

General Practice (GP) Access to Pathology Results via the Illawarra Health Clinical Information System.

We are pleased to advise that we are now able to provide local General Practitioners with direct access to our Pathology results enquiry system via the Illawarra Health Clinical Information system.

We have arranged access to this system via the Illawarra Division of General Practice. This allows a secure access to our results enquiry system via the Gateway system currently used by the Division.

This will allow GP's to access the pathology results in the same way that they access other information such as discharge summaries. Access to this information will be of assistance in the management of those patients who have received healthcare as a patient of Illawarra Health.

For further information please contact either:

Mr. Ken Lynch at the Illawarra Division of General Practice: Phone no. 42267052

Or

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The Role of Monitoring Serum Vancomycin Levels

Measurement of serum Vancomycin levels is a test commonly requested and performed in NSW public hospitals. This is presumably on the premise that Vancomycin is a toxic drug and that renal impairment can occur if serum levels of the drug are not adequately monitored. However, the potential nephrotoxicity of Vancomycin and the role of monitoring serum Vancomycin levels have been questioned widely in the literature over the last 10-15 years.

Vancomycin is a glycopeptide antibiotic that is still the antibiotic of choice for serious infections caused by multi-resistant gram-positive organisms such as MRSA, Methicillin-resistant coagulase-negative staphylococci and *Enterococcus faecium*. It also has a role in the treatment of gram-positive infections in patients with a history of immediate Penicillin hypersensitivity and in the treatment of meningitis caused by highly Penicillin-resistant pneumococci. Glycopeptide antibiotics are quite distinct from the aminoglycoside antibiotics such as Gentamicin, Tobramycin and Amikacin, which have a well established potential for nephrotoxicity and ototoxicity and for which monitoring of serum levels is strongly recommended.

Since its introduction for clinical use in the late 1950's, Vancomycin has generally been regarded as having the potential to cause nephrotoxicity. However, numerous reports over the last 10-15 years have questioned the role of Vancomycin alone in causing renal impairment and the potential for nephrotoxicity of this drug remains controversial. Most of the data obtained implying that Vancomycin has the potential for nephrotoxicity and ototoxicity was obtained some 40 years ago when the Vancomycin preparations available contained impurities not present in the preparations available nowadays. More recent data definitively proving that Vancomycin is nephrotoxic or ototoxic in humans is difficult to find. Much of the available data does not control or concomitant administration of other nephrotoxic drugs such as aminoglycosides or other underlying medical risk factors for renal impairment. Recent information suggests that Vancomycin alone has a low potential for causing nephrotoxicity, the rate of nephrotoxicity being of the order of 5% or less in the absence of other factors that can adversely affect renal function. Most studies have indicated that if Vancomycin alone causes renal impairment, this is reversible upon discontinuation of the drug. It is generally accepted from the data available that the nephrotoxicity of Vancomycin is increased to 22-35% when it is co-administered with an aminoglycoside antibiotic such as Gentamicin.

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There is no evidence in the literature to show that monitoring of serum Vancomycin levels can be used to identify or prevent nephrotoxicity or ototoxicity. Based on data regarding the pharmacodynamics of Vancomycin and concerns regarding the emergence of *Staphylococcus aureus* with reduced susceptibility to Vancomycin (hVISA), recent guidelines suggest that perhaps a more important indication for measuring serum Vancomycin levels is to ensure an adequate trough serum level for efficacy rather than to predict or prevent toxicity. Vancomycin demonstrates concentration-independent killing in its effect on bacteria. Increasing the drug concentration above a certain level does not necessarily improve bactericidal effects. The critical pharmacodynamic parameter for such antibiotics is the duration that the drug concentration at the site of infection is above the mean inhibitory concentration (MIC) of the pathogen. The objective of dosage regimes for these "time-dependent" antibiotics is to maintain the antibiotic concentration at the infection site much higher than the MIC for a substantial part of the dosing interval. Maintaining adequate trough concentrations is more important for predicting efficacy although there is little data to show a clear correlation between serum Vancomycin concentrations and clinical outcome. The most recent version of *Therapeutic Guidelines: Antibiotic* suggests that trough Vancomycin levels should be maintained between 10-20 mg/L. It should be noted that this target range for trough Vancomycin levels is higher than has been recommended in previous versions of the guidelines because of increasing data regarding the safety and pharmacodynamics of Vancomycin. Recent data suggests that development of infections caused by *Staph. aureus* with reduced susceptibility to Vancomycin is associated with low Vancomycin trough levels (<10 mg/L).

