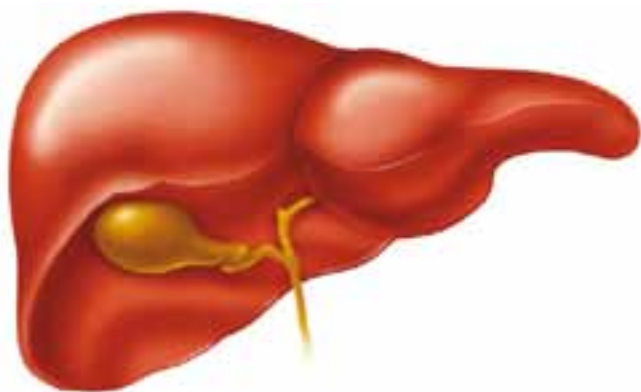




Liver special edition

SMMGP is becoming increasingly concerned about the rise in liver disease in the UK and we are pleased to bring you this special edition on the liver. People using drugs and alcohol are at particular risk of liver disease, and in this edition of Network we aim to provide the knowledge to better diagnose, refer and support the treatment of this growing problem.



Liver disease: a ticking time bomb

Liver disease in the UK is killing more people than diabetes and road deaths combined; it is the fifth biggest cause of death in England and Wales, after heart disease, cancer, stroke and respiratory disease¹. The rate of death in all these major causes of death is reducing in the UK except for one: liver disease. A total of 16,087 people died from liver disease in 2008, and if the rate continues at its current pace, deaths from liver disease are

predicted to double in the next 20 years. Despite this looming crisis it has to be remembered that the three main causes of liver disease – alcohol, obesity and blood borne infections, in particular hepatitis B and C – are all preventable and treatable.

“there can be a lack of confidence about liver disease in primary care, leading to a failure to both prevent and diagnose problems”

People dying from liver disease die young: the average age of death is 59 – and this average age is falling – as compared to over 70 for the other major killers². People with liver disease tend to be ill for 3-5 years before death. However for many the period of illness is longer and the social and economic cost is significant. A typical patient will have 5-10 hospital admissions before dying. Around 700 people will receive a liver transplant, and this number is rising. Some have calculated that the cost of liver disease could be as high as 1 billion by 2015. As with so many other conditions, health inequalities compound the problem, with socially excluded populations experiencing higher levels of liver disease.

And yet there can be a lack of confidence about liver disease in primary care, leading to a failure to both prevent and diagnose problems. One difficulty with diagnosis is that liver disease is often

1 Office for National Statistics: Health Service Quarterly, Winter 2008, No. 40 p59-60

2 A joint response on behalf of liver disease clinicians and patients by British Association for the Study of the Liver (BASL), British Liver Trust (BLT) and British Society of Gastroenterology (BSG) to the White Paper 'Equity and Excellence: Liberating the NHS'

...continued overleaf

In this issue

Jude Oben and colleagues run through the basics of non alcoholic fatty liver disease. **Page 3**

Carsten Grimm gives some hints and tips on how to diagnose alcohol related liver disease. **Page 4**

Helen's story of how her GP missed her symptoms of hepatitis C is an important reminder about diagnosis in Living with HCV and **Euan Lawson** goes on to give some useful tips on diagnosis. **Page 5**

Euan Lawson gives some practical suggestions about finding cases of hepatitis B and C on **page 6**, and discusses the ins and outs of hepatitis A and B immunisations. **Page 7**

Graham Foster and Morven Cunningham give us a glimpse into the future in their article What's new on the horizon for treatment of hepatitis C? **Page 8**

Brian Thompson gives some detail on factors that lead to progression of liver disease for those with hepatitis. **Page 10**

Martin Lombard, National Clinical Director for Liver Disease who is tasked with developing the liver strategy outlines some of the issues in a briefing paper. **Page 11**

Iain Brew takes us through the ways in which we can support people going through treatment for hepatitis C. **Page 12**

Dr Fixit **Mark Hallam** gives advice to a GP on how to support people who are in hepatitis treatment. **Page 13**

Steve Brinksman is Dr Fixit to a GP with a patient with hepatitis C who is overweight and drinking alcohol, and suggests that there is a lot primary care can do limit harm to the liver and to prepare people for treatment. **Page 14**

See all the latest courses and events. **Page 16**. We hope you enjoy this edition.

Editor



Don't forget to become a free member and receive regular clinical and policy updates - the newsletter can also be emailed to you – all for free www.smmgp.org.uk/membership

... continued from page 1

silent until it is very advanced. Once advanced, it is clearly best treated by the experts and so this can lead to a level of uncertainty about how to deal with the disease. This special edition of network will look at what primary care can do to improve prevention and diagnosis, and also to support people who are going through treatment. **Jude Oben** and colleagues run through the basics of non alcoholic fatty liver disease on **page 3**, and help is provided by **Carsten Grimm** when he gives some hints and tips on how to diagnose alcohol related liver disease on **page 4**. Helen's story of how her GP missed her symptoms of hepatitis C is an important reminder about diagnosis on **page 5**.

Although HCV detection rates are improving, the numbers going on to be treated remain low: of the 13,000 new cases of hepatitis C infection in the UK per year we are treating around 5,000³. **Euan Lawson** gives some practical suggestions about finding cases of hepatitis B and C on **page 6**.

Patients with hepatitis C will be familiar to many of our readers, but we may not always know what happens once the referral has gone to the specialist. **Brian Thompson** gives some detail on factors that lead to progression of liver disease for those with hepatitis **on page 10**. Treatment for hepatitis C has greatly improved in the

last decade and there continue to be advances. **Graham Foster and Morven Cunningham** give us a glimpse into the future in their article *What's new on the horizon for treatment of hepatitis C?* **on page 8** and **Iain Brew** take us through the ways in which we can support people going through treatment for hepatitis C in his article **on page 12**.

“Primary care is perfectly placed to prevent, diagnose and support the treatment of liver disease”

Primary care can play an important role in preventing the spread of hepatitis C and advising hepatitis C positive individuals on how to reduce harm to their liver if they do not wish to be treated: Dr Fixit **Mark Hallam** gives advice to a GP on how to do so **on page 13**. For those working with people using drugs and alcohol, liver disease is an important issue; up to 50% of injecting drug users are positive for hepatitis C, and it is important to prevent, diagnose and manage the problem. Add to this the fact that up to 25% of those in methadone treatment are problematic drinkers⁴, and the risks to the liver get worse. A recent study found that the cause of death for 1 in 5 patients in methadone treatment had liver disease as an underlying cause⁵. The final ingredient of this dangerous cocktail, the compounding effect of health inequalities, means that we must be especially aware of liver disease amongst those with drug problems. **On page 14, Steve Brinksman** is Dr Fixit to a GP with a patient with hepatitis C who is overweight and drinking alcohol, and suggests that there is a lot primary care can do limit harm to the liver and to prepare people for treatment.

The quiet killer has also been largely silent in policy. Despite the fact that we are failing to tackle the increasing harms and costs of liver disease, it has somehow failed to appear in National Service frameworks, or Quality Outcome Framework (QOF) indicators. Following increasing pressure from organisations including the British Liver Trust (BLT), the British Association for the Study of the Liver (BASL) and the British Society of Gastroenterology (BSG) the Department of Health are in the process of developing a National Strategy for Liver Disease which will begin to bridge some of the current gaps in policy. **Martin Lombard**, National Clinical Director for Liver Disease who is tasked with developing the strategy outlines some of the issues in a briefing paper on **page 11**.

Primary care is perfectly placed to prevent, diagnose and support the treatment of liver disease and it may soon play a role in commissioning services. And yet myths and a lack of confidence can hinder primary care's response. There can be a misconception that liver disease is all about alcohol use which can lead to a failure to diagnose. There can be a belief that there is nothing we can do about liver disease: and yet it is almost never too late to intervene. With the right support, primary care has the ability to play an essential role in reducing the burgeoning harm of liver disease to individuals, communities and society.

Kate Halliday SMMGP

3 The All Party Parliamentary Hepatology Group (2010) *In the dark. An audit of hospital hepatitis C services across England* London.

4 Gossop, M, Marsden, J, Stewart D (2001) National Treatment Outcome Research Study NTORs After Five Years National Addiction Centre

5 Gibson A, Randall D, Degenhardt A (2011) The increasing mortality burden of liver disease among opioid dependent people: cohort study. *Addiction* 2011. Postprint. doi:10.1111/j.1360-0443.2011.03575.x

Editorial

We feel it is important to have a special edition on the liver due to the growing problems with liver disease and are pleased to have the help of guest clinical editor **Euan Lawson**. We hope to guide you through the issues of liver disease and provide you with the knowledge to support the prevention, diagnosis, referral on and the management of liver treatment in primary care, where so much can be done.

It has been a busy time for SMMGP, with our conference on 13th October being a sell out – see www.smmgp.org.uk for presentations. One of the key messages I took from the day was the importance of clinicians and patients engaging with the new NHS Clinical Commissioning Groups and the Health and Wellbeing Boards, so watch out for more on this from SMMGP.

We have also developed materials for the RCGP Certificate in the Detection, Diagnosis and Management of Hepatitis B and C in Primary Care which was launched in September. A two hour e-module is freely available at <http://elearning.rcgp.org.uk> and can be done as a standalone or in preparation for the Part 1 Training Day (see page 16 for more details).

We are very excited to announce the 17th National RCGP Conference *Managing drug and alcohol problems in primary care* will take place in Cardiff on 11th May 2012. The title of the conference is **Going for gold: right treatment, right time, right place**. Save the date, and watch out for more details on our website.

Enjoy this issue!

