RATIONAL TESTING

Raised inflammatory markers

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Cite this as: *BMJ* 2012;344:e454
doi: 10.1136/bmj.e454

This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor, head of department of academic endocrinology, diabetes, and metabolism, Hull York Medical School; and Eric Kilpatrick, honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School. To suggest a topic for this series, please email us at practice@bmj.com.

What is the evidence for using C reactive protein, erythrocyte sedimentation rate, and plasma viscosity in diagnosis?

A 72 year old man consulted a general practitioner colleague of ours last week complaining of a non-specific feeling of malaise for about three weeks, with mild headache and pain in his left knee. He has generalised moderate osteoarthritis, mainly affecting his back and both knees. Our colleague had found nothing relevant on examination and had ordered several blood tests. A full blood count and liver and renal function were normal, but the erythrocyte sedimentation rate was moderately raised at 35 mm/h.

What is the role of inflammatory markers?

Measurement of inflammatory markers has two main functions: to detect acute inflammation that might indicate specific diseases, or to give a marker of treatment response (we will not consider this second indication here). Measurement of inflammatory markers can also be used as a general, but non-specific, test for serious underlying disease. Inflammatory markers are measured in about 4% of general practitioner consultations, for a range of indications, with 44-47% requested for specific diagnostic purposes, 27-33% for monitoring of disease, and 14-28% for non-specific diagnostic purposes.[1 2] There is considerable inter-practice variation in the measurement of inflammatory markers and in general practitioners' responses to abnormalities.[1 3 4] We found no health-economic analyses of these tests, but the total costs of testing must be considerable. For example, 63 000 primary care requests for inflammatory markers are tested annually at the University Hospitals Bristol NHS Foundation Trust, which serves a population of about 300 000 in 40 general practices (personal communication, W Woltersdorf, 2011).

LEARNING POINTS

Normal levels of inflammatory markers are valuable in ruling out a few specific conditions, notably polymyalgia rheumatica, giant cell arteritis, myeloma, and infection of hip revisions

Raised levels of inflammatory markers may be found in many other conditions, particularly infections, autoimmune conditions, and certain cancers. In these cases, they increase the probability of the condition being present, but additional information would be needed to be confident the disease is present or absent

Inflammatory markers are too non-specific to be a useful tool for diagnosing serious underlying disease and should rarely be used in this situation

In an incidental finding of raised levels of inflammatory markers, if history and examination yield no clues as to cause, it is reasonable to wait and see if symptoms develop. If levels are markedly raised (such as ESR >100 mm/h), the likelihood of disease is much higher, but history, examination, and focused investigations are usually sufficient to establish a diagnosis

Diseases with prominent activation of the inflammatory response fall into three main groups: infections, autoimmune diseases, and some haematological malignancies. Inflammatory markers include C reactive protein (CRP), erythrocyte sedimentation rate, plasma viscosity, fibrinogen, ferritin, and several other acute phase proteins, though only the first three are commonly referred to as inflammatory markers. CRP is considered to be particularly useful in detecting bacterial infection.[4] Plasma viscosity is now generally preferred to the erythrocyte sedimentation rate (ESR), as it is unaffected by anaemia or polycythaemia, or by delays between sampling and measurement, and has results independent of age or sex.[5] All these factors potentially affect the ESR. The change to use of viscosity is relatively recent, so most reports have studied the ESR or CRP. This article considers the evidence for and the rational use of CRP, ESR, and viscosity in diagnosis, both for specific diseases and non-specifically.

Diagnostic testing for specific diseases

The classic conditions for which testing may be useful are polymyalgia rheumatica or giant cell arteritis, recently reviewed in the *BMJ*.[6] Systemic features may predominate, with myalgia or headache minor or absent. A normal viscosity or ESR and normal CRP virtually rules out the condition. False negative results are rare—probably below 3%—though studies examining this required a positive result from a temporal artery biopsy, so the patients evaluated would have had more severe disease.[6] Another condition with characteristic raised inflammatory markers is myeloma.[7] If polymyalgia rheumatica, giant cell arteritis, or myeloma are suspected, measurement of inflammatory markers is a simple "rule out" test: normal inflammatory markers make the chance of any of these diseases being present so low as to allow the clinician to omit specific testing with protein electrophoresis and urinary Bence Jones protein.[7]

