The Practitioner

CPD study pack

November 2016;260(1798)
The study pack contains this month's CPD exercise plus all relevant articles:

- GPs have key role in improving outcomes in acute asthma
- Assessment and management of active and latent TB
- Improving the identification and monitoring of cirrhosis

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Practitioner CPD exercise

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- Prescribing review
- Educational meetings
- Significant event audit
- Practice meeting
- Implement a new service
- Take on new role
- Significant event audits
- Change with feedback from patients and/or colleagues

Further options for sessional GPs
- Self audit of own practice:
  - Record-keeping
  - Referrals for investigations
  - Prospective condition based reviews
  - Random case analysis with colleagues
  - Review of telephone triage outcomes
- Update drugs in emergency bag

CPD Framework

Online all articles are now associated with CPD prompts to written reflection in the form of three PDF fillable templates:
- Article review framework
- Case review framework
- Audit framework

ACUTE ASTHMA

1 Which of the statements are true?

A Macrolide antibiotics are of no benefit in asthma attacks
True ☐ **False** ☐

B Women who are pregnant should receive the same treatment for asthma attacks as those who are not
True ☐ **False** ☐

C Patients reviewed in the afternoon or evening often deteriorate following initial assessment
True ☐ **False** ☐

D Most asthma deaths occur in hospital
True ☐ **False** ☐

E Patients admitted with a mild to moderate attack should be followed up in primary care every 3 months
True ☐ **False** ☐

2 List four features that denote severe acute asthma.

3 Match the feature to the severity of asthma attack.

A PEF > 50-70% predicted

B Raised $PaCO_2$

C Exhaustion

D Hypotension

E Inability to complete sentences in one breath

1 Moderate
2 Severe
3 Life-threatening
4 Near fatal

4 List any changes to your clinical practice that you may make having read this article.

TUBERCULOSIS

5 Which of the statements are true?

A Household contacts of any patient with active TB should be screened for latent infection
True ☐ **False** ☐

B Of those infected with TB 15% will go on to develop active disease
True ☐ **False** ☐

C TB infection can only be transmitted if patients are producing sputum
True ☐ **False** ☐

D Once infected patients who are immunosuppressed are at greater risk of progression to active disease
True ☐ **False** ☐

E A positive Mantoux test is defined as an induration ≥ 5 mm irrespective of prior BCG vaccination
True ☐ **False** ☐

6 Complete the statement:

under the age of
can develop rapidly
and potentially
infection.

7 Which of the following are risk factors for the progression of latent to active TB infection?

A Treatment with biologic agents

B Chronic kidney disease

C Age under 12 years

D Alcohol misuse

»

CME - FILLABLE PDF FORM

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8 List any changes to your clinical practice that you may make having read this article.

CIRRHOSIS

9 Match the statistic to the statement:

A The proportion of patients with cirrhosis who are asymptomatic

B Three-year survival rate in cirrhosis patients with a Child Pugh score 7 to 9

C Mortality associated with acute variceal haemorrhage

D Annual risk of patients with cirrhosis developing overt hepatic encephalopathy

1 20%
2 46%
3 50%
4 59%

10 List four potential complications of cirrhosis.

11 Which of the statements are true?

A One in five patients with oesophageal varices will develop a variceal haemorrhage within two years
True ☐ **False** ☐

B Hepatocellular carcinoma is often asymptomatic until late in the disease
True ☐ **False** ☐

C A quarter of patients with compensated cirrhosis have oesophageal varices at diagnosis
True ☐ **False** ☐

D Abnormal liver function tests correlate poorly with the presence of cirrhosis
True ☐ **False** ☐

12 List any changes to your clinical practice that you may make having read this article.

Answers

ACUTE ASTHMA
1 **A** True **B** True **C** True **D** False **E** False (every 6 months)

2 PEF 33–50% best or predicted; respiratory rate ≥ 25/min; heart rate ≥ 110 bpm; unable to complete sentences in one breath

3 **A** 1 **B** 4 **C** 3 **D** 3 **E** 2

TUBERCULOSIS
5 **A** False (only contacts of patients with active pulmonary or laryngeal TB) **B** False (10%) **C** True **D** True **E** True

6 Infants; 12 months; progressive; fatal

7 A, B, D

CIRRHOSIS
9 **A** 3 **B** 4 **C** 3 **D** 1

10 Ascites, hepatocellular carcinoma, oesophageal varices, hepatic encephalopathy

11 **A** False (one in four) **B** True **C** False (a third) **D** True

The Practitioner

GPs have key role in improving outcomes in acute asthma

Grover HL, Higgins BG. GPs have key role in improving outcomes in acute asthma.
Practitioner 2016; 260(1798):15-19

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GPs have key role in improving outcomes in acute asthma

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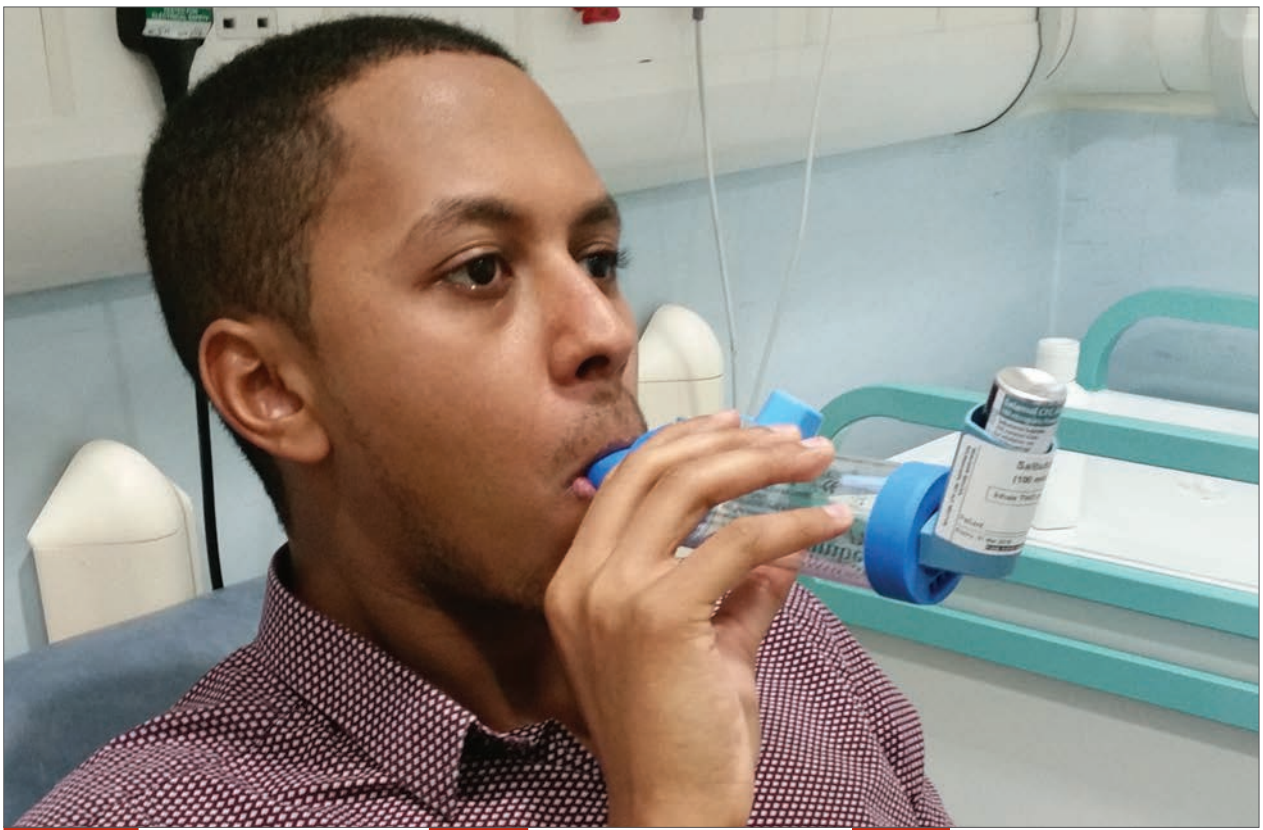

Which patients are at greatest risk?