Kate Halliday Editor



Jude Oben and colleagues run through the basics of non alcoholic fatty liver disease. Read this article to improve your diagnostic skills! **Ed**

Practical management of non alcoholic fatty liver disease in primary care

Introduction

Non alcoholic fatty liver disease (NAFLD) is the leading cause of liver dysfunction in developed countries. The predominant cause of NAFLD is obesity and its pathogenesis implicates insulin resistance and increased oxidant stress with consequent activation of fibrogenesis. Presently, NAFLD cannot be diagnosed with a single test. Given its association with obesity, the initial treatment is dietary modification and increased physical activity.

Definition

Non alcoholic fatty liver disease (NAFLD) is a spectrum of liver disease ranging from hepatosteatosis (fatty liver), to non-alcoholic steatohepatitis (NASH) (fat with inflammation), through to fibrosis and potentially cirrhosis and hepatocellular carcinoma without a history of immoderate alcohol use. NAFLD patients who become cirrhotic usually exhibit a reduction in their degree of steatosis. NASH is a more severe stage of NAFLD.

Prevalence

The population prevalence of NAFLD has been estimated at 7-35%, using alanine transaminase levels, ultrasound scanning or magnetic resonance spectroscopy (MRS), as diagnostic techniques, of which MRS is most sensitive for detecting liver fat. NAFLD prevalence is around 15% in Asian and 20-30% in Western adults. Estimates of NASH prevalence are at around 2.5%, making NASH more widespread than chronic hepatitis B and C, alcoholic liver disease and other metabolic liver diseases. The rising rates of obesity worldwide parallel rising rates of NAFLD and as such it is projected that within the next decade a greater number of patients will be transplanted for NAFLD than for end stage chronic hepatitis C.

Risk factors

Risk factors associated with NAFLD are mainly features of the (dys) metabolic syndrome: obesity, type 2 diabetes, insulin resistance, hypertension, and dyslipidaemia. Male sex and increased waist circumference are also well established risk factors. NAFLD is primarily associated with increased intra-abdominal fat mass.

NAFLD has been shown to be clustered within families and patterns of inter-ethnic variation have also been documented. It has recently been shown that maternal obesity by means of programming during neonatal and immediate perinatal development can increase susceptibility to NAFLD in adulthood.

Clinical features

Most patients with NAFLD are asymptomatic in the early stages of disease. However, symptoms can include right upper quadrant discomfort and general fatigue. Hepatomegaly and right upper quadrant tenderness may be present on examination.

Diagnosis

Presently, there is no single diagnostic test that reliably detects NAFLD. Its diagnosis is dependent on identification of hepatic triglyceride accumulation at the tissue level in an obese, insulin resistant and dyslipidaemic patient with little or no alcohol history. Diagnosis of NAFLD is also one largely of exclusion. Its presence is confirmed in the absence of focal liver lesions, positive serology for hepatitis A, B and C, aberrant autoimmune profile, copper, caeruloplasmin and ferritin.

Histological classification of hepatosteatosis is diagnostic of NAFLD. The majority of NAFLD patients have abnormal liver function tests. However, elevated transaminase and gamma glutamyltransferase (GGT) levels lack sensitivity and specificity for NAFLD. Furthermore, aberrant liver enzymes may normalise with disease progression. The aspartate transaminase to alanine transaminase ratio is usually <1 unlike alcoholic liver disease where it is >1. However, reversal of the AST/ALT ratio to >1 implies advanced fibrosis in NAFLD.

Serum albumin and bilirubin remain within physiological ranges in NAFLD patients. However, these levels become perturbed with disease progression to cirrhosis. A low level inflammatory state exists in obesity and NAFLD which is reflected by increased ferritin levels in the presence of normal iron indices. Raised anti-smooth muscle and anti-nuclear antibodies, seen in up to 25% of NAFLD patients, are indicative of more severe inflammation and injury.

Ultrasonography is a simple, cost effective and non-invasive technique used to detect hepatosteatosis. It has a sensitivity of 66-100% for a fat content >33%. CT and MRI have around the same sensitivity and specificity as ultrasonography although more expensive. MRS is the most sensitive imaging modality, detecting hepatosteatosis at around 5%.

Transient elastography (Fibroscan) is an alternative ultrasound imaging modality. It provides information on liver stiffness which correlating with hepatic fibrosis. However, it is technically difficult to use in obese patients.

Liver biopsy is the preferred diagnostic technique, although invasive. Skelley et

al. reported that, of 354 patients being investigated for abnormal liver function tests with negative liver serology, 34% required revision of diagnosis post biopsy.

Treatment

There is presently no single therapeutic intervention. NAFLD is largely the consequence of obesity, malnutrition and sedentary behaviour and thus primary prevention are lifestyle modifications. Exercise improves biochemical and histological parameters by reducing visceral fat, enhancing insulin sensitivity and lipid oxidation. However, the risk of disease progression and cardiovascular co-morbidity may warrant pharmacological intervention.

Controlled weight reduction of 5-10% of initial body mass improves or normalises liver enzymes, reduces hepatosteatosis, inflammation and fibrosis. Rapid weight loss has been correlated with accelerated disease progression in NAFLD patients. Weight loss surgery (bariatric surgery) in a cohort of NASH patients has been shown to improve hepatosteatosis, necroinflammatory changes and fibrosis. Similarly, a recent prospective study reported improvement of ballooning and steatosis post-operatively at 1 and 5 years in NASH patients.

Anti-obesity pharmacotherapy includes orlistat, sibutamine and rimonabant. Orlistat is a gastrointestinal lipase inhibitor that aids weight loss and reduces plasma FFAs in NAFLD. It is thought to be most efficacious as an adjunct to dietary intervention. Anti-oxidants and hepato-protectants may also have a therapeutic role. Cytoprotective agents include ursodeoxycholic acid (UDCA), s-adenosylmethionine, betaine, pentoxifylline and vitamin E.

Summary

The term NAFLD encompasses a spectrum of histological features from steatosis to cirrhosis. It is the most common cause of chronic liver disease worldwide, rising in tandem with obesity and type 2 diabetes. Insulin resistance and oxidative stress are important in disease progression. There is presently no single diagnostic test for NAFLD, although, emerging modalities with greater sensitivity and specificity may aid future diagnosis, staging and management.

Similarly, there are no approved treatments of NAFLD. In the majority of cases, treatment strategies commence with lifestyle modifications and may include pharmacotherapy in the form of insulin sensitizers, cholesterol lowering agents, anti-obesity and anti-oxidant agents.

Mouralidarane A, Soeda J, Oben JA, University College London, Centre for Hepatology, Royal Free Hospital, London; Guy's and St Thomas' Hospital, London

A full list of references is available at www.smmgp.org.uk

Managing alcohol-related liver disease (ALD) is a difficult clinical situation which many doctors struggle with. **Carsten Grimm** gives an overview of the current guidelines and makes the case for more cooperation between primary and secondary care. **Ed**

Alcohol and the liver

One of my pet hates is the invisible line that crosses our healthcare system: it's the one between primary and secondary care, or generalists and specialists. I am a fan of general practice, and equally admire the knowledge and dedication of consultants.

General practice requires autonomy to make decisions and judgments, otherwise it will not work as a gatekeeper in the healthcare system. Guidelines help us to make decisions, but do not replace our independent thinking. Not every chest pain will get referred to the hospital and not every abnormal liver function test (LFT) will get seen by a hepatologist. This is not bad medicine; this is good practice as long as doctors are competent, well trained and experienced.

“General practice requires autonomy to make decisions and judgments, otherwise it will not work as a gatekeeper in the healthcare system”

The National Institute for Health and Clinical Excellence (NICE) has published two clinical guidelines about alcohol misuse within the last year^{1,2}. They are comprehensive and sticking to them will make any practitioner do the right thing in the vast majority of cases. However, there are some parts of the guidelines that require us to think about how and why we need to implement them very carefully.

So what does NICE recommend regarding diagnosis of alcohol use disorders and liver disease?

1 Simple biological measures such as liver function tests are poor indicators of the presence of harmful or dependent drinking.

So let's not use them any more to determine how bad a drinking problem is. This is much better done by using either screening questionnaires like AUDIT (Alcohol Use Disorders Identification Test) and SADQ, (Severity of Alcohol Dependence Questionnaire) or even better by an expert assessment.

2 Consider blood tests to help identify physical health needs, but do not use blood tests routinely for the identification and diagnosis of alcohol use disorders.

What does this mean in practice? Anyone who is classified as a harmful, or dependent drinker should have LFTs done routinely as part of their assessment because the risk of developing liver disease is 13 times higher in harmful drinkers as compared to low risk drinkers³, so it makes a lot of sense to have a closer look at the liver. In some ways, it might be even more important to check LFTs for harmful drinkers than for dependent individuals as we have a fairly good idea what we do next for this group and how to

do it: brief intervention, which works in one in eight patients⁴. So by simply advising individuals to reduce their alcohol intake in a structured way we can reduce the risk considerably. Unlike harmful drinkers, dependent drinkers are more difficult to treat and need more interventions and considerably more resources.

We must not forget that we are only talking about risk and that even a lower risk drinker can develop serious problems with the liver, though it is far less likely. This is similar to cardiovascular disease risk assessment; even a low cardiac risk score does not rule out the risk of having a heart attack. So we still have to be aware that it might be necessary to investigate the liver in someone who does not drink too much. This is also due to the fact that some other liver diseases might be adversely affected by consuming even a low amount of alcohol. For example, someone who has chronic hepatitis C and continues to drink to hazardous levels might run a high risk of developing liver failure very soon.

3 Exclude alternative causes of liver disease in people with a history of harmful or hazardous drinking who have abnormal liver blood test results.

