A rapid review of liver disease epidemiology, treatment and service provision in England

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Final Report

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EXECUTIVE SUMMARY

This rapid review of the evidence relating to liver disease epidemiology, treatment and service provision was conducted by a research team at Newcastle University between August and October 2007. This work was commissioned by the Department of Health. The aims of this review were: to summarise from published literature and relevant unpublished data what is currently known about liver disease; to identify gaps in the evidence-base; and to suggest what might be done to tackle liver disease in England.

What the review found:

- England, in common with the rest of the UK, is seeing a marked increase in liver disease with reports of rising morbidity and mortality, particularly in younger age groups.

- These trends have become apparent over time and look set to continue into the future.

- UK trends are in the opposite direction to general world trends; where liver disease rates are falling.

- Our closest comparator countries (USA, Canada and France) have experienced a decrease in liver disease rates over recent years.

- UK patterns are now closest to those seen in Scandinavia; but they are still someway behind Eastern Europe.

- The key risk factors for liver disease are: excessive drinking, infection with hepatitis B or C, and obesity.
  - These risk factors are relevant to a large proportion of the population.
  - These risk factors are modifiable.
• People can acquire liver disease for other reasons such as genetic inheritance, immune response and paediatric conditions.
  o These factors account for a small proportion of liver disease.
  o These factors are generally not modifiable.

• Health professionals and the general public are unaware of the wider range of reasons (modifiable and unmodifiable) that can lead to liver disease.
  o Better understanding of risk factors could help preventive efforts.
  o Better uptake of screening would enable earlier treatment.
  o Better awareness that liver disease can result from mainstream behaviour may help to reduce stigma often associated with it.

• Regarding the key (modifiable) risk factors, different trends are emerging in different parts of England.
  o Heavier drinking in the North of England.
  o Higher rates of chronic viral hepatitis in the West and South East of England.
  o Higher rates of obesity particularly in areas of high social deprivation.

• The co-occurrence of key risk factors for liver disease has the potential to lead to a rapid increase in this condition in England (as recently seen in Scotland).

• There are evidence-based interventions that can be used to change lifestyle behaviour and modify the risk factors for developing liver disease.
  o Brief alcohol interventions to reduce heavy drinking.
  o Behaviour change interventions plus weight modification and exercise regimes to reduce levels of obesity.
  o Needle exchange schemes to prevent hepatitis B and C infections.

• There is also evidence to support other health care interventions and treatments which can reduce morbidity and mortality from liver disease.
  o Hepatitis B vaccination of high risk groups.
  o Early treatment for hepatitis C.
There is much less evaluative work on the prevention of liver disease than on treatment and limited economic evaluation of different treatment options for alcohol and obesity-related liver disease; although NICE recommend that treatment for chronic hepatitis B and C is effective and cost effective.

There is no central database of clinical activity on liver disease; service provision data are only available piecemeal from numerous disparate sources which limits the ability to gain a clear picture of NHS liver care.

There appears to be a lack of trained Hepatologists in England to meet the current and growing demand for liver care.

Current Hospital Episode statistics are difficult to interpret since they are based on data codes which do not clearly distinguish between all the different types and causes of liver disease.

New cases of liver disease seem to be increasing each year in English hospitals and there is more demand for treatment than services can currently meet.

Over the past 5 years, the number of liver transplants in England has risen by 62%; in 2005/6 the number of people waiting for a transplant rose by 38%.

There are 6 transplant centres in England but none in the South West or the North West of England; the latter is where some of the highest rates of liver disease are reported.

Survival rates from liver transplants are improving in both adults and children which means that more people will need specialist care whilst living with this condition for longer (for surviving children this is needed over their lifetime).

There is almost no research on the experiences of patients with liver disease who need to access care for this condition in England.
Evidence gaps have been noticed in the following areas:

- We noted a lack of high quality epidemiological data on various aspects of liver disease in England
  - Experience of liver disease in ethnic minority groups
  - Rates of liver disease by age/sex/region/socio-economic status
  - Numbers of new cases emerging in England each year
  - Total numbers of cases requiring (or likely to require) NHS treatment
  - These incidence and prevalence rates need to be derived piece meal or more often extrapolated from work in other countries

- There appear to be evidence gaps relating to prevention, treatment and palliative care for people with liver disease. Key gaps identified were:
  - How to improve screening for hepatitis B and C in high risk groups (as only 1-2% of HCV patients are aware of their disease)
  - Efficient means of reducing obesity in England
  - The utility of different methods of case identification to facilitate identification of liver disease at an early stage
  - The cost-effectiveness of different options for treating liver disease
  - Ways of improving quality of life in people with liver disease

- We need a better understanding of clinical aspects of liver disease including:
  - Progression from one form of liver disease to a more serious condition
  - The synergistic relationship between different modifiable risk factors for liver disease particularly the interaction of obesity and alcohol-related liver disease with each other and with the viral liver diseases
  - The interaction between modifiable and non-modifiable causes of liver disease
  - Reasons underlying the rising incidence of cholangiocarcinoma, where there has been a 20 fold increase in 20 years, and its treatment.

- We need to establish how best to get research evidence about liver disease prevention, treatment and palliation into clinical practice
• Dissemination routes – getting the evidence to clinicians
• Translation work – converting the evidence into models for care
• Implementation strategies – means of encouraging clinicians to change practice

• We need to evaluate different models of service provision for liver disease and explore ways of expanding the workforce including:
  o New roles (e.g. lifestyle advisors)
  o Expanded roles (dieticians, specialist nurses for alcohol interventions and delivering antiviral therapy)
  o New ways of working (shared care, different skill-mix)
  o Better division of labour (primary, secondary and tertiary care)

• We need research that includes patients’ perspective of liver disease covering:
  o Accessibility and acceptability of screening services to different sections of the population
  o What it feels like to experience a diagnosis of liver disease
  o How to access timely and appropriate care
  o How the negotiate generalist and specialist aspects of care
  o Patients’ experience of treatment and care delivery

Suggestions for tackling liver disease in England:

• Identify deaths from alcohol induced liver disease, hepatitis B, hepatitis C and obesity related cirrhosis as separate entities within the ONS reporting system.

• Implement screening and brief interventions to reduce heavy drinking

• Use behaviour change interventions to help tackle obesity

• Promote early detection (via screening) and treatment for hepatitis C

• Promote vaccination of high risk groups for hepatitis B
• Promote detection (via screening of ethnic minorities and other high risk groups) and treatment for chronic hepatitis B.

• Use effective treatment to ameliorate existing obesity

• Develop effective treatment for cholangiocarcinoma

• Educate health professionals and the public about risk factors for liver disease

• Address current misinformation and prejudice concerning liver disease

• Ensure equitable access to treatment for liver disease in all areas of England by promoting hepatology networks.

• Plan ahead in terms of the likely need for more liver services in England.

• Ensure that there is an appropriately configured and trained workforce to deal with the growing problem of liver disease in England.

• Establish a hepatology research network within the comprehensive research network (UKCRN) to develop and evaluate new therapies where there is unmet clinical need.

• Develop a national audit tool with appropriate IT support to monitor the changing incidence of liver disease in England; this would have the potential added-value of being able to capture the impact of interventions used to prevent liver disease in the future.
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1. REVIEW METHOD

1. We compiled a comprehensive list of key informants on liver disease from recently published work \(^1\) and consulted a group of expert clinicians to ensure that all relevant individuals and treatment centres were included.

2. We wrote to all key informants (individuals and agencies) to request relevant data and research reports (published or unpublished) on liver disease.

3. We used responses in 2 to access further key informants whom we emailed to request further information [see Appendix I for the full list].

4. We searched electronic medical databases (Medline, Embase, EconLit, Cochrane Library) for relevant literature on liver disease epidemiology, treatment and service provision.
   a. Given recent reviews of liver disease \(^1-5\) we focused on material from 2005/7.
   b. We used a reported search strategy for epidemiological studies \(^2\) with additional key words and a health economics search strategy developed in other work [see Appendices II-IV for search strategies and relevant acronyms].

5. We conducted key-word searches on internet search engines (Google, Google Scholar) to access recent papers and reports and tracked down hard copies via e-journals or inter-library loans.

6. Given the time-frame for this rapid review and the large volume of material, we were not able to formally appraise the research studies that were identified. However, the vast majority of the material was from peer-reviewed journals and so we felt the content was quality-assured and authoritative.
7. We did not conduct formal data abstraction of the material instead we synthesised it into a descriptive (best-evidence) summary. This narrative was structured around the patient journey into liver disease:
   a. Who develops liver disease and what are the consequences?
   b. How do people get liver disease and can it be prevented?
   c. At what stage is liver disease identified?
   d. What happens to people with liver disease in terms of NHS treatment?

8. We used the evidence to recommend what could be done to tackle liver disease now; and identified gaps in the literature to identify areas where further research is required.

9. We produced an initial report in November 2007 which was circulated to the expert clinician group and other key experts for feedback and validation of the content.

10. We incorporated suggestions and comments from the peer review process to produce this final report of our review.
2. LIVER DISEASE – GENERAL EPIDEMIOLOGY

The liver is a large organ in the upper right abdomen that aids in digestion and removes waste products from the blood.

In the simplest terms, liver disease refers to any disorder of the liver and includes the following conditions:

- Steatosis or fatty deposits in the liver
- Fibrosis or scarring of the liver;
- Hepatitis or inflammation of the liver;
- Cirrhosis where scarring and inflammation spread through the liver and irreversibly disrupt its shape or function causing permanent cell damage and ultimately liver failure and leading to liver cancer.
- Liver cancer which causes ultimately liver failure and death

Liver disease mortality

As many as one in 10 people in England have some form of liver disease \(^6\) and many of them die prematurely from this condition. Liver disease is currently the fifth most common cause of mortality in the UK for both men and women. \(^3\) However, whilst the mortality rates for the other 4 major causes of death are falling, the trend for liver disease is steadily rising in both sexes (See Figures 1 & 2).

The codes defined by the 10th revision of the International Classification of Diseases (ICD-10) for all diseases of the liver are K70-K76 [see Appendix V]. Chronic liver disease, which includes alcoholic liver disease, is specified by the codes K70 and K73-K74.
In 2006, the mortality rate for males from all types of liver disease was 161 male deaths (age standardized per million population) compared to 87 in 1996, representing an 85% increase over the last decade. The corresponding rate for females was 86 deaths compared to 52 in 1996, representing a 65% increase over the last decade.\(^3\)

Death rate changes over the last 25 years (1981 to 2006) showed a 177% increase for men and 100% for women (in 1981 there were 58 male deaths and 43 female deaths).
Recent estimates suggest that liver disease mortality may double again in the next decade. ³

Although the death rates for liver disease are lower than the other four main causes of death in the UK, the persistently increasing rates for liver disease are concerning.

The significant upward trend for both men ($R^2 = 0.98$) and women ($R^2 = 0.95$) shown in figure 3 for chronic liver disease indicates a clear need to plan ahead in terms of NHS treatment services. For context, $R^2$ is a statistical measure of how well a regression line approximates real data points; an $R^2 1.0$ (100%) indicates a perfect fit.

![Figure 3. Deaths from chronic liver disease in England and Wales. Source: ⁷](image)

Cirrhosis and primary liver cancer accounts for one in every 40 (2.5%) deaths worldwide. ⁸ Historically, the UK has experienced relatively low rates of liver disease compared to mainland Europe, particularly Mediterranean countries. However, since the 1970’s UK increases in deaths due to liver disease have been accompanied by a corresponding fall in European figures (see figure 4).
Liver Cirrhosis

The majority of liver deaths are due to cirrhosis \(^2\) and it has recently been reported that there are about 4-5000 deaths from cirrhosis in the UK each year. \(^10\) \(^11\)

A recent population-based study reported a 41\% increase in new cases of cirrhosis each year (incidence) in the UK between 1992-2001. \(^12\) In this General Practice study, 3,360 new cases were identified and the incidence rate was 14 cases per 100,000 population. Median age at diagnosis was 56 years for men and 61 years for women. \(^12\)

Detailed analyses of liver cirrhosis data between 1991 and 2001 showed that mortality in men rose by two-thirds in England and Wales (67\%) and more than doubled in Scotland (112\%). The corresponding increases in women were 35\% in England and Wales and 63\% in Scotland. \(^13\) \(^14\) This work reported particularly large increases in younger age groups (15-44) see Figure 5.

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**Figure 4.** Trends in standardised mortality rates (per 100,000 population) for chronic liver disease in the UK and in Europe, 1970-1998. Source: \(^9\)
These data are notable since liver disease has typically been considered a disease of older age. However, a growing number of reports show that cirrhosis in England is occurring in younger people. See Table 1 and Figure 6-7. Deaths of individuals in their twenties have been reported and whilst the absolute numbers are low, the proportionate increases are not.

Table 1. Numbers of deaths in England from chronic liver disease. Source: 16
Regional trends

Within England, the greatest numbers of deaths from chronic liver disease are found in the North West and North East of England. These two regions were reported to have the highest rates of heavy drinking in England and alcohol-related hospital admissions. These areas also have some of the highest rates of social deprivation in England.
Figure 7. Distribution of deaths from liver disease across England. Source: 19

*International trends*

Recent worldwide assessment of mortality due to liver cirrhosis shows a favourable downward trends in most countries of the world except for the UK, Eastern Europe and parts of Scandinavia 20 see Figures 8-10.
Figure 8. Male (top, black bars) and female (bottom, pink bars) age-standardized mortality rates for diseases of the liver. Shown are countries with increasing trend for years with available data between 1950-2005. Source 17
Figure 9. Male (top, black bars) and female (bottom, pink bars) age-standardized mortality rates for diseases of the liver. Shown are countries with decreasing trend for years with available data between 1950-2005. Source^{17}
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Liver cancer

The other main cause of death from liver disease is due to liver cancer; although it should be noted that cirrhosis is a specific precursor of liver cancer. Liver cancer can either arise in the hepatobiliary system itself (primary liver cancer) or metastasize from a tumour elsewhere in the body (secondary liver cancer).

Most liver cancer (95%) is a secondary cancer.

Nevertheless, primary liver cancer caused 2091 deaths in England and Wales in 2001 and mortality rates have steadily increased over the last three decades (West et al. 2006). There are about 2300 new cases each year, with an overall incidence of 4 per 100,000 population. Liver cancer is more common in men compared to women and it predominately occurs in older people, peaking in the 7th decade.
Primary liver cancer consists of either Hepatocellular carcinoma (HCC) which arises in liver cells (hepatocytes) or Cholangiocarcinoma (CCA) which arises in the bile ducts either within (intrahepatic) or outside of the liver (extra-hepatic). HCC is responsible for the majority (70-85%) of primary liver cancer world-wide. However, recent rises in primary liver cancer have been attributed to a rapid rate of increase in CCA.

Incidence of CCA has increased 16-fold in England and Wales since 1971 whilst HCC has increased three-fold over this time. CCA has increased dramatically in both men and women in England and Wales; it is the commonest type of primary liver cancer in English women. HCC increases have only been significant in males; it is the commonest type of primary liver cancer in English men.

**Conclusion**

A large number of people die from liver disease in England each year, and these individuals are dying earlier than they used to. The highest death rates from liver disease are found in the North of England. International data show that the pattern of liver disease in England is closer to that of Scandinavia rather than the pattern seen in our usual comparator countries (the USA, Canada, France).

In the following section we describe the patient journey into liver disease (how they developed this condition), what the consequences of liver disease are for them (morbidity and premature death); and how we can prevent and/or treat people with this condition.
3. MAJOR LIVER DISEASE

In this section we describe the key risk factors that cause individuals to develop liver disease. All these risk factors involve a behavioural component. Thus these risk factors are all potentially modifiable.

The key risk factors for liver disease in England are:

- Excessive alcohol consumption
- Infection with the hepatitis C virus (HCV)
- Infection with the hepatitis B virus (HBV)
- Obesity and the metabolic syndrome
ALCOHOLIC LIVER DISEASE (ALD)

Alcohol is responsible for 70% of cirrhosis deaths in the UK. Thus cirrhosis deaths and chronic liver disease are often used as a proxy for the prevalence of ALD in the population.

Likewise, alcohol death statistics are sometimes used as an indicator of alcoholic liver deaths. In the Office for National Statistics (ONS) data, cirrhosis accounts for 85% of the total alcohol deaths. Generally however, it is thought that liver disease accounts for between 15% and 25% of all alcohol-related deaths.

ALD has only been recorded separately from liver disease in England and Wales since January 2001. It is important to be aware of this when considering the data presented below.

Who gets ALD and what are the consequences?

Alcohol consumption accounts for the greatest proportion of liver disease in the UK; recent studies report that between 50 and 60% of liver disease is alcohol-related.

Mortality from ALD has increased rapidly in England over the last three decades. Thirty years ago the leading causes of mortality from liver disease were non-alcohol-related. However, over the past 30 years mortality from alcohol-related cirrhosis has overtaken and exceeded deaths from non-alcohol-related liver disease; the mortality rate from alcohol-related cirrhosis rose from 1 to 8 per 100,000 deaths between 1975 to 2000.

There are geographical variations in the prevalence of ALD in the UK. In 2005 the highest mortality rate from chronic liver disease was in the North West of England for both men and women, 18.7 per 100,000 in men and 10.3 per 100,000 in women. Rates were lowest in men (8.1 per 100,000) and women (5.1 per 100,000) in the South East of England.
Thus the Association of Public Health Observatories reported that there was an emerging north-south divide in mortality rates for chronic liver disease which was primarily due to alcohol. It is widely reported that Scotland has the highest rates of cirrhosis and alcohol-related deaths in the UK\textsuperscript{14,15} and there is concern that if rates continue to rise in the North of England they will soon equal those found in Scotland.

Data consistently show that cirrhosis and other alcohol-related mortality is higher amongst those in the lower socioeconomic classes.\textsuperscript{28,29} Recent trends in alcohol-related deaths in the UK, illustrate clear differences in mortality rates between the least and most deprived areas.\textsuperscript{23} For males living in the most deprived areas the rates of deaths due to alcohol was more than five times higher than those living in the least deprived areas rising, that is 31.9 compared to 6.2 deaths per 100,000. For females alcohol-related death rates in the most deprived areas were over three times those in the least deprived areas, that is 11.3 compared to 3.7 deaths per 100,000 respectively. In both males and females, the North-West of England had the highest alcohol-related death rates in the most deprived areas.\textsuperscript{28}

Few studies have considered variations in ALD by ethnicity. However there is some evidence of higher mortality rates from ALD in Black and Asian men with this condition compared to White British men.\textsuperscript{2,30} In their analysis of mortality from liver disease in the West Midlands between 1993 and 2000, Fisher et al\textsuperscript{30} found that Asian men had a mortality ratio 3.79 times greater than that of white men. This study was based on a small sample but the authors concluded that this area was worth further study. Indeed demographic analyses of alcohol-related deaths commonly excludes ethnicity and this issue needs further investigation.

Recent data for 2001-2005 reported variation in alcohol-related mortality by occupation. For males, sea-farers and coal mine operators had the highest standardised mortality ratio, while for women, publicans and bar staff had the highest rates, men in the alcohol industry also had high rates.\textsuperscript{31}

People die younger from alcohol-related liver disease compared to non-alcohol related liver disease. In 2004, the mean age at death was 53.7 years for men with alcohol-related liver disease compared to 66.4 years for men with non-alcohol related liver
Liver disease. The same data shows that the mean age at death was 54.8 years for women with alcohol-related liver disease compared to 65.6 years for women with non-alcohol related liver disease.  

Overall, the mean age of death from liver disease has decreased over the twenty years from 1984 – 2005, falling from 60 years in men in 1984 to 58 years in 2005 and from 63 years to 61 years in women during the same period.  It is likely that the increase in deaths from alcohol-related liver disease have brought down this average.

The growing levels of ALD are putting an increasing burden on the National Health Service. Hospital Episode Statistics (HES) for England reveal that hospital admissions for ALD doubled between 1997/98 and 2004/2005 rising from 17,732 to 35,335. In these patients, the average length of stay fell slightly from 8.4 days in 1999/98 to 7.1 days in 2004/2005 but still remained high.

How do people get ALD and can we prevent this?

There is a well established relationship between individuals’ daily alcohol consumption and risk of developing liver disease. Drinking above the recommended weekly limits advised in the UK results in increased risk of developing liver disease.

A US study found that for men who die between the ages of 35 and 69 years the risk of death from liver cirrhosis increases from 5 per 100,000 with no alcohol consumption to 41 per 100,000 if drinking 4 or more drinks per day.

The pattern of alcohol consumption and the types of alcohol that are consumed are important in determining the risk of ALD. A steady pattern of drinking rather than binge drinking is more likely to be harmful to the liver. Drinking without food is also likely to increase the risk of developing liver disease and some studies have shown that drinking wine carries a lower risk of developing liver disease than beer and spirits. However, a recent study has challenged this finding and identified increases in wine consumption as the main contributing factor to increases in cirrhosis mortality in the UK.
There is also emerging evidence that the majority of people admitted to hospital with ALD are not alcohol-dependent drinkers but are heavy drinkers whose social drinking has got out of control. 39

The specific risk of liver disease due to heavy drinking is concerning since numerous data sources describe a high prevalence of heavy drinking in the UK. Data from the General Household Survey (GHS) in 2005 showed that one in four men (24.5%) and one in seven women (14.5%) were consuming hazardous or harmful levels of alcohol. 27

Hazardous drinking is defined as consumption above recommended limits which increases the risk of physical or psychological harm. Harmful drinking is defined by the presence of physical or psychological symptoms.

Similarly the Alcohol Needs Assessment Research Project (ANARP) carried out in 2004 found that 26% of people aged between 16-64 years have an alcohol use disorder (AUD), which is equivalent to 8.2 million people in England. 40 In ANARP, an AUD included hazardous, harmful or dependent drinking.

