Optimal use of blood tests in acute medicine

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Abstract

The optimal use of laboratory tests requires an understanding of the many variables that may influence the result and its interpretation. This is especially important with the increasing use of point-of-care testing. In this article we cover how to request the 'right test' as well as some of the variables. Most common tests are discussed.

Keywords CRP; D-Dimer; eGFR; point of care systems; predictive values; sensitivity; specificity; test performance; troponin

Requesting the 'right test'

Almost 70% of clinical decisions in the NHS involve pathology services, and most patients being investigated by the acute medicine team will have blood drawn for laboratory testing. The results of these analyses may be used for many purposes, including making new diagnoses and the monitoring and management of previously established diagnoses.

A general understanding of the chance of a laboratory test being normal or abnormal in health or disease is helpful when trying to interpret test results. The 'reference range' of a test is calculated to encompass 95% of the results expected in a 'normal' population,[1] so 2.5% of a healthy population will have results less than the lower limit of the reference range and 2.5% will have results greater than the upper limit, usually by a relatively small amount.

Several characteristics of a test describe its utility in making or ruling out a diagnosis. Most acute physicians will be aware of the concepts of the 'sensitivity' and 'specificity' of investigations (Table 1). These are important descriptions of a test, describing how it performs when the condition being tested for is known to be present or not. However, in the real world of acute medicine this is not the question being asked; the physician does not know whether the condition is present or not, but is faced with trying to make that judgement from the results of available investigations. Under these circumstances, more useful information is provided by the positive and negative predictive values, which describe how the test performs when its results are known to be positive or negative.[2]

Sensitivity and specificity are fixed descriptions of how a test performs. In contrast, an important (and not necessarily intuitive) characteristic of predictive values is that they are not fixed but depend on the prevalence of the condition in the population being investigated. In a population with a low prevalence of the condition, the positive predictive value falls and the negative predictive value rises, and there will be increased numbers of false-positive results.[3] In practical terms, this means that if a test is requested for a condition that is unlikely to be present, a negative result will make that condition more unlikely, but a positive result is quite likely to be a false-positive, and therefore misleading and requiring further investigation. This has obvious implications in the use of 'screening' investigations in acute medicine.

'Top 20' common presentations

The use of 'request profiles' (i.e. predetermined groups of laboratory tests) to investigate common presentations is widespread in acute hospital settings. Indeed, the concept of common presentations, and protocols or pathways to investigate these, is implicit in the general internal medicine (acute medicine) curriculum, which lists the 'top 20' common presentations to acute medicine.[4] Request profiles have advantages: they improve efficiency as they can be requested by non-medically trained healthcare professionals, they aim to avoid the discomfort of repeated venepuncture for the patient and, if well designed, they can be an economical and focused use of laboratory resources. However, the requesting clinician should consider the appropriateness of each component of the panel. It can be argued that there is no such thing as a 'routine' blood test. The clinical reasons for each test requested should be considered:

- Is there a specific indication?
- How will the results be acted upon when they become available?
- Is the result going to aid patient management?
- Is it an efficient use of resources?
- Is there a high chance that a spurious or unhelpful result will be generated?
- Would an alternative test be more useful or reliable?

Clinicians should also be aware that the composition of these panels of tests has been influenced by a variety of historical and practical issues, may not always reflect current thinking, and may vary from laboratory to laboratory. There is a process now under way in the UK to harmonize common test profiles, with the aim of rationalizing their contents and ensuring that clinicians receive the results of the same tests from whatever laboratory they use.[5]

Variation

To allow reliable interpretation of blood test results, requesting physicians should have an understanding of the variables that may influence the results.

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Performance of diagnostic tests

	Condition present	Condition absent
Test positive	True-positive (TP)	False-positive (FP)
Test negative	False-negative (FN)	True-negative (TN)

Test characteristic	Formula	Question being asked
Sensitivity	TP/(TP + FN)	What proportion of people with this condition have a positive result?
Specificity	TN/(TN + FP)	What proportion of people without this condition have a negative result?
Positive predictive value	TP/(TP + FP)	What proportion of people with a positive test have this condition?
Negative predictive value	TN/(TN + FN)	What proportion of people with a negative test do not have this condition?