The good news is that this refers to a one-off array of blood tests to exclude viral hepatitis and autoimmune diseases. The bad news is that there is no national guideline that defines what exactly we need to test for. Which brings me to the next recommendation:

4 Refer people to a specialist experienced in the management of alcohol-related liver disease to confirm a clinical diagnosis of alcohol-related liver disease.

This is the one that makes me feel uneasy: taking all the above into account, can we fulfill this without sending every single person with slightly abnormal LFTs who is drinking too much to a specialist?

This is what I would recommend: liaise with your local hepatology department to establish what you want to do locally by approaching the newly established Clinical Commissioning Groups. I would be surprised to find any specialist who is keen to see all individuals with abnormal LFTs and a history of drinking too much in their clinics. We should be able to train general practitioners to a level that they are indeed competent to exclude other causes and make the diagnosis of alcohol related liver disease.

As for substance misuse specialist services, we have a well-trained, highly motivated and geographically wide spread workforce in substance misuse. As alcohol treatment services are tendered out, should we not make it part of their work to do exactly that: diagnose and manage alcohol-related liver disease?

Which brings me back to my pet hate: the division between primary and secondary care. In order to maintain good access and manageable workloads in secondary care, we need to do as much as we can in primary care. Working with vulnerable and excluded groups gives me a sense of the poor attendance rate that people with problematic alcohol use have with specialists. There are many reasons why this might be; seeing a consultant usually means an appointment in a less-than-friendly, large and busy environment (hospital) to see someone who does not know you.

I think the diagnosis and large parts of the management of alcohol-related liver disease can and should be part of general practice. Our two colleges, the Royal College of General Practitioners and the Royal College of Physicians need to work together to achieve this to prevent an unsustainable increase in referrals.

Carsten Grimm RCGP Alcohol Certificate Clinical Lead

1 National Institute for Health and Clinical Excellence (2010) Alcohol use disorders: physical complications Clinical Guideline 100
 2 National Institute for Health and Clinical Excellence (2011) Alcohol dependence and harmful use Clinical Guideline 115
 3 HM Government (2007) Safe. Sensible. Social: the next steps in the national alcohol strategy

4 Babor et al (2003) Alcohol: No Ordinary Commodity - Research and Public Policy; Mesa Grande: a methodological analysis of clinical trials of treatments for alcohol use disorders. Addiction 2002 Mar;97(3):265-77

Helen, 48, contacted the British Liver Trust earlier this year exasperated by the lack of care she was receiving from her local GP, reminding us that chronic hepatitis C can present in almost any way and we all need to think about it! Helen is unsure how she contracted hepatitis C. Here is her story, followed by a piece by Euan Lawson on how to improve diagnosis of hepatitis C. Ed.

Living with HCV

I started going to my GP in May 2006 after experiencing bad night sweats and disturbed sleeping patterns. I was waking up in the early hours of the morning, wide awake and raring to go; my legs would be itchy at night, so much so that I kept dousing my cats with flea treatment until they started avoiding me!

The GP immediately said "menopause" – I was 43.

Surprised by the initial assumption, I mentioned that none of my family had had an early menopause and he just shrugged and said it happens - he said the itchy legs were dry skin until I showed him what soft skin I have and then he shrugged. Even when I started to lose weight for no reason and I started to freak out my GP was really calm about it. I went from 55kg to 49kg in about 30 days and would wake up in the morning and wonder where the rest of me had gone.

Throughout this time I was also being treated by a consultant for rheumatoid arthritis (RA), which was diagnosed in 2003. The joint pain I had started to experience from 2009 was getting progressively worse and was affecting my hands, shoulders, neck and leg joints. The RA consultant was brilliant but he told me he couldn't reconcile the amount of joint damage he could see with the amount of pain I reported experiencing. He advised me to go back to my GP because he thought something else was going on.

After returning again to my GP, I was sent for blood tests and was diagnosed hepatitis C positive. I was referred and I went to the consultant, who was very relaxed about it and explained the treatment options available to me. I told her I was studying for a degree and working full time and I didn't want to do treatment if I didn't have to and she said no problem, come back again in a year. I did have an ultrasound and it came back clear so I forgot about the hepatitis C. It never occurred to me to look it up, or connect my symptoms with hepatitis C, because nobody suggested they could be connected.

However in May 2010 I started to get diarrhoea up to six times a day and sometimes it would occur as I was eating. Certain foods would make my digestive system spring into life, including anything sugary or with vitamin C, so I cut out fruit. I noticed all the tiny little bruises on my legs, how dry everything was, for instance my eyes were a nightmare. I wanted to pee all the time and I would eat my dinner, yet be ravenous within five minutes. This was when I wasn't off food and throwing up of course.

I had become slightly erratic in my personality and I would be very chatty with strangers including shop assistants and people in queues. There was a slight air of mania to it and people could sense it; I could see them hoping I would go away soon. It got to the point where I didn't want to go out any more, even when I had made arrangements with people I would spend all my time trying to find a reason not to go. I had also developed nervous system problems where I couldn't relax my face properly and I was holding my shoulder in a strange way that caused neck pain. It

got to the point where the pain in my jaw was so bad I couldn't bite an apple.

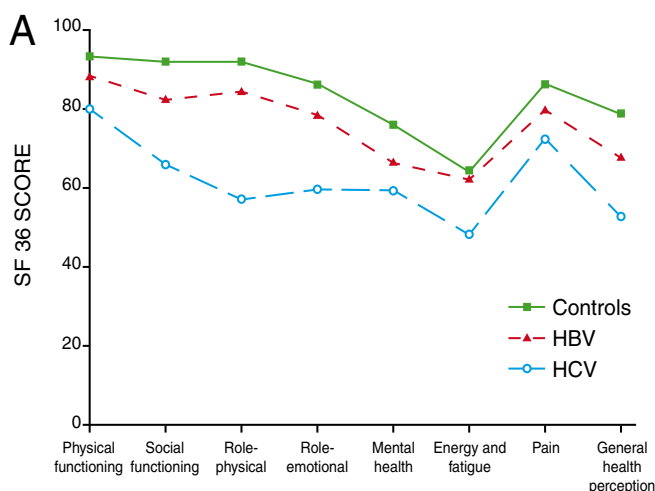
“I had become slightly erratic in my personality and I would be very chatty with strangers including shop assistants and people in queues”

I'm now five months in to a relatively symptom free treatment on a trial drug with the research team under Dr Agarwal at Kings. Hopefully I will be stopping at week 24 but I won't know until then. So here I am. Apart from the fact that I'm tired and my eyebrows seem to be packing their bags and moving, the treatment has at least given me the opportunity to follow a new career – I am thinking of phoning Maybelline or L'Oreal and offering my services as an eyelash model! *Helen is currently undergoing a clinical trial at King's College Hospital in London. She is genotype 1a and the virus was undetected at week two.*

Helen's case – going beyond the usual risk factors

Helen's case illustrates the wide range of symptoms that people with chronic hepatitis C (HCV) infection may experience and one of the key areas for GPs, as emphasised by Helen's article, is the need for those in primary care to have a high awareness of the potential for a non-specific presentation.

For many the perception remains that chronic viral hepatitis will sit relatively quiet and dormant but there is a significant impact on individuals. An important paper by Foster back in 1998 investigated quality of life in people with HCV infection¹. They used the short form 36 (SF36) questionnaire in 72 patients who were known to have chronic HCV infection but who were not undergoing active treatment. This is very similar to the position that Helen was in when she decided to defer treatment. The study showed, quite clearly, that patients with chronic hepatitis C tend to be poly-symptomatic and have significant reductions in their quality of life across all areas. The study also showed that this was not related to severity of liver disease. This reduction in quality of life also persisted when injecting drug users (who were more severely affected) were removed from the analysis.



Helen's case is entirely typical of the experience of many people with chronic hepatitis C. It is not uncommon for people to recount a long history of non-specific symptoms but particularly tiredness,

...continued overleaf

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odd skin conditions, changes and low mood and odd aches and pains, a delayed diagnosis and a realisation, after successful treatment, of how much chronic hepatitis C infection had impacted on their life.

It is clearly important that everyone in primary care has a solid understanding of the risk factors associated with viral hepatitis B and C but it is also important that we think of it when people present with an odd collection of symptoms. It may arguably be worth checking HBV, HCV and HIV alongside liver function tests in

those patients presenting with tiredness. Helen is not sure how she contracted HCV and her case highlights nicely the importance of good quality long-term relationships with patients. We need to have a better appreciation of the range of presentations and the impact on quality of life of a condition such as chronic HCV infection.

Helen's story, with thanks to Helen and the British Liver Trust

1. Foster GR, Goldin RD, Thomas HC. (1998) Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. . 1998 Jan.;27(1):209-212.

Euan Lawson gives some practical suggestions about finding cases of hepatitis B and C. **Ed**

Suggestions to find and manage hepatitis B and C in your practice

Run an audit in your practice

Almost 90% of the newly diagnosed people with hepatitis C (HCV) infections in the UK are in people who are currently injecting or have injected drugs in the past. The Health Protection Agency estimates 44% are in current injectors, 43% in past injectors, 5.6% in South Asian 'never injectors' and 7.3% in white/ other ethnicity 'never injectors'. Over 90% of cases of hepatitis B (HBV) infection are imported, particularly from Africa, Brazil, Peru, China and other South East Asia regions. An example audit would run a search for all individuals coded with past or current drug use and look to see if they have their HCV and HBV status coded and if HCV that they have had a PCR test. Those that don't could be invited in or have a screen message added to their computer notes suggesting they should be offered testing and hepatitis B immunisation opportunistically.

Alternatively, it should be possible to identify those with a diagnosis of chronic hepatitis B or C in the practice and find out if they have been offered referral in the past 2 years and support. Have they had a medical review in the past year? If not offer one and discuss new treatments and the reason for early treatment.