CRP and ESR have been studied as an aid to differentiating between minor illness and more serious disease, either in primary care or emergency departments. Some subjects have been systematically reviewed (table 1). Most of these reviews show a moderate relation between raised inflammatory markers and the target condition, but almost always the authors concluded that the sensitivities and specificities, on their own, were insufficient to rule in or rule out the condition safely. This was particularly so for primary care, where the prevalence of the target condition is usually lower. However, inflammatory markers may have some value as part of a clinical prediction rule incorporating other relevant clinical features, such as fever, although none seems to have entered mainstream clinical practice. One reason for this

Table 1 | Reviews of inflammatory markers for diagnosis of specific conditions

Target condition (test)	Setting	Study type	Outcome
Chorioamnionitis in premature delivery (CRP)	Secondary care	Systematic review (6 reports; 466 patients)[8]	Summary sensitivity 73%, specificity 76%
Serious infections in febrile children (CRP, ESR)	Secondary care	Systematic reviews (5/6 reports on CRP/ESR; 1379 patients having CRP)9 [10]	Likelihood ratio of raised CRP 3.2 (95% CI 2.7 to 3.7); negative likelihood ratio 0.33 (0.23 to 0.49).[10] Similar results in second review[9]
Bacterial chest infection in children (CRP)	Secondary care	Systematic review (8 reports; 1230 patients)[11]	Pooled odds ratio for raised CRP and bacterial infection 2.6 (1.2 to 5.6)
Bacterial chest infection in adults (CRP)	Primary care; accident and emergency departments	Systematic review (8 reports, with 2194 patients)[12]	Likelihood ratio of raised CRP 2.1 (95% CI 1.8 to 2.4); negative likelihood ratio 0.33 (0.25 to 0.43). Similar results in an earlier review[13] and a subsequent study in primary care[14]
Appendicitis in children with abdominal pain (CRP, ESR)	Secondary care (mainly emergency departments)	Systematic review of all features of appendicitis, including 5 studies of CRP, 1 of ESR; 730 and 162 children repsectivley[15]	Likelihood ratio of raised CRP increases as CRP increases: 5.2 (1.7 to 16) for CRP >25 mg/L. For normal CRP, 0.44 to 0.47. For ESR >20 mm/h, 3.8 (1.8 to 8.1)
Osteomyelitis of the leg in diabetes (ESR)	Secondary care (inpatients and outpatients)	Systematic review of all features of osteomyelitis, including 3 studies of ESR; 92 patients[16]	Summary likelihood ratio of ESR >70 mm/h 11 (1.6 to 79).
Infection in revision hip arthroplasties (CRP, ESR)	Secondary care	Cohort study of 178 patients; 202 arthroplasties [17]	ESR >30 mm/h: sensitivity 0.82 (0.65 to 0.93), specificity 0.85 (0.78 to 0.91); CRP >100 mg/L 0.96 (0.78 to 1.0), 0.92 (0.85 to 0.96). No patient with an infected arthroplasty had negative result on both tests

CRP=C reactive protein; ESR= erythrocyte sedimentation rate. 95% CI= 95% confidence interval.

may be the inevitable delay in obtaining a result if the specimen requires analysis off site.

Recent studies have examined whether CRP testing influences the decision to prescribe antibiotics for respiratory infections in primary care. One study in Norway, Sweden, and Wales found that the CRP result was the strongest influence on the decision to prescribe antibiotics, outweighing physical signs such as crackles on auscultation.[18] A cluster randomised trial in the Netherlands examined the effect of two interventions: CRP testing or training in enhanced communication skills. Antibiotic prescribing was significantly reduced in both intervention groups—from 57% in control patients to 43% for those whose doctors were in an intervention group.[19] General practitioners responded positively to having point of care access to CRP, as it enhanced patients' and general practitioners' confidence in prescribing decisions and empowered the doctors to prescribe antibiotics less often.[20] In all these studies, negative tests seemed to give the doctors additional confidence in avoiding prescription of antibiotics: this is clinically supported by the negative likelihood ratio of 0.33,[11] meaning that bacterial infection is about a third less likely once a negative test has been reported. The health economic aspects of point of care access to CRP testing would need to be examined before its use was to be recommended.

Observational studies have shown that inflammatory markers may be raised in ovarian, renal, and colorectal cancers, especially in advanced disease.[21-23] However, has been shown to have no discriminatory value in diagnosing these conditions, even in secondary care, where there is a higher prevalence than in primary care.[24]

In summary, there are a few clinical situations in which testing of inflammatory markers is the optimum test, as either a "rule in" or a "rule out" test. These include suspected polymyalgia rheumatica or giant cell arteritis, myeloma (ESR or viscosity), and infection of hip revisions (ESR or CRP). In most conditions, however, there is only a moderate association between raised inflammatory markers and the disease of interest, so they can refine the probability of disease, particularly if the test result is used in conjunction with other factors, such as symptoms.