The proportion of women drinking at hazardous and harmful levels is particular noteworthy as these figures have increased over recent years while heavy drinking in men seems to have stabilised. Self reported GHS data showed that the proportion of women drinking above recommended limits increased between 1988 and 2002 from 10% to 16% in women while in men the figure remained around 27% during this period. 27

Population studies have consistently found a strong relationship between cirrhosis mortality rates and per capita alcohol consumption in the population, see Figure 11. 41 However, there is a lag in this relationship, thus cirrhosis mortality rates are influenced by the alcohol consumption rates of several previous years. 41 42
Despite the greater risk of cirrhosis from heavy drinking, high alcohol consumption is not always the full story, since just one in five people drinking at hazardous or harmful levels progress to cirrhosis. Thus genetic and environmental factors may also be important in determining which patients progress from a fatty liver in the first instance to fibrosis and cirrhosis thereafter. However, more research is required on this issue and particularly to confirm that genetic susceptibility may be more pronounced in women compared to men.
Most studies have found that women are more likely to develop liver disease at lower doses of alcohol than men. It has been reported that the risk of developing liver disease is significant for women drinking above 7-13 drinks (84-156g) per week and in men drinking 14-27 drinks (168-324g) per week. This may be due to the fact that women have a lower amount of body water per weight than men, hence blood alcohol concentration rises higher and faster because it is dissolved in a smaller volume of water.

**Overlapping risk factors**

However, there are within-sex differences of developing ALD. Recent studies have suggested that excess weight or BMI score are independent risk factors for the development of ALD. This combined with women’s higher body fat ratio compared to men could be an additional factor influencing their increased susceptibility to ALD.

Individuals with hepatitis C infection who drink over 50/60g of alcohol per day have an increased risk of developing cirrhosis. One explanation given for the increasing rates of cirrhosis in UK men while levels of alcohol consumption have remained stable over recent years is the increased prevalence of obesity and hepatitis C infections in the population. The additional risks for hepatitis C patients that consume alcohol within recommended daily limits is currently unclear.

**Prevention**

The most effective preventative measure for alcohol-related liver disease at an individual level is not to drink alcohol. Unlike some other alcohol-related illness, such as heart disease, ALD does not occur in those people that have never consumed alcohol. However, it should be emphasised that not drinking alcohol does not prevent individuals from developing liver disease from other causes. In addition, moderate alcohol consumption is known to have coronary protective effects. Thus the safest policy recommendation is for individuals to drink within the recommended daily or weekly limits.

At a societal level there is evidence from comparative studies that increasing the price of alcohol via taxation and restricting the availability of alcohol are effective at reducing cirrhosis deaths. Methods for restricting the availability of alcohol
included increasing the drinking age and reducing the number of outlets selling alcohol.\textsuperscript{28} It has been concluded that, in populations with a relatively high number of heavy drinkers, the most cost-effective interventions to reduce hazardous drinking were increased price via taxation and restricted access.\textsuperscript{51} Brief alcohol interventions delivered in primary care were also highly effective\textsuperscript{52} but were considered more expensive to implement than the policy options.\textsuperscript{51}

The first Alcohol Harm Reduction Strategy for England included several strategies aimed at reducing the prevalence of heavy drinking in the population including: a campaign to promote responsible drinking among young people, a clampdown on irresponsible promotion, and extra funding for services for people with alcohol problems.\textsuperscript{49} However, the evidence relating to educational campaigns is weak and not regarded to be cost-effective.\textsuperscript{51,53} Also, whilst young people are an important target group in terms of future liver disease, the people currently at greatest risk are the adult population who may have been drinking heavily for a number of years. The recently refreshed Alcohol Strategy\textsuperscript{54} has broadened the focus to harmful adult drinkers which is a good step in tackling liver disease. Future work could broaden further to hazardous drinkers. Although this may be perceived as unpopular, the fact that one in five people are hazardous drinkers and one in five people are overweight or obese (it is not clear what overlap exists in these figures), brings the issue of liver disease into the mainstream population. The prevalence of heavy drinking in obese people and vice versa is a clear gap in our current knowledge.

The refreshed alcohol strategy has also proposed an independent national review into the relationship between alcohol pricing and promotion and heavy drinking.\textsuperscript{54} This is a positive development given the international evidence on this issue.

It is increasingly apparent that secondary risk factors of ALD need to be addressed if ALD is to be prevented. If firmer evidence confirms the link between genetic factors and increased likelihood of developing liver disease, then targeted counselling of those with increased risk might be a future option.\textsuperscript{55} However, more immediately, strategies which aim to reduce obesity may also achieve positive gains in the prevention of ALD. It would be very helpful to increase public awareness of the possible ‘double hit’ to the liver from excessive weight and heavy drinking. There is
also a clear opportunity to link food and drink issues in health promotion work in a ‘two for the price of one’ approach to achieving health gains in the population.

As ALD does not show symptoms until the most advanced stages, where mortality is high, detection of harmful or hazardous drinkers at an early stage in primary care settings is a key aim for secondary preventive work. There is a growing call for a roll-out of screening and brief interventions in England to help reduce hazardous and harmful drinking. These interventions are supported by robust evidence and are known to be cost-effective ways of reducing heavy drinking in health setting.

Once ALD develops the most effective form of tertiary prevention, to reduce the risk of advancing to a further stage, is to stop drinking. Improving the support provided to liver disease patients to remain abstinent and reduce their risk of progressing to a more advanced stage is key and there is evidence that nurse-led services are effective in supporting this work.

At what stage is liver disease detected?

The symptoms of ALD are slow and silent. ALD is often not detected until the advanced stages, with variceal haemorrhage or decompensated liver with ascites, at which time the prognosis is poor. Verrill et al. reported that 67% of a sample of patients with ALD were not admitted to hospital with an alcohol-related condition prior to being diagnosed with liver disease. These authors concluded that primary care has the most potential for detecting heavy drinking which puts patients at risk from liver disease. Indeed there is evidence that heavy drinkers visit their GP twice as often as lighter drinkers, making primary care the optimal setting for earlier identification of heavy drinking and brief intervention.

A recent small scale American study has shown that alcohol screening questionnaires can predict subsequent hospitalizations for alcohol-related GI conditions.

Liver function tests have been advocated for use in primary care. However 1 in 25 people have abnormal liver function results and there is concern about the
accuracy of these tests at identifying liver disease. Thus there is a need for an evidence based protocol of work-up, referral and further investigation.

Detection or diagnosis of alcohol-related cirrhosis requires liver biopsy or the presence of oesophageal varices. These are costly procedures which can carry inherent risks. Thus the ideal policy option is to promote earlier identification of risk behaviour in the population and brief (and cheap) interventions to reduce excessive drinking (and ideally associated risks factors such as weight gain) to achieve a reduction in the currently high rates of ALD in England.

What happens to patients with ALD? Treatment issues.

The stage of disease that patients present to health services and subsequent alcohol consumption are the two most important factors in prognosis of ALD.

Alcoholic fatty liver develops in the majority of people that consume heavy amounts of alcohol, however if detected early, this first stage of ALD is reversed with abstinence. Of those that continue to drink up to 30% develop cirrhosis within 10 years.

Alcoholic hepatitis develops in 10-35% of people that develop fatty liver and does not develop until 15-20 years of heavy drinking. The five year prognosis for patients that reduce their intake or abstain is almost 80% while for patients that continue to drink this decreases to 60%.

The levels of mortality in patients with alcoholic hepatitis despite abstinence, have led to the development of additional treatments. Corticosteroids are the main therapy to show benefit in some stages of the disease and in some though not all patients.

The final stage and irreversible stage of liver disease is cirrhosis. For patients developing cirrhosis prognosis varies between those with compensated and decompensated stages of the disease. If the cirrhosis is caught when it is compensated
average survival is 10 years for decompensated cirrhosis average survival is two years or less.  

Despite cirrhosis taking 10-20 years of drinking heavily to develop anecdotal evidence has revealed that in recent years individuals as young as 21 years have died from ALD.

Liver transplants are the main treatment option for patients with end-stage liver disease although transplants are only suitable for certain patients. Data from the UK Transplant 2000 -2002 showed that the greatest proportion (16.4%) of patients listed for liver transplants had a diagnosis of ALD. Six months abstinence from alcohol is one condition for patients before they will be considered for transplant. This remains controversial, as period of abstinence does not reliably predict abstinence afterwards.

A key concern for ALD patients that have transplants is whether they continue drinking post-transplant since this can lead to graft damage or non compliance. It is reported that short and long term survival for patients that have transplantation for ALD are similar to those that have other types of liver disease. Furthermore the number of patients that return to alcohol consumption after transplant is similar to those treated for other conditions. Less than 10% continue drinking more than 21 units per week and less than 5% damage their graft as a result of alcohol consumption.

More needs to be done to support ALD patients to remain abstinent for longer post-transplant. As pathways of care are currently inconsistent it is recommended that pathways of care might be best managed through a multidisciplinary approach. The British Society of Gastroenterology recently proposed a number of recommendations for the care of patients with alcohol-related disorders which included the employment of an alcohol health worker who can amongst other factors provide ongoing support to patients with alcohol-related liver disease and access to community services.
Conclusions

The Department of Health needs to recognise the importance of early detection of hazardous and harmful drinkers in primary care and the value of brief interventions to reduce risky alcohol consumption at the earliest stage when it is most responsive to change.

The patterns of drinking that leads to ALD are not confined to ‘stereotypical’ dependent drinkers, they are shown by mainstream people who drink heavily. Health professionals need to be aware that brief screening questionnaires can identify excessive drinking more easily and cheaply than blood tests.66 A more extensive programme of screening for excessive drinking in the population may be required to tackle liver disease problems now and in the future.

The key issue is to better understand the inter-relationships between obesity, chronic hepatitis infection and heavy drinking in the genesis and progression of liver disease. Future health promotion campaigns may need to consider linking the ‘big-hitting’ issues of heavy drinking and over-eating if the burden of liver disease is to be reduced in England.

Evidence gaps

There is strong evidence about the risk factors associated with ALD. However cirrhosis and alcohol-related deaths from all causes are frequently used as proxy indicators of ALD. There is a need for specific and up-to-date information about ALD including the incidence and prevalence of the different stages of the disease.

This review has found limited information about how or where the different stages of ALD are detected. There is a gap in our knowledge about identification and management of liver disease in primary care. Better data about how ALD is first detected and its stage of development would inform work on developing appropriate targeted prevention and detection pathways.
We found very little work on heavy drinking in minority groups in England or on the experience of people from these population sub-groups who receive treatment for liver disease.

We need more work on possible synergistic relationships between alcohol, obesity and chronic hepatitis in the development of liver disease.

We found no work on patient perspectives of ALD and experience of treatment. Previous work has suggested that a key barrier to tackling liver disease might be poor public perception of the types of people who acquire this condition. Given that mainstream behaviour such as heavy drinking and over-eating can increase the risk of liver disease this should be reversed. Sensitive qualitative research with people experiencing liver disease would appear to be a research priority.

There are several small studies reporting the effectiveness of nurse-based and multidisciplinary aftercare services in England and Wales for increasing abstinence from alcohol after treatment for liver disease. This evidence-base needs to be developed with an emphasis on the effectiveness of treatment services on the prognosis of patients with, or recovering from treatment for, ALD.
CHRONIC HEPATITIS INFECTION AND LIVER DISEASE.

Globally, chronic viral hepatitis infections account for the majority of liver disease, both cirrhosis of the liver and hepatocellular carcinoma (HCC), in nearly all regions of the world.\textsuperscript{8}

Chronic hepatitis is a complex syndrome with multiple causes, varying stages of inflammation and liver damage, different prognoses and responses to treatment.\textsuperscript{67}

The major sources of chronic hepatitis are due to infection with hepatitis C and B. [A brief description of the other hepatitis viruses in found in Appendix VI]

Around 25\% of all liver disease cases in the UK are due to hepatitis infections and this number is likely to increase in the future.\textsuperscript{68}
LIVER DISEASE DUE TO THE HEPATITIS C VIRUS (HCV)

Hepatitis C is a blood borne virus, which affects 180 million people worldwide. As hepatitis C is an RNA virus, it mutates rapidly and therefore the immune system is unable to locate and destroy it effectively.

There are 6 major strains of the virus, known as genotypes 1 to 6. Different strains predominante in different parts of the world. The most common viral forms in England are genotypes 3a (37%), 1a (32%) and 1b (15%). For comparison, the prevalence of genotype 1b is 78% in Japan, 68% in Italy and 21% in the USA.

Symptoms of hepatitis C infection include fatigue, pain in the liver area, digestive problems, concentration difficulties and flu-like symptoms such as headaches, shivering and aching joints. The presence or absence of symptoms is no indication of how much damage the virus is doing to the liver, which is why hepatitis C is also called 'the silent killer'.

Approximately 20-50% of those infected with hepatitis C naturally clear the virus from their body and experience no long-term affects from the infection.

A major cause of hepatitis C transmission was via blood transfusion prior to September 1991 (when screening was introduced in England) or blood products prior to 1986 (when viral inactivation measures were introduced).

A global review exploring hepatitis C transmission via blood transfusions reported that, after an average of 15 years later, approximately 75% of the adult patients tested positive for HCV, and the frequency of liver cirrhosis was 15–20%. More favourable outcomes were observed in children and young women.
Who gets HCV and what are the consequences?

The exact prevalence of hepatitis C is difficult to establish but current estimates suggest that around 200,000 to 500,000 people in the UK are infected with the virus (0.4 to 1% of the population), with many cases going undiagnosed. The recent Health Protection Agency annual report stated that 0.5% of the general population was affected by the hepatitis C virus. These figures equates to every GP having around 8 to 18 infected patients on their patient list, based on an average list size of 1,800.

Due to the asymptomatic nature of the infection, the prevalence of HCV in children in the UK is unknown. Between 1997 and 1998, the British Paediatric Surveillance Unit identified 182 infected children, most of whom were infected through blood products. However, it is now likely that most infected children are born to HCV positive mothers. It is estimated that 1150 pregnancies annually in the UK involve a woman infected with HCV, leading to approximately 70 infected babies being born each year. Transmission from mother to baby is almost always confined to women who have detectable HCV RNA.

At present, only 50,000 patients have been diagnosed with chronic hepatitis C in the UK, meaning that up to eight out of ten cases have no idea they are infected. Under diagnosis and subsequently under reporting are well documented problems with hepatitis C infection. Thus it is difficult to accurately plan treatment services since planning data are mostly educated estimates.

Compared to other countries (see Figure 12), the prevalence of hepatitis C infections in the UK is low; 4.1 million people in the USA (1.6% of the population) and 6.7 million Europeans suffer from chronic hepatitis C infection (0.9% of the population). However, it is difficult to establish if the UK rate is genuinely lower than in other countries or if we are less adept at identifying cases (see above).
The incidence of hepatitis C in the USA has declined in all ages and ethnic groups since the mid 1990s after a peak in the late 1980s. This decline is primarily due to a decrease in cases amongst injecting drug users (IDUs), as a result of harm reduction strategies within this high risk group. However, even though the number of new cases has declined, a substantial burden of chronic hepatitis C persists.

It is difficult to quantify the incidence of hepatitis C infections since the number of reported cases reflects the number of individuals being tested, rather than the actual incidence of disease. Furthermore, in the majority of identified cases the infection may have been contracted many years previously as there are no laboratory assays to detect acute infections.

Many people with hepatitis C are unaware that they have this infection and some live out their normal lifespan with no symptoms. This absence of physical symptoms also contributes enormously to the lack of detection of the disease. However, around 20% of people living with chronic hepatitis C infection will develop cirrhosis some 20 or 30 years after contracting the virus.

Recent analysis of around 50,000 laboratory-confirmed diagnoses of hepatitis C in England, demonstrated that 69% of cases were males and 53% were aged between 25
and 39 (see Figure 12). Thus hepatitis C affects relatively young people. However, it must be noted that laboratory diagnosis of hepatitis C predominantly occurs in current or former IDU’s.

![Figure 12. Age and sex distribution of laboratory reports of hepatitis C infection from England: 1996 to 2005.](image)

This age-trend is seen in the USA where the greatest incidence of hepatitis C was in the 25 to 39 age group. Interestingly however, this group has seen the greatest decline in rates since the mid-1990s; it has been found that since 1992 the incidence rate has declined by 92%. 82

There are gender variations in the prevalence, treatment and response to hepatitis C. Hepatitis C is less common in women and they tend to develop a more benign course of liver disease compared to men as they are more likely to have an enhanced response to interferon treatment. 48 However, women are more sensitive to the hepatotoxic effects of alcohol, a co-risk factor for liver disease. 48

Hepatitis C also exhibits geographical variation (see Table 2), with an apparent East/West divide. The highest number of cases are reported in the North West and South West and the lowest numbers in the North East, Yorkshire and East Midlands. 1

Incident rates of hepatitis C and B are associated with deprivation, poverty and level of education; thus socio-economic status is also a contributing risk factor. 1 80
Table 2. Laboratory reports of hepatitis C infection by English region: 1992 to 2005. Source: 69

In terms specific ethnic groups, a study conducted in the USA concluded that incidence rates were similar across ethnic/racial populations (see figure 13). 82 This finding was in contrast to previous findings in the 1990s. 82
Recently funded case finding work has begun to explore hepatitis C infections in ethnic minority populations living in East & West London, Walsall and Bradford. The results of this project will better advise the incidence rates and subsequent needs of cultural minority groups in England.

Statistical modelling of the prevalence of HCV antibodies in England and Wales (combining a variety of data sources from 1995 to 2003) reported that 231,000 people within the ages of 15-59 were predicted to have HCV antibodies in 2003. This predicted figure gave a prevalence rate of 0.53% in this age group and a ratio of infected males to females of 2.4 : 1.

This statistical modelling was unable to estimate an overall population prevalence due to the lack of data for the over 60s population. This statistical model should be updated and refined as new information becomes available.
About a third (31%) of chronic hepatitis C infections are in current IDUs, 57% are in ex-IDUs and 12% are in the non-IDU population i.e. contracted through infected blood/blood products transfusions and sexual transmission particularly men who have sex with men (MSM) and those with multiple sex partners.\(^\text{69, 83}\)

The prevalence of former IDUs in the UK is estimated at around 0.22%-0.8% of the general population, though many analysts think this is an underestimation.\(^\text{47}\) Due to the illicit and thus hidden nature of IDU, this population is difficult to study. Historical trends in the size and pattern of IDUs have significantly affected the number of people infected with hepatitis C. Therefore, modification of future injecting patterns may have the potential to produce major changes in the overall prevalence of hepatitis C.

However, there is evidence to suggest that incident rates of hepatitis C amongst IDUs may be rising; studies from abroad have suggested that 10% of current drug users may be infected every year.\(^\text{84}\) In addition, there was a noticeable increase in IDU in the UK during the 1960s to 1980’s. Given the prolonged incubation period for hepatitis C and the time-lag in the development of liver disease, it is possible that the full ramification of this activity may only come to notice over the next decade.

**How did they get HCV and can we prevent this?**

HCV is transmitted by blood-to-blood contact: via blood transfusions (before 1991); by sharing equipment and paraphernalia for injecting or snorting drugs; by medical or dental treatments with inadequate sterilisation; by sharing razors or toothbrushes that come into contact with broken skin (in both people); by tattooing, piercing or cosmetic treatments performed with unsterile equipment; or from mother to baby at birth.\(^\text{69}\)

Data collected from 1996 to 2005 demonstrated that only 23% of laboratory reports confirming hepatitis C infection included risk factor information. From this information it was shown that the single most important risk factor was injecting drug use (92% of all cases).\(^\text{69}\) Other risk factors were rare, but were listed in descending
order as, transfusion, blood product recipient, sexual exposure, renal failure, mother to baby, occupational and other unknown.\textsuperscript{69}

The introduction of mass screening for all blood and blood products by the National Blood Donor Service vastly reduced the risk of cross-contamination through blood/blood product transfusions infected with HCV, within the UK. The numbers of new blood donors who are hepatitis C positive continues to decline since the introduction of blood donor screening in 1991, 28 per 100,000 of new donors were detected whilst 1 per 100,000 of repeat donors tested positive for the virus.\textsuperscript{69} This trend is further evidence of the low incident rate of HCV in blood donors, confirming the reality that they are fundamentally a low-risk population.

Since the implementation of screening all blood donors for hepatitis C (1991) the main risk groups are past and present injecting drug users. It is well recognised that these groups are notoriously difficult to reach through health care services.\textsuperscript{85}

The effectiveness and cost effectiveness of testing for hepatitis C in former injecting drug users in a variety of settings has been evaluated.\textsuperscript{47, 86} On the basis that NHS commissioners currently view £30,000 per quality adjusted life year (QALY) an acceptable return on investment, there is a 74\% probability that case-finding for hepatitis C would be cost effective. Case-finding for HCV is likely to result in an additional life-year for an investment of £20,084 (£16,514 per QALY).\textsuperscript{47} Future development in HCV treatment to inhibit disease progression is likely to significantly improve the cost effectiveness of case-finding for HCV.

