Regular review

Treatment possibilities for unstable angina

Ajay Manhapra, Steven Borzak

Unstable angina is frequently encountered by general practitioners and cardiovascular specialists. In the United States, of the 2.5 million patients admitted to hospital every year with suspected acute coronary syndromes, 1.5 million have unstable angina. The rest have myocardial infarction with or without ST elevation.¹

Earlier published literature classified acute ischaemic episodes as unstable angina and either non-Q wave or Q wave infarction. As Q wave and non-Q wave infarctions can only be definitely distinguished by electrocardiography several days after the clinical event, the classification does not help with emergency patients. Moreover, the prognostic value of Q wave versus non-Q wave infarction classification is limited.² A new nosological scheme has derived from the need to rapidly assess patients at presentation so that powerful new treatments can be appropriately selected. All acute presentations suggesting acute coronary syndromes can be further divided into infarction with ST elevation (possibly including patients with new bundle branch blocks) and infarction without ST elevation and unstable angina combined. The distinction between the last two conditions can be reliably made by measuring serum markers. This classification makes sense because early thrombolytic treatment saves the lives of patients with infarction with ST elevation but has no beneficial, and probably some deleterious, effect in those with infarction without ST elevation or unstable angina. Moreover, the therapeutic approaches in the last two conditions are similar.³ Hence we consider unstable angina and infarction without ST elevation as a single entity, especially regarding treatment. Figure 1 shows a plan for assessment and classification of suspected acute coronary syndrome.

Methods

We extracted data from the personal collection of journal articles of the authors and from Medline whenever necessary. We also obtained information from review articles on different subtopics.

Pathophysiology of unstable angina

Braunwald described unstable angina as a syndrome with five mutually non-exclusive causes; thrombosis, mechanical obstruction, dynamic obstruction (spasm of microvasculature and macrovasculature), inflamma-

tion or infection, and increased oxygen demand.⁴ Unstable angina occurs from the interplay of these factors, with thrombosis and mechanical obstruction usually dominating. Transient or subtotal obstruction due to a platelet rich "white clot" over a fissured atherosclerotic plaque is considered causal in most episodes of unstable angina. This differs from the fibrin rich "red clot" associated with total coronary occlusion in infarction with ST elevation.

In contrast to the Braunwald model, European investigators have advocated a central role for inflammation in unstable angina.^{5,6} Increased concentrations of acute inflammatory markers, such as C reactive protein, are more often found in unstable angina than in chronic stable angina. Also, an increased concentration of C reactive protein at admission among patients with unstable angina has been correlated with worse outcomes both in hospital and after one year.⁷⁻⁹ Several authors have shown varying associations of different subpopulations of T lymphocytes, granulocytes, macrophages, and cytokines with unstable angina.^{5,6} Although the role of inflamma-

Henry Ford Heart and Vascular Institute, K-14, Detroit, MI 48202, USA

Ajay Manhapra
medical resident

Division of Cardiovascular Medicine, Henry Ford Heart and Vascular Institute
Steven Borzak
associate head

Correspondence to:
S Borzak
sborzak1@hfhs.org

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Fig 1 Assessment and classification of suspected acute coronary syndrome

tion or other mechanisms in unstable angina is not fully understood, it seems that inflammation in a coronary arterial plaque, leading to fissuring, rupture or erosions, and subsequent thrombosis is involved in the final step of most episodes of unstable angina.

Risk stratification

Guidelines for unstable angina were issued by the Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute in 1994. These differentiated patients at high risk of death if they had pulmonary oedema, persistent pain at rest for more than 20 minutes, S3 gallop, rales, new or worsening mitral regurgitation murmur, hypotension, or shifts of 1 mm or more in the ST segment.¹⁰ Patients without rest or nocturnal angina and with normal or unchanged electrocardiograms were defined as low risk, and those of neither low or high risk were defined as intermediate risk. This risk stratification was validated in a prospective study.¹¹ Elderly patients and those with a history of myocardial infarction are at a higher risk. The greatest risk is probably among patients with cardiogenic shock, with a 60% mortality.¹²