For patients who are haemodynamically stable with normal renal function and who are receiving standard recommended doses of Vancomycin, measurement of a single trough (collected just before the next dose is due) serum Vancomycin level 48-72 hours after commencing the antibiotic is all that is warranted. This is to ensure that the chosen dose and dosage interval is sufficient to achieve efficacy in the treatment of the infection. The currently recommended standard dosage regime for patients with normal renal function is 20 mg/kg up to a maximum of 1 gram given 12 hourly by intravenous infusion over at least 1 hour. Occasionally patients have an unexpected abnormal clearance or volume of distribution of the antibiotic. Adjustment of the dosage interval or the dose given should be made if the measured trough Vancomycin concentration is outside of the target range of 10-20 mg/L. The trough serum Vancomycin level should be checked again after any change to the dosage regime. Repeated monitoring of trough serum Vancomycin levels would also be indicated in the following situations:

- 1) Patients also being treated with an aminoglycoside antibiotic or other nephrotoxic agent.
- 2) Patients with renal failure being treated with infrequent Vancomycin doses.
- 3) Patients with renal impairment, including those with stable impairment, in whom Vancomycin doses have been adjusted accordingly.
- 4) Other patients with altered Vancomycin pharmacokinetics such as pre-term infants, burns patients, pregnant patients, patients with liver disease and paediatric cancer patients.
- 5) Patients receiving higher than normal Vancomycin doses such as those being treated for bacterial meningitis.

Further advice on appropriate Vancomycin dosage regimes and interpretation of serum Vancomycin levels can be obtained by contacting the Medical Microbiologist on call.

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Homocysteine: Clinical and Diagnostic Information

Introduction

Homocysteine is a sulphur-containing amino acid produced by the intracellular methylation of methionine (Fig. 1). Homocysteine is not a building block for proteins. Rather, it is an intermediate metabolite in the conversion of methionine to cysteine, a thiol-containing amino acid which is functional in many biologically important enzymes. Homocysteine is exported by the cell into the bloodstream where it circulates, in its oxidized form, bound to plasma proteins such as albumin.

Homocysteine is metabolized in cells by two alternative pathways. One pathway, the vitamin B6-dependent trans-sulphuration pathway, catabolizes homocysteine irreversibly to cysteine. A major proportion of homocysteine is metabolised by another pathway back to methionine. The latter pathway utilizes a folate and cobalamin-dependent enzyme, methionine synthase and conserves sulphur within the body

Abnormalities in metabolic pathways involving homocysteine

Homocysteine does not normally accumulate in blood because it is very unstable, and rapidly undergoes oxidation to homocystine. However, when homocysteine accumulates intracellularly, due to a decreased rate of conversion of homocysteine to cysteine, or a decrease in the rate of remethylation back to methionine, then increases in homocysteine excretion into the bloodstream occur. A number of factors can result in increases in serum homocysteine levels by virtue of their effects on metabolic pathways (Table 1).

Fig. 1. Pathway for the conversion of methionine to cysteine, with homocysteine as an intermediate metabolite.

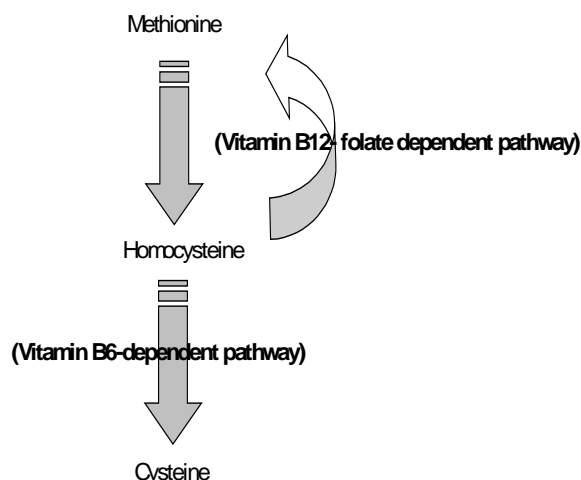


Table 1. Factors resulting in increased homocysteine levels

Nutritional deficiency of folate, vitamin B6 or vitamin B12
Renal disease due mainly to impaired excretion via the kidneys
Genetic disorders
Secondary to other diseases, such as cancer, hypothyroidism and pernicious anaemia
Smoking
Medications, such as methotrexate, anticonvulsant drugs like carbamazepine and phenytoin, corticosteroids, cyclosporine and others. Drugs affect different parts of the metabolic pathways for homocysteine and can also cause serum elevations of homocysteine

Inborn Errors of Metabolism

Grossly elevated levels of serum homocysteine are found in patients with an inborn error of metabolism in the homocysteine pathway. Normally, the concentration of homocysteine in normal urine is too low for detection. However, this defect can dramatically increase the level of homocystine in urine. Homocystinuria is a rare (1:200,000) genetic disorder. Patients with this disorder can also exhibit mental retardation, early arteriosclerosis and arterial and venous thromboembolisms. Other less severe genetic disorders of homocysteine metabolism are also found.