Audit can be a powerful tool to drive change in practice and has the potential to find cases as well as improve management of those who have been diagnosed.

Create a chronic hepatitis B and C register

Ensure you know who is being treated for hepatitis B and C in the practice. This could also be tied in to the audit work as cases are found and given appropriate Read Codes. Offer this group regular check-ups and support them through their treatment. There is much primary care can do to improve and build on care for those with chronic hepatitis infections.

Signs and symptoms

Have a low threshold for checking liver function tests (LFTs) in individuals with vague or non-specific symptoms. Anyone with abnormal LFTs should have their HBV/HCV status checked immediately - don't wait for further tests. The evidence suggests this is more cost-effective than a wait-and-see policy where LFTs are repeated¹. Just test them.

Education, education, education

Develop your skills and knowledge around hepatitis B and C. Considering attending a course such as the RCGP Part 1 course. Run a small session for practice staff or encourage them to do the e-module so that all practice staff have an improved awareness. It may also be useful to build links with the local hepatology service - be familiar with the local referral criteria and many will have nurse specialists who can help support patients in the community.

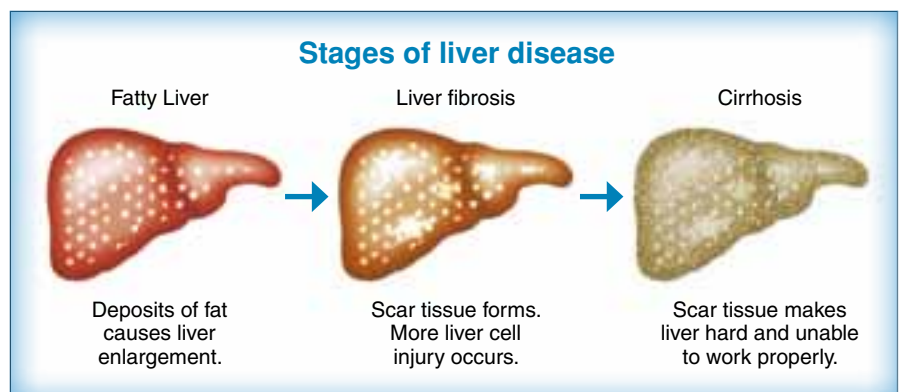
Euan Lawson Clinical Lead for the RCGP Certificate in the Detection, Diagnosis and Management of Hepatitis B and C in Primary Care

1. Arnold DT, Bentham LM, Jacob RP, Lilford RJ, Girling AJ (2011) Should patients with abnormal liver function tests in primary care be tested for chronic viral hepatitis: cost minimisation analysis based on a comprehensively tested cohort. 2011;12:9.

Harm reduction and the liver

Are we looking after people's liver health as well as we could be?

Chris Ford explains how we can take a harm reduction approach to the liver on our website www.smmgp.org.uk



Euan Lawson and discusses the ins and outs of hepatitis A and B immunisations. **Ed**



Some thoughts on managing hepatitis B and A immunisations

The Department of Health gives clear advice in *Immunisation against infectious disease* on the groups that should be vaccinated against hepatitis B¹. Known popularly as the 'Green Book' this gives detailed advice on immunisation schedules but it can be easy to feel that the chaotic circumstances found in the real world don't fit.

The standard regime recommended for hepatitis B is the 'accelerated' schedule where immunisations are given at 0, 1 and 2 months. Those at continued risk should be given at fourth dose at 12 months. The alternative of giving vaccines at 0, 1 and 6 months should only be used where there are no concerns about compliance and there is no need for immediate protection. There is a slightly reduced immunogenicity with the accelerated schedule but this is offset by a much improved compliance – particularly in groups such as injecting drug users where this can be a factor.

Partial immunisation

How do we manage people who have had partial courses of immunisation? This feels common in clinical practice and is unsurprising given that the populations that are most at risk often have fragmentary and inconsistent contacts with primary health care.

It is tempting to test for antibodies in all those who have had partial courses to assess whether or not they need further immunisation. However, the situation is not clear cut and the Green Book advises that we should only be testing for seroconversion in certain groups - such as healthcare professionals. It isn't usually appropriate to test other risk groups.

Despite the recommendations there may be some circumstances where anti-HBs has been tested. It is important not to interpret this test in isolation. Remember that it is possible for someone to be infected with hepatitis B and then go on to be a chronic carrier - they won't have any anti-HBs but they will be HBsAg positive and anti-HBc positive. If you test solely for anti-HBs then you may have just missed a case of chronic hepatitis B. It's good practice to ensure that acute and chronic hepatitis B infection have been excluded.

The overall aim of the DH's immunisation programme is to 'provide a minimum of three doses of hepatitis B vaccine to individuals at high risk of exposure to the vaccine or complications of the disease'. This is the key objective to bear in mind and, alongside the clinical history, will mean a pragmatic plan can be fleshed out to manage normal immunocompetent adults who have had a partial course of HBV immunisation. Aim to ensure three doses have been given and those individuals can be regarded as having received a course of primary immunisation. Re-starting from scratch with every single person who has a partial course is likely to be over-cautious but may be necessary if there is no clear history of immunisation at all.

“ There can be concerns from practitioners about single or combined vaccines - there isn't a 'better' vaccine but they do have slightly different characteristics ”

After primary immunisation

The full length of protection offered by hepatitis B vaccine isn't clear. It is known that vaccine-induced anti-HBs antibodies will go down over time. However, there is evidence that this doesn't give the full story in terms of someone's protection – some 'immune memory' is thought to persist. Currently, a one-off booster around 5 years after primary immunisation is recommended. Antibody testing isn't recommended before or after this booster.

Hepatitis A immunisation

Hepatitis A immunisation is recommended in a number of groups including travellers to areas with high or intermediate prevalence. It is recommended for those with chronic liver disease of any cause – including chronic hepatitis B and hepatitis C infection. This is due to concern that it may cause a more serious illness in these individuals. It is also recommended for men who have sex with men, injecting drug users and the homeless.

The vaccine is available on its own or in combination with hepatitis B. The monovalent vaccine has a bigger dose and if very rapid protection is required then a single dose of the monovalent vaccine is better and is all that is needed to provide primary immunisation. A booster is recommended at 6 to 12 months and, at present, a further booster at 20 years is also recommended. The combined vaccine primary schedule will work well for those who need immunisation against both hepatitis A and B and the schedule for Twinrix[®] consists of three vaccines at 0, 1 and 6 months. There can be concerns from practitioners about single or combined vaccines - there isn't a 'better' vaccine but they do have slightly different characteristics and the choice should be tailored to the individual's clinical circumstances.

For full information on groups to immunise then download the most current version of at the Department of Health website (tinyurl.com/DHGreenBook).

Euan Lawson Clinical Lead for the RCGP Certificate in the Detection, Diagnosis and Management of Hepatitis B and C in Primary Care

1. Department of Health. (2006). 1st ed. London: The Stationery Office; 2006.

Graham Foster and Morven Cunningham give us a glimpse into the future of hepatitis C treatment: it looks like things may be about to get better. **Ed**



What's new on the horizon for treatment of hepatitis C?

These are exciting times for those involved in treatment of patients with chronic hepatitis C infection (HCV), as the first radical new therapies for almost two decades have recently been approved in the USA. Current standard treatment, involving weekly injections of pegylated interferon alpha and twice daily oral ribavirin for 48 weeks results in a sustained virological response (SVR, defined as undetectable HCV RNA 24 weeks after treatment, which probably equates to a cure) in less than 50% of patients infected with genotype 1 HCV^{1 2}. Treatment is often poorly tolerated, with unpleasant side effects including flu-like symptoms, fatigue, mood disturbance, anaemia, dry skin and alopecia. Without improvements in treatment uptake and success the burden of chronic liver disease due to HCV in England is set to rise³, hence the pressing need for new treatments with better efficacy and tolerability.

New antiviral strategies in drug development

A number of different approaches are being taken to develop new drugs to treat chronic HCV. These include:

- Direct acting antiviral agents (DAAs), which specifically inhibit key viral proteins
- Drugs targeting host proteins which are required for viral replication
- Modifications of interferon and ribavirin to increase efficacy and reduce side effects

Other strategies which show promise, but are currently at less advanced stages of development, include viral entry inhibitors and therapeutic vaccines.

Direct-acting antiviral agents

Replication of HCV is dependent on a number of viral non-structural proteins, so these represent attractive targets for antiviral drug development. Drugs which inhibit the viral NS3/4A serine protease, the viral NS5B polymerase and agents which bind to the NS5A viral replication complex have all shown impressive anti-viral activity *in vitro* and *in vivo*. However, a significant downside to these agents is the potential for viral mutations to occur at the drug target site, conferring reduced susceptibility to the drug. Rapid emergence of drug-resistant viral variants occurs when most classes of DAA are given as monotherapy. Adding interferon and ribavirin suppresses the emergence of resistant variants, so for the time being at least these agents will need to be given together with current standard therapy.

Telaprevir and boceprevir are NS3/4A serine protease inhibitors which have recently been approved by the Food and Drug Administration in the United States and at the time of writing, approval in Europe is expected imminently. Several more protease inhibitors are in phase 2 and 3 clinical trials. In phase 3 trials, addition of either telaprevir or boceprevir to standard therapy substantially improved treatment response for patients with genotype 1 HCV, with SVR rates of over 70%. Up to two thirds of treatment-naïve patients showed an early response to therapy, and in these patients the total duration of treatment could be shortened to 24-28 weeks with no adverse effect on SVR^{4 5}. In patients who previously failed to clear the virus after a course of standard therapy, retreatment with addition of a protease inhibitor resulted in SVR in 66% (compared to 17-21% in patients retreated with standard therapy alone)^{6 7}. Notable side effects associated with these agents include rash (particularly with telaprevir, which can be severe), anaemia (particularly with boceprevir) and gastrointestinal disturbance. Patients who failed treatment with therapy containing a protease inhibitor frequently harboured drug-resistant viral variants. Although these variants declined over time after treatment, being replaced by wild-type virus⁸, whether this will compromise future treatment options for these patients is currently unknown.

