

Clinical chemistry interactive

Following are the abstracts of lectures originally presented at The Royal College of Pathologists' symposium, 'Clinical chemistry interactive', on 17 September 2003.

Which cardiac function tests should be offered and in which clinical circumstances?

The investigation of patients with suspected coronary artery disease can be broadly separated into investigation of those with suspected ACS and those with suspected ventricular dysfunction. Biochemical testing has a role in each group. It must be remembered that there is overlap between the two groups, with ACS causing ventricular dysfunction and *vice versa*.

Acute myocardial infarction (AMI) accounts for the minority of patients who present with symptoms suggestive of acute coronary syndromes. Patients with definitive ECG changes account for only 13% of those with a final diagnosis of AMI.¹ Management of these patients is straightforward and is aimed at opening the occluded artery by PCI (the preferred method) or by thrombolytic therapy. The challenge is the categorisation of the remaining patients. In patients admitted with definitive ECG changes, the probability of underlying ischaemic heart disease (IHD) is close to 100%. In patients admitted with chest pain, it is closer to 50%, while in patients seen in the emergency department, the probability is 3-5%. Conventionally, patients are assigned a diagnosis. In reality, they must be risk stratified and assigned to management pathways. Biochemical tests are part, but not the exclusive basis, of this categorisation.

The pathophysiology of acute coronary syndromes divides into three distinct but overlapping phases: myocardial ischaemia, myocardial necrosis and myocardial dysfunction. Markers are available for all of these stages. Assessment of ischaemia is currently on the basis of history and the electrocardiogram. Recently, biochemical markers of ischaemia such as whole blood choline, free fatty acid levels and ischaemia modified albumin (IMA)² have been studied. Of these, IMA is now commercially available and undergoing clinical evaluation. The measurement of cardiac troponins is now considered to be the pathognomonic test for myocardial damage. The redefinition of AMI includes troponin, as the preferred test but stipulates that troponin measurement alone is not sufficient.³ Appropriate clinical features and/or ECG data are also required. Troponin is a specific and sensitive test for myocardial damage. Myocardial damage can occur in a range of other conditions. Outside the cardiac care unit population, as many as 30% of the cases of troponin elevation are not due to ACS.

ACS can cause ventricular dysfunction and measurements of B-type natriuretic peptide (BNP) have been shown to have an independent prognostic value in patients presenting with ACS.⁴ However, unlike troponin measurement, these cannot be used to define management pathways⁵ so it is difficult to recommend their use in the differential diagnosis of ACS. There may be a role for BNP measurements as part of a rule-out strategy, since admission measurement seems to be as useful as delayed measurement. The major role is to exclude ventricular dysfunction. This has been shown in acute dyspnoea but is most useful in primary care.⁶

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What lipids should we measure and how should we express the results?

Routine lipid measurements generally include total cholesterol, high density lipoprotein (HDL)-cholesterol and triglyceride. HDL is essential for the accurate estimation of coronary heart disease (CHD) risk.^{1,2} Triglyceride is essential for the correct diagnosis of genetic hyperlipidaemias and for appropriate choice of lipid lowering treatment. 'Reference ranges' have largely been replaced by 'ideal levels' or treatment targets. It is well recognised that CHD risk is increased at 'normal' cholesterol levels, but less well recognised that 'normal' triglyceride levels can also be associated with an increased risk of CHD.³ Fasting samples allow calculation of low density lipoprotein (LDL)-cholesterol (LDL-c) from the Friedwald equation, but results derived in this way differ increasingly from measured LDL-c as triglyceride increases above 2.3 mmol/L and should not be used if levels exceed 4.5 mmol/L.⁴

Direct measurement of LDL-c avoids the problems of calculation, but, particularly in patients with an 'atherogenic lipoprotein phenotype', LDL-c does not accurately reflect LDL particle number, which is a better predictor of CHD risk. Measurement of Apo B or 'non-HDL' cholesterol may provide a better surrogate for atherogenic particles and thereby CHD risk, and both can be measured on non-fasting samples.^{5,6} Prospective studies have not been carried out to allow Apo B to be used to predict risk, but treatment targets for 'non-HDL' cholesterol have been incorporated into current guidelines. This results in stricter targets for those with elevated triglyceride, who tend to have a greater proportion of small dense LDL.