THERE ARE 5.4 MILLION PEOPLE WITH ASTHMA IN THE UK.[1] ATTENDANCE AT BOTH GP SURGERIES AND emergency departments is high and in 2011-12 there were more than 65,000 hospital admissions,[2] a higher admission rate than most comparable European countries.

Asthma deaths in the UK remain among the highest in Europe.[3] The 2014 National Review of Asthma Deaths (NRAD) looked at detailed data over a 12-month period, assessing 195 patients who died from asthma and highlighted the avoidable factors in patient deaths.

Although faults were found in secondary care, many of the problems related to poor management of patients in the community, both in terms of regular surveillance and of assessment and treatment at the onset of attacks.

How should patients be assessed?

In September 2016, the Scottish Intercollegiate Guidelines Network (SIGN) and the British Thoracic Society (BTS) published an updated version of the British guideline on asthma management.[4] Bearing in mind the frequency of acute attacks in the community, and the evidence of failings in managing these, it is timely to review this up to date advice on best practice in acute asthma care. This article will cover management of attacks of moderate severity or greater; all patients should possess an asthma action plan enabling them to self-manage milder attacks without intervention by a healthcare professional.

'Asthma deaths in the UK remain among the highest in Europe'

How should patients be followed up after an attack?

AWARENESS OF RISK

The majority of asthma deaths occur outside hospital and most patients who die from an asthma attack had chronic severe asthma. There are a minority who have a fatal attack on a background of mild to moderate asthma, although it is debatable whether these are genuinely severe episodes out of the blue rather than a case of underestimation of the true baseline severity. It is therefore important to be aware of patients who are particularly at risk, and this applies to all levels of staff beginning with receptionists; as the frontline in a GP »

surgery they should be made aware that an asthma attack is a medical emergency and requires urgent assessment by a GP or asthma nurse.

'Receptionists should be made aware that an asthma attack is a medical emergency and requires urgent assessment by a GP or asthma nurse'

An interesting UK study,[5] not yet replicated, showed benefit from setting up a formal risk register of patients considered to be most likely to experience severe problems from their asthma. These patients trigger an alert whenever they contact the practice, which among other things can be used to ensure that appointments are expedited.

This approach is worth exploring more widely, although there is an obvious danger that other patients could get less attention.

Features which indicate a high risk of severe attacks include:[5-7]

- Previous admission to intensive care, particularly if requiring mechanical ventilation
- Previous admission with asthma especially in the past year or repeated emergency department admissions
- History of worsening asthma in January or February
- Use of three or more classes of asthma medication
- Heavy use of beta-2 agonists
- Anxiety traits
- Marital stress

PERSONAL ASTHMA ACTION PLANS

More than 80% of patients in one case control study reported worsening symptoms in the previous 48 hours and had felt unwell at least seven days prior to hospital admission.[6] This suggests that there is a window of opportunity to assess and treat patients adequately before a near fatal or fatal attack develops.

The first step is appropriate action by the patient, and there is good evidence[8] that this is more likely if the patient possesses a personalised written action plan. This should include advice on self-administration of appropriate treatment and a clear escalation plan detailing when and how to access a healthcare professional for help. The NRAD report showed that only 23% of patients who died had an asthma action plan, see figure 1, opposite.

ASSESSMENT AND SEVERITY

Initial assessment by a healthcare professional should include a focused history and examination together with commencement of treatment.

The classic symptoms are breathlessness (how much can the patient say without stopping for breath?) and wheeze with attention to the timing and duration, especially noting whether symptoms disturb sleep. Key observations are those which have been shown to allow a grading of severity, specifically heart rate and respiratory rate (still regularly omitted, although less often than it used to be).

'Peak expiratory flow improves the recognition of severity when compared with examination alone'

Other signs, such as excessive use of accessory muscles of respiration or cyanosis indicate that an attack is severe or life-threatening, see table 1, left

Peak expiratory flow (PEF) is an extremely useful measurement and improves the recognition of severity when compared with examination alone.[9] PEF is expressed in terms of percentage of a patient's best peak flow measurement and is more accurate if this is known within the past two years.

It is also helpful to measure oxygen saturation to guide oxygen therapy and targets of treatment (although lack of pulse oximetry should not prevent oxygen being delivered).

Table 1

Classification of severity of asthma attack, adapted from the 2016 SIGN/BTS guideline[4]

Severity	Features
Moderate acute asthma	Increasing symptoms PEF > 50-75% best or predicted No acute features of severe asthma
Severe acute asthma	Any one of: ● PEF 33-50% best or predicted ● Respiratory rate ≥ 25/min ● Heart rate ≥ 110 bpm ● Inability to complete sentences in one breath
Life-threatening asthma	Any one of the following in a patient with severe asthma: **Clinical signs** Altered conscious level Exhaustion Arrhythmia Hypotension Cyanosis Silent chest Poor respiratory effort **Measurements** PEF < 33% SpO_2 < 92% PaO_2 < 8 kPa Normal $PaCO_2$ (4.6-6.0 kPa)
Near fatal asthma	Raised $PaCO_2$ and/or requiring mechanical ventilation with raised inflation pressures

SpO_2 = oxygen saturation; PaO_2 = partial pressure of oxygen; $PaCO_2$ = partial pressure of carbon dioxide

FIGURE 1
Asthma action plan, Asthma UK. The full template can be downloaded free from the Asthma UK website: www.asthma.org.uk

Every day asthma care:

My personal best peak flow is: ____

My **preventer** inhaler (insert name/colour): ____

I need to take my preventer inhaler every day even when I feel well

I take ____ puff(s) in the morning and ____ puff(s) at night.

My **reliever** inhaler (insert name/colour): ____

I take my reliever inhaler only if I need to

I take ____ puff(s) of my reliever inhaler if any of these things happen:

- I'm wheezing
- My chest feels tight
- I'm finding it hard to breathe
- I'm coughing.

Other medicines I take for my asthma every day:

With this daily routine I should expect/aim to have no symptoms. If I haven't had any symptoms or needed my reliever inhaler for at least 12 weeks, ask my GP or asthma nurse to review my medicines in case they can reduce the dose.

People with allergies need to be extra careful as attacks can be more severe.

When I feel worse:

- My symptoms are coming back (wheeze, tightness in my chest, feeling breathless, cough)
- I am waking up at night
- My symptoms are interfering with my usual day-to-day activities (eg at work, exercising)
- I am using my reliever inhaler ____ times a week or more
- My peak flow drops to below ____

This is what I can do straight away to get on top of my asthma:

1 **If I haven't been using my preventer inhaler, start using it regularly again or:**

Increase my preventer inhaler dose to ____ puffs ____ times a day until my symptoms have gone and my peak flow is back to normal

Take my reliever inhaler as needed (up to ____ puffs every four hours)

URGENT! If I don't improve within 24 hours make an emergency appointment to see my GP or asthma nurse.

