EASILY MISSED?

Infective endocarditis

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This is one of a series of occasional articles highlighting conditions that may be more common than many doctors realise or may be missed at first presentation. The series advisers are Anthony Harnden, university lecturer in general practice, Department of Primary Health Care, University of Oxford, and Richard Lehman, general practitioner, Banbury. If you would like to suggest a topic for this series please email us (easilymissed.bmj@bmjgroup.com).

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Previous articles in this series

- Septic arthritis in children (*BMJ* 2010;341:c4407)
- Human brucellosis (*BMJ* 2010;341:c4545)
- Primary HIV infection (*BMJ* 2010;341:c4583)
- Septic arthritis in children (*BMJ* 2010;341:c4407)
- Carcinoid syndrome (*BMJ* 2010;341:c3941)

Infective endocarditis is caused by microbial infection of the endocardial surface or of prosthetic material in the heart. More than 80% of cases are caused by *Staphylococcus aureus* or by species of *Streptococcus* or *Enterococcus*. The total incidence of infective endocarditis has remained relatively constant, but the epidemiology has changed markedly in recent years. Proportionately more cases are now seen in association with prosthetic valves and as a result of hospital acquired infections.[1]

Why is infective endocarditis missed?

Infective endocarditis is a rare disease with varied presentations. Symptoms such as loss of appetite, weight loss, arthralgia, and night sweats overlap with much more common conditions, including occult malignancy. Fever is almost invariable,[2] but many patients may initially experience only a general malaise. Given the diagnostic difficulty, some 25% of patients take longer than one month to be admitted to hospital after their first clinical signs become evident.[2]

Why does this matter?

Data from the pre-antibiotic era suggest that infective endocarditis is almost always fatal if untreated.[3] Delayed diagnosis in some groups is associated with a substantial increase in mortality.[4] Even with timely recognition and treatment, the outcome may sometimes be poor. Observational studies report one year mortality of 20-25% and 10 year mortality of 50%, outcomes worse than for many malignancies.[5]

How is it diagnosed?

Infective endocarditis should remain part of the differential diagnosis of a persistent febrile or inflammatory illness. Ironically, once infective endocarditis is suspected, confirmation of the diagnosis may be straightforward. This will usually involve referral to secondary care, where modified Duke criteria (box 1) may be applied as the diagnostic standard. These use a synthesis of clinical, microbiological, and echocardiographic findings.[6] The negative predictive value of these criteria has been estimated as more than 92%.[7] So called "culture negative" endocarditis, which occurs in 20-30% of cases, remains a difficult challenge and may be underdiagnosed by Duke criteria.[8]

The NHS Map of Medicine suggests an algorithm for early diagnosis (http://eng.mapofmedicine.com/evidence/map/infective_endocarditis3.html) but anticipates this as taking place exclusively in secondary care.

Clinical features

Pre-existing risk factors for infective endocarditis (box 2) should arouse suspicion, but previously well individuals can also become infected. In one series of endocarditis *S aureus*, only 55% of patients had a pre-existing valve lesion and 68% of patients did not show a portal of entry.[8] A fever >38ºC at some point is almost invariable,[2] so the absence of any fever should lead to consideration of an alternative diagnosis. Diagnostic "red flags" include a new regurgitant murmur, which is found in almost half of patients[2]; a regurgitant murmur across a prosthetic valve; and any systemic embolus or sepsis of unknown origin.[9] In primary care, the combination of the failure of a febrile illness to resolve, together with a murmur, may be "as good as it gets" in terms of early clinical indicators. Painless Janeway lesions on the palms or soles and immunological findings such as Roth spots and Osler nodes are now rare, being found in no more than 5% of cases of infective endocarditis,[2] but they are useful if they are present and recognised.

KEY POINTS

- Infective endocarditis is rare but is fatal in about a fifth of cases
- Infective endocarditis should be part of the differential diagnosis of a persistent febrile or inflammatory illness, particularly if there are pre-existing cardiac lesions
- Diagnosis usually requires consistent clinical findings, positive blood cultures, or other proof of infection, and positive echocardiographic findings
- Treatment is prolonged and may require cardiac surgery in addition to an extended course of antibiotics

CASE SCENARIO

Four months after prostate surgery that had been complicated by a urinary infection, a 65 year old man presented with lethargy, malaise, and mild anaemia. No further specific abnormalities were found over the next two weeks. He developed night sweats, and a new systolic murmur was heard. C reactive protein was raised at 90 mg/l. Infective endocarditis was considered as a diagnosis. Blood cultures were ordered and he was referred to hospital. *Enterococcus faecalis* was grown from all culture bottles. Transthoracic echocardiography showed mitral valve vegetations, confirming the diagnosis of bacterial endocarditis.