Non-specific testing for systemic disease

The previous paragraphs focus on the value of inflammatory markers when a specific disease is being considered. However, another use is as a general marker to differentiate between the presence and absence of disease. Several old, mostly small, studies have examined this use (table 2).[25] Generally, when general practitioners test inflammatory markers for non-specific purposes the results are afterwards seen as being of little or no clinical value.[2] "Incidental" abnormalities in inflammatory markers are difficult to interpret and can lead to expensive and potentially harmful investigations. Although doctors may be reassured by negative testing when no disease is suspected,[26] diagnostic tests yielding normal results make hardly any difference to the level of reassurance of patients.[25]

What is the interpretation of an abnormal result?

Interpreting an abnormal result is relatively straightforward if there is a clear pretest hypothesis against which the test result can be evaluated—for example, if

Table 2 | Community and primary care studies investigating the diagnostic role of inflammatory markers as diagnostic or screening tools for non-specific disease

Setting (test)	Study type	Participants	Outcome
Israeli airmen (ESR)	Prospective study, 15 year follow-up[27]	1000 healthy men aged 18-33 years: yearly ESR measurement	44 had persistently raised ESR; of these, 10 subsequently developed disease (4 myocardial infarctions, 3 ankylosing spondylitis, and one each of inflammatory bowel disease, psoriasis, benign monoclonal gammopathy)
Community study of ageing in the US (ESR)	Prospective study, 12 month follow-up[28]	100 healthy men and women aged over 70 years	9 subjects had an ESR >30 mm/h for ≥6 months; a previously undiagnosed illness was identified in 4 of these (2 polymyalgia, 1 pancytopaenia, 1 anaemia)
Primary care in the Netherlands (ESR)	Prospective study, 3 month follow-up[29]	362 patients presenting with a new complaint for which the general practitioner considered ESR to be indicated	ESR values were on average higher in those with malignancy or inflammatory diseases. Almost all diagnoses "revealed" by the raised ESR had been suspected at the initial consultation before the ESR result was known

ESR=erythrocyte sedimentation rate.

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Previous articles in this series

- Raised inflammatory markers (*BMJ* 2012;344:e454)
- Investigating recurrent angio-oedema (*BMJ* 2011;343:d6607)
- Investigation of "non-responding" presumed lower respiratory tract infection in primary care (*BMJ* 2011;343:d5840)
- Investigating mixed hyperlipidaemia (*BMJ* 2011;343:d5146)
- Interpreting asymptomatic bacteriuria (*BMJ* 2011;343:d4780)

assessing the likelihood of serious infection in a child with a fever and abdominal pain. This was best shown in a Dutch study of patients in whom the raised ESR seemed to confirm an initial diagnosis as opposed to showing unexpected disease.[29] The difficulty lies in the interpretation of an "incidental" abnormality, when no specific disease is suspected, as in our hypothetical case. A systems inquiry, focusing on infection, autoimmune conditions, and malignancy, plus examination of the patient should generally point towards specific investigations. If history and examination yield no clues, it is reasonable to wait and see if symptoms develop rather than conduct an extensive search for occult disease. This investigation plan is supported by studies that have followed up patients with unexplained increases in levels of inflammatory markers. In one large (n=1462) study of asymptomatic Swedish women, 60% of these increases were transitory; none of the women with a raised ESR developed cancer; and in 46% of the women the cause of the increase remained undiagnosed over six years of observation.[30]

In cases with markedly raised levels of inflammatory markers (such as ESR >100 mm/h) the likelihood of disease is much higher. The diagnoses found in these conditions depend on study setting, but include infection (33-60%), inflammatory disease (14-30%), and malignancy (5-28%).[7 24 31-33] No diagnosis is found in fewer than 3% of patients with an ESR of >100 mm/h. In most patients, the diagnosis is likely to be clinically apparent; once again, history, examination, focused investigations, and careful follow-up should be sufficient to establish a clear diagnosis.

Outcome

The patient was asked to reattend surgery. His headache had settled, though he still felt non-specifically unwell. Nothing untoward was found on history or examination. He gradually improved over the next two weeks without treatment or further investigation. Measurement of ESR was not repeated.