2 **If I have been given prednisolone tablets (steroid tablets) to keep at home:**

Take ____ mg of prednisolone tablets (which is ____ x 5mg) **immediately** and again every morning for ____ days or until I am fully better.

URGENT! Contact my GP or asthma nurse today and let them know I have started taking steroids and make an appointment to be seen within 24 hours.

In an asthma attack:

- My reliever inhaler is not helping or I need it more than every ____ hours
- I find it difficult to walk or talk
- I find it difficult to breathe
- I'm wheezing a lot or I have a very tight chest or I'm coughing a lot
- My peak flow is below ____

THIS IS AN EMERGENCY TAKE ACTION NOW

1. Sit up straight — don't lie down. Try to keep calm
2. Take one puff of my reliever inhaler every 30 to 60 seconds up to a maximum of 10 puffs
3. A) If I feel worse at any point while I'm using my inhaler → CALL 999
   B) If I don't feel any better after 10 puffs → CALL 999
   C) If I feel better: make an urgent same-day appointment with my GP or asthma nurse to get advice

CALL 999 → Ambulance taking longer than 15 minutes? Repeat step 2

If I feel better, and have made my urgent same-day appointment:
- Check if I've been given rescue prednisolone tablets
- If I have these I should take them as prescribed by my doctor or asthma nurse

IMPORTANT! This asthma attack information is not designed for people on a SMART or MART medicine plan. If you're on a SMART or MART medicine plan, please speak to your GP or asthma nurse to get the correct asthma attack information.

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key points

SELECTED BY

Dr Peter Savill
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Asthma deaths in the UK remain among the highest in Europe. The 2014 National Review of Asthma Deaths looked at detailed data over a 12-month period assessing 195 patients who died from asthma and highlighted the avoidable factors in patient deaths. Although faults were found in secondary care, many of the problems related to poor management of patients in the community, both in terms of regular surveillance and assessment and treatment at the onset of attacks.

Features which indicate a high risk of severe attacks include: previous admission to intensive care, particularly if requiring mechanical ventilation; previous admission with asthma especially in the past year or repeated emergency admissions; history of worsening asthma in January or February; use of three or more classes of asthma medication; heavy use of beta-2 agonists; anxiety traits; and marital stress.

More than 80% of patients in one case control study reported worsening symptoms in the previous 48 hours and had felt unwell at least seven days prior to hospital admission. This suggests that there is a window of opportunity to assess and treat patients adequately before a near fatal or fatal attack develops.

Peak expiratory flow improves the recognition of severity when compared with examination alone. Oxygen should be used to maintain oxygen saturation of 94-98% and it is recommended that GP surgeries have oxygen and an oximeter available. For anything other than life-threatening asthma, a standard metered dose inhaler administered with repeated actuations via a large volume spacer is as effective as a nebuliser. If a nebuliser is used it should ideally be driven with oxygen but nebulisers should not be withheld if oxygen is not available.

Oral steroids are required for all patients experiencing attacks of moderate severity or worse as they improve symptoms and reduce mortality, hospital admissions and the need for beta-2 agonists. The earlier steroids are administered the better the outcome. Admission is critical for patients with features of life-threatening asthma. If infection is present in asthma attacks it is usually caused by a virus and antibiotics are not appropriate. Good antibiotic stewardship is vital and antibiotics should be reserved for the minority of cases with a likely bacterial cause.

FIGURE 2
Metered dose inhaler (MDI) with large volume chamber. For anything other than life-threatening asthma a standard MDI administered with repeated actuations via a large volume spacer is as effective as a nebuliser



TREATMENT

Treatment should be implemented alongside the initial assessment of the patient. Oxygen should be used to maintain oxygen saturation of 94-98% and it is recommended that GP surgeries have oxygen and an oximeter available.

> ‘The earlier steroids are given the better the outcome’

Short-acting beta-2 agonists are quickly effective and easily administered. For anything other than life-threatening asthma a standard metered dose inhaler (MDI) administered with repeated actuations via a large volume spacer, is as effective as a nebuliser, see figure 2, above.[10] It is particularly useful to be aware of this in primary care when staff on duty may be less practised in setting up a nebuliser. The latest SIGN/BTS guideline recommends giving four separate puffs of beta-2 agonist initially, followed by two further puffs at two-minute intervals depending on response, up to a maximum of ten puffs. If a nebuliser is used it should ideally be driven by oxygen, but do not withhold nebulisers if oxygen is not available.

Oral steroids are required for all patients experiencing attacks of moderate severity or worse as they improve symptoms and reduce mortality, hospital admissions and the need for beta-2 agonists. The earlier steroids are administered the better the outcome.[11] Prednisolone 40-50 mg daily should be given for at least five days or until the patient has recovered.

REFERRAL TO HOSPITAL

Admission is critical for patients with features of life-threatening asthma. Patients with a severe asthma attack who have persisting symptoms despite treatment should also be admitted. Judgement should be applied for patients with moderate asthma attacks but with recent hospital admission, previous severe attacks or concern regarding social circumstances. These patients may still require admission to hospital. Patients being reviewed in the afternoon or evening or those with recent worsening of nocturnal symptoms may also require admission as these patients can often deteriorate again following initial assessment.

OTHER CONSIDERATIONS

The course of asthma in pregnancy is very variable but some patients experience deterioration in symptoms and have more frequent asthma attacks. A review of pregnant women with asthma attacks showed that they are often undertreated particularly with regard to steroid therapy, and

this resulted in poorer outcomes.[12] It is recommended that pregnant patients receive the same treatment for acute asthma as their counterparts who are not pregnant.

If infection is present in asthma attacks it is usually caused by a virus, and antibiotics are not appropriate. Good antibiotic stewardship is vital and antibiotics should be reserved for the minority of cases with a likely bacterial cause. Unfortunately, this advice is widely ignored. The recent AZALEA trial did not find any benefit in the use of macrolide treatment with azithromycin in asthma attacks, but a standout feature of this study was the extreme difficulty of recruiting patients because so many had already been given unnecessary antibiotic treatment.[13]

FOLLOW-UP

SIGN/BTS recommend that on discharge from hospital patients should be seen within two days by their GP or asthma nurse and that they should be seen in a specialist clinic in one month. This advice is sensible but tricky to adhere to. It will certainly never happen unless the hospital sends discharge information out promptly and GP surgeries are organised to react appropriately when they receive this. Follow-up provides a key time to check adherence to treatment, inhaler technique and to construct or amend personal asthma action plans.

'Those who have had a near fatal attack should be under specialist follow-up indefinitely'

Those patients who have had a severe attack should be followed up by an asthma specialist for at least a year afterwards, and those with a near fatal attack should be under specialist follow-up indefinitely.

It is advisable that patients who are admitted to hospital with a mild to moderate asthma attack should be followed up in primary care every six months and all other patients seen on an annual basis.

CONCLUSIONS

Asthma attacks remain a common presentation in both primary and secondary care. All patients should recover and most do, but the NRAD report is an important warning against complacency in managing this medical emergency. The updated SIGN/BTS guideline is a valuable reminder of current best practice for acute asthma management.