Electrocardiography is critical in the assessment and further management of patients with acute coronary syndrome (fig 1). It helps to differentiate infarction with ST elevation (requiring reperfusion therapy) from unstable angina and infarction without ST elevation. Electrocardiography is also a powerful prognostic tool. The global utilisation of streptokinase and tissue plasminogen for occluded coronary arteries (GUSTO) IIb trial enrolled patients with symptoms of cardiac ischaemia and electrocardiographic changes suggesting ischaemia. T wave inversion on initial electrocardiography was associated with a lower chance of death or reinfarction at 30 days and six months than with transient ST elevation, ST depression, or both. ST depression predicted the worst outcomes, more so than ST elevation alone.¹³ In the thrombolysis in myocardial infarction (TIMI) III study (patients with unstable angina and infarction without ST elevation), death and reinfarction at one year were higher in patients with ST deviation and left bundle branch block than in those with T wave changes or no electrocardiographic changes.¹⁴ Extensive ST deviation and involvement of a large number of leads have also been correlated with adverse outcomes.^{14 15} Nor does a normal electrocardiogram exclude the risk of cardiac events: the thrombolysis in myocardial infarction III study showed an 8.2% rate of death or myocardial infarction among patients with unstable angina without any electrocardiographic changes.¹⁴

Various measurements of serum markers, including concentrations of total creatine phosphokinase, the MB subfraction, myoglobin, and troponins are available for the diagnosis and risk stratification of patients with unstable angina and myocardial infarction. Measurements of concentrations of total creatine phosphokinase have low specificity and a high false positive rate. For some time, measurement of the concentration of creatine phosphokinase MB (two or more high values within 24 hours) has been used worldwide as the gold standard, reflecting myocardial necrosis.

The recent availability of troponin measurements has led to some confusion. Zimmerman et al note that

experimental data linking myocardial ischaemia or necrosis to cardiac troponin concentrations are lacking.¹⁶ Rarely, troponin concentrations may be increased in patients without coronary disease and in those with coronary disease without other clinical evidence of infarction, in which case diagnostic classification becomes murky. None the less, an increased concentration of cardiac troponin is a powerful predictor of adverse outcome and treatment benefit in patients with ischaemic symptoms.¹⁷⁻²⁰ Increased concentrations of troponin T or I carry a higher relative risk of death and adverse outcome (5 and 3.9 respectively) among patients with suspected acute coronary syndrome or unstable angina (3.8 for combined events).²¹ This predictive power is sustained even in patients with unstable angina with no electrocardiographic changes and normal creatine phosphokinase MB concentrations.^{18 22} Moreover, the higher the concentration of cardiac troponin the higher the risk of adverse outcomes and the better the benefits of treatment with inhibitors of platelet glycoprotein IIb/IIIa receptors and low molecular weight heparins.^{17 18 22-24} Myoglobin concentration seems to be reliable only for ruling out myocardial infarction when the result is negative.¹⁶

Treatment options

Nitrates (by various routes) and morphine (intravenously) are the standard initial management of chest pain and discomfort. Although there is good evidence for the beneficial role of intravenous or oral β blockers in acute myocardial infarction or recent myocardial infarction, they show only a modest effect (13% reduction) in preventing the progression of unstable angina to acute myocardial infarction.²⁵ They are, however, still recommended as routine treatment in the absence of any contraindications.

Combined data from trials of calcium channel blockers in acute myocardial infarction showed a trend towards higher mortality among those treated with these agents. Agents that increase heart rate (for example, nifedipine) were associated with a trend towards increased mortality, and long acting agents that decrease heart rate (verapamil and diltiazem) were associated with a trend towards better survival, but none of the trends were important.²⁶ Diltiazem reduces reinfarction and refractory angina in patients with non-Q wave infarction.²⁷⁻²⁹

Data suggest that calcium channel blockers that decrease heart rate (diltiazem and verapamil) can be used as a second line or third line drug after nitrates and β blockers to control symptoms and when β blockers are not tolerated. Short acting dihydropyridines such as nifedipine, which increase heart rate, should not be used. Calcium channel blockers increase mortality in patients with congestive heart failure and should be avoided.²⁷

