi:10.1210/jc.2009-2198 (2009).

5 Gussekloo, J. *et al.* Thyroid status, disability and cognitive function, and survival in old age. *Jama* **292**, 2591-2599 (2004).

6 Atzmon, G., Barzilai, N., Hollowell, J. G., Surks, M. I. & Gabriely, I. Extreme longevity is associated with increased serum thyrotropin. *J Clin Endocrinol Metab* **94**, 1251-1254, doi:10.1210/jc.2008-2325 (2009).

7 Chaker, L., Bianco, A. C., Jonklaas, J. & Peeters, R. P. Hypothyroidism. *Lancet*, doi:10.1016/s0140-6736(17)30703-1 (2017).

8 Razvi, S., Weaver, J. U., Butler, T. J. & Pearce, S. H. Levothyroxine Treatment of Subclinical Hypothyroidism, Fatal and Nonfatal Cardiovascular Events, and Mortality. *Arch Intern Med*, doi:10.1001/archinternmed.2012.1159 (2012).

9 Stott, D. J. *et al.* Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism. *New England Journal of Medicine* **376**, 2534-2544, doi:10.1056/NEJMoa1603825 (2017).

10 De Leo, S., Lee, S. Y. & Braverman, L. E. Hyperthyroidism. *Lancet* **388**, 906-918, doi:10.1016/s0140-6736(16)00278-6 (2016).

Author: Dr Peter Taylor Clinical Senior Lecturer/ Consultant Endocrinologist
For any queries please contact Dr Peter Taylor: taylorpn@cf.ac.uk

To discuss laboratory investigations please contact: Dr Carol Evans, Consultant Clinical Biochemist, Department of Medical Biochemistry, UHW Carol.evans9@wales.nhs.uk
Tel 02920748367

Urine Sampling

URINE Sampling		
Container type:	**Microbiology**	**Biochemistry**
Red Top universal with BORIC acid 	**Microscopy culture and sensitivity (M,C&S)**	**NEVER TO BE USED FOR BIOCHEMISTRY**
White top Standard Universal 	**Schistosoma/parasites** **Pregnancy test** **Urine for Mycobacterium (TB)** **Investigations**	**Biochemistry urine analysis** **Please see the Lab Test Handbook on the intranet pages for full sample collection details**

Please ensure that urine samples for Microbiology (mc&s) investigations are collected in a **RED TOPPED UNIVERSAL.** These contain boric acid as a urine preservative, which ensures the sample contents (bacteria, white cells, yeasts etc) will remain stable during transport from user to laboratory, and when samples are stored in the laboratories.
If mc&c samples are received in white topped containers, then the laboratory frequently sees overgrowth of bacteria, which can lead to inaccurate results. This is a quality improvement change which will result in more accurate microscopy reports being issued to our users.

Surgeries will need to ensure they have a stock of both red topped universals and white topped universals to cover all of the test requests in the table above.

Suspected Carbon Monoxide (CO) Exposure

'Tis the season to be.....cautious?'

With the flick of a switch or the strike of a match, the nation settles down to a nice, warm, cosy winter. Or do we? Home heating appliances, such as boilers and wood burners can pose serious risk of carbon monoxide poisoning if faulty, incorrectly fitted or poorly maintained. Carbon monoxide (CO) combines with haemoglobin to produce carboxyhaemoglobin (COHb), reducing the oxygen carrying capacity of the blood. CO is known as the 'silent killer' because it is colourless and odourless. Pregnant women, young children, the elderly and housebound are most at risk.

So what can GPs do?

Firstly, be aware of the six signs of CO poisoning:

Remember that the symptoms of CO poisoning can appear to be similar to that of flu, migraine, food poisoning, tension headaches and depression. Headache is the most common feature, with 90% of patients reporting headache, followed by nausea and vomiting (50% of patients) and vertigo (50% of patients). If your patient presents with a headache, particularly one that has developed after midnight or early in the morning and has syncope, consider CO poisoning. Another indicator can be if your patient reports that their symptoms have improved after they have left their home. This is because, once removed from the source of exposure, CO levels in the blood decline rapidly (the half-life is four to six hours), and this, plus the non-specific symptoms, mean that cases of CO are often missed.