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Useful information

Asthma UK
www.asthma.org.uk

The British guideline on asthma management. SIGN 153
Copies of the full guideline and quick reference guide can be downloaded from: www.sign.ac.uk

We welcome your feedback

If you wish to comment on this article or have a question for the authors, write to:
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The Practitioner®

Assessment and management of active and latent TB

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Assessment and management of active and latent TB

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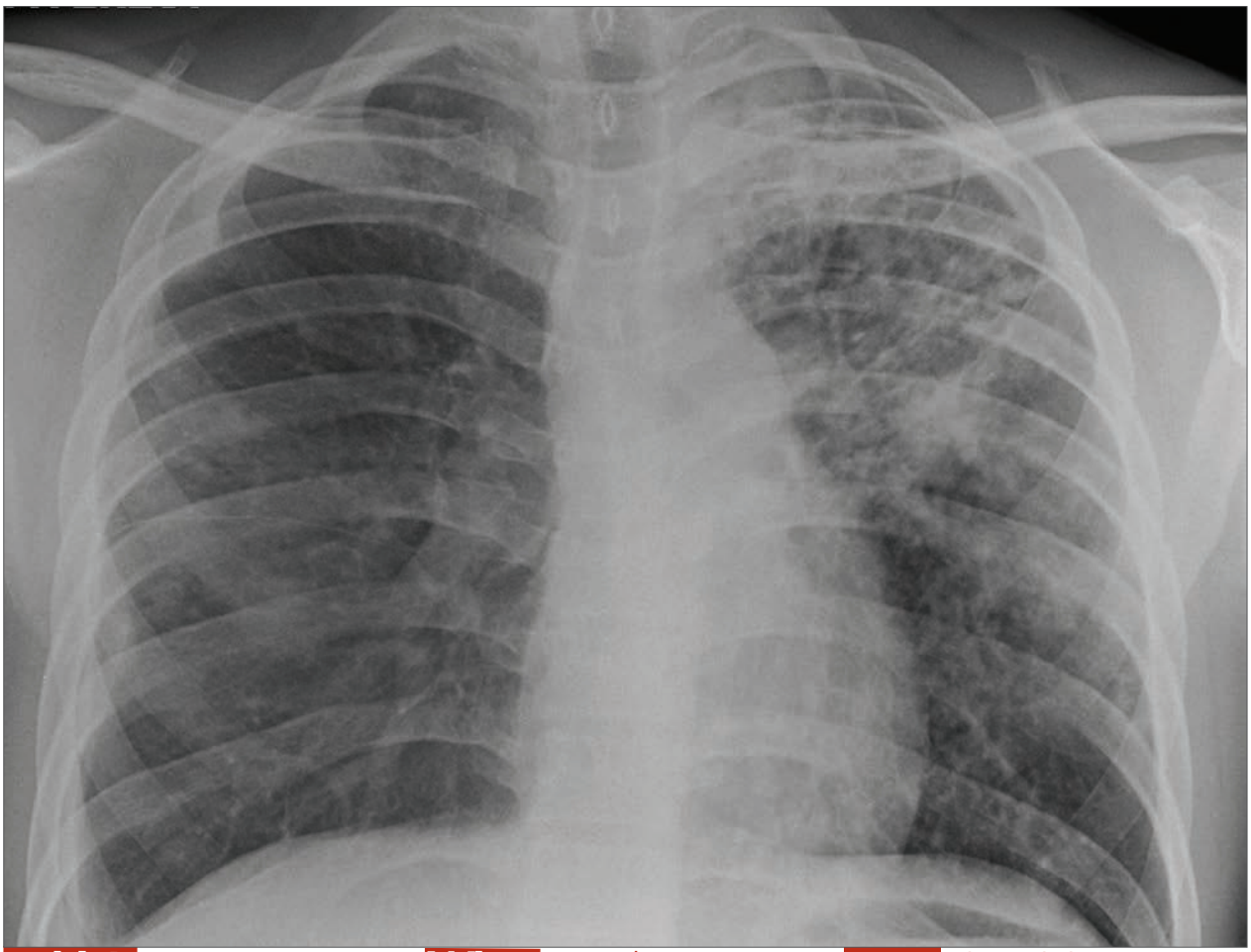

FIGURE 1
Chest x-ray of a patient with active pulmonary TB showing characteristic upper lobe consolidation with cavitation

Which groups are at increased risk of TB?

TUBERCULOSIS (TB) IS ONE OF THE LEADING GLOBAL CAUSES OF MORTALITY.[1] IT IS ESTIMATED THAT MORE than 25% of the world population has been infected, however only 10% of infected individuals will ever develop active disease.[2]

In the majority of exposed individuals, the immune system either eradicates the infection in its early stages or achieves a degree of containment, resulting in the bacterium entering a dormant state known as latent TB infection (LTBI). Active infection resulting in clinically significant disease occurs through progression of primary infection or through later reactivation of LTBI; this is most likely to occur in the first few years following infection, although late reactivation can occur several decades later, particularly in individuals who become immunosuppressed through disease or therapy.

There were an estimated 10.4 million new TB cases globally in 2015. Worldwide incidence and mortality have steadily fallen since 2003.[3] Although the UK is a low incidence country with a robust healthcare infrastructure, TB notifications in England and Wales rose in the first decade of the 21st century, reaching a peak of 8,371 in 2011 before falling to 5,859 in 2015.[4,5] The bulk of cases are among migrants: 73% of those diagnosed with active TB in 2015 were born outside the UK.

UK incidence remains significantly higher than similar developed countries, prompting a reorganisation of national TB control as set out in Public Health England's Collaborative Tuberculosis Strategy for England 2015.[6] NICE published an updated guideline on TB earlier this year.[7] One aim of the 2016 »

What are the management strategies?

How should contacts be screened?

guideline was to provide a comprehensive resource for TB services incorporating all the areas previously covered in NICE clinical and public health guidelines.

TB is spread through inhalation of respiratory droplets from patients with active pulmonary or laryngeal TB; infection can only be transmitted if patients are producing sputum.

It is important to consider the risk of both acquisition of TB and also of progression to active infection. Risk of acquisition is increased in people who have come to the UK from high incidence countries or who are born in the UK but come from high-risk ethnic minority groups. Other risk groups in the UK include those who are homeless, in prison or who misuse drugs or alcohol. Once infected, people who are immunosuppressed are at greater risk of progression to active disease, see table 1, below. One group at particularly high risk are infants below the age of 12 months who can develop rapidly progressive and potentially fatal infection. For this reason, it is important for TB teams to be aware of infants who may have been exposed to an infectious case and to refer the child to paediatric services as a matter of urgency.

Table 1

Risk factors for progression to active TB

- HIV infection
- Excessive alcohol intake
- Injecting drug use
- Solid organ transplantation
- Haematological malignancy
- Chemotherapy
- Jejunoileal bypass or gastrectomy
- Diabetes mellitus
- Chronic glucocorticoid therapy
- Treatment with anti-TNF-alpha or other biologic agents
- Chronic kidney disease or haemodialysis
- Silicosis
- Age under five years

ACTIVE TB

Assessment of active disease

A clear distinction should be drawn between the investigation of suspected active TB and the detection of LTBI, as the diagnostic and therapeutic pathways differ significantly.

The presenting symptoms of active TB are common in primary care and as such a high degree of suspicion is necessary to make the diagnosis. Cough is the main symptom in pulmonary disease but is not always accompanied by sputum production. Malaise, weight loss, fever and night sweats are common to both pulmonary and extrapulmonary disease. The presence of such symptoms, particularly in a patient with risk factors for TB, should prompt further investigation.