Contributors: JW and WH did the searches and drafted the article. All authors made revisions. WH is the guarantor.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review: Commissioned; externally peer reviewed.

Patient consent not required (patient anonymised, dead, or hypothetical).

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10-MINUTE CONSULTATION

Reviewing a patient with coeliac disease

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Cite this as: *BMJ* 2012;344:d8152
doi: 10.1136/bmj.d8152

This is part of a series of occasional articles on common problems in primary care. The *BMJ* welcomes contributions from GPs.

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Previous articles in this series
- Dyspepsia (*BMJ* 2011;343:d6234)
- The Hajj (*BMJ* 2011;343:d5593)
- Measles, mumps, and rubella vaccination in a child with suspected egg allergy (*BMJ* 2011;343:d4536)
- Osgood-Schlatter disease (*BMJ* 2011;343:d4534)

A 44 year old woman diagnosed with coeliac disease 10 years ago presents to her general practitioner with symptoms of bloating and diarrhoea that have developed over the past two months.

What you should cover

Coeliac disease is a common gastrointestinal disease, with international population studies reporting a prevalence of 0.5-1%. Inflammation of the small bowel mucosa occurs as a result of an immunological response to dietary gluten. The mainstay of treatment is a gluten-free diet.

The most appropriate method of follow-up for patients with coeliac disease is still debated. Evidence suggests that regular follow-up improves compliance with a gluten-free diet. Survey data have shown that patients would prefer a model allowing regular follow-up with a dietitian, with specialist medical expertise available if needed. However, limited resources and the ability of patients to self manage means that many patients consult their general practitioner only when they have concerns. This consultation presents an opportunity to review their management.

In patients with a relapse of symptoms:

- Reconsider the diagnosis: is this definitely coeliac disease? Review the levels of antibodies to tissue transglutaminase and the histological findings.
- Ascertain whether symptoms improved after starting a gluten-free diet; most patients report improvement of symptoms in the first few weeks. Of those whose symptoms do not improve with the diet, only a very small minority have true refractory coeliac disease, with about 90% having an alternative underlying cause identified.
- Discuss the patient's diet. The commonest cause of persistent or recurring symptoms is ingestion of gluten. Ongoing exposure to gluten will usually result in raised levels of tissue transglutaminase antibodies. A gluten-free diet can be a major undertaking for patients, so explore and resolve any perceived barriers or difficulties (such as availability of gluten-free foods, impact on social life and "eating out," and social stigma). A review by a dietitian is essential as following a gluten-free diet will require education on which foods contain gluten and how to obtain gluten-free products. Highlight further sources of information and support, such as the association Coeliac UK.
- Acknowledge that some patients may not wish to follow a gluten-free diet or may wish to have phases of compliance depending on their symptoms. Explain the long term risks associated with this strategy and help patients to make an informed decision, providing support as needed. Explain that many food products do not contain gluten, such as fruit, egg, cheese, vegetables, meat, and fish.
- Identify if the patient has any "red flag" symptoms that require urgent investigation to exclude alternative gastrointestinal disease. Ask about vomiting, rectal bleeding, and weight loss. The diagnosis of coeliac disease does not exclude coincidental disease, and for any patients developing new alarm symptoms or iron deficiency anaemia consider referral for further investigation.

What you should do

Clinical examination

- Identify signs of nutritional deficiency (oral aphthous ulceration, angular stomatitis, koilonychia) and skin rashes (dermatitis herpetiformis).
- Record the patient's weight so that objective evidence of change in weight will be available.

Blood tests

- Arrange a full blood count, ferritin, vitamin B_{12}, and folate. Half of patients with coeliac disease are anaemic at presentation, and although their anaemia will improve if they follow a gluten-free diet, specific deficiencies may need to be corrected to aid recovery.
- Arrange liver function tests. Transient hepatitis may be present at diagnosis and will resolve with introduction of a gluten-free diet; however, persistent abnormalities may be the result of associated autoimmune conditions such as primary biliary cirrhosis or autoimmune hepatitis.
- Check glucose and thyroid function levels because of the association of coeliac disease with diabetes and autoimmune thyroid disease.
- Check tissue transglutaminase antibody levels if ongoing gluten ingestion is suspected.