Antithrombins

Unfractionated heparin and the newer low molecular weight heparins, which are enzymatic or chemical degradation fragments of unfractionated heparin, produce their anticoagulant effect after binding antithrombin (fig 2). Unfractionated heparin inhibits both thrombin and factor Xa with the same potency (1:1), whereas low

molecular weight heparin has a greater inhibitory effect on factor Xa (1:2 to 1:4). Low molecular weight heparin also binds less to plasma proteins than does unfractionated heparin and has a dose independent clearance and longer half life, which gives more reliable and sustained anticoagulation with one or two doses a day. Because of this, monitoring of anticoagulant activity is not required with low molecular weight heparins and they can be given effectively without an intravenous pump. They cannot, however, be used in place of heparin in patients with heparin induced thrombocytopenia because of shared antibodies.³⁰ Hirudin and the analogue bivalirudin, however, inhibit thrombin directly without the help of antithrombin III and can inhibit both free thrombin and that bound to clots, whereas heparin inhibits only free thrombin.³¹

Various trials have shown that, when given early, unfractionated heparin is associated with a reduced incidence of acute infarction and ischaemia in patients with unstable angina and infarction without ST elevation. The effect on mortality, however, is not so evident. Meta-analyses of studies of combined aspirin and unfractionated heparin have shown a 20% reduction in death or myocardial infarction over aspirin alone.³²⁻³³ When using unfractionated heparin, weight adjusted dosing with close monitoring should be followed to keep the activated partial thromboplastin time within 1.5 to 2 times the control value: higher activated partial thromboplastin times, in addition to higher bleeding rates, have been independently associated with higher mortality.³⁴

The fragmin during instability in coronary artery disease (FRISC) trial compared a low molecular weight heparin, dalteparin (120 IU/kg twice daily subcutaneously), with placebo in 1506 patients with chest pain within 72 hours and ST depression or T wave inversion of 0.1 mV on electrocardiography. Dalteparin was associated with a 63% risk reduction (4.8% *v* 1.8%) in death or myocardial infarction after six days, and treatment benefits were maintained at 40 days.³⁵ The fragmin in unstable coronary artery disease (FRIC) trial compared a similar dosing strategy of dalteparin with unfractionated heparin in patients with unstable angina or non-Q wave infarction. No difference was found between unfractionated heparin and dalteparin in the rate of the primary end point of death, myocardial infarction, or recurrence of angina at both six days (7.6% and 9.3% respectively, *P*=0.33) and 45 days (12.3% in both groups).³⁶ Nor was any difference between the two groups observed in the rate of individual end points or composite end point of death or myocardial infarction. The incidence of adverse events was also similar and infrequent.

The efficacy and safety of subcutaneous enoxaparin in the non-Q wave coronary events (ESSENCE) trial compared the low molecular weight heparin, enoxaparin (1 mg/kg subcutaneously every 12 hours), with standard unfractionated heparin dosing for two to eight days in 3171 patients with angina at rest or non-Q wave infarction. A 16% reduction (16.6% *v* 19.8%) in the combined end point of death, myocardial infarction, or recurrent angina was found at 14 days and a 19% reduction (19.8% *v* 23.3%) at the end of 30 days among those treated with enoxaparin.³⁷ The two groups showed no major differences in death alone at 30 days.

The thrombolysis in myocardial infarction 11B trial randomly assigned 3910 patients with unstable angina or infarction without ST elevation to enoxaparin 30 mg intravenous bolus initially, followed by 1 mg/kg subcutaneous injections twice daily, or to weight adjusted unfractionated heparin. The composite end point of death, myocardial infarction, or need for urgent revascularisation was reduced by 14.6% at 14 days and 12.3% at 43 days among patients treated with enoxaparin. No reduction in death rate and no increased benefit was found among patients whose treatment was continued after discharge.³⁸ The fraxiparin in ischaemic syndrome (FRAXIS) trial randomised 3468 patients with unstable angina or non-Q wave infarction to nadroparin in two arms (for six and 14 days) and a third arm to unfractionated heparin (six days). No difference was found between the three arms in the primary outcome of cardiac death, myocardial infarction, refractory angina, or recurrence of unstable angina at 14 days.³⁹ In the fraxiparin in ischaemic syndrome trial, unlike the previous four trials, nadroparin was associated with a higher rate of major haemorrhage (3.5% *v* 1.6% with heparin).

These results suggest that low molecular weight heparins, especially enoxaparin, are more beneficial than unfractionated heparin. Moreover, because low molecular weight heparins are easy to give and require no monitoring they are a viable alternative to unfractionated heparin. A cost analysis showed that, largely because of fewer revascularisation procedures in patients treated with enoxaparin, the higher drug costs of low molecular weight heparins were offset by reduced administration and monitoring costs and enhanced efficacy.⁴⁰ Data regarding the safety and beneficial effect of enoxaparin in conjunction with catheter based interventions and glycoprotein IIb/IIIa inhibitors are awaited.