Drugs targeting the NS5B RNA polymerase can be divided into nucleoside and non-nucleoside inhibitors. Nucleoside analogues, such as RG7128, effectively act as polymerase chain terminators. Whilst they show lower antiviral potency than protease inhibitors, they have other distinct advantages. They appear less susceptible to development of drug resistant viral variants than other DAAs, and they show similar antiviral activity

1 Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncalves FL, Jr., et al. (2002) Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med.* 2002 Sep 26;347(13):975-82.

2 Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. (2001) Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet.* 2001 Sep 22;358(9286):958-65.

3 Health Protection Agency Centre for Infections (2009) Hepatitis C in the UK 2009. London

4 Poordad F, McCone J, Jr., Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. (2011) Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med.* 2011 Mar 31;364(13):1195-206.

5 Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. (2011) Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med.* 2011 Jun 23;364(25):2405-16.

6 Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. (2011) Telaprevir for retreatment of HCV infection. *N Engl J Med.* 2011 Jun 23;364(25):2417-28.

7 Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al. (2011) Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med.* 2011 Mar 31;364(13):1207-17.

8 Sullivan JC, De Meyer S, Bartels DJ, Dierynck I, Zhang E, Spanks J, et al. Evolution of treatment-emergent resistant variants in telaprevir phase 3 clinical trials. *Journal of Hepatology.* 2011;54(S1):S4.

against a range of viral genotypes, not just genotype 1⁹. Non-nucleoside analogues, such as filibuvir, inhibit polymerase activity by binding to enzyme active sites and thus act as non-nucleoside inhibitors. Antiviral activity in short term monotherapy studies is comparable to nucleoside inhibitors, but, like protease inhibitors, efficacy as monotherapy is limited by rapid emergence of antiviral resistance, and poor efficacy against genotypes other than genotype 1¹⁰. However, as part of combination therapy these agents may provide a further valuable option for many patients.

The precise function of the viral NS5A protein is unknown, but it is essential for viral replication and therefore presents another target for DAAs. The NS5A inhibitor BMS-790052 showed impressive antiviral potency and in dose-finding studies, but also rapid emergence of drug-resistant variants¹¹. These variants remained sensitive to interferon, protease and polymerase inhibitors, so again NS5A inhibitors are promising agents in the armament of antiviral combination therapy.

Inhibition of host targets

The host protein cyclophilin A is required for HCV replication. DEB025 (alisporivir) is a cyclophilin inhibitor which has shown potent anti-HCV activity alone, with additive effects when combined with interferon and ribavirin. Specific advantages are the high barrier to development of antiviral resistance, and efficacy against genotypes 2, 3 and 4 as well as genotype 1¹². Trials of alisporivir with interferon and ribavirin for treatment-naïve and treatment-experienced genotype 1 patients are currently in progress. Alisporivir is also being investigated in interferon- and/or ribavirin-free regimens in patients with genotype 2 and 3 infection and the results are eagerly awaited.

Improving tolerability of current therapy

Interferon lambda has similar intracellular antiviral effects to interferon alpha, but affects fewer cell types due to differences in receptor distribution. Phase 1 studies support the hope that this may translate to equivalent antiviral efficacy with a reduced side effect profile¹³, and further clinical trials comparing pegylated interferons alpha and lambda are underway.

Ribavirin is associated with anaemia, often managed by ribavirin dose reduction, which could compromise achievement of SVR. Taribavirin is an oral prodrug of ribavirin which is not concentrated in erythrocytes. A comparison of weight-based taribavirin with ribavirin did show less anaemia, but no improvement in SVR

rates amongst those receiving taribavirin¹⁴. Whether there is a role for taribavirin in future combination therapy is not yet clear. It may perhaps prove useful in combination with DAAs which are themselves associated with anaemia, or in patients at particular risk of this side effect (such as those with renal impairment).

“With the gathering pace of drug development, the goal of combination oral therapy which dispenses with the need for interferon may not be too far over the horizon”

Combination therapy for HCV

Following the success of combination therapy using a number of drugs with varying resistance profiles in treatment of HIV infection, this strategy is likely to be employed in HCV therapy. Unlike HIV, HCV does not establish latency and so should be inherently curable. The ideal drug combinations, number of agents and duration of therapy remain to be established, and in the short term therapies will most likely comprise one or two DAAs together with interferon and ribavirin. With the gathering pace of drug development, the goal of combination oral therapy which dispenses with the need for interferon may not be too far over the horizon.

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and The London School of Medicine and Dentistry, Queen
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g.r.foster@qmul.ac.uk

9 Le Pogam S, Seshadri A, Ewing A, Kang H, Kosaka A, Yan JM, et al. RG7128 alone or in combination with pegylated interferon-alpha2a and ribavirin prevents hepatitis C virus (HCV) Replication and selection of resistant variants in HCV-infected patients. *J Infect Dis.* Nov 15;202(10):1510-9.

10 Wagner F, Thompson R, Kantaridis C, Simpson P, Troke PJ, Jagannatha S, et al. (2011) Antiviral activity of the hepatitis C virus polymerase inhibitor filibuvir in genotype 1-infected patients. *Hepatology.* 2011 Jul;54(1):50-9.

11 Nettles RE, Gao M, Bifano M, Chung E, Persson A, Marbury TC, et al. (2011) Multiple ascending dose study of BMS-790052, an NS5A replication complex inhibitor, in patients infected with hepatitis C virus genotype 1. *Hepatology.* 2011 Aug 11.

12 Flisiak R, Feinman SV, Jablkowski M, Horban A, Kryczka W, Pawlowska M, et al. (2009) The cyclophilin inhibitor Debio 025 combined with PEG IFNalpha2a significantly reduces viral load in treatment-naïve hepatitis C patients. *Hepatology.* 2009 May;49(5):1460-8.

13 Muir AJ, Shiffman ML, Zaman A, Yoffe B, de la Torre A, Flamm S, et al. (2010) Phase 1b study of pegylated interferon lambda 1 with or without ribavirin in patients with chronic genotype 1 hepatitis C virus infection. *Hepatology.* 2010 Sep;52(3):822-32.

14 Poordad F, Lawitz E, Shiffman ML, Hassanein T, Muir AJ, Bacon BR, et al. (2010) Virologic response rates of weight-based taribavirin versus ribavirin in treatment-naïve patients with genotype 1 chronic hepatitis C. *Hepatology.* 2010 Oct;52(4):1208-15.

Brian Thompson gives some detail on factors that lead to progression of liver disease for those with hepatitis. **Ed**

Viral hepatitis and liver disease – individual outcomes

Introduction

The UK Health Protection Agency has estimated that almost 6000 individuals with hepatitis C virus (HCV) currently have cirrhosis, and up to 1500 have either end-stage liver disease or hepatocellular carcinoma (HCC). These figures are predicted to rise dramatically in the next three decades. Equivalent data for hepatitis B virus (HBV) are not yet available, but the prevalence of infection in populations from high risk areas, such as Sub-Saharan Africa and Asia is rising, and HBV related liver disease is a common presentation in many secondary care clinics. Chronic infection with hepatitis viruses is therefore a major burden on the NHS.

Mechanisms of liver damage

The mechanisms by which hepatotropic viruses lead to liver injury remain unclear. Most studies have concluded that cell mediated immune responses to viral infection is the principle mechanism of liver damage. This is consistent with the observation that HBV is associated with minimal liver damage in the early 'immune tolerant phase' of infection, despite very high levels of viral replication. HBV and HCV can, however, cause severe disease in individuals with impaired immune responses, including those with co-existing HIV infection and following liver transplantation, and it is likely that both viruses are capable of exerting a direct cytopathic effect.

In most circumstances, HBV and HCV infection is associated with histological evidence of necroinflammatory change in the liver. Each virus is associated with distinct pathological features, suggestive of virus-specific mechanisms of injury. No consistent relationship has been demonstrated between necroinflammation and disease outcomes, but several studies have shown a correlation between median elevations in ALT, which is a surrogate marker of inflammatory damage to hepatocytes, and disease progression¹. Whatever the driver, the key underlying lesion in disease progression is liver fibrosis. The rate of fibrosis progression, as assessed either by prospective grading on sequential histological assessment, or estimates based on estimated time from infection to the development of cirrhosis, is the index of disease progression.

Cohort studies suggest that individuals with severe liver fibrosis secondary to hepatitis C may progress more quickly than those with fibrosis of other aetiologies². HCC is a particularly important complication of HCV infection. The 5-year cumulative incidence of HCC in HCV-infected individuals is 17% in Western countries and 30% in Japan. HBV infection carries a similar high risk of HCC. As a comparator, the five-year cumulative incidence of HCC is 8% in alcoholic cirrhosis and 4% in cirrhosis of auto-immune aetiology³.

1 Williams M, Lang-Lenton M on behalf of the Trent Group (2010). Progression of initially mild hepatic fibrosis in patients with chronic hepatitis C infection. *Journal of Viral Hepatitis*; 18: 17-22.
 2 Lawson A, Hagan S, Rye K et al (2007). The natural history of hepatitis C with severe hepatic fibrosis. *Journal of Hepatology*; 47: 37-45.
 3 Thomson BJ (2009). Hepatitis C virus: the growing challenge. *British Medical Bulletin*; 89: 153-167.

What determines the outcome of infection in individuals?