Management

For patients who have difficulty adhering to a gluten-free diet, offer referral to a dietitian. The types of food that can be prescribed have been reviewed recently; for information see Coeliac UK's revised prescribing guide ("Useful resources" box). In some regions, supply of gluten-free products is led by community pharmacies. The table shows examples of monthly prescriptions for different patient groups, according to the number of "units" of gluten-free food products they

USEFUL RESOURCES

Primary Care Society of Gastroenterology. The management of adults with coeliac disease in primary care. 2006. www.pcsg.org.uk/downloads/pcsg-publications.

British Society of Gastroenterology. Management of adults with coeliac disease. 2010. www.bsg.org.uk/images/stories/clinical/bsg_coeliac_10.pdf

National Institute for Health and Clinical Excellence. Recognition and assessment of coeliac disease. (Clinical guideline 86.) 2009. http://guidance.nice.org.uk/CG86.

Coeliac UK (www.coeliac.org.uk/). Charity providing help and support to people with coeliac disease.

Coeliac UK. Gluten-free foods: a revised prescribing guide 2011. www.coeliac.org.uk/sites/files/coeliac/prescribing_guidelines_2.pdf.

Approximate monthly requirement of gluten-free products for various patient groups. Adapted from *Gluten-free Foods: A Revised Prescribing Guide 2011* (see Resources box)

Age group (years)	Recommended number of units*	Example of monthly prescription
1-3	10	6 × 400 g bread, 2 × 500 g pasta
4-6	11	6 × 400 g bread, 2 × 500 g pasta, 1 × (2 × 110-180 g pizza bases)
7-10	13	8 × 400 g bread, 2 × 500 g pasta, 1 × (2 × 110-180 g pizza bases)
11-14	15	8 × 400 g bread, 3 × 500 g pasta, 1 × (2 × 110-180 g pizza bases)
15-18	18	8 × 400 g bread, 4 × 500 g pasta, 2 × (2 × 110-180 g pizza bases)
Men		
19-59	18	8 × 400 g bread, 4 × 500 g pasta, 1 × (2 × 110-180 g pizza bases), 1 × 200 g crackers or crispbreads
60-74	16	8 × 400 g bread, 2 × 500 g pasta, 2 × 200 g crackers or crispbreads
≥75	14	8 × 400 g bread, 2 × 500 g pasta, 2 × 200 g crackers or crispbreads
Women		
19-74	14	8 × 400 g bread, 2 × 500 g pasta, 2 × 200 g crackers/crispbreads
≥75	12	6 × 400 g bread, 2 × 500 g pasta, 2 × 200 g crackers/crispbreads

*For prescribing purposes, each prescribable gluten-free food is allocated a unit on the basis of its carbohydrate and energy content and its cost. Thus: 400 g bread = 1 unit; 500 g pasta = 2 units; two pizza bases (110-180 g each) = 1 unit; 200 g crackers or crispbreads = 1 unit. For breast feeding, add an extra four units to the mother's requirement, and for third trimester of pregnancy add one unit.

need (units are allocated to each prescribable food on the basis of its carbohydrate and energy content and its cost).

Pancreatic insufficiency can be associated with coeliac disease and presents with diarrhoea or steatorrhoea. To diagnose pancreatic insufficiency send a stool sample for measurement of faecal elastase; if the level is low, consider a trial of pancreatin granules (such as Creon; Abbott Healthcare)—the dose can be adjusted to control symptoms, and a dietitian's advice is useful.

Although small bowel lymphoma is more common in people with coeliac disease, the annual incidence in the general population is low (0.5-1 per million), resulting in a very small increase in absolute risk for patients with coeliac disease. The increased risk reduces to a normal level after a gluten-free diet has been followed for three years. However, unexplained weight loss, abdominal pain, a palpable mass, and hypoalbuminaemia should alert you to the possibility of lymphoma and warrants referral for investigation (tissue transglutaminase antibody levels may be normal in this scenario).

If the cause of symptoms is still not clear, referral for gastroenterology opinion may be needed to exclude other associated conditions such as lactose intolerance, microscopic colitis, small bowel bacterial overgrowth, or irritable bowel syndrome. Seek specialist opinion if you suspect refractory coeliac disease.

Longer term aspects of management

The risk of developing osteoporosis is substantial, with 40% of patients having decreased bone mineral density at the time of diagnosis. However, in most cases the density will improve with a gluten-free diet. Current guidance suggests measurement of bone mineral density in all patients at diagnosis, with the subsequent frequency of assessment dictated by the baseline result together with patients' other risk factors for developing osteoporosis. Discuss relevant lifestyle measures, including regular exercise, reducing alcohol intake, and smoking cessation, and prescribe calcium supplements if necessary to ensure a daily intake of 1500 mg.