Fig 2 Site of action of antiplatelet and antithrombin agents

Because thrombotic processes and clinical events may continue after the index ischaemic event, investigators have explored the use of low molecular weight heparins for a longer duration, even after discharge. The fragmin during instability in coronary artery disease trial, the fragmin in unstable coronary artery disease trial, the fraxiparin in ischaemic syndrome trial, and the thrombolysis in myocardial infarction 11B trial all had a long term treatment protocol and showed no advantage on longer term follow up.^{35 36 38} In the fragmin during instability in coronary artery disease II trial patients were randomised to placebo or continued treatment for 90 days with dalteparin after an initial five day treatment with the drug. The composite end point of death or myocardial infarction was reduced at 30 days but not at three or six months.⁴¹ Direct thrombin inhibitors, hirudin and bivalirudin, have been evaluated in large clinical trials but no convincing benefit was found over standard heparin treatment.⁴²⁻⁴⁴

Antiplatelet agents

Aspirin has been shown to reduce the development of myocardial infarction and death in unstable angina by over 50% when used alone or with heparin.⁴⁵⁻⁴⁸ It has also been shown to decrease mortality after acute myocardial infarction with or without thrombolytic therapy, and this was sustained over two years.^{49 50} Ticlopidine, another antiplatelet drug that inhibits platelet aggregation mediated by adenosine diphosphate, reduced fatal and non-fatal myocardial infarction by 46% in patients with unstable angina compared with standard treatment without aspirin (fig 3). The use of ticlopidine is, however, limited both by side effects

such as neutropenia and thrombotic thrombocytopenic purpura and by the delay in onset of action.⁵¹ It can be used when aspirin is not tolerated.⁵² Clopidogrel has a similar mechanism of action to ticlopidine but a better safety profile and more rapid onset of action and is as effective as 325 mg of aspirin in secondary prevention.⁵³ Clopidogrel could be used in place of ticlopidine if aspirin is contraindicated because of hypersensitivity or intolerance.

Inhibitors of glycoprotein IIb/IIIa receptors

Activation of glycoprotein IIb/IIIa receptors and attachment of platelets by these receptors to fibrinogen and von Willebrand factor is the final step in the formation of platelet clots. In the past few years, various inhibitors of these receptors have been prominent in the management of patients undergoing percutaneous coronary intervention and those with unstable angina and infarction without ST elevation. Abciximab, a chimeric human-mouse monoclonal antibody, is different from eptifibatide and tirofiban, the other two approved members of this drug class. Because abciximab has higher affinity for glycoprotein IIb/IIIa receptors, the platelets take longer to recover after discontinuation of the drug (≥ 12 v ≤ 4 hours in others). Whereas eptifibatide and tirofiban are specific for the glycoprotein IIb/IIIa receptors, abciximab also binds to vitronectin and Mac-1 receptors.¹

Adjunct to percutaneous catheterisation

Glycoprotein IIb/IIIa inhibitors have been shown to be beneficial in patients with unstable angina and infarction without ST elevation undergoing high risk percutaneous revascularisation procedures. A sub-analysis of the evaluation of 7E3 for prevention of ischaemic complications (EPIC) trial (an angioplasty trial) showed that the benefit with abciximab was pronounced among those who underwent percutaneous revascularisation because of unstable angina; death, myocardial infarction, or urgent revascularisation occurred in 4.8% of patients in the treatment group and 12.8% in the placebo group at 30 days.⁵⁴ The c7E3 fab antiplatelet therapy in unstable refractory angina (CAPTURE) trial was confined to patients with refractory unstable angina (not infarction without ST elevation) who had lesions suitable for balloon angioplasty on cardiac catheterisation. The composite end point of death, myocardial infarction, or urgent reintervention at 30 days was significantly reduced among those who received abciximab bolus and infusion (15.9% v 11.4%, $P = 0.012$).⁵⁵