The laboratory can facilitate interpretation and effective use of lipid results by reporting derived parameters such as TC:HDL ratio and 'non-HDL' cholesterol. In the future, measurements such as Apo B, or methods to estimate LDL subfractions directly, suitable for use in routine laboratories, may be available to further guide treatment.

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Are prenatal and neonatal screening programmes effective and ethical?

The first routine antenatal screening programme for Down's syndrome screening began in Newport, Gwent as an extension to the existing neural tube defect screen.¹ It was introduced as a routine test and research done using the results was not referred to an ethics committee. Indeed, even today this could be the case because retrospective research based on case notes is usually considered 'audit'. Within weeks of its inception, a local resident with a Down's-affected child questioned whether it was 'right' to screen for the condition at all. At the International Down's Syndrome Screening Group conference in 2003, there was an interruption to the planned programme of events when a girl with Down's syndrome entered the auditorium and read out a speech questioning whether screening should be allowed.

A recent survey of 20% of the ethics committees in the UK demonstrated that if a Down's screening programme were to be presented *de novo* to an ethics committee today, it would be rejected as being as unethical as screening for red hair and freckles would be. This decision was marginally less clear-cut when a negative 'spin' was placed on the description of Down's syndrome and when a test with no risk to an unaffected fetus was presumed.²

The ethics of antenatal screening are complex. One of the primary tenets of screening is that there is no benefit from a screening program if there is no treatment available. Clearly, in the case of Down's syndrome screening there is usually only one treatment possibility: termination of pregnancy. In this case, if the patient is the fetus, this does not seem to be beneficial; but if the patient is the mother, it may be.

The 1980s and '90s were marked by two contradictory developments: social movements against exclusion leading to antidiscrimination laws, and developments in genetic technology leading to improved identification methods. Thus disability rights and genetics may represent, at their extremes, two polarised paradigms.³ Some disability radicals complain of 'Nazi eugenics' or genetics as a 'search and destroy' mission directed against disabled people.⁴ Others welcome genetics in the hope that it will produce therapy or cures for their problems. A third strand of thought believes in a woman's right to choose, but some studies show that the design of screening programmes may make the 'right decision' inevitable, thus removing the element of informed choice.⁵

The UK National Screening Committee is currently setting standards to ensure the efficiency of Down's screening programmes across the UK. In some screening schemes, e.g. breast screening, there are not only strict targets for detection rates, but also targets for the proportion of patients who should be screened. Some Down's programmes have noticed significant decreases in uptake as time progresses, more women understand about testing and counselling improves. Down's screening has been a controversial issue for many years and it looks as if this will continue for many more.⁶

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Can we manage thyroid function testing in a rational way?

Thyroid function tests are essential to ensure the accurate diagnosis and appropriate management of patients with thyroid disorders. The American College of Physicians (ACP), The American Thyroid Association (ATA), The American Association of Clinical Endocrinologists (AACE) and The National Academy of Clinical Biochemistry (NACB) are good examples of influential bodies who have issued recent guidelines regarding the appropriate use of thyroid function tests.¹⁻⁴ These guidelines are widely available on the web and thus many patients have expectations regarding what tests and treatment are most appropriate for their thyroid disorder. Guidelines thus tend to have a significant impact on laboratory workload and patterns of requesting. Unfortunately, the evidence base behind some of the recommendations made in the above guidelines is not strong. Such uncertainty leads to non-conformity in some of the more important areas relating to diagnosis and patient management. These include the value of screening, time intervals for follow-up testing and the target concentration for TSH for patients treated with thyroxine. The list of clinical circumstances where first line TSH is considered inappropriate to assess thyroid function is also expanding^{3,4} and, if adopted in the UK, would cause problems for laboratories using such a strategy unless excellent clinical details were available. The presentation included a case-based study to explore participants' views on the appropriate use of thyroid function tests to illustrate how these agree with current guidelines. A joint group formed from representatives of the ACB, BTA and BTF is currently preparing guidelines for the UK to update the recommendations from the 'Consensus statement for good practice and audit measures in the management of hypothyroidism and hyperthyroidism' published in 1996.⁴

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EDINBURGH ROYAL INFIRMARY

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