About 30% of patients with coeliac disease have hyposplenism. As a result of this increased prevalence and the consequent susceptibility to infection, England's Department of Health recommends offering pneumococcal vaccination to all patients, and some experts also suggest offering vaccines against haemophilus and influenza.

Discuss the risk of family members developing coeliac disease. First degree relatives have a 1 in 10 chance of being affected and should be assessed if symptoms develop.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; SB performs consultancy as a primary care adviser to Juvela (a gluten-free food manufacturer); SB and GS are members of the health advisory committee to Coeliac UK.
Provenance and peer review: Not commissioned; externally peer reviewed.
Accepted: 15 November 2011

LESSON OF THE WEEK

Cholestasis secondary to anabolic steroid use in young men

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Cite this as: *BMJ* 2012;344:e468
doi: 10.1136/bmj.e468

Ask about use of anabolic steroids in young men with unexplained cholestasis to prevent progressive liver injury

In the face of increasing societal pressure to achieve bodily perfection, young men in particular sometimes turn to anabolic steroids to help them achieve the body they want. The health consequences of this choice are often overlooked. We describe two cases of severe cholestatic liver disease in young men who had taken anabolic steroids with the aim of enhancing their body image.

Case reports

Case 1

A 32 year old man presented with a seven day history of nausea, vomiting, and jaundice associated with severe itching. He had no medical history of note and had not taken any prescribed medications for several years. He did not drink alcohol regularly and denied having used recreational drugs, although he eventually admitted having taken 5 mg a day of methandrostenolone for the first time in the previous two months. He stated that he took the drug to enhance his body image.

Blood tests on admission showed bilirubin 651 µmol/L (normal range 0 to 19), alanine aminotranferase 76 IU/L

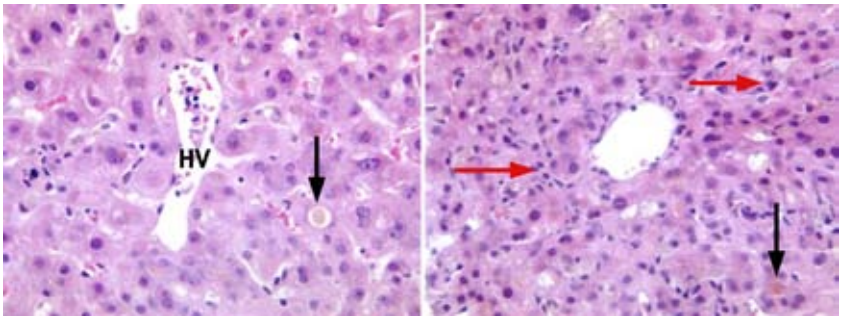

Fig 1 | Left (case 1): Bland cholestasis with canalicular bilirubinostasis (arrow) and minimal inflammation (HV=hepatic vein). Right (case 2): Cholestatic liver disease with hepatocellular bilirubinostasis (vertical arrow), accompanied by a mild lymphocytic (horizontal arrows) and macrophage infiltrate (cholestatic hepatitis)

(0 to 45), alkaline phosphatase 262 IU/L (35 to 120), and international normalised ratio 1.3. An extended liver screen (including serological testing for hepatitis A, B, C, and E as well as for cytomegalovirus and Epstein-Barr virus, full autoantibody profile, and markers of metabolic liver diseases), abdominal ultrasonography, and magnetic resonance cholangiopancreatography failed to identify any alternative causes. Cholestasis induced by anabolic steroids was diagnosed clinically (after his history of use of anabolic steroids had been ascertained). He was initially treated with ursodeoxycholic acid and observed. He became severely hypertensive on day 2, needing treatment with amlodipine. A liver biopsy on day 4 (performed because of a progressive rise in bilirubin concentration) showed bland cholestasis, in keeping with liver injury induced by anabolic steroids (fig 1 (left)). He complained of severe itching throughout the admission and needed treatment with chlorphenamine and colestyramine. His bilirubin started to fall from its peak (day 4) and he was discharged on day 7. Over the next four months his liver function gradually returned to normal (fig 2 (top)).