Cardiovascular Disease

Although severe elevations in homocysteine are rare, moderate elevations occur in about 5-7% of the general population. People with mild homocysteinaemia are typically asymptomatic until the third or fourth decade of life, when premature coronary artery disease develops.

The potential involvement of homocysteine in the development of atherosclerosis was suggested in 1969. However, homocysteine measurement has only recently gained prominence as a result of several studies (for example, Women's Health Study, Framingham Heart Study) that have confirmed its association with cardiovascular disease. These studies, based on cardiovascular endpoints such as acute myocardial infarction, stroke, coronary artery disease or death, show that elevated serum homocysteine is an independent risk factor for cardiovascular disease.

The findings of the different studies demonstrated that many subjects who developed cardiovascular events had significantly higher baseline homocysteine levels. One study estimated that 10% of the risk of coronary artery disease in the general population is attributable to moderate elevations in homocysteine. An increase in homocysteine of 5 $\mu\text{mol/L}$ above the normal range (5-15 $\mu\text{mol/L}$) is associated with an odds ratio

for coronary artery disease of 1.6 for men and 1.8 for women. The increased risk is the same as that associated with an increase in cholesterol of 0.5 mmol/L.

The mechanism by which homocysteine promotes atherothrombogenesis is unclear. Injury to endothelium, platelet activation and thrombus formation may be the final result of persistently elevated homocysteine.

Homocysteine assay and reference ranges

IPATH: Illawarra Pathology measures homocysteine by an automated immunoassay procedure. Assays are currently performed once per week, on Monday. Serum (minimum volume of 200 uL) is required for the assay. The reference ranges for adult healthy individuals are:

Male: 6 – 16 umol/L

Females: 3 – 20 umol/L

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Test numbers (with associated workload units), consumable costs, asset depreciation and maintenance costs, staff salaries, work distribution and financial data is submitted to the program on a six-monthly basis. Costs Centres within Pathology are identified so that internal comparisons can be made.

The basic unit for comparison is the Benchmarking Complexity Unit is a modified cost/test based on the concept that the level of complexity of a test reflects the amount of staff time involved. The unit provides a "Dow Jones"/"NASDAQ" type index. These values summarise and compare the overall performance of similar organisations, corrected for size, complexity, location and market type. Based on the complexity of work performed at each site it allows for a comparison with peers.

Ipath – Illawarra Pathology is considered to be in the Associated Teaching Hospital peer group and as such is benchmarked against other Pathology sites of similar size and complexity. In the recently reported comparison IPATH had the second highest level of comparative complexity of the work performed with the third lowest cost per complexity unit. This means the IPATH provides a large range of relatively complex tests for its users and provides them at a comparatively lower cost than that provided by Pathology laboratories of similar size and complexity. IPATH Illawarra Pathology will endeavour to maintain and improve to provide the best quality test range at the most cost-efficient price to its customers.

Benchmarking in Pathology – a peer group KPI

As part of its commitment to quality improvement, IPATH - Illawarra Pathology has been a contributor to the Benchmarking in Pathology Program for three years. The Program is one part of the quality assurance programs run by the Royal College of Pathologists of Australasia (RCPA) in conjunction with the Centre for Clinical Epidemiology and Biostatistics at the University of Newcastle.

The purpose of the Benchmarking program is to encourage superior performance within the Pathology services by comparing the product (test results/reports) of participating laboratories with other services providing a similar product. The Benchmarking program aims to provide basic information on the costs of supplying the pathology services required by the client of the service. The lowest unit cost service is not necessarily the best or the most cost efficient. Therefore, the quality of the product is ensured by simultaneous participation in the accuracy and precision proficiency surveys, also run by the RCPA Quality Assurance Program. All participants in the program, therefore, are encouraged by comparison with services of similar size and complexity to provide quality results that are considered to be best practice in terms of cost efficiency.

PATHOLOGY COLLECTION CENTRE

IPATH Illawarra Pathology now has a fully operational Approved Collection centre situated at Shellharbour Hospital.

This collection centre caters for all Renal, pre-Natal, Pre-operative and Cardiology Outpatient, Children and Neonates and privately referred outpatients. As part of our service we can also provide GTT's and Modified GTT's

Opening times

Mon-Frid 7:30am – 5:00pm

Sat. 7:30am –12:30pm

Patients using this service will be Bulk Billed