Acute (severe) CO poisoning can be confirmed by measuring COHb levels in blood. However, because COHb has a short half-life of just 4-6 hours it can be an unreliable indicator of exposure. The link between COHb concentration and clinical outcome is also weak. Non-smokers will typically have a baseline COHb concentration of 1-2% while in smokers this baseline will be raised (5-10%). It is also possible to measure CO in breath and you may have access to breath CO detectors which are used in smoking cessation programmes. However, while high breath CO concentrations may suggest exposure, CO can also be elevated by smoking and, as with blood tests, the tests become increasingly unreliable if several hours have elapsed since exposure. Therefore, low concentrations of COHb in blood and CO in breath cannot be used to exclude poisoning **if several hours have elapsed since exposure.**

Suspected Carbon Monoxide (CO) Exposure (Continued)

The best action that you can take if you suspect that your patient has CO poisoning is to ensure that they are removed from the source of exposure. Do not let them go home without the likely source of CO being identified and managed. If you are treating a case, or suspected case, you should call Public Health Wales' Environmental Health Protection Team on 0300 003 0032. If you are concerned that your patient has received a high exposure to CO, refer immediately to hospital for high flow oxygen treatment.

Public Health Wales has some helpful information on CO:
http://www.wales.nhs.uk/sitesplus/888/page/50368

It has also developed an algorithm to help you determine whether your patient may have been exposed and the action to take (see overleaf).

Further advice on how the manage CO exposure can also be obtained from TOXBASE (www.toxbase.org) or the National Poisons Information Service (NPIS) (Telephone: 0344 892 0111— professional use only).

This advice has also been summarised in the recent Welsh Health Circular (041)
https://gov.wales/docs/dhss/publications/whc2018-041en.pdf

Authors:
Sarah Jones, Andrew Kibble, Paul Callow, Environmental Public Health Service, Public Health Wales.
For any queries please contact publichealth.environment@wales.nhs.uk

Suspected Carbon Monoxide (CO) Exposure: A Guide for use in hospital Emergency Departments and Primary

GIG CYMRU NHS WALES | Iechyd Cyhoeddus Cymru Public Health Wales

Presenting Complaint

Headache, nausea/vomiting, drowsiness, dizziness, dyspnoea, chest pain, falls, neurological symptoms, 'tired all the time'

Could this be a case of CO poisoning?

Considerations

If you are suspicious then ask the patient:

C Cohabitees/companions
Is anyone else in the property affected (including pets)?

O Outdoors
Do symptoms improve when out of the building? ('better outdoors')

M Maintenance
Over a year since heating appliances/boilers serviced?

A Alarm
Has your CO alarm been activated?

Yes to any

Acute or Chronic Exposure

Follow TOXBASE ADVICE for symptoms, signs and management of acute and chronic cases of CO poisoning. www.toxbase.org

For ACUTE EXPOSURES, TOXBASE recommends HIGH FLOW OXYGEN and, if in primary care, urgent referral to hospital.

The half-life of carboxyhaemoglobin is reduced by the administration of high concentration supplemental oxygen.
Contact the National Poisons Information Service (NPIS) 0344 892 0111
DO NOT allow your patient to go home until the likely CO source is managed

No to all

Less suggestive of CO poisoning

Still clinically suspicious

If you suspect CO exposure you must notify the Environmental Public Health Wales Health Protection Team (HPT) on 0300 00 30032 (office hours) or via ambulance control (24 hours)

Remember to complete an online notification after discussing the case with the Health Protection Team. Available at:
www.publichealthwales.org/environmental-incident-form

Carbon monoxide poisoning can simulate conditions such as flu, migraine, food poisoning, tension headaches and depression. Headache is the most common symptom: ***THINK CO!***

Sources of Carbon Monoxide

CO may be in the home, car, workplace or in tents or caravans. Malfunctioning gas, oil, coal, coke- and wood-fuelled heating and cooking appliances are the most common sources in the home.

Poisoning can occur in all income groups and types of housing. CO can leak into houses from neighbouring premises. Pregnant women, young children, the elderly and housebound are most at risk.

Testing for Exposure

Breath tests and blood samples may prove inconclusive hours after exposure has ended: CO levels in the blood decline with a half-life of about 6 hours.

A normal concentration of carboxyhaemoglobin (COHb) does not disprove CO poisoning unless the sample has been taken during or soon after exposure ended.

For interpretation of results and detailed advice on CO poisoning see TOXBASE and call the NPIS.