HOW COMMON IS INFECTIVE ENDOCARDITIS?

- The annual incidence is 3-10 cases per 100 000
- A general practitioner is unlikely to see more than one case every 8-10 years

Box 1 | Duke criteria for diagnosis of endocarditis*

Requirements for diagnosis of "definite" infective endocarditis†

Pathological criteria

- Histological diagnosis from tissue, or culture of tissue or intracardiac abscess

Clinical criteria

- Two major criteria or
- One major criterion and three minor criteria or
- Five minor criteria

Requirements for diagnosis of "possible" infective endocarditis

Clinical criteria

- One major criterion and one minor criterion or
- Three minor criteria

Rejection of infective endocarditis if one of the following conditions is met

- Firm, alternative diagnosis explaining the evidence suggesting infective endocarditis
- Resolution of clinical findings of infective endocarditis with antibiotic course lasting four days or less
- No pathological evidence of infective endocarditis at surgery or autopsy with antibiotic course lasting four days or less
- The condition does not meet criteria for "definite" or "possible" infective endocarditis

Major blood culture criteria

- Two positive blood cultures for typical infective endocarditis organisms
- Persistently positive cultures for such organisms taken >12 hours apart
- Three or more positive cultures taken at least one hour apart

Major echocardiographic criteria

- Echocardiogram indicating infective endocarditis with no alternative explanation
- Myocardial abscess
- New partial dehiscence of prosthetic valve
- New valvular regurgitation

Minor criteria

- Predisposing cardiac condition
- Intravenous drug use
- Fever (≥38°C)
- Raised C reactive protein or erythrocyte sedimentation rate
- Vascular lesions including major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway lesions
- Immunological phenomena, including glomerulonephritis, Roth spots, Osler's nodes, and positive rheumatoid factor
- Positive cultures not meeting a major criterion or serological evidence of active infection with an organism consistent with infective endocarditis
- Echocardiographic results consistent with infective endocarditis but not meeting a major criterion

*Adapted from the American Heart Association[6]

†Either the pathological or the clinical criteria need to be met

Box 2 | Risk factors (and prevalence) found in patients in Europe who were subsequently diagnosed with "definite" endocarditis according to Duke criteria[2]

- Predisposing native valve condition (31%)
- Invasive procedure within previous 60 days (25%)
- Prosthetic valve (20%)
- Presence of pacemaker (12%)
- Congenital heart disease (10%)
- Current intravenous drug use (9%)
- Previous endocarditis (7%)

Investigations

A definitive diagnosis of infective endocarditis will almost certainly require referral to secondary care. Initial testing in primary care may prompt earlier referral or, conversely, provide reassurance that an inflammatory condition seems to be settling. Although markers of inflammation such as erythrocyte sedimentation rate and C reactive protein are raised in over 60% of patients with infective endocarditis,[2] these tests alone are too non-discriminatory to make or exclude the diagnosis.[10] However, raised concentrations (considered to be minor Duke criteria) may aid a decision to refer. A positive rheumatoid factor is potentially useful as a minor criterion. Positive blood cultures for *S aureus*, *Streptococcus*, or *Enterococcus* species suggest an important infection in any context and should be referred for hospital assessment.

Positive blood cultures or other serology and cardiac imaging in secondary care are the mainstays of definitive diagnosis. Transthoracic echocardiography is readily available, but transoesophageal studies are the current best imaging modality, particularly if prosthetic material is present. Specificity for detecting vegetations, abscesses, or other evidence of infective endocarditis can approach 100%.[11] Serial studies should be performed if the initial diagnosis remains in doubt.

How is it managed?

Hospital care is mandatory for at least the initial treatment of infective endocarditis in order to assess the early response to antibiotics and to monitor and treat any complications. Little controlled trial evidence exists to guide treatment, but a substantial body of clinical experience does exist.[6 9] Rational management involves extended courses of high dose antibiotic treatment, ideally guided by microbiological sensitivity testing. In one series of over 200 patients, 38% of patients needed surgical treatment.[5] Indications for surgery include failure to control the infection, threatened or actual embolus of septic material, and development of heart failure. Some patients may be suitable for outpatient intravenous antibiotic treatment after an initial inpatient assessment and treatment period.[9] After discharge from hospital, patients need monitoring for relapse or recurrent infection. Patients remain at risk of further episodes of infective endocarditis and should be counselled to report any potentially relevant symptoms.