For suspected pulmonary disease the initial clinical assessment has not changed in decades, with chest radiography and the collection of three deep respiratory samples for smear microscopy and culture remaining the standard of care, see figure 1, p21. If the patient is suspected of having active TB but is unable to produce a sputum sample, GPs should refer the patient to their local TB team for further assessment, which may include an induced sputum procedure or bronchoscopy.

Recent laboratory advances have improved the sensitivity and speed of TB diagnosis, for example the use of fluorescence microscopy, rather than traditional Ziehl-Neelsen staining, for sputum smear examination.[8]

'NAAT assays are recommended only in cases where rapid confirmation of TB and/or rifampicin sensitivity is important'

Additionally, molecular diagnostic tests known as nucleic acid amplification tests (NAATs) can be performed directly on sputum, produce rapid results, and have a significantly higher sensitivity than smear microscopy. Some NAATs are able to detect the presence of genes signifying rifampicin resistance, a valuable tool in the assessment of potentially multidrug-resistant disease.[9] However, in view of their cost NAAT assays are recommended only in situations where rapid confirmation of TB and/or rifampicin sensitivity is important, for example where there may be a need for a large contact tracing exercise or where multidrug resistance is suspected.

Table 2

Changes in NICE guidance on diagnosis and treatment of latent TB infection (LTBI) in household contacts and new entrants from high incidence countries (incidence > 40 per 100,000 per year)

Recommendation	NICE 2011 guidance	NICE 2016 guidance
Index case site of infection (household contacts only)	All TB sites	Pulmonary and laryngeal TB only
Age cut-off for screening	≤ 35 years	≤ 65 years
Preferred testing strategy	TST then confirmation of positive result with IGRA	TST alone in most cases
Definition of positive Mantoux test (mm induration)	≥ 6 mm if no BCG ≥ 15 mm if prior BCG	≥ 5 mm regardless of prior BCG
Age cut-off for treatment of LTBI	≤ 35 years	≤ 65 years (≤ 35 years if concern about hepatotoxicity)

TST= tuberculin skin test IGRA= interferon gamma release assay

key points

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More than 25% of the world population has been infected with tuberculosis (TB), however only 10% of those infected will ever develop active disease. Clinically significant disease occurs through progression of primary infection or through later reactivation of latent TB infection (LTBI); this is most likely to occur in the first few years following infection, although late reactivation can occur several decades later, particularly in individuals who become immunosuppressed through disease or therapy.

TB infection can only be transmitted if patients are producing sputum. Risk of acquisition is increased in people who have come to the UK from high incidence countries or who are born in the UK but come from high-risk ethnic minority groups. In 2015, 73% of those diagnosed with active TB were born outside the UK. Other risk groups in the UK include those who are homeless, in prison or who misuse drugs or alcohol. Once infected people who are immunosuppressed are at greater risk of progression to active disease. Infants below the age of 12 months can develop rapidly progressive and potentially fatal infection. It is important for TB teams to be aware of infants who may have been exposed to an infectious case and to refer the child to paediatric services as a matter of urgency.

A clear distinction should be drawn between the investigation of suspected active TB and the detection of LTBI, as the diagnostic and therapeutic pathways differ significantly. Cough is the main symptom in pulmonary disease but is not always accompanied by production of sputum. Malaise, weight loss, fever and night sweats are common to both pulmonary and extrapulmonary disease.

Initial clinical assessment with chest radiography and the collection of three deep respiratory samples for smear microscopy and culture remain the standard of care. The management of active TB has not changed significantly over many years. The most significant changes in the 2016 NICE guidance relate to screening for LTBI in individuals who are contacts of a patient with active TB, or who are recent entrants to the UK from a high incidence country. NICE recommends that only contacts of patients with active pulmonary or laryngeal TB be screened in order to focus resources on contacts of the most highly infectious cases.

Standard treatment for LTBI is with three months of rifampicin and isoniazid, or six months of isoniazid alone. The former regimen is associated with reduced hepatotoxicity and improved compliance. The isoniazid only regimen is of value in patients where there is risk of drug interactions with rifampicin: important interactions occur with oral or implanted contraceptives, warfarin and methadone, among many other drugs. The upper age limit for offering to test and treat individuals for LTBI is now 65.

Management of active disease

The management of active TB has not changed significantly over many years.[10] Attempts to shorten treatment courses using novel agents such as fluoroquinolones have not yet been successful.[11]

The standard regimen has two stages: a two-month initiation phase involving a four-drug combination of rifampicin, isoniazid, pyrazinamide and ethambutol, followed by a continuation phase of rifampicin and isoniazid lasting at least four months. In the initiation stage ethambutol is included in case of drug resistance and can be discontinued early once there is confirmation of fully sensitive disease. Fixed dose combination tablets are available for both the initiation and continuation phases, and their use is recommended by NICE to aid compliance and reduce pill burden.

Although the standard regimen is generally well tolerated it can be associated with serious side effects. Isoniazid, rifampicin and pyrazinamide have the potential to induce hepatotoxicity, and patients should be warned of this and advised to report symptoms such as nausea, vomiting or jaundice. Liver enzymes should be measured before starting treatment, however serial monitoring on therapy is only indicated if there are abnormalities at baseline.

Ethambutol can cause optic neuritis so visual acuity should be measured before starting therapy and the patient should contact the TB team or their GP if they become aware of any changes in their vision. Symptoms such as rashes and nausea are more common but usually respond to symptomatic measures.

LATENT TB INFECTION (LTBI)

Assessment of latent disease

The most significant changes in the 2016 NICE guidance relate to recommendations on screening for LTBI in individuals who are contacts of a patient with active TB, or who are recent entrants to the UK from a high incidence country, see table 2, opposite.

The tuberculin skin test (TST) in the form of the Heaf (now discontinued) or Mantoux test has been used for decades for the detection of LTBI and was the only test available until the introduction of the interferon gamma release assays (IGRAs) in the mid 2000s.

IGRAs are blood based in vitro tests that measure T cell responses to specific antigens of *M. tuberculosis*. As with the TST, a positive reaction indicates immunological memory of mycobacterial antigens and acts as a surrogate marker for LTBI. IGRAs are more specific than Mantoux and are not affected by prior BCG vaccination or exposure to most non-tuberculous mycobacteria.[12] Additionally, they are not subject to the logistical constraints of TST, with results potentially available within 24 hours and no requirement for a follow-up appointment for results to be interpreted.

The drawback of IGRAs is their high cost relative to Mantoux. As such, NICE had previously recommended a strategy of an initial Mantoux screening test followed by a confirmatory IGRA in most circumstances. However, the recent guidance has returned to predominant use of the TST on grounds of cost effectiveness. In addition, the evidence considered by the NICE guideline development group supported a change in the cut-off between a positive and negative Mantoux test, such that a positive result is now defined as an induration of 5 mm or greater irrespective of prior BCG vaccination.

'NICE recommends that only contacts of patients with active pulmonary or laryngeal TB should be screened'

Previously it was recommended that household contacts of any patient with active TB should be screened for latent infection. The recent guidance recommends that only contacts of patients with active pulmonary or laryngeal TB should be screened in order to focus resources on contacts of the most highly infectious cases.

Although this approach will in theory result in fewer contacts being screened with a higher proportion of contacts being found to have LTBI, one potential disadvantage is that we lose the opportunity to identify people with LTBI who may not have acquired infection from the non-infectious index case in question, but from a third party acting as a common source. Conversely, the reduction in the Mantoux threshold, and increase in age cut-off for screening, may increase screening workload. It will be important to assess the impact of these changes on future TB epidemiology in the UK.