The issue of proactive case finding for hepatitis C in primary care has been explored using a cost-utility modelling approach.\textsuperscript{74} This study reported a 75\% probability that such initiatives would be cost effectiveness in primary care.\textsuperscript{74} A recent initiative, the Sentinel Surveillance scheme gives individuals the opportunity to access testing via their GP Surgeries and, although there has been limited uptake of the scheme, around 9,000 tests were performed in 2006.\textsuperscript{79, 69, 79} A recent paper exploring the sentinel laboratory surveillance of hepatitis C antibody testing in England concluded that these data provide valuable supplementary data to national surveillance.\textsuperscript{87} In addition, it has been proposed that testing for the hepatitis C virus among prisoners as part of an
active case finding campaign would also be beneficial, given that the last extensive study of the prevalence of hepatitis B and C in the prison population was conducted between 1997-98.\(^8^8\)

**Overlapping risk factors**

Co-factors influencing the progression of hepatitis C to chronic liver disease include alcohol abuse, the age at which the infection was acquired, duration of the infection, overweight, male sex and co-infection with hepatitis A, B or HIV.\(^3^\) It has also been stated that heavy alcohol consumption, diabetes and viral hepatitis exert independent and synergistic effects on the risk of developing HCC in the USA.\(^8^9\)

In people with hepatitis C, alcohol consumption over 50-60g/day has been associated with a 60% increase in risk of cirrhosis.\(^4^8\) Thus moderating alcohol consumption in people with liver disease due to HCV would be beneficial. In addition, 40% of IDUs are thought to have high alcohol intake in addition to their drug use.\(^4^7\) Thus alcohol risk reduction would be beneficial in this high-risk group.

There has been a suggestion of a link between hepatitis C and Non-alcoholic Fatty Liver Disease (NAFLD), as these conditions co-exist more frequently than would be expected by chance.\(^9^0-9^2\) A prospective study concluded that patients with chronic hepatitis C and Non-alcoholic steatohepatitis (NASH) differ significantly from those with this virus and fatty changes (steatosis), and those with HCV alone in terms of biological and metabolic factors and more advanced liver cell damage.\(^9^1\)

It has also been suggested that genotype 3 form of the hepatitis virus and a high BMI may interact to cause steatosis in patients with hepatitis C.\(^9^0\) This possible linkage between hepatitis C infection and metabolic causes of liver disease, including NASH, need to be explored in more detail.\(^9^1\)

**Prevention**

The FaCe-It campaign, launched nationally in December 2004, aimed to raise public awareness of hepatitis C; its prevention, diagnosis and treatment in support of the Government’s Hepatitis C Action Plan for England.\(^7^8\) FaCE-It also aimed to raise professional awareness of hepatitis C by encouraging the provision of advice about
the risks of hepatitis C infection, and testing to individuals at risk. The FaCe It exhibition had a potential audience of 16 million people and more than 1.2 million leaflets were distributed. The impact of this 3 year campaign has recently been evaluated, which demonstrated that public awareness of the disease increased from 15% to 29%, whilst testing for hepatitis C by Primary Health Care professionals had increased by 60% since 2002. The campaign also proved to be a useful resource as over a quarter of a million people accessed the website.

Other health promotion campaigns include World Hepatitis Awareness Day, the 1st October and ‘What not to share’, a Hepatitis C Trust campaign which has received celebrity endorsement.

There is currently no vaccination for hepatitis C due mainly to the complexity of the virus and the rapid rate at which the virus can mutate. However encouragingly, two pharmaceutical companies have recently announced promising results from the early phases of small drug trials. This ongoing development of Vertex VX-950 and AVI-4065 NEUGENE signifies a possible new approach to tackling the hepatitis C disease for the future.

Currently however, the primary aim in controlling HCV is to prevent exposure to the infection in first instance, whilst the secondary emphasis for preventing hepatitis induced liver disease is focused on early detection followed by anti-viral treatment.

The National Screening Committee and National Institute for Health and Clinical Excellence (NICE) have not recommended an antenatal screening programme as there is still insufficient evidence regarding effective interventions to prevent mother-to-baby transmission.

Thus early identification of hepatitis C infection is important to improve outcomes from this condition and for broader public health. Early diagnosis increases the probability of successful treatment for hepatitis C (see below) and also the impact of positive lifestyle changes can limit cross-infection in the population.

An Italian survey examined the impact of a hepatitis C diagnosis on patients’ lifestyle and concluded that most drinkers (74%) modified their alcohol consumption
whilst a minority of smokers (21%) modified their habits. These changes were long-lasting as the time period between diagnosis and the survey was 5 years. Thus early detection of hepatitis C can generate positive changes in behaviour which can ameliorate the effects of the infection.

At what stage is liver disease from HCV detected?

Chronic hepatitis C infection is often asymptomatic until liver failure becomes apparent. The rate of progression to cirrhosis is unpredictable but usually slow, with decades elapsing between infection and the development of serious complications.

Screening tests for hepatitis C infections use Enzyme Linked Immunosorbent Assays (ELISA). Antibody tests cannot reliability diagnose acute hepatitis C as the incubation period of acute hepatitis C is usually between 6 and 9 weeks, with specific antibodies only present after 3 months from infection, and in some cases it may take up to 6 months before antibody is detected. Also hepatitis C antibodies usually appear relatively late in the course of infection, which causes false negative results. Finally, there are currently no laboratory tests which differentiate between acute or chronic or resolved presentations of the virus.

Thus HCV antibody tests can only detect if exposure to HCV has occurred in patients, they cannot determine if patients are still exposed to the virus or if it has resolved naturally. HCV RNA tests are needed to identify whether the virus itself is in the blood stream. This test may also be used after treatment to see if the virus has been eliminated from the body.

The timely management of acute hepatitis C infections is imperative as there is strong evidence to suggest that the rate of chronicity is reduced from 80% to 50% in those who have received interferon treatment.

In the UK there are 4 clinical specialities that deal with hepatitis C; Gastroenterology (GI), Genito-Urinary Medicine (GUM), Hepatology and Infectious Disease Specialists (ID). Diagnostic and treatment pathways for patients with hepatitis C in these different departments are unclear. A study conducted by Parkes et al. found
that over half of the patients who were referred to a comprehensive service provider (CSP) had been previously diagnosed with hepatitis C; 41% came from Primary Care, 24% from drug and alcohol services, 14% from Prisons and 14% from GUM physicians.

Since many IDU’s spend a period of time in prison, it is an extremely important opportunity to target this high risk population. 99

Screening for HCV in prisons has been explored and the uptake of testing found to be very low due to personal and institutional factors. 99 Encouragingly, prisoners were reasonably familiar with harm minimisation strategies, such as needle and other paraphernalia exchanges, and had utilised these facilities in the community. 99

Some innovative health promotion programmes are currently underway in the English prison service including: the development of the Music4Messages CD with specially commissioned ‘rap’ music and a discussion of health issue which provides primary prevention information to juveniles and young offenders on the risks of Hepatitis C; and an educational DVD, called Hepatitis C: Inside and Out, produced by Offender Health in collaboration with Munro and Forster (a media Company who worked on the national FaCe It campaign). These initiatives are attempting to address the need to improve health promotion activity in prisons and, in particular, to reduce the stigma associated with hepatitis C infection and treatment options.

What happens to people with HCV liver disease? Treatment issues

Treatments for hepatitis C are expensive but have success rates now around 50% for genotype 1 and 80% for genotypes 2 and 3. 78 For 55% of patients with varying genotypes who have moderate to severe hepatitis, the combination therapy of pegylated interferon and ribavirin is successful in clearing the infection, leaving no detectable virus in the blood 6 months after treatment. The issue of whether the infection with genotype 1b carries a worse prognosis than other genotypes due to lower responsiveness to interferon treatment remains unclear. 36 However, recent findings suggest that independent risk factors associated with end-stage liver disease included HCV genotype 1, alcohol abuse and HIV co-infection. 100
The duration of treatment is usually 6 months for patients with genotype 2 and 3, and 12 months for genotype 1. Current NICE guidance acknowledges the fact that the duration of treatment will vary depending on individual case factors such as: the specific drug; viral genotype; initial viral load; response to treatment; and treatment regime.

Drug treatments are associated with significant side effects. Thus if patients default or if they are unresponsive to treatment, they can progress to liver cirrhosis and/or liver cancer with many needing a liver transplant. Approximately 20-40% of all liver transplants performed in Europe and the USA are due to cirrhosis caused by chronic hepatitis C. However, in England, about 15% of liver transplants are due to liver damage caused by the hepatitis C.

Although fulminant or acute liver failure associated with hepatitis C infection is rare, the co-occurrence of hepatitis C with another chronic liver condition (e.g. chronic hepatitis B) may act synergistically and precipitate liver failure. In patients with chronic hepatitis C, who develop cirrhosis, approximately 1-4% progress to Hepatocellular Carcinoma (HCC). The development of HCC is rare in patients with chronic hepatitis C who do not have cirrhosis.

At present the most effective treatment for hepatitis C involves viral eradication therapy through the use of a combination of anti-viral agents, which is supported by NICE guidance published in 2004 for patients with moderate to severe chronic hepatitis C. In addition, NICE have since conducted a review on treatment guidance aimed at patients with mild chronic forms of the virus, which has been published as an extension to the original document (2006).

NICE guidance state that combination therapy, comprising peginterferon alfa-2a and ribavirin or peginterferon alfa-2b and ribavirin, is recommended for the treatment of mild chronic hepatitis C. Monotherapy with peginterferon alfa-2a or peginterferon alfa-2b is also recommended for the treatment of mild chronic hepatitis C in people who are unable to tolerate ribavirin, or for whom ribavirin is contraindicated.
In general, the treatment modality of interferon and ribavirin has also been proven to be cost-effective, except for patients aged over 65 with genotype 1 strain of the virus. Due to current under-diagnosis, it is estimated that only 1-2% of those infected with hepatitis C are currently receiving NICE recommended therapy.

Furthermore, not all patients diagnosed with HCV are able to undergo anti-viral treatment. Recent work found that in newly diagnosed hepatitis C patients only 10-24% were eligible for the anti-viral drug treatment. Eligibility criteria include age, gender, genotype, severity of hepatitis and co-morbidities e.g. (current/future drug/alcohol abuse).

Many factors can increase the progression of liver disease as well as decrease the response to interferon treatment, for example alcohol misuse. The most important single reason reported for ineligibility was ongoing illicit drug use. However, recent US work concluded that a history of injecting drug use was not negatively associated with HCV treatment candidacy or outcomes. Thus former IDU patients should be assessed on a case-by-case basis for HCV treatment.

There is no licensed treatment for children with HCV infection. Strategies have followed those in adults. Combination therapy of ribavirin and interferon has reported better responses than interferon monotherapy. However side effects have been found to be common and sometimes severe. A multicentre European Study of combination therapy in children is currently in progress.

Cirrhosis due to chronic hepatitis C is the most common indicator for liver transplantation in the western world. However, recurrence of the disease is virtually universal and current research focuses on factors which determine the pattern and severity of recurrence.

The management of patients with chronic hepatitis C who fail to respond to antiviral treatments is a key issue which has lead to exploration of new therapies for HCV. The main developments concentrate on the orally available anti-viral agent, Vx-950 which
is known as telaprevir. Findings have shown that telaprevir and in combination with peginterferon results in a continuing decline of viral levels and thus the two agents perform a potentially synergistic elimination of the infection. Preliminary results have suggested that the most effective treatment regime may be a short course of telaprevir followed by the combination of peginterferon and ribavirin as 70% of patients had no detectable virus after 12 weeks compared to 39% with the current conventional therapy.

Conclusions

With an increasing incidence of hepatitis C it is predicted that the future burden on healthcare services from consequent liver disease will increase by 60% by 2008. This equates to a five-fold increased demand for liver transplantation.

Inequity of health care provision for hepatitis C may occur at all stages of the patient pathway. Thus there should be an expansion of services, particularly in key geographical locations such as the West of England, to facilitate an increased uptake and comparable service delivery throughout the UK.

The majority of hepatitis C positive patients in the UK are not receiving anti-viral treatment, which contrasts greatly with situation in Europe. This should be addressed.

At present, there is not extensive screening for hepatitis C in England, other than in the blood donor programme. France and Germany amongst others have more robust screening programmes to detect early stage hepatitis C. Increasing opportunities for hepatitis C screening should be considered, if not in the mainstream population then this should occur routinely in prisons.

A recent review found that just 8% of PCTs had effectively implemented the National Action plan for hepatitis C; 56% had partially implemented it and 36% had minimally implemented it. In addition, 46% of hospitals reported significant delays in hepatitis C treatment. Thus there needs to be more encouragement of such work.
in primary and secondary care; including performance monitoring of this activity in necessary.

A number of authors have reported the need to construct a comprehensive computerised IM&T strategy as a matter of urgency. The development of a nationally-recognised database would enable evaluation of clinical data (sporadically collected at present) from which epidemiological trends and future treatment recommendations could be made.

**Evidence gaps**

There is currently no vaccine for hepatitis C. The work into the development of a vaccine should continue.

More research is required on the experiences of people with hepatitis C, from detection through to treatment. The perception that hepatitis C is only experienced by particular subgroups (e.g. IDU groups) perpetuates unsympathetic attitudes to this condition which acts as a barrier to the uptake of health education work.
LIVER DISEASE FROM THE HEPATITIS B VIRUS (HBV)

Who gets liver disease from HBV and what are the consequences?

Hepatitis B accounts for about a fifth of the reported cases of chronic hepatitis infections in UK. \(^1\)

The prevalence of hepatitis B in the UK has been reported as 0.1% of the population i.e. approximately 60,000 people. \(^1\) However, a Department of Health strategy document on infectious diseases suggested that 180,000 people in the UK may have chronic hepatitis B. \(^{105}\) The most recent prevalence estimate from the Hepatitis B Foundation is 325,000 individuals. \(^{106}\) Given this wide range of prevalence estimates from different agencies, there is an urgent need for clarity on this matter.

Although HBV infection in children is low, infection during childhood contributes to an estimated 20–65% of new chronic infections (this wide range is due to different prevalence rates in different ethnic groups). The number of infections in children in England and Wales between 1995 and 2000 was 13 per year, 75 overall. Childhood infection contributed to 2% of all laboratory reports, and to an estimated 21% of all new chronic infections. Among South Asians, infections in infants were much more common, contributing to 65% of new chronic infections. \(^{107}\)

Of those people chronically infected with HBV approximately 15% to 40% will develop cirrhosis, liver failure, or hepatocellular carcinoma. \(^{108,109}\) Chronic hepatitis B infection is defined as the persistence of hepatitis B antibodies (HBsAg) in the blood serum for six months or longer. \(^{109}\)

Internationally, it is estimated that approximately 400 million people are infected with HBV worldwide, \(^{110}\) with around 1 million people in Europe becoming infected with the virus every year. Globally, hepatitis B is the leading cause of cirrhosis \(^{111}\) and is the ninth most common cause of death, killing around 2 million people each year. In the USA, it is estimated that around 1.25 million people are affected by the virus at a cost of $700 million annually. \(^{112}\)
Hepatitis B is most common in the Far East, the Middle East, Africa and southern Europe. The World Health Organisation regards hepatitis B infection in China as endemic. Around 130 million people in China are carriers of HBV (almost a third of the people infected with HBV worldwide); 30 million people in the country are chronically infected. The World Health Organisation categorised countries relating to the prevalence of hepatitis B which is based on the prevalence of HBsAg into high (more than 8%), intermediate (2 to 8%) and low (less than 2%) infection-rate countries. Currently, England is a low infection-rate country.

There is a variation in the geographical prevalence of hepatitis B in England; inner cities have a higher rate of infection than their rural counterparts. The prevalence of hepatitis B in the UK is also greatly affected by the settlement of legal immigrant populations into England, from countries with high or intermediate prevalence of the virus. For example, London has one of the lowest average rates of alcohol consumption yet liver disease mortality is one of the highest in England, due predominately to virally induced liver disease deaths. Furthermore, incident rates of both hepatitis B and C are linked to deprivation and poverty; thus socio-economic status is also a contributing risk factor for chronic hepatitis.

The incidence of hepatitis B in the UK has been falling since the mid 80s, which coincided with the introduction of vaccination in high risk groups such as drug users and healthcare workers. Furthermore, in the USA, progress has been made to reduce the racial/ethnic disparities in hepatitis B rates. Historically in the USA, Asians and Pacific Islanders had disproportionately higher rates of hepatitis B and this disparity has declined with the successful implementation of routine hepatitis B vaccination in infancy. However, although Hispanic rates have declined in recent years they still remain more than two-fold higher than those amongst other racial/ethnic groups in the United States.

HBV is only transmitted through exposure to the blood or body fluids of an infected person. In the England, the people most at risk of contracting hepatitis B are IDUs, people who have unprotected sex with different partners, close family members of someone with the infection, babies born to infected mothers and travellers to high-risk countries who come into contact with infected blood and other bodily fluids.
It is a common misconception that the hepatitis viruses are only caught by drug users. This stigma prevents diagnosis and treatment of existing cases. Better education and health promotion messages are needed to overcome this view. 3

Hepatitis B is an occupational hazard for health workers and emergency responders due to exposure to trauma, needle-stick and other injuries. 109 Social contact carries no risk of infection and good hygiene procedures easily eliminate the virus on external surfaces. Thus clothing contaminated with the virus can be put through a normal hot wash in a washing machine to kill the virus. Similarly, washing-up liquid and hot water is effective for plates and cutlery.

Surveillance in the USA found that HBV rates vary with age, consistently 25 to 44 year olds had the highest rates (approx 3.6 per 100,000) whilst under 15 year olds had the lowest rates (approx 0.03 per 100,000). 82 There are also gender differences, the incidence in males is 1.6 times greater than in females. 82 In the USA, this gender divide is increasing. 82

The incidence of hepatitis B varies across ethnic groups (see figure 14). In the USA, non-Hispanic blacks have the highest incidence rates at 2.9 per 100,000 compared to non-Hispanic whites with rates of approximately 1.1 per 100,000. 82 At present, there is a study being conducted exploring the prevalence of hepatitis B in South Asian communities living in the UK. 69
How do people get HBV and can we prevent this?

In areas of the world where HBV is endemic (e.g. sub-Saharan Africa, Pacific regions and Asia) or in areas where incidence rates are high (e.g. Southern parts of Eastern and Central Europe and the Middle East) the majority of individuals become infected during childhood. However, in Western and Northern Europe and North America where the prevalence of hepatitis B is relatively low, the virus is acquired primarily during adulthood.  

The age at which infection is acquired is also a major risk factor of the virus developing into chronic hepatitis B infection.  

It has been estimated that around 6400 cases of chronic hepatitis B arrive in the UK annually as a result of legal immigration from countries with a higher prevalence of hepatitis B. Consequently, in UK regions where there are high levels of immigration,
prevalence of hepatitis B is higher than the general prevalence rate of 0.1% of the population; some areas have a prevalence of 2% of the population.\textsuperscript{1}

\textit{Overlapping risk factors}

It has been suggested that co-morbidity with other risk factors, such as alcohol abuse, male gender, obesity, age at which the infection is acquired and any co-infection with hepatitis A or C, can increase the risk of hepatitis B progressing to chronic liver disease.\textsuperscript{109} However, is an evidence gap on whether the source of the contracted infection effects the progression to liver disease. Furthermore, there is no conclusive evidence on disease progression when more than one risk factor is present.

\textit{Prevention}

Compared to the high prevalence of HBV imported into the UK by migrant communities, chronic cases of hepatitis B arising from acute infection acquired in the UK by the resident population is approximately 250 cases annually.\textsuperscript{3} Thus mass infant immunisation would only prevent this small number of cases, consequently a policy of selective immunisation was adopted.\textsuperscript{115}

Most studies of mass immunisation in children and high risk groups have not been applicable to the UK context so it is difficult to draw conclusions on the cost-effectiveness of such strategies in England.\textsuperscript{3} Thus, the UK remains one of a minority of developed countries not to implement universal neonatal hepatitis B vaccination.\textsuperscript{116} Preliminary work has estimated a cost of hepatitis B to the NHS as between £26m-£375m, with total societal costs ranging up to £429m.\textsuperscript{117} The forecasted cost of implementing an infant immunisation programme in the UK, which could potentially be added to the routine childhood vaccination programme currently in place, is approximately £10.4m.\textsuperscript{117} At face value, these figures suggest that an infant immunisation programme could produce costs savings. However, evaluating the cost-effectiveness of a universal vaccination programme is extremely complex with many variables and differing perspectives to consider. Hence more rigorous economic evaluation is required in this area.

Due to mounting international evidence on immunisation, the BMA has recently endorsed the suggestion of universal vaccination for hepatitis B in the UK.\textsuperscript{118} The
basis of this recommendation was the growing financial burden the disease puts on the NHS and an escalating risk of exposure to the UK population due to increased foreign travel and migration from overseas. Furthermore, as age of infection is a major risk factor for developing chronic hepatitis, the importance of childhood prevention programmes to limit the severity of the disease has been reinforced.

The USA has used a safe and effective vaccination for hepatitis B since 1981. Vaccination for hepatitis B in the UK is available on request to high risk groups (e.g. health workers, those travelling to high risk countries, men who have sex with men, current or former injecting drug users and prisoners.). Vaccination is delivered within GP surgeries, acute hospitals or high street travel clinics.

The use of a combination vaccination combating hepatitis A and B has been proposed in high-risk groups, studies have concluded that a combination vaccine can reduce mortality, morbidity and costs associated with treating infections. No guidance has been published to date for the proposed use of the combination vaccine in the UK.

Infants born to mothers known to carry HBV can be treated with antibodies to this virus. If this vaccine is given within 12 hours of birth, the risk of acquiring hepatitis B is reduced by 95%. This treatment also allows a mother to safely breastfeed her child. Thus the family and other household members of someone with hepatitis B should be vaccinated.

Whilst the debate about mass immunisation in childhood continues, the best preventive strategy for England is to avoid new cases of infection by focusing on increasing awareness and promoting positive behavioural change in high-risk groups.

**At what stage is HBV liver disease detected? Treatment issues.**

The majority of people infected with HBV do not need specific treatment, other than rest, and they eventually make a full recovery. This is because hepatitis B can cause an acute illness that resolves quickly without causing long-term liver damage; up to 95% of adults clear the infection spontaneously without treatment. However, hepatitis B can also cause chronic illness that lasts more than six months or more with ongoing
symptoms. Nevertheless less than 10% adults who contract hepatitis B progress to chronic liver infection. The incubation period for hepatitis B ranges from 40 to 160 days, with an average of 60 to 90 days.