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LESSON OF THE WEEK

Acute liver failure after administration of paracetamol at the maximum recommended daily dose in adults

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A total of 4 g of paracetamol repeated daily may be hepatotoxic in malnourished adults with low body weight

Paracetamol is the most commonly used analgesic and antipyretic in the world; it can be bought without prescription in most countries despite being the commonest cause of acute liver failure in western Europe. Prescribing information suggests that it is safe to use in adults in divided doses that total 4 g daily. Malnutrition, starvation, chronic alcohol misuse, and concomitant use of drugs that induce cytochrome P450 enzymes increase the risk of hepatotoxicity induced by paracetamol. Nevertheless, doctors commonly regard paracetamol 4 g daily as being safe as well as an effective analgesic. We describe two cases (one fatal) of acute liver failure secondary to maximum dose oral paracetamol; these highlight the importance of considering dose reduction in those with low body weight and/or other risk factors for hepatotoxicity.

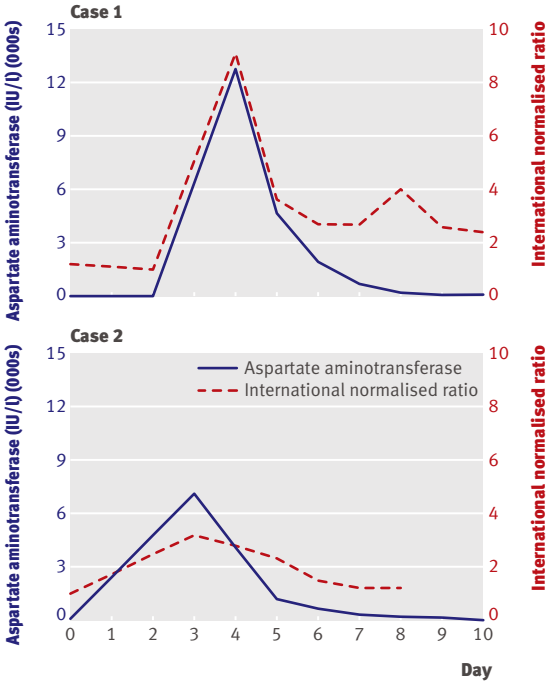
Case reports

Case 1

A 43 year old man was admitted with an exacerbation of Crohn's colitis. His nutritional status was poor, with an admission weight of 30 kg and a body mass index (weight (kg)/(height (m)^2)) of 12. He received intravenous hydrocortisone and metronidazole along with oral paracetamol at a total dose of 4 g daily. Four days later he became confused and tachypnoeic and was found to have developed acute liver failure with an aspartate aminotransferase of 12 769 IU/l, international normalised ratio of 9.1 (figure), and severe lactic acidosis. Liver function tests were normal at the time of his admission. His paracetamol concentration was raised (92 mg/l) despite him having received the standard maximum adult dose under direct supervision. No other cause of liver failure could be identified; he was never hypotensive, and serological studies for acute viral infection were negative. He was transferred to the regional liver failure service, but despite treatment with *N*-acetylcysteine and supportive care on the liver intensive care unit he died 12 days later of multiorgan failure.

Case 2

A 32 year old woman with a history of chronic alcoholism was admitted with acute alcohol withdrawal and abdominal pain secondary to alcoholic gastritis. She was prescribed vitamin supplements, chlordiazepoxide, and oral paracetamol (total 4 g daily). She weighed 44 kg on admission (body mass index 17). Blood tests and abdominal ultrasound on admission were unremarkable (aspartate aminotransferase 56 IU/l). Three days later she became increasingly agitated and complained of nausea. She was found to be in acute liver failure with a peak aspartate aminotransferase of 7116 IU/l and international normalised ratio of 3.2 (figure). Her paracetamol concentration was raised (105 mg/l). She was transferred to the liver intensive care unit and received full supportive care



Dynamic changes in aspartate aminotransferase (left axis) and international normalised ratio (right axis) for each patient. Both patients received oral paracetamol, each at a total dose of 4 g daily from the time of admission to hospital (day 0)

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- Delayed diagnosis of primary hyperaldosteronism (*BMJ* 2010;340:c2461)
- Sexual precocity in a 4 year old boy (*BMJ* 2010;340:c2319)
- Treatment for lymph node tuberculosis (*BMJ* 2010;340:c63)

including *N*-acetylcysteine. Her liver function gradually recovered and she was discharged 15 days later.