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Management of latent disease

Standard treatment for LTBI is with three months of rifampicin and isoniazid, or six months of isoniazid alone. The former regimen is associated with reduced hepatotoxicity and improved compliance. The isoniazid only regimen is of value in patients where there is risk of drug interactions with rifampicin: important interactions occur with oral or implanted contraceptives, warfarin and methadone, among many other drugs.

'The upper age limit for offering to test and treat individuals for LTBI is now 65 years'

One further significant change in LTBI management relates to the age cut-off for treatment of LTBI. In previous guidance this cut-off was 35 years, based on increasing risk of hepatotoxicity and reducing efficacy with increasing age. Notably, the upper age limit for offering to test and treat individuals for LTBI is now 65 years, with the caveat that individuals aged 35 to 65 years should only be treated if there is no concern about hepatotoxicity.

CONCLUSIONS

The expansion in the use of immunosuppressive medications exposes more individuals to the risk of reactivation of LTBI. As such it is important that healthcare professionals in frontline services are aware of the local epidemiology and common presenting symptoms of TB.

Clear referral pathways from GP and emergency departments are required to ensure possible cases of active TB are assessed rapidly and treatment started as soon as possible to minimise clinical severity and public health impact.

Despite developments in novel diagnostics it is important to bear in mind that sputum samples and chest radiography remain the mainstay of diagnosis for suspected active pulmonary disease.

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Improving the identification and monitoring of cirrhosis

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Improving the identification and monitoring of cirrhosis

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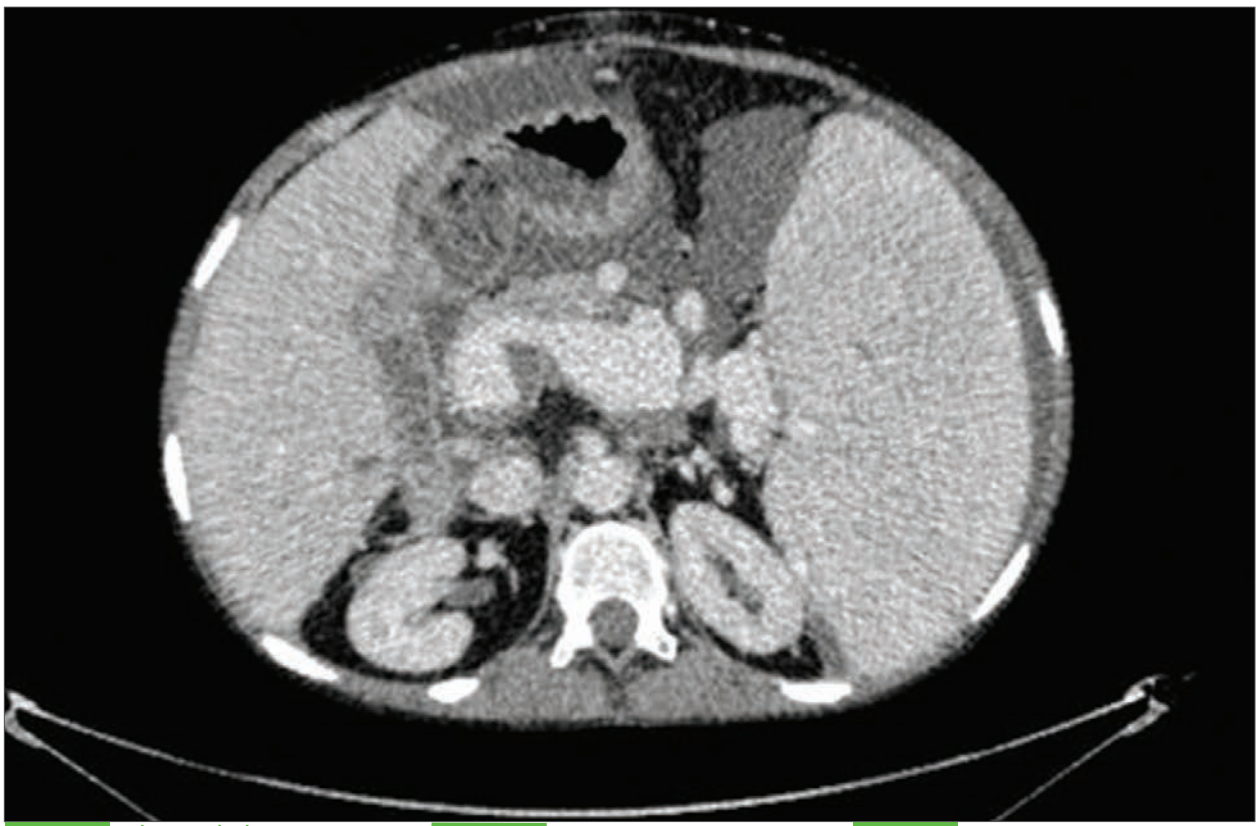

CT scan showing decompensated liver disease with portal hypertension and ascites

How should cirrhosis be diagnosed?

BOTH THE MORBIDITY AND MORTALITY ASSOCIATED WITH CIRRHOSIS ARE ON THE INCREASE.

In a recent UK cohort study the incidence of cirrhosis increased by 50.6% between 1998 and 2009. By 2009 the authors estimated there to be approximately 17,000 new cases per year with a disease burden greater than the fifth leading cause of cancer. Although all causes of liver disease increased during this period, this trend was primarily attributed to rising levels of alcohol misuse and obesity.[1]

By 2012, cirrhotic patients admitted to hospital were six times more likely to die compared with patients admitted for any other reason. Nearly half of liver disease admissions were for alcohol-related liver disease and were associated with a 12.3% mortality.[2]

What are the potential complications?

Cirrhosis is more common in urban and socially deprived areas.[3] The NHS Atlas of Variation in Healthcare for People with Liver Disease found that the highest rates of hospital admission for end-stage liver disease due to chronic hepatitis C virus were in central London and the North West of England. Admissions for alcohol-related liver disease were also most common in the North West.[4]

Consequently, the Chief Medical Officer has advised that liver disease should be one of the key issues for health in England and earlier this year NICE published an evidence-based guideline on assessment and management of cirrhosis (NG50).[2]

How should patients be monitored?

DIAGNOSIS

Cirrhosis generally results from chronic liver damage over many years. It is characterised by fibrosis and nodularity of the liver parenchyma, which interferes with the synthetic, metabolic and excretory functions of the liver.

Common causes include: alcohol misuse, hepatitis B (± delta) and C, and non-alcoholic fatty liver disease (NAFLD). Less common causes include: primary or secondary biliary cirrhosis; autoimmune hepatitis; primary sclerosing cholangitis: haemochromatosis; Wilson's disease; alpha 1-antitrypsin deficiency; cystic fibrosis; certain drugs e.g. methotrexate, isoniazid, amiodarone; right-sided heart failure, tricuspid regurgitation, pericarditis and veno-occlusive disease e.g. Budd-Chiari syndrome. »

INVESTIGATIONS

Abnormal liver function tests (LFTs) are a common finding in primary care but correlate poorly with the presence of cirrhosis. Alanine amino transaminase (ALT) is only elevated in 1-4% of asymptomatic patients with cirrhosis,[5] and therefore routine blood tests cannot rule out cirrhosis.[2]

Ultrasound

Abdominal ultrasonography is a good first-line investigation in patients with suspected liver disease. It has a high sensitivity (91%) and specificity (94%) for the detection of the gross features of cirrhosis,[6] can detect > 90% of gallstones,[7] and differentiate between solid and cystic lesions within the liver parenchyma.