US surveillance in 2005 reported that of hospital patients infected with hepatitis B, 77% presented with jaundice, 40% were hospitalised and 1% died. However, in England it has been reported that jaundice only occurs in about 10% of younger children and in 30 to 50% of adults.

NICE guidance published in 2006 on chronic hepatitis B outlined the most effective treatment options. However, these treatments do not relate to patients co-infected with hepatitis C, hepatitis D or HIV. Unlike the treatment for hepatitis C, treatment for hepatitis B takes longer as it suppresses the virus rather than eliminates it.

Treatment with interferon or peginterferon alfa 2-a is used in the first instance. NICE guidelines also recommend Adefovir dipivoxil as another option for adults with chronic hepatitis B. In addition, the guidance states that Adefovir dipivoxil could also be used in combination with Lamivudine, but it is implicit that it should not be given before treatment with Lamivudine. At present, none of these drugs clear the infection completely but rather they stop the virus from replicating, and so prevent further liver damage such as cirrhosis and/or liver cancer.

Treatment options for children also include Interferon, Lamivudine and Adefovir dipivoxil, although it is stated that the long term effectiveness and side effects of these treatments need further investigation. No trials are yet underway to investigate pegylated interferon in children.

Drug resistance in the treatment of hepatitis B presents a serious problem to providing effective long-term treatment against the viral disease. It has been demonstrated that only 30-40% of white adults have a sustained response to interferon alfa treatment, and poorer response rates are seen in Asian patients. This lack of performance has led to the exploration and development of antiviral agents, such as lamivudine and adefovir, as an alternative treatment option. However, resistance to antiviral
monotherapy predictably presents a similar obstacle and work is now ongoing to evaluate the effectiveness of combination therapy in the fight against hepatitis B.  

Combined therapies capable of producing a sustained response against the hepatitis B are still not entirely proven, and they have yet to achieve the dramatic benefits such treatments have produced against other infections such as HIV, hepatitis C and tuberculosis. Recently published results from a clinical trial comparing the antiviral efficacy of telbivudine and adefovir and the effects of switching treatments demonstrated that telbivudine achieved a more consistent HBV DNA suppression. This is encouraging, but more work is needed in this field.

The cost effectiveness of the various treatments combinations for adults have been explored by a number of studies. One of the most recent studies concluded that both Entecavir and Adefovir treatment methods are cost effective for patients with hepatitis B induced cirrhosis, however, selecting which treatment to use is highly dependant on available budgets.

A systematic review exploring the cost-effectiveness of adefovir, dipivoxil and pegylated interferon alfa-2a stated that the in most cases treatments induced a remission of HBV and offered protection from the risk of progression to cirrhosis, HCC and liver transplant. However, some cases did not respond to the treatment or suffered a relapse and in these instances another treatment modality was suggested, occurring obvious cost implications.

The conclusion on the cost-effectiveness of treatment for hepatitis B is that more evidence is required to develop comprehensive guidance on the effectiveness of anti-viral treatments in specific sub-groups such as patients with cirrhosis, different genotypes, different ethnic groups and those with co-infections and /or co-morbidities.

Conclusions

We should improve immunisation of high-risk groups for HBV as outlined by the Chief Medical Office for England in 2001. We recognise current UK policy to offer
all pregnant women screening for hepatitis B to allow babies born to infected mothers to be immunised soon after birth. This primary prevention protects infants from becoming chronic carriers of the virus and developing hepatitis induced cirrhosis in the future. However, more could be done to increase the uptake of the complete course of vaccine to ensure immunity among babies born to infected mothers.

We need to improve HBV screening in high risk groups (IDU, MSM, those with multiple sex partners) where new infections continue to occur. Better screening approaches would help to strengthen vaccination efforts.

The majority of chronic hepatitis B cases occur in first generation migrants to the UK and account for 6500 cases of chronic hepatitis B per year. These cases cannot be prevented by vaccination programs in the UK and can only be addressed by better systems of case identification. This is essential because currently therapy reduces progression of the disease by around 50%.

PCTs should focus more attention on prison health since 60% of IDUs have been in prison at some stage in their life. Prison is currently the most common source of hepatitis B infection in the UK; better health education and sensitive encouragement of HBV testing could also decrease incidence rates in this usually hard to reach population.

**Evidence gaps**

We need to assess if demanding treatments regimes for HBV, currently delivered entirely in secondary care, could be at least partly delivered in primary care. This could include specialist nurses working within the primary care setting. Whilst secondary care is better equipped to deliver specialist treatment, patients may be more likely to adhere to prolonged therapy if it is located in more familiar surroundings and closer to their home. Further work is needed to explore the possibilities of shared-care in this area.
LIVER DISEASE DUE TO OBESITY

There is increasing evidence that obesity can lead to liver disease.

There is concern that growing obesity levels in the UK, especially in younger age groups, may lead to a rapid rise in future liver disease cases.\(^2\)\(^{129}\)

Approximately 23% of adults and 20% of children in England are obese (defined as a Body Mass Index (BMI) of >30 kg/m\(^2\)); this proportion has grown steadily over recent years and, if unchecked, will continue to increase.\(^1\)\(^{30}\)

**Who gets liver disease from obesity and what are the consequences?**

Obesity is a risk factor for Non-Alcoholic Fatty Liver Disease (NAFLD) and a more severe (progressive) form of damage called Non-Alcoholic Steatohepatitis (NASH).

Essentially, fat accumulation in the liver (steatosis) leads to scarring (fibrosis) and inflammation (hepatitis). If this scarring and inflammation becomes irreversible the liver becomes cirrhotic.\(^3\)\(^{131}\)\(^{132}\)

Not everyone who is overweight or obese will develop fatty liver and not everyone who has a fatty liver is overweight. However the majority of people with NAFLD are overweight or obese.\(^1\)\(^{33}\)

A growing number of studies have documented obesity as a risk factor for both ALD\(^1\)\(^{34-136}\) and NAFLD.\(^4\)\(^{5}\)\(^{135}\)\(^{137-140}\) Thus the development of liver disease from metabolic causes appears to be a robust phenomenon.

NAFLD affects a substantial proportion of the general population and is associated with many features of the metabolic syndrome. It is currently the most common cause of abnormal liver function tests in Hepatology practice and affects approximately 15-25% of the general population in various countries, this proportion increases to 70-90% of obese patients, or patients with Type II diabetes.\(^1\)\(^{41}\)
Trends in NAFLD/NASH are strongly associated with patterns of obesity and Type 2 diabetes in a population. US data show that prevalence of NAFLD is rising with levels of obesity. Obesity and NAFLD is present in 65-90% of liver disease cases in the UK, however, many people with NAFLD remain undiagnosed.

Although NAFLD and NASH have risen over recent years, there are currently no clear data showing a concomitant rise in mortality figures, which may be due to a time-lag in the development of this disease or a lack of research. However, a rise in mortality due to NASH is expected in the future due to the substantial shift in the prevalence of obesity over recent years.

It is highly likely that future increases in obesity will result in further cases of liver disease which will have an impact on health services; however the extent of this possible increase is not currently clear.

According to Hospital Episode Statistics (HES) data, obesity is mentioned in less than 1% of cases of liver disease (see Figure 15 below).

These findings suggest that HES data may under-record obesity as a contributing factor for liver disease; previous research has found that hospital physicians do not always record obesity in patients’ notes.
NAFLD has been described in persons of all ages and it is the most common liver disease among obese adolescents in North America\textsuperscript{144} with a prevalence of between 17\% and 34\%.\textsuperscript{132, 145} NASH has been reported to be present in around a third (33\%) of these individuals and some may progress to cirrhosis.\textsuperscript{146}

Childhood obesity is an important, early risk-factor for a substantial amount of ill-health and premature mortality in adulthood.\textsuperscript{147} Research on 102 obese children and adolescents in a paediatric weight management clinic concluded that obesity in childhood creates the metabolic platform for adult CVD and NAFLD. In this US study, African-American and Hispanic children appeared to be at the greatest risk.\textsuperscript{147}

Although most of the populations in which NAFLD has been studied have been predominantly white, work on minority ethnic groups is increasing. One US study has

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure15.png}
\caption{Relative proportion of admissions for non-alcoholic liver disease (including NAFLD/NASH) and ALD. Source\textsuperscript{3}}
\end{figure}
looked at the clinical presentation of NAFLD in different racial and ethnic groups in a geographically representative and racially diverse segment of the population. They found that of 159 study patients, 44% were white, 28% were Hispanic, 17% were Asian, 6% were American Indian and 5% were mixed-race. These data were against local population figures and it was concluded NAFLD may be more common in Hispanic groups.

Asian-Indian men appear to have an increased susceptibility to NAFLD due to its linkage with the metabolic syndrome and type 2 diabetes.

Until recently, NASH was thought to be confined largely to middle-aged obese women with diabetes. However, it also occurs in men and people who are not obese. Studies of ‘high risk’ groups (i.e. obese populations) have reported a prevalence of NASH of around 25%.

One study reported progression from steatosis to cirrhosis in 3% of NAFLD patients over a 10-year period. Progression from NASH to cirrhosis occurred in 20% of patients and from NASH to liver-related death of 12% of patients. This progression through various degrees of liver disease is a cause for concern.

Studies have also shown that obesity and Type 2 diabetes are associated with cryptogenic cirrhosis (cirrhosis due to unidentified causes).

How do people get liver disease due to obesity and can we prevent this?

The risk factors for obesity are also risk factors for NAFLD. Risk factors for obesity include behavioural components (exercise and weight control measures), social components (food choices and eating patterns in different cultural groups) and components of the metabolic syndrome (impaired glucose tolerance or insulin resistance, high blood pressure, high triglycerides, dyslipidaemia, decreased ADL Cholesterol, central adiposity).

People with the metabolic syndrome are at increased risk of coronary heart disease (CHD), peripheral coronary vascular disease (CVD), stroke, type 2 diabetes and liver
However, it is currently unclear whether the metabolic syndrome causes liver disease or if a fatty liver causes hepatic insulin resistance and consequent metabolic changes. 155

Recent studies have reported an association between NAFLD and CVD. 141 NAFLD is also associated with an increased risk of all-cause death and predicts future CVD events independently of other prognostic factors, including components of the metabolic syndrome. Thus it is important to assess the global CVD risk in patients with NAFLD. 141

The mechanism of liver injury in NAFLD/NASH is thought to follow a ‘two hit phenomenon’ whereby steatosis sensitizes the liver to a variety of second hits which lead to fibrosis and inflammation. 156 In the first hit insulin resistance and free fatty acids seem to play a major role. 157 In most subjects this is related to obesity, abdominal fat and aspects of the metabolic syndrome, including type 2 diabetes. In the second hit, oxidative stress (which can come from a number of causes) appear to be key. 156

*Overlapping risk factors*

A number of studies report a synergistic relationship between different risk factors for liver disease. 3, 89, 158 Thus a potent ‘triple hit’ has been described from a combination of obesity, hepatitis C infection and alcohol use which interact to hasten progression of chronic liver disease. 2

Being overweight appears to interact with alcohol leading to increased risk of ALD. 2 A study carried out in France by Naverau found that being overweight was also associated with cirrhosis in a study of alcoholic patients. 45

*Prevention*

The key way to prevent the development of NAFLD/NASH is to reduce the numbers of people who are overweight or obese in the population.
Targeting child obesity in addition to obesity in adulthood has been emphasised in recent health policy. The 2005 White Paper “Choosing Health: Making healthier choices easier”\(^{159}\), linked action plans focused on improving diet and increasing physical activity.\(^{160,161}\) More recently, child obesity became an indicator in the 2007 Child Health PSA which was set to improve the health and wellbeing of children and young people. The Secretary of State for Health and the Secretary of State for Children, Schools and Families share joint responsibility for the progress of this target.

There are, of course, other drivers for the focus on obesity in health policy, but success in implementing these strategies could lead to a reduction in liver disease.\(^{3}\)

Weight loss through low-energy diet and increasing levels of physical activity are recommended for tackling obesity.\(^{162}\) A recent systematic review of psychological interventions for the treatment of obesity.\(^{163}\) reported that people who are obese or overweight can benefit from behavioural and cognitive behavioural interventions and that these types of interventions are particularly effective when combined with dietary and exercise advice.\(^{163}\)

Studies which have attempted to improve community health via educational campaigns focused on individual behaviour (e.g. on diet and physical activity) have not reported significant effects.\(^{3}\) Research on the potential effectiveness of policy interventions is required.\(^{72}\) Suggestions have included: restricting the advertising of unhealthy foods to children and changing the formulation of processed foods to reduce the consumption of fat, sugar and salt in the population\(^{72}\); improving the nutritional labelling of foods, social marketing work, promotion of leisure-time sports and activities, and promoting healthy schools and active transport policies.\(^{164}\)

Clinical trials of a number of drugs for the treatment of NASH in adults and children are under way in the USA.\(^{165,166}\) Preliminary evidence suggests that the anti-diabetic drugs metformin and the thioglitazones, together with pentoxifylline, may have a valuable role in improving NASH.\(^{3}\) Controlled trials of weight reduction and physical activity to improve insulin sensitivity in obese patients should be a priority.\(^{167}\) Evidence on both clinical effectiveness and cost-effectiveness are required.
The challenge of reversing the epidemic of obesity and type 2 diabetes is enormous. Better control of Type 2 diabetes after implementation of the Diabetes NSF may lead to a reduction in NAFLD/NASH.

**At what stage is liver disease due to obesity detected?**

Most patients with NAFLD typically have no symptoms or clinical signs of liver disease at the time of diagnosis, although some patients may report fatigue and a sensation of fullness or abdominal discomfort. Thus many patients are either identified via chance in primary care (via liver function tests for other conditions) or they are diagnosed when their condition has progressed to more severe liver disease where symptoms become apparent, which has a negative effect on prognosis.

The presence of elevated serum liver enzymes (mild to moderate) are the most common, and often the only abnormality found in NAFLD patients. Other abnormalities may be found in patients with more advanced disease (cirrhosis). However, liver enzymes may be in the normal range in up to 70% of patients and thus are relatively insensitive for the detection of NAFLD.

Patients with persistently raised liver enzymes may be referred to secondary care for further tests. Histological manifestations of NAFLD are similar to those observed in patients with ALD and of other secondary causes of chronic liver disease. 141

**What happens to patients with liver disease due to obesity? Treatment issues.**

At present there is no therapy for NAFLD per se. 149 168 Treatment for all patients, whatever the severity of their disease, is generally directed at the associated risk factors, obesity, type 2 DM, hyperlipidemia and hypertension. 149 This strategy will reduce morbidity and mortality and may also be beneficial to the liver. 140

The role of increased BMI and steatosis as comorbidity factors in the progression of fibrosis has important therapeutic implications. Gradual weight reduction is
recommended as a first step in the management of patients with obesity-related fatty liver. However, there is a lack of long-term outcome data on the effect of modest weight loss on liver disease or associated metabolic factors.\textsuperscript{162}

Recent work has shown that modest weight loss accompanied by increased physical activity is beneficial in patients with NAFLD, characterised by a decrease in serum alanine aminotransferase (ALT) levels (17 to 26%).\textsuperscript{162} In patients who maintained their weight loss, ALT levels stabilised at the reduced level, however, patients who regained weight showed increased ALT levels (a return to baseline levels).

Weight reduction may also bring about positive improvements in steatosis, fibrosis and fasting insulin levels.\textsuperscript{162} The amount of physical activity per week is significant in the overall success of weight loss and maintenance. Patients who maintained weight loss were more likely to attain realistic levels of exercise (as recommended) and continue exercising long term.

In addition to lifestyle and behavioural interventions, the most recent NICE guidelines on the prevention and management of obesity have guidance on drug and surgical interventions.\textsuperscript{169} In relation to surgical interventions, NICE recommends bariatric surgery for individuals with a BMI over 40 when all non-surgical interventions have been unsuccessful or for individuals with a BMI over 50 for whom non-surgical intervention is not considered appropriate. Importantly recent studies have found that patients with NAFLD show significant improvements after bariatric surgery.\textsuperscript{168,170} Although the authors do recommend that larger studies are needed with more long term follow up.

Furthermore, NICE has recommended two pharmaceutical interventions (Orlistat and Sibutramine) as part of an overall plan for obesity. Studies have reported that achieving weight control with these medications is associated with improvement of NASH although again more work is needed to determine the long-term efficacy.\textsuperscript{168,171}

It has been reported that the use of thiazolidinediones to change the balance between visceral and subcutaneous fat and muscle lipids can improve insulin sensitivity and so may improve NAFLD and NASH.\textsuperscript{147}
Once cirrhosis has developed, the natural history of NAFLD is broadly similar to other causes of cirrhosis, with secondary complications arising due to portal hypertension, liver failure and hepatocellular carcinoma (HCC). The latter is significant as obesity is an independent risk factor for HCC.

A recent comparison of outcome for patients with compensated cirrhosis due to NAFLD, compared to those with hepatitis C, found that the former had lower mortality and less frequent ascites, hyperbilirubinaemia and HCC but higher cardiovascular mortality.

Up until 2003, liver transplantation in patients with NASH was uncommon. However, the proportion of patients with NASH receiving a liver transplant has increased over the past four years. Initial data suggests that their post-transplant survival outcomes may be better than those for patients with ALD or cirrhosis due to viral hepatitis.

Conclusions

The characteristic of the liver as the only organ to regenerate creates an opportunity for strategies to be developed aimed at the prevention of harm from liver diseases by targeting the contributory causes of liver disease. The development of public awareness about the link between obesity and liver disease is essential.

There is a need to raise awareness in the public health workforce on the link between obesity and liver disease. Most health professionals are likely to be unaware of this link. The recent document ‘Foresight Tackling Obesities: Future Choices’ included a limited reference to NAFLD/NASH. Thus health professionals need specific education to improve their knowledge and thence to improve preventive work focused on NAFLD and NASH.

The evidence on the benefit of weight reduction and exercise on NAFLD indicates a clear need for dieticians and nutritional support in the treatment of NAFLD as suggested in other reports.
Given the clear links between Obesity, diabetes, CHD, CVD and NAFLD/NASH it is imperative that effective treatment of patients involves a chronic disease management work including support to patients regarding self-management.  

**Evidence Gaps**

Further research is needed into the links between obesity and liver disease including progression from NAFLD to NASH. This research will enable us to better understand the impact that increasing levels of obesity may place on liver services.

There are gaps in knowledge about the incidence of NAFLD in general and in different population groups. Most of the work on ethnic groups has been conducted in the USA. UK specific work is important, given the high prevalence of obesity and type 2 diabetes in people from the South Asian continent.

It is also not clear whether fatty liver triggers metabolic complications or vice versa. Given the high prevalence of obesity in the UK, unravelling this relationship is essential.

The progression from NAFLD to NASH to cirrhosis is unclear. Better understanding of this process will help the development of specific/targeted prevention and treatment for these conditions.

More controlled trials of weight reduction and physical activity to improve insulin sensitivity in obese patients should be a priority. Evidence on clinical effectiveness and cost-effectiveness are required.
4. LESS COMMON LIVER DISEASE

In this section, we describe a range of other causes of liver disease. These conditions are generally uncommon. In addition they are typically not directly due to subjects’ behaviour. Hence these liver diseases, in the main, are not easily modifiable. Thus we have not made specific recommendations for practice and policy in this section.

However, two points should be noted:

- Primary liver cancer often results from progressive development of earlier stage liver disease; thus its earliest origins may be behavioural. However, once a precursor condition has developed (e.g. cirrhosis), the onward development to liver cancer may be hard to modify via behavioural interventions.

- Drug-induced liver disease due to paracetamol over-dose can be considered behavioural. However, an intentional suicide or parasuicide is likely to be triggered by psychological factors or an underlying mental health condition. Hence its inclusion in this section.

We have categorised these non-behavioural causes of liver disease as follows:

- Primary liver cancers
- Autoimmune liver disease
- Genetic or inherited liver disease
- Liver disease due to Vascular conditions
- Drug-induced liver disease
- Specific Paediatric liver disease
PRIMARY LIVER CANCER

In England and Wales, the incidence of cancers of the liver, gallbladder and biliary tract has increased over the last three decades of the 20th century, particularly in males. ¹

In 1999–2001, liver cell cancer (Hepatocellular carcinoma or HCC) was the most common subsite in males and was twice as common as intrahepatic bile duct cancer (Cholangiocarcinoma or CCA). In contrast, intrahepatic bile duct cancer was the most common in females.

Rates of intrahepatic bile duct cancer increased dramatically in both sexes, whereas the rate of liver cell cancer increased significantly in males, but not in females.

These incidence trends show some divergence from the previously reported mortality statistics. In addition, there were dramatic reductions in the incidence of extrahepatic bile duct and gallbladder cancers in both men and women. ²²

<table>
<thead>
<tr>
<th>Table 3. Incidence of cancers of the liver, gallbladder and biliary tract in England and Wales by subsite and sex per 100,000 (using 3-year rolling averages for the calculation of rates)</th>
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<tbody>
<tr>
<td>----------------------------------------------------------------</td>
</tr>
<tr>
<td>Liver, gallbladder &amp; biliary tract</td>
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<tr>
<td>Liver cell cancer</td>
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<tr>
<td>Intrahepatic bile ducts</td>
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<td>Liver unspecified</td>
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<td>Gallbladder</td>
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<tr>
<td>Extrahepatic bile ducts</td>
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<td>Other biliary tract cancer</td>
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CI, confidence interval. (a)1979-1981. Source: ²²
Liver disease – A rapid review of epidemiology, treatment and service provision

Hepatocellular carcinoma (HCC)

Liver cell cancer or HCC is one of the most common malignant tumours worldwide but, despite scientific advances, survival rates have not improved during the last three decades due to the advanced stage of the disease at diagnosis and due to the limited therapeutic options. ¹⁷⁴

Who gets HCC and what are the consequences?