Case 2

A 16 year old boy presented to his general practitioner with a three week history of severe itching, nausea, and abdominal discomfort. He was noted to be jaundiced. He did not have any notable medical, travel, or family history. He was not taking any prescribed medications or herbal remedies and denied having used recreational drugs. On direct questioning later in hospital, he admitted having taken 10 mg of methandrostenolone three times a day for five days before the onset of his symptoms. This was his first use of anabolic steroids. The reason behind his use of anabolic steroids was not ascertained at the time.

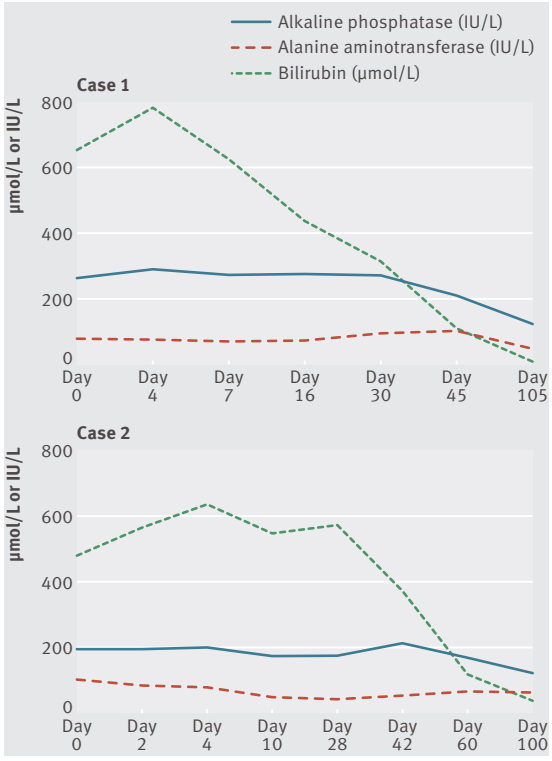

Fig 2 | Serial values for alkaline phosphatase, alanine aminotransferase, and bilirubin for case 1 (top) and case 2 (bottom)

His blood tests on admission showed bilirubin 441 µmol/l, alanine aminotranferase 156 IU/L, alkaline phosphatase 203 IU/L, and international normalised ratio 1.1. An extended liver screen and abdominal ultrasonography failed to identify an alternative cause for his jaundice, and cholestasis induced by methandrostenolone was subsequently diagnosed clinically. His bilirubin peaked at 635 µmol/l on day 7, and his liver biopsy confirmed cholestatic liver disease with a mild element of hepatitis (fig 1 (right)). He had a prolonged admission (15 days) with severe refractory pruritus despite administration of colestyramine, chlorphenamine, ursodeoxycholic acid, rifampacin, and naltrexone. Once discharged, he was increasingly anxious and depressed and refused to attend school because of his jaundice. His liver function returned to normal over four months (fig 2 (bottom)).

Discussion

The use of anabolic steroids is no longer limited to elite athletes. Figures from the Department of Health in the United Kingdom showed that 0.2% of young people had tried anabolic steroids in 2001-4 and 0.5% in 2006.[1 2] A questionnaire study of 3403 12th grade students (final year of secondary school) in the United States found that 6.6% admitted to taking anabolic steroids.[3] Worryingly, two thirds of those had started using anabolic steroids when they were aged 16 or younger.

A study of homosexual men who regularly attended gyms in London in 2000 found that 15.2% of the 792 men surveyed had used anabolic steroids in the preceding year, with 11.7% of them having injected the drugs.[4] Two thirds of the respondents used more than one agent (so called "stacking"). The high prevalence of use of injectable anabolic steroids correlates with our local experience, where 43% of new registrations for needle exchanges were users of anabolic steroids.[5] This figure might be an underestimate as many users of anabolic steroids will collect needles and syringes for friends and other users as well.[5]

Many different formulations and types of anabolic steroids are available to users. However, it is the 17α alkylated steroids, such as methandrostenolone and methyltestosterone, that have the most capacity to be hepatotoxic—17α alkylation slows down metabolism of the steroids in the liver, thereby exposing hepatocytes and cholangiocytes to the drug for longer.[5] Fewer of the injectable anabolic steroids are 17α alkylated, so use of oral anabolic steroids is more commonly associated with abnormal liver function. Anabolic steroids vary in their androgenic and anabolic properties, and body builders often use several steroids with the intent of producing differing results. Most of these drugs are sourced either illegally or via the internet. The actual anabolic steroids used, and the true dosage, are often unknown to the user.