Primary treatment

The platelet receptor inhibition for ischaemic syndrome management (PRISM) trial compared tirofiban with heparin among patients with unstable angina or infarction without ST elevation. Tirofiban reduced the composite end point of death, myocardial infarction, or refractory ischaemia by 32% at 48 hours. At 30 days a similar rate of composite end points was observed in both groups.⁵⁶ The platelet receptor inhibition for ischaemic syndrome management in patients limited by unstable signs and symptoms (PRISM-PLUS) trial compared a minimum of 48 hour infusion of tirofiban and heparin, tirofiban alone, and heparin alone among patients with unstable angina and electrocardiographic

Fig 3 Plan for treatment decisions in patients admitted with unstable angina or infarction without ST elevation

changes or increases in concentrations of creatine kinase and the MB subfraction and prolonged angina within the previous 12 hours (a higher risk population than those in the platelet receptor inhibition for ischaemic syndrome management trial). The composite end point was significantly reduced in the tirofiban and heparin group (12.9% *v* 17.9% in heparin only, $P=0.004$) at seven days.⁵⁷ The benefit of tirofiban with heparin persisted at both 30 days (18.5% *v* 22.3%) and six months (27.7% *v* 32.1%). The benefit occurred irrespective of whether patients received medical treatment alone or additional revascularisation. The tirofiban alone arm was discontinued early owing to increased mortality.

The platelet glycoprotein IIb/IIIa in unstable angina: receptor suppression using integrilin therapy (PURSUIT) trial compared eptifibatide with placebo in patients with unstable angina and infarction without ST elevation and showed a 1.5% absolute reduction in the primary end point of death or myocardial infarction at 30 days (14.2 *v* 15.7%; $P=0.042$).¹² In this international study the benefit was similar across all management strategies (medical management, percutaneous intervention, or coronary artery bypass grafting) and in all geographical areas.

The combined data show that when glycoprotein IIb/IIIa inhibitors are given with aspirin and standard dose heparin they result in a small but important clinical improvement in the management of high risk patients with unstable angina (refractory angina with electrocardiographic changes or increases in serum marker concentration) and infarction without ST elevation, irrespective of the management strategy.⁵⁸ Tirofiban and eptifibatide have proved benefits as primary treatment in unstable angina and infarction without ST elevation.

Statins

The beneficial role of lipid lowering treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors among patients with a history of myocardial infarction and increased or average low density lipoprotein cholesterol concentrations has been established.⁵⁹⁻⁶⁰ A recent trial showed that long term treatment with pravastatin reduced the risk of death from coronary heart disease by 29% among those who had a history of admission to hospital for unstable angina with varying plasma cholesterol concentrations.⁶¹ All patients with unstable angina or infarction without ST elevation should have their cholesterol concentration measured, and treatment should be aimed at achieving a target concentration of low density lipoprotein cholesterol of less than 1000 mg/l.

Angiotensin converting enzyme inhibitors

Angiotensin converting enzyme inhibitors are well established in the treatment of anterior myocardial infarction and heart failure after infarction.⁶² Recently, however, the heart outcomes prevention evaluation (HOPE) study showed that treatment with the angiotensin converting enzyme inhibitor ramipril reduced mortality in patients with a history of any vascular disease and no history of heart failure.⁶³

Management strategies

General agreement prevails that patients with ongoing or recurrent ischaemia and life threatening complications should undergo coronary angiography and revascularisation. In the past few years, follow up management by early conservative strategy or early invasive strategy has been considered for stabilised patients with unstable angina or infarction without ST elevation. Early conservative strategy involves risk stratification by using clinical data and non-invasive testing and by resorting to coronary angiography only for patients who have recurrent symptoms or a stress test result that is positive for ischaemia. In early invasive strategy, coronary angiography is routinely recommended and further revascularisation performed if anatomically appropriate.

The thrombolysis in myocardial infarction 3B trial compared early conservative and invasive strategies in 1473 patients with unstable angina or infarction without ST elevation randomised within 18-48 hours.⁶⁴ The outcomes were similar for both strategies. The veterans affairs non-Q wave infarction strategies in hospital (VANQWISH) trial compared the two strategies in patients with infarction without ST elevation and found a favourable trend with conservative strategy.⁶⁵ A benefit from delayed early invasive strategy (intervention four days after index event) for the combined end point of death and myocardial infarction at six months was found in the fragmin and fast revascularisation during instability in coronary artery disease II trial.⁶⁶ This benefit was mainly because of the reduction in rate of myocardial infarction, and no major difference in mortality was noted. At one year, however, a 43% lower mortality (2.2% versus 3.9%) was found in the invasive strategy group.⁶⁷ The retrospective data from the Organization to Assess Strategies for Ischemic Syndromes (OASIS) registry did not show any improvement in mortality of patients from countries with high utilisation of invasive procedures.⁶⁸ In fact, the death rate or myocardial infarction rate at six months was lower among patients treated in hospitals without cardiac catheterisation facilities.