HCC is the cause of death of more than 19,000 adults per year in the US. The primary etiology is infection with hepatitis B and/or hepatitis C virus. ¹⁷⁵

The US the incidence of HCC rose from 14 per million population in 1976-80 to 24 per million population by 1991-95. ²,¹⁷⁶ These rates were twice as high in Blacks compared to Whites and the increase was particularly in the younger ages. In general, HCC is three times more common in males than females (see Figure 15) and the incidence increases with age, see Figures 16-17. ¹⁷⁴

Figure 15. Directly standardised HCC mortality rates for men and women using European standard population
A recent study examined 30,423 HCC cases in Europe and 6,976 in the US (1982-1994) to look at incidence and survival rates. In southern Europe, incidence was 12/100,000 in men and 3/100,000 women in 1992-1994 whilst in northern Europe the
rates were similar to the US at 3/100,000 in men and <1/100,000 in women). Over this study period incidence remained stable in the US and most of Europe except for a notable increase in southern Europe. Five year relative survival was <10% in Europe, ranging from 8% (southern Europe) to 5% Eastern Europe and 6% in the US. It was unaffected by sex but was better in younger patients. 177

**How do people get HCC and can we prevent this?**

A large majority of HCC arises in cirrhotic livers. 2 Whilst HCC is relatively uncommon in the UK, accounting for about 2% of all cancers, it is the commonest cancer worldwide due to high carrier rates of hepatitis B and C. 2

*Risk factors*

The three commonest risk factors for HCC in the US are infection with hepatitis C (HCV) and/or hepatitis B (HBV) virus and Alcoholic Liver Disease (ALD). 2 The incidence of HCC is estimated to rise in US because of the large pool of HCV infected individuals, even though the incidence of new HCV infection is falling. Modelling in US suggest that HCC incidence might double within the next 1-2 decades. 80 Since alcoholic cirrhosis mortality and alcohol consumption have been declining in Canada, the upward HCC trend has been attributed to the long-term effect of hepatitis B and C infection. 178

*Prevention*

HCC prevention falls into two categories: primary prevention aimed at reducing chronic liver diseases from occurring in the first place and secondary prevention aimed at preventing the recurrence and/or the development of new HCC lesions after successful surgical or non-surgical HCC treatment. 174

Blum argues that in order to reduce morbidity and mortality from HCC early diagnosis and the development of novel systematic therapies for advanced disease, including drugs, gene and immune therapies as well as primary HCC prevention after successful therapeutic interventions needs to be improved in order to make an impact
on survival of patients. New technologies, including gene expression profiling and proteomic analyses, should allow to further elucidate the molecular events underlying HCC developments and to identify novel diagnostic markers as well as therapeutic and preventive targets.

**At what stage do patients present with HCC?**

Despite scientific advances and the implementation of measures for early HCC detection in patients at risk, patient survival has not improved during the last three decades. This was due to both the advanced stage of the disease at the time of clinical presentation and limited therapeutic options.

**What happens to patients with primary liver cancer? Treatment approaches**

Between Jan 1989 and 2004, 1619 liver transplantations were performed in 1471 patients including 163 with a HCC in cirrhosis. The primary diagnosis of patients was hepatitis C (41%); alcohol toxic cirrhosis (21%), cryptogenic cirrhosis (10%), haemochromatosis (2%); primary schlerosing cholangitis, PBC, autoimmune hepatitis, porphyria cutaneatuara or Budd Chiari syndrome accounted for one patient each. The post-operative mortality rate was 1.7%. One, 5 and 10 year survival rates were 88%, 62% and 51%.
Cholangiocarcinoma (CCA)

In CCA, the tumour can arise in ductular epithelium of the biliary tree, either within the liver (intrahepatic) or more commonly in the bile ducts outside the liver (extrahepatic). 21

Who gets CCA and what are the consequences of this?

CCA is rare. Worldwide, CCA accounts for 3% of all gastrointestinal cancers and is the second commonest primary hepatic tumour. 21 The peak age for patients with the disease is in their seventies with a slight male preponderance. 21 However, there have been rising incidence rates, paralleled by mortality rates around the world – see Figure 18. 21

How did they get CC – can we prevent it?:

CCA has been reported to occur coincidentally with a range of diseases including ulcerative colitis, polycystic disease and other less common gastrointestinal complaints.180 181 However, primary sclerosing cholagitis is the commonest known predisposing condition for CCA; rates of 8-40% have been reported in patients with primary sclerosing cholangitis. 21

In one US study, all patients (aged 65+) with intrahepatic CCA were identified between 1993-1999. 182 Controls were randomly chosen from individuals without any cancer diagnosis. A total of 625 cases and 90,834 controls satisfied the inclusion/exclusion criteria. Cases were older than controls and more likely to be male but the ethnic profile was similar. Several risk factors were significantly more prevalent amongst ‘cases’. These included non-specific cirrhosis, hepatitis C or human immunodeficiency virus (HIV) infection, diabetes and inflammatory bowel disease. 182
Figure 18. World-wide incidence of intra (top) and extra-hepatic CCA (bottom).
Source: 21

Prevention

Due to the difficulties in diagnosing CCA, it is often only detected in a late stage and so it is usually considered to be a fatal condition. 21 Thus it is difficult to achieve effective preventive work for CCA itself, preventive approaches need to focus on the precursors of CCA.

At what stage do patients present with CCA?

The disease is usually detected late primarily because many of the early symptoms are non-specific. The most common sign of the disease is abdominal pain. 181 (see table 4).
Table 4. Signs and symptoms of 162 patients with cholangiocellular carcinoma

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Patients (n)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain (RUQ and/or epigastric)</td>
<td>137</td>
<td>84.6</td>
</tr>
<tr>
<td>Fever, chills</td>
<td>85</td>
<td>52.5</td>
</tr>
<tr>
<td>Abdominal tenderness</td>
<td>35</td>
<td>21.6</td>
</tr>
<tr>
<td>Jaundice</td>
<td>46</td>
<td>28.4</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>56</td>
<td>34.6</td>
</tr>
<tr>
<td>Body weight loss</td>
<td>126</td>
<td>77.8</td>
</tr>
<tr>
<td>Weakness, fatigue</td>
<td>50</td>
<td>30.1</td>
</tr>
<tr>
<td>Anaemia</td>
<td>132</td>
<td>81.5</td>
</tr>
</tbody>
</table>

RUQ, right upper quadrant. Summarized from Chen et al.8

What happens to people with CCA? Treatment issues

Most patients with CCA die within 12 months of presenting with the disease.21 A review of survival rates is shown in Table 5 below.181 It has been reported that an aggressive surgical approach provides the best chance for overall survival.181 There is a lack of effective non-surgical therapeutic approaches for CCA.183

Table 5. Cumulative survival rates of peripheral CCA after resection in Western and Eastern. Source:181

<table>
<thead>
<tr>
<th>Resected cases</th>
<th>1-year</th>
<th>5-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schlinkert et al.90</td>
<td>6</td>
<td>33.3%</td>
</tr>
<tr>
<td>Berdah et al.21</td>
<td>17</td>
<td>67%</td>
</tr>
<tr>
<td>Casavilla et al.47</td>
<td>34</td>
<td>60%</td>
</tr>
<tr>
<td>Roayae et al.48</td>
<td>16</td>
<td>87%</td>
</tr>
<tr>
<td>Kawarabu et al.50</td>
<td>16</td>
<td>63.6%</td>
</tr>
<tr>
<td>Chen et al.8,43,45</td>
<td>48*</td>
<td>55.5%</td>
</tr>
</tbody>
</table>

* Hepatolithiasis was associated with cholangiocarcinoma in 33 of 48 cases.

However, not all cases are suitable for surgery and there is a shortage of liver donors. Hence palliative approaches are also important in people with CCA. The one and five years survival rates in un-resected patients are 20% and 1.5% respectively.
AUTOIMMUNE CONDITIONS

Autoimmune conditions arise when the body’s immune system attacks the liver. This process can lead to inflammation or hepatitis which, if untreated, can lead to cirrhosis or liver failure.

The main autoimmune conditions that lead to liver disease are:

- primary biliary cirrhosis
- primary sclerosing cholangitis
- autoimmune hepatitis
Primary Biliary Cirrhosis (PBC)

PBC is a chronic progressive disease, which leads to a progressive destruction of the small intrahepatic bile ducts with portal inflammation leading to fibrosis and cirrhosis. PBC takes approximately 15 years to lead to liver fibrosis and cirrhosis.

Who gets PBC and what are the consequences?

Estimates of PBC vary between 20 and 240 cases per million population, with an incidence between 4 and 30 cases million per year. At this time there is no cure for PBC.

Much of the UK data on incidence and prevalence come from North East England. A study in Newcastle (1987-1994) found an incidence of definite adult cases between of 22 per million population with no obvious trend; prevalence rose from 180 to 240 per million population over this time period. Data from the wider region reported a rising prevalence rate (probable cases) from 202 to 335 per million population in adults between 1987 and 1994. The ELDIT database from Tayside reported an incidence of 43 per million population in the period 1980-98 though they did not report on time trends. However, a United States study found no change in incidence in the period 1975-95.

It is currently not clear why regional or national difference in PBC incidence and/or prevalence rates occur.

PBC typically occurs later in life and is thought to affect women more than men, with an annual mortality rate of 1-2 cases per 100,000 (see Figure 19 below).
How did they acquire PBC?

Why people get PBC is unknown. It is thought that individuals may inherit a predisposition for this condition which is subsequently triggered by environmental factors (an infection or some form of poison taken in from the environment). Occasionally PBC occurs during pregnancy, although it is not clear why.

We currently do not know if specific risk factors lead to the development of PBC and we do not know how to prevent this condition.

At what stage is PBC detected?

PBC is generally detected via blood tests. Most people who have PBC have anti-mitochondrial antibodies in their blood. A liver function test (LFTs) is carried out to determine how well the liver is working.

Specific diagnosis requires ultrasound or liver biopsy.
What happens to people with PBC? Treatment issues

It has been suggested that Ursodexoycholic acid (URSO) may help some people with PBC, although it is unclear how effective this drug is. A recent study investigated whether the risk of mortality and malignancy in people with PBC is reduced by the use of ursodeoxycholic acid. 189 930 PBC cases were compared to 9,202 control subjects from the GP research database in the UK. Patients with PBC had a 3-fold mortality increase when compared with the general population. 189 The use of ursodeoxycholic acid appeared to reduce mortality, but this effect was not statistically significant. 189

The other treatment for PBC is a liver transplant once the liver is seriously damaged. 190

Controversy exists as to whether people with primary biliary cirrhosis (PBC) have an increased risk of developing osteoporosis and the extent to which this may translate into an increased risk of fracture. 191 In a recent case-control study, 930 people with PBC were compared to 9202 age and sex matched controls. Results showed that there were approximately a 2-fold relative increases in the risk of any fracture, hip fracture, and ulna/radius fracture for the PBC cohort compared with the general population. 191
Primary Schlerosing Cholangitis (PSC)

PSC is a chronic disease which causes inflammatory fibrosis of the biliary tract which is immune mediated although the aetiology remains unknown. PSC can progress to cirrhosis and it also causes an increased risk of CCA.

Who gets PSC and what are the consequences?

There is limited epidemiological work on PSC. It appears to be more common in Northern Europe. A study in Norway found an incidence of 13 per million population, and a prevalence of 85 per million population.

PSC can occur at any age, however, is a rare disorder in young adults and it seems not to exist in children. It occurs at twice the rate in males as females and patients are usually diagnosed in their thirties.

Mortality from PSC has increased from around 100 deaths per annum in mid-1980s to 200 deaths per annum by 2000, despite the use of liver transplantation. Analysis of HES data shows no apparent increase in those aged under 64.

How do people get PSC – can we prevent this?

Risk factors

Risk factors seem to include hepatitis C infection, human immunodeficiency virus (HIV), liver cirrhosis and diabetes.

Prevention

We currently do not have clear information on how to prevent PSC.
At what stage is PSC detected

Cases are often diagnosed in early adult life. Prevalence estimates for PSC for the US were 10-40 per million population and in Sweden of 60 per million population. There are no epidemiological data on trends in PSC. In most cases, PSC arises as a complication of ulcerative colitis (figures range from 20-80%). Analysis of HES data for ulcerative colitis show very little rise in hospitalisation between 1989-2000 in England.

What happens to patients with PSC – Treatment issues

There is no treatment for PSC except transplantation. Although PSC is an uncommon disease, it is among the most common indications for liver transplantation in Europe and in the United States. Prognosis partly depends on the stage in the disease of diagnosis; because of a lead time effect—whether at first symptoms or abnormal LFT test or definitive diagnosis by ERCP (Endoscopic Retrograde Cholangiopancreatography).

A recent case series of 9 patients who underwent live donor liver transplantation for PSC described the clinical course and genetic disposition of these patients. Cumulated 5 year patient and graft survival rates were 90% and 70% respectively. The mean time to reocurrence was 3.3 years and recurrent PSC was diagnosed in 50% of patients. This report concluded that overall patient survival seemed to equal that of deceased donor liver transplantations, although more longer-term follow-up was required.
Autoimmune Hepatitis (AIH)

AIH is a progressive chronic hepatitis of unknown cause in which gradual destruction of the hepatic parenchyma occurs, frequently leading to cirrhosis. 199, 200

Variant, overlapping or mixed forms of autoimmune hepatitis share features with other autoimmune liver diseases: primary biliary cirrhosis and primary sclerosing cholangitis, however these similarities amongst these disorders at the moment are descriptive. 199

It is however important to distinguish autoimmune hepatitis from other forms of chronic hepatitis because a large percentage do respond to anti-inflammatory or immunosuppressive therapy or both. 199

Who gets AIH and what are the consequences of this?

There is limited epidemiological work on AIH. The incidence of type 1 AIH in caucasian populations in Europe and North America ranges from 0.1 to 1.9 per 100,000 population annually. 201

Autoimmune hepatitis is more common among women than men. 199

How did they get AIH and can we prevent this?

We currently have no clear information on risk factors or prevention.

At what stage is AIH detected?

Patients with Auto-immune hepatitis may present with non-specific symptoms of varying severity, such as fatigue, lethargy, malaise, anorexia, nausea, abdominal pain and itching. Physical examination may reveal no abnormalities. 199
AIH is the one of the most poorly diagnosed and managed liver diseases in Hepatology and patients commonly present late with what could have been avoidable cirrhosis since AIH is a treatable condition. 202

**What happens to people with AIH? Treatment issues**

A large number of AIH cases respond well to anti-inflammatory or immunosuppressive therapy or both. 199 In recent trials ten year survival rates among those treated are now considered to be over 90% 203 however the 20 year survival rate may be less that 80% among those without cirrhosis and less than 40% of those with cirrhosis. 203

Although survival can be prolonged and improved the quality of a person’s life and avoid the need for liver transplantations, there are still considerable therapeutic challenges remaining. 204
GENETIC (INHERITED) LIVER DISEASE

Inherited liver disease is rare. Although the burden of the condition for sufferers may be great, the small numbers of people affected by these conditions are vastly outweighed by the larger numbers where liver disease is caused by the other factors. ³

There are a number of inherited conditions that can lead to liver disease including:

- Wilson’s Disease
- Alpha₁-Antitrypsin Deficiency
- Haemochromatosis
Wilson’s Disease

Wilson's disease (or progressive hepatolenticular degeneration) is a genetic disorder of copper metabolism, characterised by hepatic and neurological disease. For those affected there is an accumulation of excess copper in the liver caused by reduced excretion of it in bile. It is progressive and can remain undiagnosed and thought to be fatal if not treated. 205 206

Wilson’s disease is caused by an autosomal recessive disorder of hepatic copper disposition caused by mutations in the gene ATP7B, located on chromosome 13. 2

Who gets it and what are the consequences?

Wilson’ Disease affects between one in 30 000 and one in 100 000 individuals. Most symptoms first appear in the second and third decades of life. 3 205 206

How did they get it – can we prevent it?

Wilson’s disease is a genetic condition and so currently not preventable. However, the discovery of new genes and new patterns of regulation of recently identified gene products may in the future lead to novel interventions for the treatment of these disorders. 205

At what stage is it detected?

In Wilson’s disease, the usual age range for clinical presentation is 5–45 years, younger children although older adults may present with this disease. 207
What happens to patients with it? Treatment issues

If left untreated it will invariably result in severe disability and death, however if discovered early there are effective treatments available.\textsuperscript{205} There is growing evidence for the use of trientine for the treatment of Wilson’s disease.\textsuperscript{205} Marcellini found that in children treated with oral zinc therapy for 10 years the disease was controlled effectively and safely and prevented its progression.\textsuperscript{206}

The outlook for liver transplantation for people with Wilson’s disease is best when it is identified early.\textsuperscript{207}
Alpha 1 Anti-trypsin deficiency (A1AD)

In Alpha 1 Anti-trypsin deficiency (A1AD) the body does not produce enough of the enzyme Alpha 1 Anti-trypsin that digests damaged or ageing cells. \(^2\) A1AD predisposes to chronic obstructive pulmonary disease (COPD) \(^{208}\) and is the most frequent cause of liver disease in children. \(^{209}\)

Who gets it?

The American National Institutes for Health statistics estimate that 1 in 2,500 people have A1AD. \(^3\) It is estimated that there are between 70,000 and 120,000 individuals with A1AD in Western European countries. \(^{210}\)

A1AD is the most frequent genetic cause of liver disease in children; however it may also be discovered first in late childhood or early adolescence. \(^{209}\)

How did they get A1AD and can we prevent this?

This is a genetic (inherited) condition and currently not preventable.

At what stage is it detected:

A1AD is usually first discovered at birth, however, it may be discovered later in late childhood or early adolescence when the affected individual is seen with abdominal distention from hepatosplenomegaly or ascites, or has bleeding that is caused by esophageal variceal haemorrhage. \(^{209}\)
What happens to patients with it? Treatment issues

The World Health Organization recommends screening for α1-antitrypsin deficiency at least once in all patients with chronic obstructive pulmonary disease, and in adolescents and adults with asthma. The most important principle in the treatment of A1AD is stopping smoking. Treatment options include orthotopic liver transplantation; shunt surgery, pharmacologic therapy, protein replacement therapy and gene replacement therapy.
Haemochromatosis

The most common genetic liver disease is Haemochromatosis, an autosomal recessive trait which causes iron overload in the liver and affects its functioning.

Clinical manifestations of Heamochromatosis are liver disease but also diabetes, hypermelanotic pigmentation of the skin and heart failure. 211

Who gets it and what are the consequences?

Estimates vary widely. Gagne reports a prevalence of 1–5 per thousand in Caucasian populations. 211 Other reports suggest that as many as 1 in 8 of the Caucasian population has the point mutation that can lead to Haemachromatosis. 2

In haemochromatosis cases, 1 in 200-400 are at risk of developing iron overload. 212

How do they get it – can we prevent it?

Haemachromatosis is a genetic (inherited) condition and we currently do not know how to prevent it.

At what stage is it detected?

Screening is not yet implemented in clinical practice for haemochromatosis. Gagne evaluated the cost-effectiveness of population screening for haemochromatosis via computer modelling of different screening scenarios. Input data were government estimates of health services data and costs and a virtual population with user-defined demographic characteristics. With HCC and cirrhosis as the cost driving complications, population based screening was not significantly more cost efficient than no screening, however, the life expectancy of individuals with hereditary haemochromatosis who were treated improved by 7 years. 211 Whitlock et al. 213 concluded that the current evidence did not support widespread screening.
What happens to patients with it? Treatment issues

The complications that arise in haemochromatosis of iron overload can be avoided if identified early and managed appropriately. The treatment used is therapeutic phlebotomy which is used to remove excess iron and maintain low normal body iron stores.
VASCULAR CONDITIONS

Abnormalities of circulation that affect the liver include congestive heart failure, which leads to reduced outflow of blood from the liver, constrictive pericarditis and obstruction of the inferior vena cava.

A condition more specific to the liver results from obstruction of the hepatic veins is Budd-Chiari syndrome.\textsuperscript{215} Here increased resistance to hepatic venous outflow results in an enlarged liver due to blood pooling which can lead to hypoxia. The hypoxia in turn causes hepatocyte damage with possible fibrosis and cirrhosis; the latter can be termed cardiac cirrhosis.\textsuperscript{215}
**Budd–Chiari Syndrome (BCS)**

Budd-Chiari syndrome is a liver condition caused by blockage of hepatic veins.\(^{216}\) It is a rare condition with unknown etiology. However, it is thought to predominantly arise in people who have a tendency towards blood clotting. Hence it is best regarded as a vascular condition although there may be a genetic component.

Two of the hepatic veins must be blocked for clinically evident disease. Liver congestion and hypoxic damage of hepatocytes eventually results in fibrosis.\(^{216}\) BCS occurs when venous outflow from the liver is obstructed. The obstruction may occur at any point from the hepatic venules to the left atrium.\(^{217}\)

**Who gets it and what are the consequences?**

It occurs in 1/100 000 in the general population. Hypercoagulable state could be identified in 75% of the patients; more than one etiologic factor may play a role in 25% of patients.\(^{216}\)

**How did they get it – can we prevent it?**

The syndrome occurs in patients with underlying thrombotic disorders such as polycythemia rubra vera, paroxysmal nocturnal hemoglobinuria and pregnancy.\(^{217}\)

BCS should be suspected in patients with: (1) Abrupt onset of ascites and painful hepatomegaly; (2) Massive ascites with relatively preserved liver functions; (3) Sinusoidal dilation in liver biopsy without heart disease; (4) Fulminant hepatic failure associated with hepatomegaly and ascites; (5) Unexplained chronic liver disease; (6) Liver disease with thrombogenic disorder.\(^{216}\)
We currently do not know how to prevent this condition. Given the occurrence of BCS in people with blood clotting disorders, there is a possibility that anti-clotting measures may be beneficial.