It is clear that the outcome of chronic hepatitis infection is highly variable. But what factors determine whether an individual with HBV or HCV viraemia develops liver disease and how quickly do they do so? Demographic, host and environmental factors clearly modulate outcomes of hepatitis virus infection and consideration of these factors should inform our strategy of engagement.

Demographic factors

The most informative studies of the influence of age and gender are based on well characterised cohorts of mothers infected with HCV by contaminated anti-D in Ireland and Germany and a cohort of plasma donors infected in Austria^{4,5,6}. These studies share the invaluable advantage of accurate identification of the time of infection, but are otherwise strikingly different. Only 2% of the Irish cohort had developed cirrhosis after 17 years of follow up and rates were similar in the German group after 25 years. In contrast, 34% of the Austrian cohort had severe fibrosis and 15% end stage liver disease or HCC at 31 years of follow up.

What are the reasons for such diversity?

The two most obvious differences are that: i) recipients of anti-D were female, while plasma donors were predominantly male and ii) the plasma donor cohort was older at the point of analysis. Other studies have confirmed that male gender and older age are predictive of a poor outcome in both HCV and HBV infection. Age in particular is consistently identified as a dominant risk factor for disease progression. This is not only for the obvious reasons that older individuals are likely to have been infected for longer, but because disease appears to accelerate with age. Retrospective analysis of a large French HCV cohort found that patients infected at age 20 took 44 years to develop cirrhosis, whereas those infected over the age of 50 progressed to cirrhosis in only 12 years⁷. Prospective studies have confirmed the non-linear nature of fibrosis progression. The impact of age and associated liver disease is equally striking in response to current antiviral therapies. Men aged 30 infected with HCV genotype 1 and no underlying liver disease had a sustained response to therapy of >70%, whereas males aged 50 with cirrhosis had a response rate of <10%⁸. These observations provide a compelling argument for the early identification and treatment of chronic hepatitis C virus infection.

Alcohol

A strong consensus has emerged that alcohol consumption of >30g/day is a major co-factor in hepatitis disease progression. This is particularly important in populations of intravenous drug users, who are at greatest risk of the acquisition of HCV, and in whom excess alcohol consumption is common. The Dionysus study, a large prospective community based study in Northern Italy, has demonstrated that ethanol intake of more than 30g/day is the most important risk factor for cirrhosis and death in patients with

4 340:5. 43:6. 47:7. 349: 8. Thomson BJ, Kwong G, Ratib S et al. (2008). Response rates to combination therapy for chronic HCV infection in a clinical setting and derivation of probability tables for individual patient management. *Journal of Viral Hepatitis*; 15: 271-278
 5 Wiese M, Grüngreiff K, Güthoff W, et al (2005). Outcome in a hepatitis C (genotype 1b) single source outbreak in Germany – a 25 year multicentre study. *Journal of Hepatology*; 43: 590-598.
 6 Ferenci P, Ferenci S, Datz C, Rezman I, Oberaigner M, Strauss R (2007). Morbidity and mortality in paid Austrian plasma donors infected with hepatitis C at plasma donation in the 1970s. *Journal of Hepatology*; 47: 31-36.
 7 Poynard T, Bedossa P, Opolon P (1997). Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet*; 349: 825-832.
 8 Thomson BJ, Kwong G, Ratib S et al. (2008). Response rates to combination therapy for chronic HCV infection in a clinical setting and derivation of probability tables for individual patient management. *Journal of Viral Hepatitis*; 15: 271-278.

chronic HCV or HBV infection⁹. Conversely, HCV and HBV infection increase the risk of cirrhosis in individuals with an alcohol intake of >30g/day¹⁰. A meta-analysis of 47 studies of the natural history of HCV infection in injecting drug users (IDUs) found generally poor outcomes in this group, and identified high levels of alcohol as a strong predictor of rapid disease progression¹¹. A separate study found that alcohol consumption of less than 30g/day does not appear to be associated with increased fibrosis in patients with chronic HCV infection¹². There is also encouraging evidence that behavioural programmes in young IDUs with HCV infection can lead to significant improvement of alanine transaminase (ALT) in those who reduce alcohol consumption¹³.

Diabetes

HCV infection has been robustly associated with the development

9 Bellentani S, Scaglioni F, Ciccia S, Bedogni G, Tribelli C (2011). HCV, HBV and alcohol—the Dionysos study. *Digestive Diseases*; 28: 799-801.

10 Stroffolini T, Cotticelli G, Medda E et al (2010) Interaction of alcohol intake and cofactors on the risk of cirrhosis. *Liver International*; 30: 867-870.

11 John-Baptiste A, Krahn M, Heathcote J, Laporte A, Tomlinson G (2010). The natural history of hepatitis C virus infection acquired through injection drug use: meta-analysis and meta-regression. *Journal of Hepatology*; 53: 245-251.

12 Cheung O, Sterling RK, Salvatori J et al (2011) Mild chronic alcohol consumption is not associated with increased fibrosis in patients with chronic hepatitis C. *Journal of Clinical Gastroenterology*; 45: 76-82.

13 Drumright LN, Hagan H, Thomas DL et al (2011) Predictors and effects of alcohol use on liver function among young HCV-infected injection drug users in a behavioural intervention. *Journal of Hepatology*; 55: 45-52.

of insulin resistance and type 2 diabetes mellitus. The insulin resistant state associated with hepatitis C leads to accelerated progression of liver fibrosis and reduced response to anti-viral therapy¹⁴.

Host genetics

Although demographic and environmental factors have an important effect on disease outcomes, they do not fully explain the heterogeneity of response, and the host genetic background is likely to play a major role. Evidence from twin studies is consistent with this concept. A variety of molecular techniques, including candidate gene association studies and genome-wide association studies have interrogated the relationship between molecular variation and diversity of outcome in HBV and HCV infection. These studies have found a number of reproducible associations, particularly in immune response genes¹⁵. The most striking has been the identification of a locus within the interleukin (IL) 28-29 region which appears to have a dominant effect on the outcome of treatment for HCV infection. It is likely that IL-28B genotyping will become part of routine clinical practice in the foreseeable future.

Brian J Thomson PhD, FRCP, Associate Clinical Professor, University of Nottingham and Nottingham University Hospital

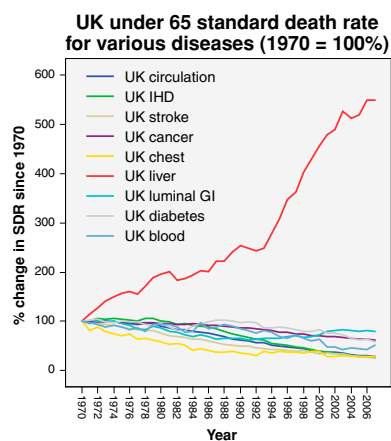
14 Alaei M, Negro F. Hepatitis C virus and glucose and lipid metabolism (2008). *Diabetes & Metabolism*; 34: 692-700.

15 Thurz M, Yee L, Khakoo S (2011). Understanding the host genetics of chronic hepatitis B and C. *Seminars in Liver Disease*; 31: 115-127

Martin Lombard, National Clinical Director for Liver Disease outlines some of the issues for the liver strategy, and encourages us to get involved by joining the NHS Liver Networks Site. Ed

Liver disease and primary care: a briefing paper

Patients with liver disease can present in primary care in a number of ways and this paper sets out ways in which we would like to engage primary care doctors, nurses and other health care workers in helping to reduce the prevalence of progressive liver disease and to manage the increasing burden on the NHS.



Many doctors in primary care are unaware of what is happening to the relative mortality rate from liver disease compared to other disease. As shown in the graph on the left, the death rates from cardiovascular disease, cancers, respiratory disease and strokes are decreasing year on year since 1970. By contrast the red line which is rising represents the relative mortality from liver disease since 1970.

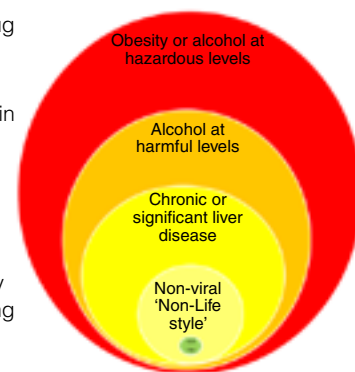
This is why we need to engage primary care in helping us to tackle this important and growing problem. In addition, the average age of death for liver disease is much lower (59 years) than the other main causes (72-84 years) and the trends for liver disease in the UK are opposite to those in other European countries.

The growth of liver disease:

- 30% of blood tests from primary care show abnormal liver enzymes
- >60% of all gastroenterology inpatients are due to liver disease
- >25% referrals to gastroenterology outpatients are due to liver disease
- Cirrhosis rates in the UK have more than doubled in the past 10 years
- There are 700 liver transplants a year in the UK, but 700,000 people with significant liver disease

The principal reasons for the growth in liver disease:

- Alcohol: especially resulting in liver disease in 35-65 year age groups
- Hepatitis C: especially in current or former drug users, it is potentially a curable condition
- Hepatitis B: especially in immigrant populations, its progression can be delayed/avoided by treatment
- Fatty liver disease associated with obesity and diabetes; becoming the most common reason for referral and fastest growing cause for cirrhosis



For more information please join the NHS Liver Networks Site by emailing liverstrategy@dh.gsi.gov.uk

Martin Lombard, National Clinical Director for Liver Disease

Iain Brew takes us through the ways in which we can support people going through treatment for hepatitis C. **Ed**

Management of hepatitis C treatment and side effects

Current antiviral treatment for hepatitis C consists of weekly subcutaneous injections of pegylated interferon alpha, which has virucidal activity with daily oral ribavirin, which interferes with viral replication. Pegylated interferon has a molecule of polyethylene glycol attached, which causes the interferon to remain in the body for longer.