Anabolic steroids have been linked to many adverse

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health effects, including cardiomyopathy, cerebrovascular events, hypertension, aggression, prostatic hypertrophy, and cholestatic liver injury.[6 7] In one study, 96% of users of anabolic steroids reported at least one side effect.[4] However, the absolute risks have not been fully evaluated. Users typically take them in "cycles" that vary in length (often 8-12 weeks) to minimise side effects, with a similar amount of time "off cycle." The agent implicated in both cases of severe cholestatic liver injury presented here was methandrostenolone. This is a weak androgen receptor agonist and has long been recognised as a cause of liver damage.[5] This fact seems to be well known among users of anabolic steroids as many internet steroid forums recommend taking the drugs for no more than four weeks to avoid going "yellow."

Anabolic steroids are freely available online and there seems to be no regulation of the quality or quantity of drugs dispensed in the various formulations.[8] Several "dietary supplements" have been found to contain substantial amounts of anabolic steroids.[9] A recent report from Portugal described a case in which cardiomyopathy induced by anabolic steroids had caused fulminant liver failure in a bodybuilder who took large doses of anabolic steroids.[10] A further, Canadian case report has described the simultaneous occurrence of cholestatic jaundice, acute kidney injury, and acute pancreatitis.[11]

Neither of our patients had evidence of renal dysfunction or acute pancreatitis. Although we have yet to see any cases of fulminant liver failure resulting from use of anabolic steroids, our two cases presented here illustrate that the cholestatic injury is not always benign. Both patients needed a prolonged stay in hospital for treatment resistant pruritus. The second case was associated with considerable psychological morbidity, so much so that the patient felt he had to leave school.

When our two patients sought medical help, both initially denied using anabolic steroids and both had to be directly questioned further about this. Therefore, we highlight that it is especially important to consider anabolic steroid use in young men with abnormal liver function to prevent progressive liver injury.

Contributors: AME, SMcP, and SM wrote the first draft of the report. AME made subsequent changes. ADB was responsible for histological analysis. RTD provided the background on community use of anabolic steroids. SMcP and MH were responsible for the hepatological management of patient 1, and SM was responsible for the hepatological management of patient 2. All authors were involved in revisions of the documents and approved the final version. MH is the guarantor.
Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.
Provenance and peer review: Not commissioned, externally peer reviewed.
Patient consent obtained.

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Accepted: 21 November 2011

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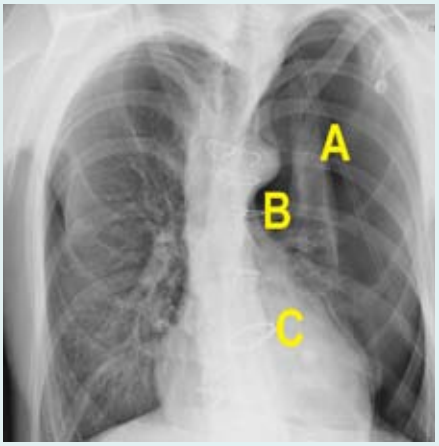
PICTURE QUIZ An unfortunate teenager



Chest radiograph showing a large left sided pneumothorax (A), with visible sternotomy sutures (B) and a mechanical aortic valve replacement (C)

1 A large left sided pneumothorax is present. A mechanical valve is seen in situ in the aortic position with some overlying metallic sternal sutures. Allowing for rotation, there is a degree of thoracic spine scoliosis.
2 This patient has Marfan's syndrome, which explains his scoliosis, recurrent pneumothoraxes, and aortic valve replacement at such an early age.
3 Marfan's syndrome is diagnosed using the modified Ghent criteria (2010).
4 Common clinical manifestations include dilation of the aortic root, aortic dissection, aortic or mitral valve incompetence, wide arm span, arachnodactyly, high arched palate, scoliosis, ectopia lentis, and spontaneous pneumothoraxes.
5 Marfan's syndrome is an autosomal dominant connective tissue disease that is caused by a mutation in the *FBN1* gene, which encodes the matrix protein fibrillin. However, about 25% of cases are thought to occur as a result of de novo mutations.

STATISTICAL QUESTION "n of 1" trials

Statements *a*, *b*, and *c* are true, whereas *d* is false.

CASE REPORT Exertional dyspnoea and syncope

1 Cardiac amyloidosis.
2 Orthostatic hypotension exacerbated by β blockade.
3 Oral anticoagulants and cardioversion.
4 Perform cardiac biopsy to confirm the diagnosis and to guide specific treatment for the type of amyloid identified.