**At what stage is it detected?**

BCS is complex and hard to diagnosis however increasing nurse practitioners awareness about this rare condition through a case presentation and review of the literature emphasizes the major factors for accurate diagnosis. \(^{218}\)

**What happens to patients with it? Treatment issues**

Liver transplantation for BCS is an effective treatment, irrespective of the underlying cause and should be considered before renal failure occurs. \(^{219}\)
DRUG-INDUCED LIVER INJURY

Drug-induced liver injury can be classified as predictable or non-predictable/idiosyncratic hepatotoxicity.

Predictable reactions occur in response to drugs that are known to have a dose dependent response; paracetamol (acetaminophen) is the main drug taken in overdose in the UK.\(^\text{220}\)

Non-predictable/idiosyncratic drug-induced liver injury occurs sporadically in a small number of individuals at recommended doses because of genetic make-up or because they have difficulty metabolising them. It is reported that almost 1000 drugs can cause drug-induced liver injury; antibacterial drugs, particularly those used to treat tuberculosis, are the major class of drug responsible.\(^\text{221}\)

Who gets drug induced liver disease and what are the consequences?

There are approximately 70,000 new cases of paracetamol overdose per year in Britain\(^\text{222}\) and these overdoses cause approximately 150 deaths annually.\(^\text{220}\)

Therefore, although death from paracetamol overdose is relatively rare, it is still the most common cause of mortality from acute liver disease in the UK; accounting for 60-65% of cases of acute liver disease.\(^\text{220}\)

An American review found that drugs excluding paracetamol are responsible for 12% of liver failure, while paracetamol is responsible for nearly 50% of cases.\(^\text{221 223}\)

Incidence of idiosyncratic drug-induced liver injury is likely to be relatively low as drugs that are known to be hepatotoxic do not usually make it to the market. However it is not possible to find a figure for the incidence of this condition. Indeed, there is criticism of the current reporting of drug-induced liver injury because it relies on spontaneous reports from clinicians who do not have fail-proof means of detection.\(^\text{221 223}\)
How do they get liver disease – can we prevent this?

*Risk factors*

Different risk factors have come to be associated with different drugs. However, common risk factors include: genetic variations, being female, underlying disease states (including hepatitis B or hepatitis C, or infection with human immunodeficiency), increased age, combination therapy, alcohol use and malnutrition.\(^\text{221} 223\)

It is likely that certain genetic dispositions are the greatest risk factor associated with drug-induced liver injury. Associations with strong evidence include N-Acetyltransferase 2 and CYP2E1 associated with susceptibility to drug induced hepatotoxicity caused by antituberculous drugs.\(^\text{221}\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>Chronic alcohol use, fasting, isoniazid use (an antituberculous drug)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Female sex, osteoarthritis</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Young age</td>
</tr>
<tr>
<td>Halothane</td>
<td>Obesity</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Hepatitis B virus, hepatitis C virus, alcohol use, older age, female sex, rifampicin (rifampin) use</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Chronic alcohol use, obesity, diabetes mellitus, chronic hepatitis, psoriasis</td>
</tr>
<tr>
<td>Valpoate sodium</td>
<td>Young age, antiepileptic drug use</td>
</tr>
</tbody>
</table>

*Table 6. Examples of risk factors for drug-induced liver injury. Source: \(^\text{221}\)*
**Prevention**

A primary preventative measure to reduce the number of paracetamol related deaths was introduced in 1998 in the UK. This was a legislation that restricted the sale of paracetamol to 16 tablets in a pack (from 25) in all outlets other than pharmacies. In a review of evidence on this measure it was concluded that paracetamol associated mortality rates, hospital admissions, severity of the overdose, admissions to liver units and for liver transplants have decreased since this measure came into place. But they caution that the evidence is based on a small number of studies with limited follow up and therefore the impacts of the measure are still unclear.

The two main types of prevention for non-predictable/ idiosyncratic drug-induced liver injury are: clinical trials for signs of toxicity prior to a drug going on the market and monitoring of liver abnormalities in patients in primary or secondary care.

Rigorous tests are run prior to drugs going on the market and those that detect hepatic injury, usually by serum enzyme activity increasing, are usually rejected for public use. However studies report several problems with clinical trials for detecting idiosyncratic toxicity. The first is that they are often conducted in samples of the population which would not be large enough to detect idiosyncratic reactions as these range from 1:1,000 to 1:10,000. Furthermore the threshold of ALT (alanine transaminase) abnormalities at which a drug is thought to cause significant risk of liver toxicity, and is thus withdrawn from the market, does not always predict severe outcomes and some drugs might be being withdrawn that don’t lead to severe injury.

For drugs that do show liver toxicity a benefit-risk analysis is carried out. The drugs that do have a risk of toxicity but where the benefits are thought to outweigh the costs and make it onto the market regular monitoring of ALT is recommended.

Correspondingly, the second approach to preventing liver injury would be the monitoring of patients for liver injury in primary or secondary care and when injury is shown their use of the drug would be ceased. However, it is noted that there are several problems with this method; one is that compliance to screening has been poor.
and another is that ALT abnormalities do not always indicate severe reactions. Furthermore, reactions can occur following months of treatment despite normal test results, reactions also occur after patients have ceased taking drugs. \(^{221}\)

**At what stage is drug induced liver disease detected?**

A definitive diagnosis of drug-induced liver injury is not possible, even through liver biopsy, because drug-induced liver injury changes can resemble other liver disease states. Therefore, detection is often carried out through elimination of other causes of liver disease and then identification of a ‘drug-specific clinical signature’. Abbound and Kaplowitz (2007) summarise that these clinical signatures include:

- The pattern of liver test abnormality
- Duration of latency to symptomatic presentation
- Presence or absence of immune mediated hypersensitivity
- Response to drug withdrawal

The Roussel - Uclaf causality assessment method (RUCAM) developed in 1990 is a validated tool used to predict likelihood of drug-induced liver injury. There are some criticisms of the tool however in that the scoring factors are not all evidence based. \(^{223}\)

**What happens to patients with this liver disease? Treatment issues**

Treatment options for drug-induced liver injury are cessation of the drug, and support and monitoring for hepatic failure. \(^{221}\) There are only two proven antidotes to drug-induced liver injury acetylcysteine for paracetamol toxicity and intravenous carntine for valproate sodium overdose. \(^{221}\) For acute liver failure, liver transplant would be the only cure.

It is reported that survival is better for paracetamol reactions than for idiosyncratic cases, 62% compared to 26% respectively. \(^{221}\)
SPECIFIC PAEDIATRIC LIVER DISEASE

Liver disease in children is uncommon but the effect on the lives of sufferers is great. In addition, treatment services will be involved in the case of these individuals for many years.

The specific liver conditions most relevant to children are:

- Biliary atresia
- Cystic fibrosis.
Biliary Atresia (BA)

BA is the most common and important neonatal hepatobiliary disorder. It is characterised by complete obstruction of all or part of the extrahepatic bile duct and is always associated with abnormalities of the intrahepatic bile duct and results in death if left untreated.

BA occurs exclusively in newborns and was, therefore, called ‘congenital extrahepatic biliary atresia’. However, this condition is not thought to be immunological in origin.

Who gets BA and what are the consequences?

Rates are thought to be higher in Asian countries than others although this has not been well investigated. Tiao looked at the National Health Insurance database to explore at this. They identified 327 new cases of BA from 1996-2003. The overall incidence of BA was 1.46 cases per 10 000 live births (0.89-1.90 per 10 000). The 5 year overall survival rate during 1999-2003 was higher that during 1996-1998 (74.8% vs 61.1%, p=0.014). Taiwan has the 2nd highest levels of BA however the management has been improving with a better 5 year overall survival rate.

How did they get BA and can we prevent this?

It was thought that BA was a genetic (inherited condition). However, research suggests that BA might be due to an immune response, triggered by environmental factors (possibly viral) during the perinatal period.

BA may be triggered by environmental factors (possibly viral) during the perinatal period. We currently do not know how to prevent this condition.
At what stage is BA detected?

BA is exclusively found in newborns.\(^{227}\)

BA is identified in an infant with prolonged jaundice (beyond 2 weeks of age), pale stools, or dark urine.\(^{225,230}\) An examination of the colour of a fresh stool specimen is also useful in differentiating cholestasis (pale stools) from indirect hyperbilirubinemia (bright yellow stools). One promising early screening strategy is to give a stool colour card given to new parents and their primary care provider which will alert them to abnormal stools.\(^{225}\)

What happens to patients with BA? Treatment issues.

The main treatment option is corrective surgery to unblock the bile ducts. The best time to operate is six weeks after birth, although not all children recover fully. In the majority of cases the bile flow will still remain insufficient and the liver fibrosis worsens making a liver transplant the only option.\(^{230}\)

It is argued that current treatment is inadequate\(^{224,225}\) and it has been shown that earlier diagnosis (<30-45 days of life) is associated with improved outcomes.\(^{225}\)

The gold standard for operating on BA patients is Kasai’s portoenterostomy.\(^{227}\) A study of long term prognosis of children undergoing the Kasai operation for BA showed the twenty year survival rate was significantly better in children with BA restricted to the hepatic ducts or with cysts at the porta hepatis.\(^{226}\) This work showed that less than 18% of infants with BA who are treated with corrective surgery may avoid liver transplantation, but even these patients require lifelong care.\(^{226}\)
Cystic Fibrosis (CF)

CF is an inherited disorder of epithelial transport which affects the lungs, pancreas, gut, liver and exocrine glands and results from mutations of a gene located on chromosome 7. A genetic mutation affects the Cystic fibrosis transmembrane conductance regulator (CFTR); a transmembrane chloride channel.

CF is usually identified in children and it is increasingly associated with liver disease. A genetic mutation affects the Cystic fibrosis transmembrane conductance regulator (CFTR); a transmembrane chloride channel.

Who gets CF and what are the consequences?

Although all CF patients have abnormal CFTR, not all people with this mutation develop significant liver disease. Thus it is hard to estimate the true risk of liver disease in people with CF.

A US study of all children who attended a CF clinic (195 patients underwent tests) showed that 19% had abnormal liver sonograms and of these 63% had abnormal test results. Furthermore, 8 children with abnormal results had signs of portal hypertension; 82% (14/17) of those with signs of cirrhosis had abnormal liver function. It was concluded that there was a significant relationship between abnormal liver architecture at ultrasound and results of liver function tests in children with CF. The most specific ultrasound abnormalities are signs suggestive of portal hypertension and cirrhosis.

How did they get it and can we prevent it?

This is a genetic (inherited) condition and we do not know how to prevent it.
What happens to patients with it?

A case study of 2 female patients with CF who had simultaneous pancreas and liver transplantation reported that both recovered well with liver functions, resolution of portal hypertension and normal blood glucoses independent of insulin. This report conclude that transplantation provided normalization of glucose and improved nutrition for patients; thus it should be considered in CF patients with CFRD.
5. TREATMENT EFFECTIVENESS – THE EVIDENCE BASE

In earlier sections on risk factors for (and other causes of) liver disease we described a range of treatment approaches, used by clinicians, to manage the wide range of liver diseases encountered in practice.

Where relevant we reported evidence supporting prevention, treatment and palliation of liver disease and its symptoms.

In this section we briefly overview the evaluative literature on the treatment of liver disease to help describe:

- The balance of research on prevention and treatment of liver disease

- To assess the strength of evidence guiding liver disease work.

To do this we have:

Summarised the recent literature in terms of the types of papers being published.

Summarised evidence reviews on prevention and treatment for liver disease published on the Cochrane library.

Summarised current guidance for clinicians on treatments for liver disease.

Appraised the health economics literature on liver disease treatment.
Summary of the literature on liver treatment

In our search of electronic databases (2005-7) and the internet for research on liver disease, we identified 402 relevant references.

The majority of this work (39%) was descriptive epidemiology and much of this work was from outside the UK.

About a third (30%) of the papers reported on the treatment of liver disease, whilst just 13% focused on preventive care.

Just 7% of papers described service provision for liver disease and a quarter (25%) included economic aspects of care.

The rows in Table 7 breakdown the literature for specific liver disease.

<table>
<thead>
<tr>
<th></th>
<th>Epidemiology (156)</th>
<th>Treatment (119)</th>
<th>Prevention (52)</th>
<th>Services (29)</th>
<th>Economics (99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General liver disease (63)</td>
<td>36</td>
<td>31</td>
<td>11</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Alcohol (58)</td>
<td>36</td>
<td>8</td>
<td>13</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Obesity (52)</td>
<td>38</td>
<td>16</td>
<td>14</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis (87)</td>
<td>23</td>
<td>17</td>
<td>7</td>
<td>3</td>
<td>35</td>
</tr>
<tr>
<td>Autoimmune (31)</td>
<td>22</td>
<td>17</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Genetic (14)</td>
<td>8</td>
<td>10</td>
<td>6</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Vascular (14)</td>
<td>7</td>
<td>9</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Drugs (9)</td>
<td>38</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Paediatric (11)</td>
<td>8</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Economics (99)</td>
<td>3</td>
<td>62</td>
<td>22</td>
<td>11</td>
<td>99</td>
</tr>
<tr>
<td>Transplant (41)</td>
<td>3</td>
<td>35</td>
<td>2</td>
<td>4</td>
<td>13</td>
</tr>
</tbody>
</table>

*Please note as some papers cover more than one aspect of liver disease the rows and columns do not add up.

Table 7. Summary of the literature identified in this rapid review
Effectiveness of prevention and treatment for liver disease

To make a rapid assessment of the treatment literature on liver disease we looked at systematic reviews and review protocols published on the Cochrane Library. The breakdown of material was as follows (See Table 8):

- 263 reviews/protocols relating to Hepato-biliary conditions
- 126 were relevant to our review; although 7 had been withdrawn
- 119 reviews and protocol contained 47 were duplicate entries
- 71 separate entries (about half were reviews and half were protocols)
  - 58 (82%) covered treatment for liver disease
  - 13 (18%) covered preventive care

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>Prevention</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review</td>
<td>29</td>
<td>5</td>
<td>34</td>
</tr>
<tr>
<td>Protocol</td>
<td>29</td>
<td>8</td>
<td>37</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>58</strong></td>
<td><strong>13</strong></td>
<td><strong>71</strong></td>
</tr>
</tbody>
</table>

Table 8. shows the breakdown of reviews/protocols by treatment/preventive work

<table>
<thead>
<tr>
<th></th>
<th>Effective</th>
<th>Not effective</th>
<th>Inconclusive</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>5</td>
<td>2</td>
<td>22</td>
<td>29</td>
</tr>
<tr>
<td>Prevention</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>8</strong></td>
<td><strong>2</strong></td>
<td><strong>24</strong></td>
<td><strong>34</strong></td>
</tr>
</tbody>
</table>

Table 9 provides a summary of conclusions drawn in published reviews

Just 8 reviews identified effective interventions (for summary see Table 9 and for details Table 10). [Appendix VII has a synopsis of all reviews]

- Six focused on the prevention or treatment of hepatitis infection.
  - Two of the reviews on hepatitis infection concluded that vaccination strategies were effective at preventing acute hepatitis B infection.
Four reviews of treatment for hepatitis C (acute and chronic) reported that the use of interferon (in varying forms) was effective at reducing or clearing the viral load.

- Two reviews focused on recurrent bleeding in liver disease.
  - One review, on the prevention of bleeding from gastric varices, reported that the use of prophylactic antibiotics was effective.
  - The other, on the treatment of acute oesophageal varices, concluded that Terlipressin was an effective treatment.

**Conclusion**

Despite a large initial number of Cochrane reviews focusing on Hepato-Biliary conditions, only a small number identified effective preventive or treatment and most of these focused on hepatitis infection.

More evaluative research is required and this should focus on preventing as well as treating liver disease. In addition, there is a need for research which identifies effective means of disseminating and encouraging implementation of evidence-based interventions since most physicians have not had specific training in Hepatology, and thus are not using the most effective interventions in liver care.\(^{234}\)

Work in other areas of the Cochrane library (Drugs and Alcohol; Metabolic Conditions) has reported on preventive interventions that are likely to have a positive impact on the field of liver disease.

Brief behaviour change interventions are effective at reducing excessive drinking in primary care settings\(^{52}\) which could help to reduce the numbers of people developing ALD.

Behaviour change interventions are effective at producing weight-loss outcomes in people who are obese, particularly when used in combination with diet and physical
activity. Non-pharmacological interventions focused on diet or physical activity alone produced small improvements and pharmacological approaches had a limited impact on obesity but were beneficial in conjunction with weight-loss programmes. Use of these approaches, particularly behaviour change interventions, could play a positive role in preventing NAFLD/NASH.

Better cross-linkages across different areas of the Cochrane library would help to inform clinicians about current practice to prevent liver disease.

<table>
<thead>
<tr>
<th>Treatment/Prevention</th>
<th>Target condition (or group)</th>
<th>Reference (1st author, year &amp; title)</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention</td>
<td>acute hepatitis B carriers of hepatitis B virus</td>
<td>Lee et al. 2006 Hepatitis B immunisation for newborn infants of hepatitis B surface antigen-positive mothers.</td>
<td>Vaccine, hepatitis B immunoglobulin, and vaccine plus hepatitis B immunoglobulin prevent hepatitis B occurrence in newborn infants of HBsAg positive mothers.</td>
</tr>
<tr>
<td>Prevention</td>
<td>acute hepatitis B</td>
<td>Chen et al. 2005 Vaccines for preventing hepatitis B in health-care workers.</td>
<td>Plasma-derived vaccines (PDV) significantly prevents hepatitis B events. Recombinant vaccines (RV) seem to be able to elicit similar protective anti-HBs levels.</td>
</tr>
<tr>
<td>Treatment</td>
<td>acute hepatitis C</td>
<td>Myers et al. 2001 Interferon for acute hepatitis C.</td>
<td>Interferon α improves liver biochemistry and viral clearance in transfusion-acquired acute hepatitis C. More work needed about long-term clinical outcomes.</td>
</tr>
<tr>
<td>Treatment</td>
<td>chronic hepatitis C</td>
<td>Myers et al. 2002 Interferon for interferon naive patients with chronic hepatitis C.</td>
<td>Interferon is effective in interferon naive patients with chronic hepatitis C but the efficacy in patients with normal aminotransferases is unproven.</td>
</tr>
<tr>
<td>Treatment</td>
<td>Chronic hepatitis C</td>
<td>Myers et al. 2002 Interferon for</td>
<td>Re-treatment with interferon leads to sustained HCV clearance</td>
</tr>
</tbody>
</table>
interferon-nonresponding and relapsing patients with chronic hepatitis

from the blood in patients with previous nonresponse to or relapse from interferon therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Chronic hepatitis C</th>
<th>Brok et al. 2005</th>
<th>Adding ribavirin to interferon increases the number that clear HCV but also increases the risk of several adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ribavirin plus interferon versus interferon for chronic hepatitis C.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention</td>
<td>Recurrent bleeding from gastric varices</td>
<td>Soares-Weiser et al 2002</td>
<td>Antibiotic prophylaxis for cirrhotic inpatients with gastrointestinal bleeding is effective in reducing the number of deaths and bacterial infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antibiotic prophylaxis for cirrhotic patients with gastrointestinal bleeding.</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Recurrent bleeding from oesophageal varices</td>
<td>Ioannou et al. 2003</td>
<td>Terlipressin should be considered to be effective in the treatment of acute variceal haemorrhage.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Terlipressin for acute oesophageal variceal haemorrhage</td>
<td></td>
</tr>
</tbody>
</table>

Table 10. Summary of effective interventions for the prevention or treatment of liver disease. A full list of work with inconclusive and null-effect interventions can be found in the Appendix VII.
Clinical guidance on treatment for liver disease

We considered the current official guidance from the National Institute for Health and Clinical Excellence (NICE) which appraises the evidence for clinicians on a range of treatment approaches in liver disease.

It is not clear how these sets of guidance relate to work reported on the Cochrane library (above).

NICE conducts an assessment of evidence of effectiveness and cost-effectiveness of treatments for the Department of Health.

There are 13 sets of guidance relating to liver disease published by NICE. A brief summary is outlined below along with a hyperlink to the publication.

A number of approaches that were supported required a Hepatobiliary surgeon and/or a specialized multidisciplinary team or specific training to conduct the procedure (1, 4, 5, 7). Others required special arrangements for consenting of patients and audit/research on outcomes (2, 3, 4, 7, 8, 11, 13).

Some treatments were not recommended for practice (2, 6).

   
   Current evidence of safety and efficacy appears adequate to support the use of the procedure, provided that normal arrangements are in place for consent, audit and clinical governance. Recommendations state that patient selection should be carried out by a multidisciplinary team that includes a hepatobiliary surgeon and should be monitored by CT or ultrasound.
   
   Radiofrequency ablation of hepatocellular carcinoma

2. Photodynamic therapy for bile duct cancer, 2005

   Current evidence on the safety and efficacy of photodynamic therapy (PDT) for bile duct cancer does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research
Photodynamic therapy for bile duct cancer

3. Liver-donor liver transplantation, 2006

Current evidence suggests that living donor liver transplantation carries significant risk of morbidity and a small risk of death for donors. Thus clinicians wishing to undertake this procedure should take the following actions: inform the clinical governance leads in their trusts; ensure that donors and recipients undergo thorough physical and psychological screening, and receive counselling about the morbidity and risks associated with this procedure. They should also be provided with clear, written information. An audit and review of clinical outcomes of all people donating liver tissue for transplantation should be carried out.