Both drugs can produce a number of side effects; some are more serious than others, but careful monitoring of patients is essential during and immediately after treatment. Duration of antiviral medication is decided on genotype and viral load. Genotypes 2 and 3 with low viral load may be cleared with as little as twelve weeks treatment, but types 1 and 4 require 48 weeks.

Interferon

Common side effects mimic other viral infections – lethargy, loss of appetite, nausea and diarrhoea are particularly likely in the first six to eight weeks of treatment. Many patients describe symptoms of “flu” and may need rest or time off work, but supportive and symptomatic treatment is usually all that is required. It is perfectly reasonable to use paracetamol in hepatitis C patients as long as the dose does not exceed recommendations and there is no evidence of decompensated liver cirrhosis. Weight monitoring is important and the provision of nutritional support should be considered in patients with weight loss and doses may need to be adjusted if the weight loss is particularly bad.

Treating clinicians will arrange for regular blood test monitoring; both interferon and ribavirin can cause myelosuppression affecting red cell, white cell and platelet production. If the neutrophil count is consistently below 0.5, granulocyte colony stimulating factor (GCSF) may be considered and erythropoietin (EPO) may be necessary to reverse anaemia in severe cases. As with haematological side effects in chemotherapy for cancers, treatment

holidays or dose reductions have been used to manage these serious side effects effectively, but it is important to maximize the chances of sustained viral response (SVR) by getting the maximum possible dose of treatment into the minimum time. Unless a patient presents with fever or acute illness, there should be no need for further blood testing by other clinicians.

“Many patients describe symptoms of “flu” and may need rest or time off work, but supportive and symptomatic treatment is usually all that is required”

Less common adverse effects include thyroid disturbances; either hyper- or hypothyroid may result. Thyroid function is another part of routine monitoring of patients whilst in treatment. Although patients are often concerned about alopecia, this is not common and is rarely significant.

Local reactions at the injection site are common: pain, redness and induration are effectively managed with 1% hydrocortisone cream. It is normal to alternate between the left and right side of the anterior abdominal wall to reduce the chances of these reactions. Hard lumps in the subcutaneous tissue may remain for several months even after treatment is complete.

Ribavirin

Many of the side effects of ribavirin are similar to interferon, especially flu-like symptoms and gastrointestinal effects. Chest pain, cough and palpitation may also occur, but the management of these simply consists of excluding serious pathology and offering reassurance to the patient.

Patients with pre-existing heart disease or ophthalmological problems should be monitored for any deterioration in their diseases and should be referred for expert assessment in case of concern. Such deterioration may lead to antiviral treatment being abandoned.

Psychiatric side effects may include depression, poor concentration and memory loss, suicidal ideation and

psychosis. It is important that patients with a history of serious mental health problems be stabilised before treatment is considered. Any prescribed psychotropic medication should be at a stable dose and patients should be advised to avoid self-medication with alcohol or drugs of abuse, which may further increase the risk of psychiatric side effects. All health workers who are involved with patients undergoing antiviral therapy for hepatitis C should be alive to the development of psychiatric symptoms and should manage these as soon as possible.

As with interferon, haematological monitoring is important. Ribavirin may cause haemolytic anaemia and thrombocytopenia, although the latter is not normally clinically important. It is not uncommon to see platelet counts below 50 and these may worry haematology laboratories and primary care clinicians alike, but spontaneous bleeding is unlikely unless the platelet count is below 10. No treatment is needed for mild to moderate thrombocytopenia, although the clinician in charge of antiviral treatment should be made aware. As above, there should normally be no need for additional blood monitoring in primary care unless there is good cause.

Ribavirin is teratogenic in animals, so should be avoided during pregnancy and adequate contraception is important for both men and women undergoing treatment.

During treatment with ribavirin, patients may suffer worsening dental problems, glossitis and stomatitis. There should be adequate provision for dental care and oral hygiene is very important. Glossitis and stomatitis respond well to barriers such as Vaseline or topical steroids if more severe, but any opportunistic candida infection should be treated at the same time.

Skin rashes resembling psoriasis or eczema should be managed with emollients with mild steroids being used only where really necessary. Stevens Johnson syndrome occurs rarely, but needs vigorous treatment.

Iain Brew, GPSI Hepatitis C, Leeds Community Health Services NHS Trust



Dr Fixit on management of hepatitis C in primary care

Dear Dr Fixit,

Jim is a 28 year old a patient of mine who has a history of heroin use. I have been treating him for the last 4 years at my surgery and he is on 60mls methadone. He has really reduced his drug use and now only uses heroin, which he injects twice a month. He recently had a positive PCR test for hepatitis C which he says he was expecting as he has shared injecting equipment. He is very clear that he does not want treatment at the moment because he has a lot going on in his life as he has recently started a new job, has moved into his own flat where he lives on his own, and has a new circle of non drug using friends and is socialising a lot more. He says he would like to think about treatment in a year's time. Is there anything I can do in the meantime to help him?

Reply by Mark Hallam, CDT & Blood Borne Virus Medical Lead in Leeds, St Martin's Health Services

Jim's request is not unreasonable. He obviously understands that treatment of his hepatitis C may be challenging and that it may be too much for him to cope with on top of all the other things going on in his life. At the age of 28, he is still relatively young. We know that treatment is best started when people are young, but treatment effectiveness starts to diminish from around the age of 40 and he is a few years short of this¹. Nonetheless a few issues are raised, particularly in terms of harm reduction, whether to Jim himself or those he may

potentially pass his infection on to. There is evidence that interventions in primary care can be very effective².

“Not only does fatty liver potentially accelerate liver damage, but there is also an association between insulin resistance and treatment resistance”

The first obvious issue is he continues to inject heroin twice per month. Jim clearly has some knowledge of the potential for spread of infection from sharing injecting equipment since he said he was not surprised by his positive hepatitis C result. Nonetheless it is worth exploring this issue further: can he be encouraged not to inject? If he cannot stop injecting, can he be supported not to share equipment? Is he aware that sharing of all 'works' including spoons, filters and water is risky? Is he using a needle exchange^{3,4,7}?

He should also know that sharing of even non-injecting drug use paraphernalia can pass on hepatitis infections. Jim isn't disclosing cocaine use, but it is known that sharing of equipment such as crack pipes and cocaine 'straws' can pass on infection via the mucous membrane injury associated with both these practices^{3,4,5}.

Another crucial issue is whether he is on the right dose of methadone? At 60mls he is at the bottom end of the optimum 60-120ml range^{6,7}. Is he getting withdrawal symptoms? He will be unlikely to succeed in reducing his heroin use

and stopping injecting if he continues to suffer even very mild withdrawal.

We also need to ensure he is protected from hepatitis A and B which could potentially be much worse, if caught on top of hepatitis C. Hepatitis A and B are preventable and it is essential that Jim is offered vaccination for both as soon as possible^{8,9,10}.

There are a few other factors which can potentially be modified, to limit the damage of chronic hepatitis C to Jim's liver. Is he using alcohol? It is clear that alcohol use even in relatively modest amounts is undesirable for two reasons: first there is a danger of accelerating the progression of liver fibrosis towards cirrhosis; second it is known that alcohol reduces the effectiveness of hepatitis C treatment¹. Jim should be advised that total abstinence from alcohol is the safest option. Failing that, he should be advised to limit consumption to as little as possible and well below the standard 21 units per week recommended as the limit for a (healthy) man¹¹.

If Jim is a higher risk drinker, every effort should be made to motivate him to address the issue before he reaches the point where he starts on any future treatment for his hepatitis C. It is worth noting that smoking can also accelerate progression of hepatitis C^{1,12}.

Another important factor which can also potentially be modified is weight. Hepatic steatosis (fatty liver) is increasingly recognised as being an important cause of liver disease. It is often (but not always) associated with obesity. If Jim has a body mass index of over 29, efforts should be made to encourage him to lose weight through a program of healthy eating and exercise. Not only does fatty liver potentially accelerate liver damage, but there

1 Royal College of General Practitioners (2007) Guidance for the prevention, testing, treatment and management of hepatitis C in primary care 2007

2 Wright NMJ and Tompkins CNE (2006) A review of the evidence for the effectiveness of Primary Prevention interventions for hepatitis C among injecting drug users? *Harm Reduction Journal* 2006, 3:27.

3 Health Protection Agency (2009) Shooting Up: Infections among injecting drug users in the UK

4 Karmochkine M, Carrat F, Dos Santos O, Cacoub P, Raguin G (2006) A case control study of risk factors for hepatitis C infection in patients with unexplained routes of infection. *J Viral Hep* 2006; 13:775-782

5 Royal College of General Practitioners (2004) Guidance for Working with Cocaine & Crack Users in Primary Care

6 Department of Health (2007) Drug Misuse & Dependence: UK guidelines on clinical management.

7 Royal College of General Practitioners (2011) Guidance for the use of substitute prescribing in treatment of opioid dependence in primary care 2011.

8 Department of Health (2011) Immunisation against infectious disease: "the Green Book": Update

9 Vento S, Garofano T, Renzini C, et al. (1998) Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *N Engl J Med* 1998; 338(5):286-90.

10 Sundkvist T, et al (2003) Outbreak of hepatitis A infection among intravenous drug users in Suffolk and suspected risk factors. *Communicable Disease and Public Health*, 2003. 6(2): p. 101-5.

11 Hutchinson SJ, Bird SM, Goldberg DJ. (2005) Influence of alcohol on the progression of hepatitis C virus infection: a meta-analysis. *Clinical Gastroenterology & Hepatology*. 2005 Nov; 3(11):1150-9

12 Hezode C, Lonjon I, Roudot-Thoraval F, et al (2003) Impact of smoking on histological liver lesions in chronic hepatitis C. *Gut* 2003;52(1):126-9

... continued overleaf

is also an association between insulin resistance and treatment resistance^{13,14}.