Conflicting data exist as to whether an early invasive strategy or conservative strategy is best. A recent trial showed that dipyridamole stress testing can be done as early as two to three days after a myocardial infarction and can effectively predict adverse events.⁶⁹ Such early non-invasive testing might lead to more extensive use of conservative strategy in the future.

Conclusion

Treatment options for the management of unstable angina and infarction without ST elevation are considerable. Figure 3 gives a plan for treatment decisions in patients admitted with unstable angina or infarction without ST elevation. The judicious use of treatment options on the basis of an ongoing risk stratification throughout the hospital stay and outpatient follow up and the use of all possible diagnostic data will provide patients with the best medical care.

Competing interests: None declared.

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Lesson of the week

Unsuspected central hypothyroidism

A Waise, P E Belchetz

Thyroid testing is increasingly used as a tool for identifying cases of thyroid disease in both primary and secondary care even in the absence of a strong clinical suspicion of disease. Patients with unsuspected thyroid disease are, therefore, likely to be identified, and among those identified are a few patients who have pituitary tumours or hypopituitarism. In the United Kingdom there is variation in which tests are offered for first line thyroid testing. In a 1994 survey of endocrinological testing in clinical biochemistry laboratories in the United Kingdom, Barth et al found that 30 different combinations of first line and second line profiles were being used.¹ In a total of 186 replies 34% of laboratories reported offering testing for free thyroxine concentrations and thyroid stimulating hormone, 32% offered testing only for thyroid stimulating hormone, and 18% offered testing for total thyroxine concentration. The cases of the six patients described here highlight the fact that offering testing only for thyroid stimulating hormone (TSH) may be inappropriate.

The first five patients discussed had concentrations of free thyroxine hormone and thyroid stimulating hormone measured using a highly sensitive, third generation method (Amerlite hTSH, Kodak Clinical Diagnostics, Amersham). In the sixth patient these were measured by a two step, second generation method (Beckman Instruments, High Wycombe). Prolactin, luteinising hormone, and follicle stimulating hormone were measured using the Abbott IMX fluoroimmunoassay (Abbott Diagnostics, Maidenhead).

Growth hormone was measured using the Nichols Diagnostics immunoassay (Nichols Institute Diagnostics, Bad-Nauheim, Germany). Testosterone was measured by radioimmunoassay. Anterior pituitary function was investigated in five patients using glucagon, thyrotrophin releasing hormone, and gonadotrophin releasing hormone challenge. Insulin was used instead of glucagon in one instance.

Case reports

Case 1

A 75 year old man with a three year history of anaemia was referred by his general practitioner to a general physician. The patient's haemoglobin was 10.8 g/dl with contracted red cells. Hypothyroidism was suggested as a possible cause. On thyroid testing serum concentration of TSH was 1.34 mU/l (reference range 0.15-3.5 mU/l) and free thyroxine concentration was 8 pmol/l (10-30 pmol/l).

The patient's anaemia and the biochemical evidence of central hypothyroidism triggered referral for clinical endocrine assessment. The patient reported a 12 year history of feeling cold and of sexual dysfunction. He was kyphotic and had postural hypotension, sparse body hair, and thin skin. Pituitary stimulation testing confirmed the diagnosis of hypopituitarism and computed tomography identified a pituitary tumour. He received hydrocortisone and levothyroxine sodium (thyroxine sodium) and had transsphenoidal surgery for a non-secretory pituitary adenoma.

Testing only for thyroid stimulating hormone will miss unsuspected cases of central hypothyroidism

Department of Clinical Biochemistry, Friarage Hospital, Northallerton, North Yorkshire DL6 1JG
A Waise
consultant chemical pathologist

Department of Medicine, General Infirmary, Leeds LS1 3EX
P E Belchetz
consultant physician

Correspondence to:
A Waise
a.waise@nhs.uk
northy.nhs.uk

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