Living-donor liver transplantation

4. Microwave ablation for the treatment of Metastases in the liver, 2007

Current evidence on the safety and efficacy of this procedure does not appear adequate for it to be used without special arrangements for consent and for audit or research. Clinicians wishing to use this procedure should take the following actions: Inform the clinical governance leads in their trusts; ensure that patients understand the uncertainty about the procedures safety and efficacy and provide them with clear written information, including about other treatment options. Furthermore, an audit and review of all clinical outcomes for all patients should be carried out. Patient selection should be carried out by a multidisciplinary team that includes a hepatobiliary surgeon and the procedure should be performed under appropriate imaging guidance. Adverse events relating to this procedure should be reported to the Medicines and Healthcare products Regulatory Agency.

Microwave ablation for the treatment of metastases in the liver

5. Laparoscopic liver resection, 2005

Current evidence on the safety and efficacy of laparoscopic liver resection appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance. Patient selection for laparoscopic liver resection should be carried out by a multidisciplinary team. Surgeons undertaking laparoscopic liver resection should
have specialist training and expertise both in laparoscopic techniques and in the specific issues relating to liver surgery.

**Laparoscopic liver resection**

6. **Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C, 2006**

The Committee did not believe that there was sufficient evidence to recommend combination therapy or mono-therapy with peg-interferon-alfa for people with mild chronic hepatitis C who are under the age of 18 years, or those who have had a liver transplant

**Hepatitis C - peginterferon alfa and ribavirin**

7. **Microwave ablation of hepatocellular carcinoma, 2007**

Current evidence on the safety and efficacy of microwave ablation of hepatocellular carcinoma appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance. Patient selection should be carried out by a multidisciplinary team that includes a hepatobiliary surgeon; and the procedure should be performed under appropriate imaging guidance. A number of devices are available, and there is some uncertainty about the energy levels that should be used. NICE recommends that any adverse events relating to this procedure should be reported to the Medicines and Healthcare products Regulatory Agency. Further research on long-term survival outcomes and comparisons of microwave ablation with other ablative techniques will be beneficial/useful

**Microwave ablation of hepatocellular carcinoma**

8. **Extracorporeal albumin dialysis for acute –on-chronic liver failure, 2004**

Current evidence on the safety and efficacy of extracorporeal albumin dialysis for acute-on-chronic liver failure (AoCLF) does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research. Clinicians wishing to undertake extracorporeal albumin dialysis for AoCLF should take the following action: Inform the clinical governance leads in their Trusts; ensure that patients understand the uncertainty about the procedure’s safety and efficacy and provide them with clear written information (Use of the
Institute’s Information for the Public is recommended). An audit and review should be carried out to look at the clinical outcomes of all patients having extracorporeal albumin dialysis for AoCLF and publication of safety and efficacy outcomes will be useful in reducing the current uncertainty.

**Extracorporeal albumin dialysis for acute-on-chronic liver failure**

9. **Radio frequency (RF) assisted liver resection, 2007**

Although the evidence is limited on the safety and efficacy of radiofrequency (RF)-assisted liver resection, it appears adequate to support the use of this procedure as one of the options for liver resection, provided that the normal arrangements are in place for consent, audit and clinical governance.

**Radiofrequency-assisted liver resection**

10. **Adefovir dipivoxil and peginterferon alfa-2a- for the treatment of chronic hepatitis B, 2006**

Drug treatment with peginterferon alfa-2a or adefovir dipivoxil should be initiated only by an appropriately qualified healthcare professional with expertise in the management of viral hepatitis. Continuation of therapy under shared-care arrangements with a general practitioner is appropriate.

**Hepatitis B (chronic) - adefovir dipivoxil and pegylated interferon alpha-2a**

11. **Radiofrequency ablation for the treatment of colorectal metastases in the liver, 2004**

Current evidence on safety of radiofrequency ablation of colorectal metastases in the liver appears adequate. However, the evidence of its effect on survival is not yet adequate to support the use of this procedure without special arrangements for consent and for audit or research.

**Radiofrequency ablation for the treatment of colorectal metastases in the liver**
12. Selective internal radiation therapy for colorectal metastases in the liver

Current evidence on the safety of SIRT for colorectal metastases in the liver appears adequate. With regard to efficacy, the procedure may reduce tumour bulk, but there is a lack of evidence of symptom relief or increased survival, and combination with other treatments makes interpretation of the published literature difficult.

Selective internal radiation therapy for colorectal metastases in the liver

13. Complete cytoreduction and heated intraperitoneal intraoperative chemotherapy (Sugarbaker technique) for peritoneal carcinomatosis

Current evidence on the safety and efficacy of complete cytoreduction and heated intraoperative intra-peritoneal chemotherapy (the sugarbaker technique) for peritoneal carcinomas does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research.

Complete cytoreduction and heated intraperitoneal intraoperative chemotherapy (Sugarbaker technique) for peritoneal carcinomatosis

14. NICE guidance currently in progress

Recognition and treatment of neonatal jaundice
Health Economics of liver disease treatment

To date, economic evaluation in the area of liver disease appears to have been limited. One of the challenges in this field is the ethical issue of assessing costs and effects of differing care options in patients with a severe, and often life threatening condition. One promising approach is the use of decision-analysis modelling.

Economic modelling in liver disease

Decision analysis models do not use actual patients but instead use a hypothetical cohort of people who are assigned characteristics similar to the actual patient population. A model brings together data from a variety of sources such as clinical trials, meta-analysis databases and hospital records. Use of a decision model allows the investigator to combine data on costs and effects, including quality of life, to produce data on lifetime costs, life expectancy and quality of life for alternative treatments for the same condition. The hypothetical cohort enters the model, and if they go down the ‘no treatment’ or ‘control’ branch, the model will assign proportions of the cohort to different health states, according to epidemiological evidence. For example, these states might be different Child-Pugh classifications. Based on epidemiological evidence, cases move between the states in pre-specified time periods (e.g. annually) until the cohort dies out. The different health states have costs and health outcomes associated with them, and so, once the cohort dies out, it is possible to aggregate the costs and outcomes to obtain a cost per unit of health gain. Alternatively, the cohort could be modelled to go down the ‘new treatment’ arm where, according to data from randomised trials, they will experience health states at different rates and at different points in time, thus producing a different cost per unit of health gain which can be compared with that for the ‘control’ arm.

Such ‘modelling’ allows us to see how ratios of cost to effectiveness change if key variables in the model are altered. This would not be possible with primary data. However, although it is recognised that modelling has a key role to play in health economic evaluation, there are concerns about the quality and comparability of the data that enter into the model. These concerns about modelling have led to some restrictions being placed on their use.
Economic evaluation of liver disease treatment

Our search of the published literature (for the search strategy see Appendix III) found that, until recently, economic evaluations had focused on two main areas; screening and treatment for Hepatocellular carcinoma (HCC) and prophylaxis and treatment for variceal bleeding (VB).

We are aware of an emerging literature on liver transplantation and a recent work on screening, vaccination and treatment of chronic hepatitis which was covered in the relevant section. However, in the time available for this review, we focused our attention on HCC and VB where there is a clear body of literature.

The literature review identified 22 economic evaluation papers in these two key areas of liver disease treatment: 7 relating to HCC and 15 relating to VB. Each of these studies was assessed against six key criteria for economic evaluations as set out in Laupacis et al. All of the studies are summarised in Appendix VIII and IX.

Hepatocellular carcinoma (HCC)

Screening

Due to an increased incidence of HCC in patients with cirrhosis, surveillance for HCC in patients with liver cirrhosis may seem appropriate. We identified 5 studies involving economic evaluation in the area of screening for HCC (Appendix VIII). The method of screening for HCC in all 5 economic evaluations involved Alpha Fetoprotein (AFP) and ultra-sound.

Sarasin et al used a modelling approach to assess the cost-effectiveness of screening Child-Pugh A patients. Child-Pugh B and C patients were not used as they would not be medically able to stand the treatment given if HCC were found. The treatment option given was partial hepatic resection. The model compared the cost of each life year saved from screening every six months and detection from clinical symptoms only. The model used a set of assumptions which included that:
small HCC would be undetected without screening; small tumours do not increase mortality above that of the underlying cirrhosis; and the sensitivity and specificity of the ultra sound and AFP in detecting large HCC is 100%. The model used a hypothetical cohort of 55 year old males and conducted extensive sensitivity analysis to estimate an incremental cost per life year gained of screening over not screening of between $26,000 and $284,000. The results also gave a maximum gain in life expectancy of nine months as a result of screening in the best case scenario. Therefore, it was concluded that, for most patients, screening did not prove to be worthwhile.

This was also the conclusion of the Bolondi et al study. Using a prospective cohort study of patients with cirrhosis but not HCC, they report a cost per life year saved of US$113,534. However, Farinati and Gianni concluded that screening for HCC increased mean survival time and was not as costly as a priori expectations. Their mean cost per year of life saved was based on the cost of the screening plus the cost of treatment. The treatment options considered were orthotopic liver transplantation (OLTx), percutaneous ethanol injection (PEI), trans-catheter arterial chemo-embolization (TACE) and surgical resection. The combined screening and treatment cost per year of life saved for a treatable HCC is $9152.

Finally a recent health technology assessment (HTA) review in the UK developed a number of decision analysis models to assess the cost effectiveness of various strategies of screening using AFP and ultra sound either individually or in combination and either annually or six monthly versus no screening. This study reported a number of incremental cost per QALY ratios which ranged from £20,700 per QALY for AFP annually versus no screening through to £60,100 per QALY for AFP and ultra sound every six month versus no screening.

**Treatment**

Once HCC has been diagnosed, the treatment options open to patients are limited. Despite this there is still no conclusive evidence on which treatment is the best way forward. In patients in the early stages of HCC the choice of which treatment to give is still debatable with some favouring resection and some OLTx. With this
issue still undecided the cost and effectiveness of the treatments may become a factor in the decision; especially in hospitals where resources are limited. In a small cohort study of compensated cirrhosis patients, four treatment options (OLTx, Surgical resection, PEI and TACE) were compared with best supportive care. The cost per life year saved for OLTx was $21,664; however, only the cost of the treatment was taken into account and the extra cost of the treatment over best supportive care was not presented. The cost per life year for TACE was $4009, for surgical resection $1959 and for PEI was $1233. These estimates, like that of OLTx, are based only on the costs of treatment.

Variceal bleeding (VB)

Screening

Variceal bleeding (VB) is one of the most severe and life threatening symptoms of cirrhosis of the liver. Interest has arisen in the prevention of an initial episode of VB due to the mortality rates associated with it; about 20-30% of deaths of cirrhosis patients are associated with VB. Fifteen economic evaluations have been conducted in the area of VB; of which, eight studies examine interventions for primary prophylaxis of VB and 7 studies evaluate interventions following an initial episode of VB (Appendix IX).

Screening for varices has been recommended for all patients with cirrhosis. The evidence to support the cost effectiveness of universal screening is mixed. From the published economic evaluations of screening for VB, it is difficult to give a definitive recommendation as the studies have examined different methods of screening and other forms of primary prophylaxis such as universal β-blockers and endoscopic variceal ligation. In each study a different comparator is chosen, thus it is difficult to compare the results across studies.

The study by Chalasani et al was designed to determine whether it was possible to use clinical variables to predict the presence of large esophageal varices. Two different interventions were evaluated against a baseline of ‘do nothing’, these were screen all cirrhosis patients or screen only those considered as high risk. The
incremental cost effectiveness ratios (ICER) were: US$15,160 per case of VB averted for the screen all strategy; and US$3,533 per VB case averted for the screen only high risk patients strategy. This study was the only one in this area which did not use decision analysis modelling approach.

Imperiale et al \(^{255}\) carried out a cost utility analysis which incorporated data on patients’ quality of life in the form of utility data. In this health context, ‘utility’ is a judgement of how ‘good’ or ‘bad’ a health state is. Thus different degrees of impairment are weighted (or given a utility value) between 0 and 1, where 0 is assumed to be equated to ‘being dead’ and 1 is equated with ‘full/normal health’. These weights can be used to ‘quality adjust’ survival gains or remaining years of life, and are used in the calculation of quality adjusted life years (QALYs). The authors estimated an incremental cost per QALY of £25,548 for using endoscopic variceal ligation as primary prophylaxis for VB versus \(\beta\)-blockers. Within the field of liver disease there are very few studies which have estimated quality of life data for health states associate with different stages of liver disease. \(^{269}\)

**Treatment**

Treatments for active VB that have been evaluated include; transjugular intrahepatic portosystemic shunt (TIPS), H-graft portacaval shunt and endoscopic sclerotherapy. TIPS has been recommended as an initial treatment as it appeared to offer cost-savings over other forms of treatment. \(^{270-272}\) However, this is subject to debate. In the studies by Rosemurgy et al \(^{260}\) and Helton et al \(^{261}\) only the total costs of treatment and follow up have been reported with both reporting higher total cost for TIPS over other forms of surgical treatment. However, these studies did not combined the information on costs and outcomes together, thus, it is not possible to determine an ICER and make a judgment about the interventions.

In the area of secondary prophylaxis of VB there have been three studies published which used decision analysis models. \(^{262-264}\) However, only the study by Targownik et al 2004 \(^{262}\) reported on cost-effectiveness using an ICER. They evaluated the cost-effectiveness of reducing the incidence of VB by measuring hepatic venous pressure
gradient monitoring (HVPG) following treatment with β-blockers and nitrates versus endoscopic band ligation. The reports an ICER of $5974 per recurrent bleed prevented.

Conclusion

The evidence on cost and effectiveness of screening and treatment in both HCC and VB is mixed.

In HCC screening, all the studies found that screening using AFP and/or ultrasound increased costs compared with the option of not screening. The evidence on effectiveness was more mixed but it suggests that screening would result in only a small increase in life expectancy. A key issue is whether it is worthwhile screening to detect cases of HCC earlier if the relevant treatment (OLTx through the transplant programme) cannot be provided for these cases i.e. due to donor shortage.

The limited number of studies of treatment for HCC reviewed in this report makes it difficult to draw a conclusion on which form of treatment would be recommended, especially as these studies date from the 1990’s and may not represent the latest state of the art in treatment for HCC.

The studies which evaluated screening and pharmacoprophylaxis for VB generally reported that it was cost-effective. However, for endoscopy screening followed by prophylaxis using β-blockers, there was no clear consensus on whether this approach should be universal or just for patients with a higher risk of developing VB (decompensated cirrhosis patients).

A more recent addition to the treatment of VB is the incorporation of haemodynamic monitoring alongside prophylaxis with β-blockers which is used to determine the effectiveness of the drug treatment. There was conflicting evidence from the studies which incorporated additional haemodynamic monitoring of the pharmacoprophylaxis; one study reported cost-savings from HVPG whilst another reported very large cost per year of life saved values. The decision on whether to add HVPG measurement is
dependent on the local costs of measuring HVPG and the life expectancy of the patient group being screened.

The large variation in the ways in which each of these studies were conducted means that it is not easy to interpret the ICERs calculated. Screening and treatment for HCC and VB increases costs. Thus the decision on whether an intervention is ‘cost effective’ must be based on considering the opportunity costs of allocating resources for these interventions away from other currently provided treatments if there is to be no increase in the overall health care budget.

Most of the studies reviewed did not meet all the quality requirements for economic evaluations. The most common areas to be excluded are the year and country the study took part in, and discounting of the costs. Without this the interventions evaluated can look more (or less) attractive than they really are.

Similarly, by only providing the total cost of the treatment or intervention rather than an incremental analysis the true return on any additional resource use cannot be determined, which diminishes the usefulness of the study for making decisions on allocation of resources. The studies which were based on decision models did however meet more of these criteria. It is easier to do in a decision model because it is designed to include such factors as discounting and sensitivity analysis which clinically based economic evaluations often miss out.
6. SERVICE PROVISION FOR LIVER DISEASE

In earlier sections we described the key risk factors for liver disease in England (heavy drinking, chronic hepatitis infections and obesity) and outlined ways of preventing these cases of liver disease.

Liver disease of behavioural origin may be ameliorated by changes in patterns of risky behaviour (heavy drinking, excess calorie intake leading to obesity).

Identifying liver disease early in its development is ideal. However, liver function tests are often inaccurate (not particularly specific) at identifying liver disease.\textsuperscript{273} In addition, abnormal results for liver function are often not adequately investigated, thus the opportunity for early identification of treatable liver disease is often missed.\textsuperscript{62}

There are treatments which have beneficial effects on liver disease, particularly if it is identified at an early stage (e.g. interferon treatment to tackle hepatitis C). Hence it is important to encourage individuals in high-risk groups to come forward for testing.

However, we also described a range of hepatic conditions that were caused by genetic, auto-immune and other factors which are not currently modifiable.

As liver disease progresses to cirrhosis and primary liver cancer, the damage becomes permanent and significantly life-limiting.

Median survival with compensated cirrhosis (without complications) is 12 years compared to around 2 years for decompensated cirrhosis (symptoms include bleeding from varices, ascites, jaundice and encephalopathy).\textsuperscript{274}. Transition from compensated to decompensated cirrhosis occur at a rate of 5-7\% per year.\textsuperscript{274}

In the following section we describe current treatment demand and service provision for liver disease in England.
Service Demand

Tables 11 and 12 show finished hospital episodes (HES data) per 100,000 population by English government region during 2005/2006 (from April 1st 2005 until March 31st 2006). Relevant ICD-10 codes for liver disease are reported in Appendix V.

For men and women, the highest incidence of alcoholic liver disease (K70) occurs in the North West of England. However, the highest incidence of all other types of liver disease and liver cancer is generally found in London; although there appears to be a North East spike for women in chronic hepatitis (K73) and fibrosis and cirrhosis of the liver (K74).

<table>
<thead>
<tr>
<th>Region</th>
<th>K70</th>
<th>K73_K74</th>
<th>K71_K72_K75_K76</th>
<th>C22</th>
</tr>
</thead>
<tbody>
<tr>
<td>North East</td>
<td>36.3</td>
<td>9.4</td>
<td>20.0</td>
<td>12.1</td>
</tr>
<tr>
<td>North West</td>
<td>41.8</td>
<td>4.7</td>
<td>15.3</td>
<td>8.9</td>
</tr>
<tr>
<td>Yorkshire and The Humber</td>
<td>33.3</td>
<td>5.3</td>
<td>17.7</td>
<td>7.3</td>
</tr>
<tr>
<td>East Midlands</td>
<td>26.7</td>
<td>7.3</td>
<td>18.8</td>
<td>6.1</td>
</tr>
<tr>
<td>West Midlands</td>
<td>30.9</td>
<td>7.5</td>
<td>20.0</td>
<td>8.8</td>
</tr>
<tr>
<td>East of England</td>
<td>23.8</td>
<td>7.6</td>
<td>16.7</td>
<td>6.1</td>
</tr>
<tr>
<td>London</td>
<td>34.9</td>
<td>11.9</td>
<td>25.5</td>
<td>15.8</td>
</tr>
<tr>
<td>South East</td>
<td>22.8</td>
<td>5.4</td>
<td>13.5</td>
<td>6.3</td>
</tr>
<tr>
<td>South West</td>
<td>28.4</td>
<td>7.8</td>
<td>18.8</td>
<td>6.7</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>30.8</td>
<td>7.3</td>
<td>18.3</td>
<td>8.7</td>
</tr>
</tbody>
</table>

Table 11. Male Patients (based on finished episodes in HES 2005/2006) per 100,000 population of each English government region Source: HES 2005/2006

<table>
<thead>
<tr>
<th>Region</th>
<th>K70</th>
<th>K73_K74</th>
<th>K71_K72_K75_K76</th>
<th>C22</th>
</tr>
</thead>
<tbody>
<tr>
<td>North East</td>
<td>18.5</td>
<td>11.4</td>
<td>19.4</td>
<td>5.3</td>
</tr>
<tr>
<td>North West</td>
<td>24.7</td>
<td>7.9</td>
<td>15.8</td>
<td>6.0</td>
</tr>
<tr>
<td>Yorkshire and The Humber</td>
<td>15.1</td>
<td>8.6</td>
<td>17.8</td>
<td>4.3</td>
</tr>
<tr>
<td>East Midlands</td>
<td>14.4</td>
<td>8.4</td>
<td>15.5</td>
<td>3.9</td>
</tr>
<tr>
<td>West Midlands</td>
<td>14.8</td>
<td>9.3</td>
<td>19.0</td>
<td>5.0</td>
</tr>
<tr>
<td>East of England</td>
<td>13.0</td>
<td>7.3</td>
<td>13.1</td>
<td>4.0</td>
</tr>
<tr>
<td>London</td>
<td>12.0</td>
<td>9.1</td>
<td>21.4</td>
<td>7.6</td>
</tr>
<tr>
<td>South East</td>
<td>10.1</td>
<td>6.0</td>
<td>11.7</td>
<td>3.9</td>
</tr>
<tr>
<td>South West</td>
<td>13.5</td>
<td>7.0</td>
<td>14.7</td>
<td>4.7</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>14.9</td>
<td>8.0</td>
<td>16.2</td>
<td>5.1</td>
</tr>
</tbody>
</table>

Table 12. Female Patients (based on finished episodes in HES 2005/2006) per 100,000 population of each English government region Source: HES 2005/2006
Tables 13 and 14 show similar HES data by ethnicity. For men and women, the highest incidence of alcoholic liver disease (K70) occurs in people classified as White British and White Other. The incidence of other types of liver disease shows a less clear pattern by ethnicity. However, new cases of liver cell cancer (C22) are highest in men and women who are classified as Black or Mixed Black.