It is important that Jim doesn't pass his infection on. Aside from activities associated with his drug use, there are a number of ways this can happen. The common denominator is blood. Although the hepatitis C virus can be identified in various bodily fluids, blood is pretty much the only medium when it comes to spread of infection^{1,15}. Thus, it is important to reassure him that normal person to person contact, including such as hugging or kissing, cannot pass on hepatitis C. The activities which he needs to be concerned about involve inoculation of blood. Even in minute amounts, blood passing from an infected to the bloodstream of an uninfected person, carries risk of transmitting the infection^{1,4,16}.

There is some risk of an exchange of blood occurring through sharing of items such as toothbrushes and razor blades. Many suffer from mild gum disease and if two such share a toothbrush, minute deposits of blood may be picked up on the bristles and inoculated into the bleeding surfaces of the gums of another. It is not difficult to imagine how this may occur with razor blades – but similarly nail clippers also may be a source of risk¹.

You mention Jim lives alone; people may come to stay or he may embark on a relationship where inadvertent sharing of such implements may take place and he should be advised on the risks. The issue of sexual risk needs to be covered, even if Jim has no partner at the moment. Because minute amounts of blood can be exchanged during sex there is some risk of transmission of hepatitis C. However, evidence suggests that the risk associated with 'non-rough' heterosexual sex is low. One study of nearly 900 heterosexual monogamous couples failed to find a single case of intra-spousal transmission and other sources have quoted life-time risk for same type of couple as 2-3%^{1,16}.

13 Hu KQ, Kyulo NL, Esrailian E, et al. (2004) Overweight and obesity, hepatic steatosis and progression of chronic hepatitis C: a retrospective study on a large cohort of patients in the United States. *J Hepatol* 2004; 40(1): 147– 54

14 Bressler B, Guindi M, Tomlinson G, et al. (2003) High body mass index is an independent risk factor for non response to antiviral treatment in chronic hepatitis C. *Hepatology* 2003; 38:639-44

15 World Health Organization Hepatitis C fact sheet No 164 June 2011

16 Vandelli C, et al. *Am J Gastro* (2004) Lack of Evidence of Sexual Transmission of Hepatitis C among Monogamous Couples: Results of a 10-Year Prospective Follow-Up Study; 99: 855-859.

There is higher risk with 'rough' sex, sex with multiple partners – or with men having sex with men. In all these scenarios use of condoms considerably diminishes risks of transmission of infection.

It is worth returning to the issue of why Jim is choosing to delay his treatment. As already mentioned, his reasoning may be sound. With his age being somewhat less than 40 and a presumed relatively short history of hepatitis C, it is unlikely that delay of a year would result in significant worsening of either his condition or of his chances of successful treatment.

It is worth considering other issues which may influence his decision to delay. Jim may believe he cannot be referred for treatment because he continues to inject heroin. NICE guidance is now in favour of offering hepatitis C treatment to people who are still injecting (NB not all hepatology departments will have adopted this principle, but should be challenged if they have not)^{1,17}. Some additional blood tests could also help him reach a decision. Knowing his genotype would be helpful to give him an idea of the success rates of treatment, and knowing a bit more about the state of his liver could also be helpful. If there was any sign of damage to his liver I would advise him to go for early treatment.

Jim may fear having a liver biopsy as part of assessment for treatment of his hepatitis C. It is worth pointing out that most people don't need a liver biopsy before treatment, especially if they are young, have genotype 2 or 3 have no liver damage, no significant history of problematic alcohol use and a less complex history (and the advent of 'Fibroscan' tests may reduce the need to carry out diagnostic liver biopsy still further).

Finally Jim may have misconceptions about hepatitis C treatment and you can really help here and explain the main side-effects, explain he will be supported through treatment by a specialist hepatology nurse and that he can talk to someone who has been through treatment. He could be put in contact with an organisation such as the Hepatitis C Trust or a local support network to address particular anxieties and misconceptions he may have – about any aspects of the disease or its treatment.

17 National Institute for Clinical Excellence Guidance on Hepatitis C, peginterferon alfa & ribavirin – see references TA 75, 106 & 200.



Dr Fixit on alcohol, obesity and hepatitis C

Dear Dr Fixit

Shaun is a 49 year old patient who has been in drug treatment at my surgery for 7 years. During this time he has ceased all illicit drug use. However over the past 2 years his alcohol use has increased and he is now drinking 3 cans of strong lager a day, he says to cope with boredom and to cheer him up. He lives alone, but has regular contact with his son and daughter who are in their 20's. He has also steadily put on weight whilst he has been in treatment and now has a BMI of 34. He smokes ½ ounce of tobacco a day. He has recently tested PCR positive for hepatitis C and wants to start treatment but I have heard that people drinking this much don't get accepted for treatment programmes. How can I help him?

Answer provided by Steve Brinksman, Clinical Director SMMGP

When teaching medical students and GP registrars at Fixit Health Centre I make a point of stressing to them early on that a basic issue in primary care is to learn to deal with uncertainty and at the same time to be aware of the fundamental interconnectedness of all things¹. Shaun presents with multiple possible pathologies that can interact with each other to potentiate the level of morbidity that occurs. Like Dirk Gently we must learn to take a holistic approach in which our relationship with the patient is equally as vital as our diagnostic acumen and our prescription pad. Whilst acknowledging the importance of understanding the disease processes involved we must also

1 Douglas Adams: Dirk Gently's Holistic Detective Agency

provide information and psycho-social support to try and effect behavioural change².

Faced with the three commonest causes of cirrhosis the outlook for Shaun's liver would appear bleak. However there is evidence that two of these problems, alcohol and obesity, can be resolved or at least be significantly ameliorated by behavioural change and the third, hepatitis C, is potentially treatable by medical intervention.³

The fact that Shaun is keen to get into a treatment programme suggests he is aware of some of the issues surrounding chronic viral hepatitis and that he has some motivation to change. This may well provide the impetus to promote other changes. It will be important to assess any underlying liver damage but I would not wait for the results of investigations before trying to engage him in making the significant alterations necessary in his life. I find that referring to significant weight loss and reductions or preferably abstinence from alcohol can be difficult and you may need outside help if you have it available. The focus should be on the fact that there are treatments for these conditions which have been shown to have significant results.

Arrange LFTs and also send him for an ultrasound scan of his liver. Viral hepatitis, alcoholic and non-alcoholic fatty liver disease (sometimes referred to as steatosis) can all produce abnormal LFTs. However very high levels would be best managed with an urgent hepatology assessment. The ultrasound scan may show evidence of fatty change within the liver and if associated with abnormal LFTs referral for liver biopsy or if available a fibroscan should be considered.

Trying to maintain a holistic approach we should remain aware of other possible non-hepatic problems. Non-Alcoholic Fatty Liver Disease is one of the components of metabolic syndrome so the possibility exists that he may have associated co-morbidities such as hypertension, hyperlipidaemia and impaired glucose tolerance or even type 2 diabetes. Should any of these problems co-exist then they should be treated and

2 Miller W, Rollnick S (2002). *Motivational interviewing; preparing people for change*. Second edition. New York: Guilford Press

3 National Institute for Health and Clinical Excellence CE TA75 Hepatitis C pegylated interferons, ribavirin and alpha interferon: guidance

there is some evidence that statins may reduce the hepatic risk in NAFLD as well as the cardiovascular risk.

Shaun has already mentioned that his alcohol consumption is linked to boredom and to "cheer him up" and there is a large overlap between common mental health problems such as depression and anxiety and excess alcohol and drug use. Clinical judgement and a validated screening questionnaire should be used to assess if this may be true for Shaun. If so then treatment for his mental health may help him reduce or stop his alcohol. Referral to mutual aid groups and local day services may also help him reduce his boredom and improve his mood and motivation.

“you can give practical advice such as reducing the strength of alcohol he is consuming”

Hepatitis C treatment should no longer be denied to patients purely because they are in opiate substitution treatment and increasingly evidence suggests that even those continuing to use illicit drugs may benefit from treatment. However it is well established that not only does excess alcohol hasten the progression of the disease but it also adversely interferes with treatment, an effect exacerbated by both obesity and cigarette smoking, and for this reason some services may decline treatment until he has reduced or stopped his alcohol use. Shaun is also older and male both of which reduce the chance of treatment success, highlighting the need for him to make as much positive change as possible.

With Shaun drinking over 100 units a week, he probably has a degree of physical dependence and so may need a community or in-patient detox. If he is not motivated to take this step, brief interventions have been shown to be effective⁴ and as part of this you can give practical advice such as reducing the strength of alcohol he is consuming such as reducing from 9.8% ABV lager to 5.6% ABV. This will reduce his units by over a third even if he continues to drink 3 cans a day. If he manages this,

4 Dunn C, Deroo L, Rivara F (2001). The use of brief interventions adapted from motivational interviewing across behavioural domains; a systematic review. *Addiction*;96:1725-1742

then set him another goal for example to reduce his weekly units to under 50. Work with him at each stage, encourage him and celebrate that he is a step nearer to treatment. Keep working with him and if available get support from an alcohol counsellor or project.

Shaun should also be encouraged to lose weight and as he lives alone he may need help and advice on preparing healthy lower calorie meals as well as increasing his exercise. Before recommending a significant increase in exercise it would be a sensible precaution to assess his risk of cardiovascular disease. Regular review around weight loss is effective and when coupled with peer support is one of the reasons that weight watchers and similar groups can be successful. There would also be benefit from smoking cessation.

Most of us find so much change at one time daunting and may choose to make smaller changes or concentrate on one area at a time. This approach may give the confidence to later effect other changes and in the absence of evidence of significant liver disease then I feel it should be agreed with him as to the order in which these are tackled.

COURSES AND EVENTS

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