Discussion

Paracetamol is metabolised in the liver by processes of glucuronidation and sulfation. Most of the drug is metabolised into non-toxic metabolites, but 5-10% is converted by the cytochrome P450 system into the reactive toxic intermediate *N*-acetyl-*p*-benzoquinoneimine (NAPQI).[1] In healthy individuals taking therapeutic doses of paracetamol this metabolite is usually rendered non-toxic by binding to glutathione.[2] Overdose of paracetamol, induction of cytochrome P450 enzymes, or glutathione deficiency may result in the metabolic pathway becoming overwhelmed, producing an excess of NAPQI, which binds to hepatocyte macromolecules causing enzymatic dysfunction, structural and metabolic disarray, and eventually necrotic cell death. Hepatocytes are increasingly susceptible to oxidative stress when glutathione is depleted.[3]

Glutathione is synthesised from glutamate, cysteine, and glycine by two cytosolic enzymes (γ-glutamylcysteine synthetase and glutathione synthetase).[4] Thus protein or amino acid deficiency secondary to malnutrition, malabsorption, or synthetic failure leads to glutathione deficiency. Alcoholics have low serum and intrahepatic glutathione concentrations, and chronic illness and fasting are risk factors for glutathione deficiency.[5]

Paracetamol has a narrow therapeutic index, and severe hepatocellular necrosis may follow the oral ingestion of a single dose of 150 mg/kg. Both of the patients we describe were underweight and had additional factors that made them at increased risk of hepatotoxicity. Patient 1 weighed 30 kg and his daily dose of 4 g was therefore 133 mg/kg. The daily dose received by patient 2 was 91 mg/kg. Doses of this magnitude repeated daily in individuals with inadequate metabolic capacity may lead to liver injury, which in severe cases may result in acute liver failure.

Several cases of acute liver failure secondary to oral paracetamol at the maximum recommended daily dose have been reported, and in all these cases the patients had identifiable risk factors for hepatotoxicity.[6-10] Although these cases are rare, it is likely that they are an underrepresentation of the true incidence as some practitioners may not identify the correct cause of liver injury owing to a low index of suspicion. Patients who develop milder hepatic impairment may not be identified at all if liver function tests are not measured. A prospective study of acute liver failure at 17 tertiary care centres in the United States identified 21 patients with acute liver failure secondary to paracetamol at doses of ≤4 g daily over a 41 month period.[11]

The widespread use of paracetamol in hospitals and in the community, coupled with the high prevalence of chronic alcoholism and malnutrition, particularly in hospital inpatients, means that more cases will probably occur. However, if awareness is raised, further cases of acute liver failure may be preventable through reduced doses in those who are most at risk.

Intravenous paracetamol is now increasingly used in secondary care; at our hospital the annual number of prescriptions for intravenous paracetamol rose by 30% between 2007 and 2009 (from 2438 to 3174). The bioavailability of intravenous paracetamol (1.0) is higher than that of oral paracetamol, which is dose dependent and ranges from 0.7 to 0.9.[12] Thus, there may be a greater potential for liver injury if a total of 4 g daily intravenous paracetamol is prescribed to malnourished patients with low body weight.

The *British National Formulary* (*BNF*) states that the daily dose of intravenous paracetamol should not exceed 60 mg/kg when prescribed for adults weighing <50 kg.[13] The latest edition also cautions for the first time that the maximum daily dose of infusions should be reduced to 3 g for patients with hepatocellular insufficiency, chronic alcoholism, chronic malnutrition, or dehydration. However, it contains no recommendations to reduce the dose of oral paracetamol for adults weighing <50 kg or in the presence of other risk factors. This disparity between the maximum recommended dose of oral and intravenous paracetamol for adults with low body weight and/or other risk factors for hepatotoxicity is surprising, given that the systemic bioavailability of oral paracetamol may be as high as 90%.

We reviewed oral and intravenous paracetamol prescriptions issued at our hospital to adults weighing <50 kg over eight weeks. Eighty two per cent (47/57) of patients were prescribed oral paracetamol at the maximum recommended daily dose. Two of these patients had a transient rise in aspartate aminotransferase during treatment (from 29 IU/l to a peak of 526 IU/l over four days in a patient weighing 39 kg, and from 29 IU/l to 138 IU/l over three days in a patient weighing 40 kg). Moreover, in 17 of the 18 patients given intravenous paracetamol, the dose was not reduced as recommended by the *British National Formulary*. This shows that few practitioners in secondary care reduce the dose of either oral or intravenous paracetamol in adults with a low body weight and confirms that many patients are potentially at risk. The fact that we were able to identify two susceptible adults with evidence of liver injury secondary to maximum dose paracetamol at a single centre in a period as short as eight weeks suggests that these cases may be under-recognised.

We have raised awareness of this matter locally via email bulletins, pharmacists, and the introduction of an alert message on our electronic prescribing system recommending the reduction of the daily dose of paracetamol (oral and intravenous) to 2 g for adults weighing <50 kg.

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