Biopsy

The gold standard test for the diagnosis of cirrhosis remains a liver biopsy. However, it is associated with adverse events such as sub-capsular haemorrhage in up to 1% of cases. Liver biopsy samples < 1/50,000 of the liver parenchyma,[8] so sampling errors are possible. It is also relatively expensive, invasive and disliked by patients, making serial measurements challenging.

Noninvasive serum markers have therefore been developed to improve identification of patients with advanced fibrosis or cirrhosis who require further assessment or referral to secondary care.

Enhanced liver fibrosis panel

The most commonly used serum biomarker is the enhanced liver fibrosis panel, see box 1, below.[9] When interpreting these tests it is recognised that extra-hepatic inflammation may result in a false-positive result and alternatively significant fibrogenesis may go undetected if there is minimal hepatic inflammation. Overall these markers are becoming increasingly reliable at detecting fibrosis although they correlate poorly with the stage of fibrosis and may be less specific if there is concurrent hepatitis.[10]

'Compared with a standard biopsy, transient elastography will assess a much larger proportion of the liver and therefore sampling errors should be reduced'

Transient elastography

This is a specialist radiological test, which quantifies liver compliance or stiffness using a probe that produces a shear ultrasound wave that passes through the liver.

The velocity of the wave moving through liver tissue acts as a proxy for fibrotic change. A measurement > 7 kPa is indicative of significant fibrosis (METAVIR grade F2-F4) and > 11-14 kPa is consistent with cirrhosis.

Compared with a standard biopsy, transient elastography will assess a much larger proportion of the liver and therefore sampling errors should be reduced. The measurements are painless and quick and as a consequence serial measurements for monitoring treatment response e.g. in chronic viral hepatitis, are feasible and acceptable to patients. Although reproducibility is generally very good, intraobserver variation still exists and its sensitivity is reduced in obese patients, those with significant ascites or active hepatitis — in these patients liver biopsy remains the optimal method of detecting cirrhosis.

Acoustic radiation force impulse (ARFI) imaging

ARFI is similar to transient elastography as it measures the propagation speed of an acoustic wave produced by the probe, that is increased in fibrotic tissue. Unlike transient elastography this technique uses a standard ultrasound machine but with an additional probe.[11] A meta-analysis comparing ARFI and transient elastography found that there was no significant difference in reliability between the techniques.[12]

RISK FACTORS

Nearly 50% of patients with cirrhosis are asymptomatic.[13] As a result the condition may only be discovered incidentally as a result of abnormalities in LFTs or imaging of the abdomen performed for other reasons, or by the targeted screening of high-risk groups. In the UK the most common risk factors for developing cirrhosis, and therefore the patients who should be targeted for screening include those with: hepatitis B or C infection, alcohol misuse, obesity (BMI ≥ 30 kg/m^2) or type 2 diabetes. NICE guidelines recommend that this is done with transient elastography in patients with hepatitis C, men who drink > 50 units or women who drink > 35 units of alcohol per week and have done so for several months and in patients who have been diagnosed with alcohol-related liver disease.[2]

In patients who are at risk of NAFLD i.e. those who are obese, have diabetes or metabolic syndrome, there is limited evidence to support routine screening, but they are recognised to be at a higher risk of developing cirrhosis. Therefore initially screening should be performed with an enhanced liver fibrosis panel, see box 1, left, to stratify those patients who potentially have advanced liver fibrosis. In patients with an enhanced liver fibrosis score > 10.51 further investigation by transient elastography or ARFI is recommended.[2,14]

If initial screening tests for cirrhosis are negative in high-risk groups (alcohol-related liver disease, chronic hepatitis C which has not shown a

Box 1

Enhanced liver fibrosis (ELF) panel [28]

ELF score calculation

ELF = 2.494 + 0.846 ln([HA]) + 0.735 ln([PIIINP]) + 0.391 ln([TIMP-1])

Cut-off values

< 7.7 = No fibrosis to moderate fibrosis
≥ 7.7 to < 9.8 = Moderate fibrosis
≥ 9.8 = Severe fibrosis

*NB: In patients with NAFLD NICE guidelines suggest using a cutoff of 10.51 for further investigation of cirrhosis[2]

HA = hyaluronic acid PIIINP = procollagen III amino terminal peptide
TIMP-1 = tissue inhibitor of metalloproteinase 1

Table1

Risk factors for the development of hepatocellular carcinoma (HCC)

Risk factor	
Age	> 60[29]
Gender	Male[29]
Hepatitis B and C	Worldwide approximately half of cases of HCC are attributed to hepatitis B and a third to hepatitis C[29] Co-infection with HIV further increases risk[30]
Cirrhosis	One third of cirrhotic patients will develop HCC during their lifetime[31]
Alcohol	Alcohol misuse is a risk factor for HCC independent of cirrhosis[29,32]
Metabolic syndrome	Diabetes, obesity and fatty liver[32,33]
Smoking[32,34]	
Haemochromatosis	Up to half of patients with iron overload will develop HCC in their lifetime, although most will be cirrhotic at the time of HCC diagnosis[35]
Toxins	Aflatoxin B,[36] anabolic steroids [37]
Genetic predisposition	BRCA 1/ BRCA 2/ EGF gene [38,39]

Table 2a

Calculating the Child-Pugh score

Score	1	2	3
Bilirubin (μmol/L)	< 34	34-51	> 51
Prothrombin time in seconds (INR)	< 4 (< 1.7)	4-6 (1.7-2.3)	> 6 (> 2.3)
Albumin (g/L)	> 35	28-35	< 28
Ascites	Absent	Mild-moderate (diuretic responsive)	Severe (diuretic refractory)
Encephalopathy	Absent	Grade 1-2 (or precipitant induced)	Grade 3-4 (or chronic)

Table 2b

Three-year survival based on Child-Pugh score

The Child-Pugh score ranks the severity of cirrhosis into three classes

Disease severity	Child-Pugh score	Three-year survival[40]
Class A	≤ 6	73%
Class B	7 to 9	59%
Class C	≥ 10	46%

sustained virological response to antiviral therapy and those with NAFLD and an elevated enhanced liver fibrosis panel), repeat testing should be performed with transient elastography every two years.

ASSESSMENT FOR COMPLICATIONS

Patients with confirmed cirrhosis should be assessed for potential complications (ascites, encephalopathy, oesophageal varices or hepatocellular carcinoma). Decompensation or complications of cirrhosis should be detectable by all clinicians. Screening and surveillance for hepatocellular carcinoma and varices is the responsibility of secondary care. GPs should ensure patients are getting the appropriate investigations when they see patients with known cirrhosis for any reason.

In patients with compensated disease the risk of developing complications can be predicted using clinical scoring systems such as the Model for End-Stage Liver Disease (MELD). In patients with cirrhosis, MELD scores should be repeated six monthly; those with a MELD score > 12 are at an increased risk of developing complications. Once the MELD score is > 30, patients have a mortality of > 50% at three months.[15] All patients with cirrhosis and especially those who have decompensated disease and/or an elevated MELD score (> 12) should be under the care of a specialist hepatology centre.[2]

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide, with an estimated 750,000 new cases per year. Incidence varies globally with the highest prevalence in China, South East Asia and sub-Saharan Africa where carriage of chronic viral hepatitis is high. In the UK, there has also been an increase in the incidence of primary liver cancers in the past decade. The trend has been more profound in men than women.[16] Ninety per cent of cases are associated with one or more risk factors, see table 1, above left.