Table 1

Pre-analytical variables

Pre-analytical variables include intra-individual biological and physiological variation (e.g. time of sampling, posture, intercurrent pathology),[6] as well as the intrinsic variability of a biological system around a homeostatic set-point.[7] Some of the biological variables can be minimized, for example avoiding large meat-based meals before sampling blood for creatinine, whereas others, such as race and sex, are fixed. Other non-biological factors that can contribute to pre-analytical variation include specimen storage, transport time and sampling technique. The causes and degree of variation will vary greatly with the analyte. For example, the effects of fasting status on plasma glucose or vigorous exercise on serum creatine kinase can significantly influence results and subsequent clinical decisions. However, some pre-analytical variables (e.g. the diurnal variation of thyroid-stimulating hormone) are of negligible effect.

Analytical variables

Analytical methods and instruments in blood sciences are thoroughly evaluated before being introduced into routine clinical use to make sure that reliable results will be generated with minimal delay. These include accuracy (how close the generated result is to the 'true' value), precision (the variation from the mean value on repeat analysis), interfering substances (e.g. the effect of lipaemia on serum sodium measurement), specificity and sensitivity. External quality assurance and internal quality control, as well as pre-, peri- and post-analytical review by laboratory staff, are all employed by laboratories to ensure the results are as reliable as possible.

Commonly used tests in acute medicine

The pressures in acute medicine mean that there can be a tendency to request large panels of tests in a relatively unthinking manner. Some tests that are particularly frequently requested have well recognized pitfalls, including estimated glomerular filtration rate (eGFR), troponin, D-dimer and C-reactive protein (CRP).

eGFR: until recently serum creatinine has been the usual measure of glomerular function, through its inverse relation to creatinine clearance and hence glomerular filtration rate. It suffers from the disadvantage that it is also related to muscle mass (and therefore to sex and age). A serum creatinine concentration that is entirely 'normal' for a muscular young man may indicate impaired glomerular function in a frail elderly woman. The derivation of a formula for calculating an eGFR from a large study of patients with impaired renal function has therefore been helpful in avoiding this potential problem.[8] The usual form of this equation uses serum creatinine concentration, age, sex and race (but in practice information about race is seldom provided to laboratories and is therefore not incorporated). Many laboratory computer systems automatically provide this result whenever a serum creatinine is requested. However, the calculation is not valid at extremes of weight or age, in pregnancy, or in patients with an abnormal muscle mass such as those with amputations, skeletal muscle disease or paraplegia. Even more importantly in the context of acute medicine, it is not valid under circumstances where renal function is changing rapidly or in patients with 'normal' renal function (since the equation was derived in patients with renal failure). The eGFR also suffers from significant imprecision, such that only 90% of eGFRs will be within 30% of the true GFR. Nevertheless, in stable patients with impaired renal function, eGFR has been a significant advance on the use of serum creatinine or creatinine clearance.

Troponin: troponin T and troponin I are components of the troponin complex, which is exclusively present in striated muscle. Isoforms of both of these troponins exist that are specific to cardiac muscle. These are normally undetectable in the circulation, but are released and become detectable following cardiac muscle necrosis. A small proportion of troponin is present as a soluble fraction within the cytoplasm of the myocyte and is rapidly released, becoming detectable after 3–6 hours, and peaking at 12–24 hours. More gradual release of the insoluble fraction accounts for the prolonged plateau of troponin release, which may remain detectable for up to a week or more. A negative troponin, in an appropriately timed sample (certainly 6 hours, and ideally 12 hours, after the episode of chest pain), can therefore provide useful evidence to exclude myocardial damage. There is also evidence that serial rather than single troponin measurements (e.g. taken at baseline and 3 hours after admission) may also be effective in diagnosing or excluding an acute myocardial infarction.[9] A positive result in a sample taken at any stage after the episode of chest pain is usually interpreted as indicating some degree of myocardial damage. While this may often be the case, troponin may be elevated in a variety of other conditions, including myocarditis, heart failure, kidney disease,

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