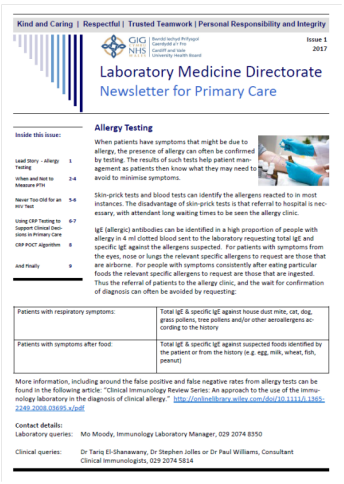
If you strongly suspect CO poisoning, do not wait for results, contact your local Public Health Wales HPT immediately

Actions the HPT will take to prevent further exposure

Notify others (including the gas emergency helpline on 0800 111 999)
Investigate and assess the risk of exposure to others
Recommend action to mitigate risk
Provide advice on prevention
Update the patient and clinician

Clinical follow-up is important as further consequences of chronic exposure to CO may be delayed, or mild symptoms may persist, multiply or intensify.
Recommend the purchase of an approved audible CO alarm (EN50291 compliant) for installation in the home.

And Finally..


Kind and Caring | Respectful | Trusted Teamwork | Personal Responsibility and Integrity

Issue 1
2017

Laboratory Medicine Directorate
Newsletter for Primary Care

Inside this issue:

Lead Story – Allergy Testing 1
When and Not to Measure PTH 2-4
Never Too Old for an HIV Test 5-6
Using CRP Testing to Support Clinical Decisions in Primary Care 6-7
CRP POCT Algorithm 8
And Finally 9

Allergy Testing

When patients have symptoms that might be due to allergy, the presence of allergy can often be confirmed by testing. The results of such tests help patient management as patients then know what they may need to avoid to minimise symptoms.

Skin-prick tests and blood tests can identify the allergens reacted to in most instances. The disadvantage of skin-prick tests is that referral to hospital is necessary, with attendant long waiting times to be seen the allergy clinic.

IgE (allergic) antibodies can be identified in a high proportion of people with allergy in 4 ml clotted blood sent to the laboratory requesting total IgE and specific IgE against the allergens suspected. For patients with symptoms from the eyes, nose or lungs the relevant specific allergens to request are those that are airborne. For people with symptoms consistently after eating particular foods the relevant specific allergens to request are those that are ingested. Thus the referral of patients to the allergy clinic, and the wait for confirmation of diagnosis can often be avoided by requesting:

Patients with respiratory symptoms:	Total IgE & specific IgE against house dust mite, cat, dog, grass pollens, tree pollens and/or other aeroallergens according to the history
Patients with symptoms after food:	Total IgE & specific IgE against suspected foods identified by the patient or from the history (e.g. egg, milk, wheat, fish, peanut)

More information, including around the false positive and false negative rates from allergy tests can be found in the following article: "Clinical Immunology Review Series: An approach to the use of the immunology laboratory in the diagnosis of clinical allergy." http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2249.2008.03695.x/pdf

Contact details:
Laboratory queries: Mo Moody, Immunology Laboratory Manager, 029 2074 8350
Clinical queries: Dr Tariq El-Shanawany, Dr Stephen Jolles or Dr Paul Williams, Consultant Clinical Immunologists, 029 2074 5814

Did You Know?

Back copies of the Laboratory Medicine Newsletter for Primary Care can found on the Laboratory Medicine pages on the Cardiff and Vale UHB intranet: http://nww.cardiffandvale.wales.nhs.uk/portal/page?_pageid=253,972415,253_972431&_dad=portal&_schema=PORTAL

and the Bro Taf Local Medical Committee Website: http://www.brotaflmc.org.uk/

Viewing Biochemistry Test Results Out of Hours

GPs with access to Welsh Clinical Portal (WCP), can now view results (in WCP) that are in preliminary status before they have been fully authorised from the laboratory information system. This means that any results that are telephoned out of hours can be viewed for confirmation.

Contact Us:

Laboratory Medicine would welcome your suggestions for service improvements. If you use any of our services and you have an idea about how we can improve, please email: lisa.griffiths3@wales.nhs.uk

For feedback and comments on the newsletter in general, please contact either:

Dr Carol Evans, Laboratory Director, Department of Medical Biochemistry & Immunology: carol.evans9@wales.nhs.uk

Helen Jenkins, Clinical Diagnostics and Therapeutics Clinical Board Management Office: helen.jenkins2@wales.nhs.uk