HCC is often asymptomatic until late in the disease. The European Association for the Study of the Liver (EASL) therefore recommends HCC surveillance in the following high-risk groups to enable earlier detection of these lesions:[17]

- Cirrhotic patients, Child-Pugh stage A and B (see table 2a and 2b, left) and Child-Pugh stage C awaiting liver transplantation
- Non-cirrhotic hepatitis B carriers with active hepatitis or family history of HCC

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key points

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Morbidity and mortality associated with cirrhosis are on the increase. In a recent UK cohort study the incidence of cirrhosis increased by 50.6% between 1998 and 2009. By 2009 the authors estimated there to be around 17,000 new cases per year with a disease burden greater than the fifth leading cause of cancer. Although all causes of liver disease increased during this period, this trend was primarily attributed to rising levels of alcohol misuse and obesity.

Cirrhosis generally results from chronic liver damage over many years. It is characterised by fibrosis and nodularity of the parenchyma, which interferes with the synthetic, metabolic and excretory functions of the liver. Common causes include: alcohol misuse, hepatitis B (± delta) and hepatitis C and non-alcoholic fatty liver disease.

Abnormal liver function tests are a common finding in primary care but correlate poorly with the presence of cirrhosis. Alanine amino transaminase is only elevated in 1-4% of asymptomatic patients with cirrhosis, and so routine blood tests cannot rule out cirrhosis. Abdominal ultrasonography is a good first-line investigation in patients with suspected liver disease. The most commonly used serum biomarker is the enhanced liver fibrosis panel. Transient elastography is a specialist radiological test, which quantifies liver compliance or stiffness. Compared with a standard biopsy, it will assess a much larger proportion of the liver and therefore sampling errors should be reduced. The measurements are painless and quick and serial measurements for monitoring treatment response e.g. in chronic viral hepatitis, are feasible and acceptable to patients.

In the UK, the most common risk factors for developing cirrhosis, and therefore the patients who should be targeted for screening, include those with: hepatitis B or C infection, alcohol misuse, obesity (BMI $\geq$ 30 kg/m^2) or type 2 diabetes. NICE recommends that this is done with transient elastography in patients with hepatitis C, men who drink > 50 units or women who drink > 35 units of alcohol per week, and have done so for several months, and in people who have been diagnosed with alcohol-related liver disease.

Patients with confirmed cirrhosis should be assessed for potential complications (ascites, encephalopathy, oesophageal varices or hepatocellular carcinoma). Reviewing cirrhotic patients regularly in primary care provides a valuable opportunity to ensure hepatocellular carcinoma and variceal surveillance is being undertaken and enables further opportunities to provide lifestyle advice such as losing weight or reducing alcohol intake. One in four patients with oesophageal varices will develop a variceal haemorrhage within two years. Acute variceal haemorrhage is associated with a mortality of up to 50%. Patients with a new diagnosis of cirrhosis should be offered a gastroscopy for detection of varices.

and non-cirrhotic patients with chronic hepatitis C and advanced liver fibrosis

NICE guidelines also suggest surveillance in all patients with established cirrhosis who do not have hepatitis B infection and are not receiving end of life care. NICE, the British Society of Gastroenterology (BSG) and EASL all recommend that surveillance should be performed by abdominal ultrasound every six months.[18] NICE and the BSG also suggest ultrasound can be combined with serum alpha fetoprotein (AFP).[19] In up to 90% of small HCCs the AFP will be normal so it cannot be used alone for surveillance.[19,20]

'Patients with a new diagnosis of cirrhosis should be offered a gastroscopy for detection of varices'

Despite multiple surveillance guidelines HCC surveillance continues to be performed poorly even in large centres.[21,22] Therefore reviewing cirrhotic patients regularly in primary care provides a valuable opportunity to ensure HCC and variceal surveillance is being undertaken and enables further opportunities to provide lifestyle advice such as losing weight or reducing alcohol intake.

Oesophageal varices

Oesophageal varices are present in approximately one-third of patients with compensated cirrhosis and two-thirds of those with decompensated disease at diagnosis.[23] In those with established cirrhosis 5-7% will develop oesophageal varices annually. Once established, small oesophageal varices progress to large varices at a rate of approximately 8% per year.

Risk factors for variceal rupture include: size of varix, severity of liver disease, sepsis, HCC and an elevated portal pressure gradient. One in four patients with oesophageal varices will develop a variceal haemorrhage within two years.[24] Acute variceal haemorrhage is associated with a mortality of up to 50%.[25]

Patients with a new diagnosis of cirrhosis should be offered a gastroscopy for detection of varices. Surveillance endoscopy should be repeated three yearly if no varices are detected.[2] If moderate to large varices are seen, endoscopic variceal band ligation should be performed and in cases of variceal haemorrhage antibiotic prophylaxis should be commenced in addition to standard resuscitation and endoscopic management.

The management of small varices is controversial and has been omitted from the current NICE guidelines because of lack of evidence.

Ascites

A further complication of cirrhosis leading to portal hypertension and subsequent activation of the renin-angiotensin-aldosterone system is the development of ascites and fluid retention. Ascites is usually managed with diuretics in combination with a low-salt diet and fluid restriction. If ascites is unresponsive to this initial management or the patient develops complications such as hepatorenal syndrome, then transcatheter intrahepatic portosystemic shunt (TIPS) should be considered.

Encephalopathy, cardiac failure and severe liver disease are contraindications to TIPS and in these cases regular large volume paracentesis is an alternative. When the ascitic protein concentration is < 15 g/L prophylactic ciprofloxacin or norfloxacin is recommended until the ascites has resolved, to prevent spontaneous bacterial peritonitis.[2]

Hepatic encephalopathy

Hepatic encephalopathy is defined as a spectrum of neuropsychiatric abnormalities in patients with cirrhosis, after exclusion of other causes.

The condition is characterised by changes in personality, intellectual impairment and drowsiness. It can be subdivided into two main categories: overt and minimal.

Overt hepatic encephalopathy is evident clinically, whereas minimal hepatic encephalopathy requires neuropsychological testing for confirmation. Overt hepatic encephalopathy occurs in around 30-45% of cirrhosis patients in their lifetime, although it is suspected that up to 70% may experience a subclinical minimal encephalopathy state at some point.[26] Patients with cirrhosis have an annual risk of developing overt hepatic encephalopathy of approximately 20%.[27]

Common precipitants include non-compliance with hepatic encephalopathy therapy, increased protein ingestion, gastrointestinal bleeding, constipation, renal failure, electrolyte imbalance e.g. hyponatraemia, hypovolaemia, drugs (e.g. opiates, benzodiazepines, diuretics) and sepsis.[17]

CONCLUSIONS

Noninvasive markers to detect advanced fibrosis are increasingly available allowing better differentiation of those with advanced liver disease from the much larger population with abnormal liver enzymes or risk factors for liver disease. In light of these markers becoming more available in routine practice, the recent NICE guideline provides clinicians with a framework for identifying those at risk of cirrhosis and who should be further assessed by enhanced liver fibrosis panel and/or transient elastography and ultimately who warrants referral to secondary care hepatology services.

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