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>K70</td>
<td>K73_K42</td>
</tr>
<tr>
<td>White British</td>
<td>24.8</td>
<td>5.2</td>
</tr>
<tr>
<td>White Other</td>
<td>31.7</td>
<td>10.6</td>
</tr>
<tr>
<td>Asian or mixed Asian</td>
<td>21</td>
<td>8.5</td>
</tr>
<tr>
<td>Black or mixed black</td>
<td>8.6</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>16.8</td>
<td>10.2</td>
</tr>
<tr>
<td>general_population (excluding unspecified ethnicity)</td>
<td>24.7</td>
<td>5.8</td>
</tr>
<tr>
<td>general_population (including unspecified ethnicity)</td>
<td>30</td>
<td>7.1</td>
</tr>
</tbody>
</table>

Table 13. Male Patients (based on finished episodes in HES 2005/2006) per 100,000 population of each ethnic group Source: HES 2005/2006

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>K70</td>
</tr>
<tr>
<td>White British</td>
<td>12.8</td>
</tr>
<tr>
<td>White Other</td>
<td>11.1</td>
</tr>
<tr>
<td>Asian or mixed Asian</td>
<td>1.7</td>
</tr>
<tr>
<td>Black or mixed black</td>
<td>4.1</td>
</tr>
<tr>
<td>Other</td>
<td>3.6</td>
</tr>
<tr>
<td>general_population (excluding unspecified ethnicity)</td>
<td>12</td>
</tr>
<tr>
<td>general_population (including unspecified ethnicity)</td>
<td>14.5</td>
</tr>
</tbody>
</table>

Table 14. Female Patients (based on finished episodes in HES 2005/2006) per 100,000 population of each ethnic group Source: HES 2005/2006

There is a difficulty in interpreting HES data since they are reliant on current ICD-10 codes which do not clearly distinguish between different forms of liver disease. Also, current analyses tend to group several codes together (K71-72 and K75-76). Thus whilst it is relatively clear to identify Alcoholic Liver Disease (K70), it is not easy to ascertain the number of new cases of liver disease due to other causes and, in particular, Non-Alcoholic Fatty Liver Disease.
Service Distribution

Three categories of hospital provide liver services in the UK: 5

• District general and university-associated hospitals that usually have a gastroenterologist with a primary interest in liver disease (District hospitals).
• Teaching hospitals with a major interest in liver disease that do not undertake liver transplantation (Hepatology centres).
• Liver transplant centres (Transplant centres).

Although we were not provided with any data on general hospital activity or from primary care, it is widely recognised that the majority of liver disease is managed in district general hospitals with no trained hepatologist and the majority of patients initially present and are cared for in primary care.

A recent survey in England 275 identified 89 hospitals where some Hepatology services were provided; 34 identified themselves as a Hepatology centre and six were liver transplant centres. Thus 49 District hospitals provided liver services but did not consider themselves to be Hepatology centres. Of these 49, only 2 had designated a hepatologist. In the remaining 47 district hospitals, the workload was managed either by gastroenterologists alone (n=21) or with support from general physicians in (n=26). 275

In the 34 Hepatology centres, 28 (82%) reported a severe shortage of key staff. Nearly a third did not have a consultant Hepatologist in post. 275 276

All six Transplant centres with core funding for tertiary liver care had more than one hepatologist and half had more than 3. Patients referred to these centres that do not need a transplant (30-60% of total referrals) benefit from the broader range of services available as well as more expert staff. 276

Appendix X shows the geographical distribution of Transplant and Hepatology centres in England.
The six adult transplant centres in England are located in Birmingham, Cambridge, London (Kings and the Royal Free), Leeds, and Newcastle (see Table 15). It is notable that there are no transplant centres in the North West of England which has one of the highest rates of liver disease and there is no coverage of the South West. Recent data reported that each of the six transplant centres received referrals from all over the country and from more than 50 PCTs.  

<table>
<thead>
<tr>
<th>Liver Transplant Centres</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birmingham</td>
</tr>
<tr>
<td>Cambridge</td>
</tr>
<tr>
<td>Leeds</td>
</tr>
<tr>
<td>London</td>
</tr>
<tr>
<td>London</td>
</tr>
<tr>
<td>Newcastle</td>
</tr>
</tbody>
</table>

Table 15. Location of Liver Transplant Centres in England. Source:  

This unequal distribution of services is of concern and it has been reported that a patient living in Leeds is four times more likely to be referred for a liver transplant than a patient living in Cornwall.  

Despite 34 hospitals reporting that they provide specialist liver services, the National Plan for Liver Services UK reported that only 10-15 hospitals in the UK (including 7 transplant centres, 6 English and 1 Scottish) would qualify as Hepatology centres; defined as having the clinical expertise and treatment facilities to deliver specialised care for liver disease.  

Workforce Training  

Gastroenterologists manage the majority of liver disease in the UK. However the increasing burden of liver disease and the increasing complexity of managing complicated liver conditions has led for calls from clinicians for the better training and the recruitment of more hepatologists that that have received adequate training.  

\[1\]  

\[5\]
The current specialist registrar (SpR) training programme (where one of a 5 year training programme is spent in a “liver post”) has been reported to be insufficient. In a report published by the British Association for the Study of the Liver (BASL) it was noted that the 3 Consultant hepatologists appointed in the first 6 months of 2007 all received their specialist training as clinical research fellows in Liver Transplant Units rather than in the SpR training programme. Furthermore there were only two applicants for each of these positions compared to 10+ for consultant gastroenterologist posts, suggesting a rarity of adequately trained hepatologists in England.

Thus BASL recommended that:

- Hepatology becomes recognised as a sub-speciality normally entered by CCST – accredited gastroenterologists.
- Approximately 14 new posts need to be created to enable SPRs accredited in Gastroenterology to spend a sixth year in training in the sub-speciality of Hepatology
- Sub-speciality accreditation should only be available to SpRs who have spent, in total, a minimum of two years training in designated Liver Units, 18 months of which should be spent in clinical posts.
- A minimum of six months of the 2 years should be spent training in a designated Liver Unit with an active liver transplant programme and at least six months should also be spent in a designated Liver Unit with no transplant programme.
- As for other trainees in Gastroenterology, trainees in Hepatology will be expected to be trained in diagnostic and therapeutic endoscopy to JAG standards.

A 2002 survey of gastroenterologists also concluded that the number of consultant hepatologists needs to increase to meet the growing demand of increasing liver disease in England and to provide an appropriate level of care in large district general hospitals as well as in specialist centres. It was estimated in 2002 that to provide an appropriate level of care there would need to be one hepatologist to every four gastroenterologists appointed.
Hospital activity - Liver transplantation

Transplantation is a successful treatment for end-stage cirrhosis, with a 75% five year survival rate. However, there is limited availability of organs for donation. Also, issues of compatibility and comorbidity factors mean that not every person with liver disease can be transplanted.

The age of liver donors has increased significantly over the last 15 years in Europe and this has had an adverse impact on graft and patient survival in patients with Alcoholic Liver Disease (ALD) and cirrhosis due to hepatitis C virus (HCV).

In 2000-1, there were 896 episodes of liver surgery resection and this number rose to 1451 by 2004-5; this represented a 62% increase over this five year time period.

The highest numbers of liver transplants occur in the South East of England and London. Whilst the highest number of liver disease cases are found in the North West and North East.

The lowest rates of liver transplants occurred in the South West of England.

There is a suggestion that transplant surgery rates are led by the availability of services (specialist transplant centres) rather than by case need.

The number of deceased liver donors and transplants in the UK has remained relatively constant in the last ten years. In 2006/7, 636 organs were retrieved and 588 used in transplantation. (see Figure 20).

However, the number of patients waiting for a liver transplant has steadily increased. In 2006, the number of people on the active liver transplant list was 38% greater than in the previous year.
Figure 20. Liver transplant figures for the UK (1997-2007).

Prior to transplantation, patients attend Hepatology clinics for general management and assessment for transplantation. Data supplied by University Hospital Birmingham show that 591 men attending the Hepatology clinic had 1565 episodes of care and 322 women had 896 episodes of care. 173

Of these Hepatology episodes in men: 67% were related to ALD; 21% to NAFLD and 12% to NASH. 173 Of these Hepatology episodes in women: 62% were related to ALD; 26% to NAFLD; and 11% to NASH. 173

The age range of patients attending Hepatology clinics was wide (patients in their 20’s to their 70’s). 173 However, the modal age group was 50-59 for ALD and NASH and 40-49 for NAFLD (see Figure 21).
Figure 21. Age of patients attending Hepatology clinics in Birmingham in 2007.

Source: 173

The numbers of new referrals seems to be rising exponentially each year; the tailing off in 2007 is due to incomplete data for the current year (see Figure 22). 173
Figure 22. Year of original referral of patients attending Hepatology clinics at the University Hospital Birmingham. Source: 173

Although ALD is the most common presenting condition, the number of referrals due to NAFLD and NASH has been growing steadily since the 1990’s (see Figure 22).

If NAFLD and NASH cases are added together then the cases of liver disease due to obesity and the metabolic syndrome almost reach those for ALD. It would be important to see if this trend is similar in other parts of the country.
Hospital activity - Non-transplant specialist care

Data supplied by the Plymouth Hospitals NHS Trust in the South West of England show that specialist hospital (non-transplant) activity on liver disease has steadily increased over recent years (see Tables 13-17).

This activity includes treatment for primary and secondary liver cancer, liver biopsies, drainage of ascites and management of different forms of liver disease.

Patients with advanced liver disease tend to have multiple admissions each year.

Hospital activity includes liver disease as a main diagnosis or as a secondary diagnosis (often much higher figures), where patients present for other reasons.

In all these aspects of liver disease treatment, clinical activity seems to be rising year on year.

<table>
<thead>
<tr>
<th>year</th>
<th>Admissions – main diagnosis</th>
<th>Admissions – any diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>20 (9)</td>
<td>30 (14)</td>
</tr>
<tr>
<td>2002</td>
<td>33 (17)</td>
<td>41 (20)</td>
</tr>
<tr>
<td>2003</td>
<td>22 (15)</td>
<td>31 (19)</td>
</tr>
<tr>
<td>2004</td>
<td>39 (18)</td>
<td>36 (17)</td>
</tr>
<tr>
<td>2005</td>
<td>56 (26)</td>
<td>25 (11)</td>
</tr>
<tr>
<td>2006</td>
<td>82 (34)</td>
<td>70 (30)</td>
</tr>
</tbody>
</table>

Table 13. Counts per finished consultant episode (FCE) – the figure in the bracket is the number of patients that made up the admissions total. Source: 283
### Secondary liver tumours C76.7

<table>
<thead>
<tr>
<th>year</th>
<th>Admissions – main diagnosis</th>
<th>Admissions – any diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>216 (51)</td>
<td>1454 (327)</td>
</tr>
<tr>
<td>2002</td>
<td>196 (42)</td>
<td>1236 (342)</td>
</tr>
<tr>
<td>2003</td>
<td>176 (43)</td>
<td>1225 (324)</td>
</tr>
<tr>
<td>2004</td>
<td>148 (52)</td>
<td>1005 (307)</td>
</tr>
<tr>
<td>2005</td>
<td>169 (46)</td>
<td>1448 (342)</td>
</tr>
<tr>
<td>2006</td>
<td>216 (69)</td>
<td>1544 (378)</td>
</tr>
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</table>

Table 14. Counts per FCE (number of patients that made up the admission total). Source: 283

### Management of Alcoholic liver disease K700-709

<table>
<thead>
<tr>
<th>year</th>
<th>Admissions – main diagnosis</th>
<th>Admissions – any diagnosis</th>
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<tbody>
<tr>
<td>2001</td>
<td>120 (70)</td>
<td>285 (153)</td>
</tr>
<tr>
<td>2002</td>
<td>126 (98)</td>
<td>341 (186)</td>
</tr>
<tr>
<td>2003</td>
<td>141 (102)</td>
<td>353 (195)</td>
</tr>
<tr>
<td>2004</td>
<td>126 (68)</td>
<td>342 (135)</td>
</tr>
<tr>
<td>2005</td>
<td>142 (70)</td>
<td>365 (138)</td>
</tr>
<tr>
<td>2006</td>
<td>182 (98)</td>
<td>512 (169)</td>
</tr>
</tbody>
</table>

Table 15. Counts per FCE (number of patients that made up the admission total). Source: 283

### Liver biopsies – OPCS J091-92, J131-2, J141, J171

<table>
<thead>
<tr>
<th>year</th>
<th>Admissions – main diagnosis</th>
<th>Admissions – any diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>13 (13)</td>
<td>148 (141)</td>
</tr>
<tr>
<td>2005</td>
<td>16 (16)</td>
<td>161 (152)</td>
</tr>
<tr>
<td>2006</td>
<td>12 (12)</td>
<td>215 (204)</td>
</tr>
</tbody>
</table>

Table 16 Counts per FCE (number of patients that made up the admission total). Source: 283
<table>
<thead>
<tr>
<th>Year</th>
<th>Admissions – main diagnosis</th>
<th>Admissions – any diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>23 (23)</td>
<td>51 (42)</td>
</tr>
<tr>
<td>2005</td>
<td>30 (29)</td>
<td>118 (86)</td>
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<tr>
<td>2006</td>
<td>31 (30)</td>
<td>141 (99)</td>
</tr>
</tbody>
</table>

Table 17 Counts per FCE (number of patients that made up the admission total).

Source: 283
**Hospital activity – Paediatric liver care**

In paediatric liver disease, children are often born with a liver condition and require life-long care.

Paediatric liver services are available in 3 centres in England: Birmingham (Birmingham Children’s Hospital), London (King’s College Hospital) and Leeds (St James’s University Hospital).

Outcomes of liver transplantation in children have improved over time, particularly children under one year of age; one-year patient and graft survival rates improved from 50-58% in the 1986-9 to 81-88% in 2000-3. A corollary of this positive outcome is the likely need for more care of young people living with liver disease.

Data supplied by King’s College Hospital in London show 614 referrals and/or admissions for paediatric liver disease in 2006, 313 cases were new referrals (see Figure 23).

There appears to have been a slight increase in the number of cases of liver disease treated in this paediatric centre since 2003/4 (see Figure 23).

As with adults, individual patients present repeatedly for care each year and so there are more hospital episodes compared to patient cases (see Figure 24).
Figure 23. All cases of paediatric liver disease and new cases each year. Source: 285

Figure 24. Numbers of day and outpatient cases by child and hospital episode. Source: 285
The most common conditions were genetic in origin (biliary atresia in children <1 year old and 1-5 years old). However, children also present with acute liver failure (n=29 in 2006/7).

However, paediatric services treat a wide range of liver disease including (2006/7 figures) autoimmune disease (n=25), hepatitis B (n=4), hepatitis C (n=1), metabolic liver disease (n=11), non-alcoholic fatty liver disease (n=10), primary liver tumours (n=17) and disorders of the bile duct (n=19).
7. PATIENT PERSPECTIVE

We were unable to find any published research on patients’ perspectives of being diagnosed with, or of accessing treatment for, liver disease. The only in-depth research identified was with prisoners (service users and potential service users) who were interviewed about views on hepatitis C testing in the prison setting. 99

However, we were sent some qualitative data by the British Liver Trust (BLT) which describes patient and carers’ experiences of liver services. 286 These data were obtained from a survey of patients and carers at a conference organised by the Charity in October 2007 and visitors to their website and helpline during October and November 2007. Although based on a small and self-selected sample these data provide a valuable insight into service user views.

The following is a broad summary of the patients’ views of liver services:

- Respondents seemed to highly value specialist treatment and care for liver problems. Those people that have received specialised treatment praised the quality of their care. However some patients reported having to travel up to 300 miles to access specialist care. Conversely, others reported travelling less than five miles for their care, suggesting that at least some of these people were not receiving care from doctors with specialist expertise i.e. in Hepatology centres.

- Some respondents reported a reluctance from GPs to refer them to specialist centres. The survey found an average a 564 day delay from the onset of symptoms to diagnosis. It was perceived that this wait was due to delays in primary care rather than waiting lists for specialists.

- In some cases patients with health conditions which can have major liver implications were never seen by a hepatologist because the liver disease was not considered to be the primary aetiology. For example, patients with NASH managed purely by a cardio-vascular specialist. Furthermore patients with
mental health problems who had taken drug overdoses had not received liver treatment after they have had emergency care.

- Many respondents reported experiencing stigma due to their condition. This arose from misconceptions about alcohol use (e.g. it was presumed to be excessive when alcohol might not have be the causal factor for their liver disease) or acquisition of the hepatitis virus (e.g. it was assumed to be due to injecting drug use or risky sexual behaviour rather than contaminated blood products). Many patients felt that these misconceptions had led to poor quality of care and may have influenced referral and treatment decisions.

- Patients reported that they would like to receive more holistic treatment. Centres that offered the additional support of specialist nurses, counsellors, social workers and seamless access to other professionals seemed to be very much valued by patients.

- Respondents reported a common experience of administrative errors regarding communication about test results or liaison between different treatment providers. Thus test results went missing or were miscommunicated between different clinicians. It was not clear if this was particular to Hepatology or an inherent problem in situations where patients have complex needs.

The lack of rigorously conducted research on patients’ views is a significant gap in our knowledge about liver disease treatment and service provision and should be addressed as a priority in future research work.
8. CONCLUSIONS

Liver disease in England is increasing; there are more cases developing each year and people are dying earlier from this condition.

The steady rise in liver disease in England is in contrast to most countries of the world.

Most cases of liver disease are due to modifiable (lifestyle) factors.

The largest numbers of liver disease cases in England are due to excessive drinking in the population and to chronic hepatitis infections.

Obesity can also cause liver disease and high obesity rates in England are likely to lead to a rapid increase in liver disease in the near future.

The NHS needs more capacity to respond to liver disease in England, particularly in the North West and the South West of England.

The NHS needs to prepare for a potentially large future burden of liver disease.

Current research tends to focus on treating existing liver disease; future work needs to address effective means of preventing liver disease.

Behaviour change interventions are effective at reducing excessive drinking and obesity and should be implemented in England.

We need better screening for hepatitis infections and early treatment of hepatitis C.

Patient s’ perspectives of living with (and often dying early from) liver disease are absent from the current literature and this needs to be rectified.
9. ACKNOWLEDGEMENTS

This work was undertaken by the Institute of Health and Society who received funding from the Department of Health, Policy Research Programme (grant reference LVR/012). The views expressed in the publication are those of the authors and not necessarily those of the Department of Health.

We would particularly like to acknowledge the hard work of our secretarial and administrative colleagues who have provided us with a tremendous amount of support in carrying out this rapid review work.

Most of the tracking-down of references, arranging inter-library loans and printing fell to Beth Edgar who did this amazingly efficiently and she was provided with helpful cover by Lynne Oliver. Thanks also to Miriam Lowes for tracking down key papers.

We would also like to thank Laura Stokoe (Professor Kaner’s personal assistant) who always manages to keep the show on the road, no matter how challenging or last minute the request.

Wayne Younger and Gillian Paczynski helped arrange the finance and contract

We would like to thank all the individuals and agencies who responded to our request for information. We have experienced a tremendous amount of energy and motivation from a wide range of individuals (clinicians, statutory agencies and the voluntary sector) who are eager to improve services for people with liver disease in England.
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    unpublished report from the British Liver Trust, 2007
    Efficacy of a Recombinant Hepatitis E Vaccine. *New England Journal of
APPENDICES
## Appendix I

### Liver review – Key Informants contacted

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Appendix II

Search strategy for epidemiology papers.

Original source for the search strategy (1-20) Roderick et al. 2004

1. exp INCIDENCE/
2. exp PREVALENCE/
3. (incidence or prevalence).ti,ab.
4. 1 or 2 or 3
5. exp Risk Factors/ 
6. exp Time Factors/ 
7. exp Cohort Studies/
8. epidemiol$.ti,ab.
9. aetio$.ti,ab.
10. etiolog$.ti,ab.
11. 8 or 9 or 10
12. ((natural or disease$) adj (progress$ or course$ or histor$)).ti,ab.
13. 4 or 5 or 6 or 7 or 11 or 12
14. time trends$.mp 
15. trends$.mp.
16. projection$.mp
17. model$.mp.
18. 13 or 14 or 15 or 16 or 17
19. limit 18 to human
20. 18 and 19

21. Liver disease
22. [relevant key word terms – see below)
23. 21 or 22
24. 20 and 23

Keywords
Alcohol, alcoholic, alcohol-related, drugs, substance
hepatitis, infections, hepatitis C, hepatitis B, HCV, HBV
Obesity, overweight, metabolic syndrome, NAFLD, NASH
Genetic, inherited, heritable
Autoimmune, acquired, immune system
Cancer, tumours, primary liver cancer
Paediatric, childhood, child, infant
Budd Chiari, Primary Biliary Cirrhosis, Schlerosing Cholangitis, Biliary Atresia
Appendix III

Search strategy - Economic Evaluations of treatment for liver disease

**Medline/PubMed (National Library of Medicine) 1966 to May 2003**
((((alcohol-related disorders OR alcohol drinking OR alcoholism[MeSH Subjects]) AND (liver OR liver diseases[MeSH Subjects]) OR liver diseases, alcoholic OR liver cirrhosis, alcoholic[MeSH Subjects])

AND

cost of illness OR economics OR health planning[MeSH Subjects] OR economics[subheading] OR burden of illness OR cost of illness OR cost OR costs[TextWords])

**Embase (OVID) 1980 to May 2003**
((((Alcoholism[Embase Subject Headings] OR alcohol*[Text Word] AND (liver disease OR liver)) OR alcohol liver disease OR alcohol liver cirrhosis[Embase Subject Headings])

AND

cost of Illness OR economics OR health economics OR economic aspect OR health care cost OR cost of health care planning[Embase Subject Headings] OR “cost of illness” OR “burden of illness” OR cost OR costs[Text Words])

**EconLit (EBSCO) & Business Source Premiere (EBSCO) Mid 1960s to 2003**
alcohol* AND liver* [Default Fields]

AND

cost* OR burden of illness OR economic* [Default Fields]

**Sociological Abstracts (WebSPIRS) 1963 to 2003**
alcoholism OR alcohol[Descriptors] AND liver*[TextWord]

AND

costs OR health care costs OR economics[Descriptors] OR cost of illness OR burden of illness OR cost OR economic*[Text Words]

**Social Sciences Abstracts (Wilson Web) 1983 to 2003**
(alcoholism[Descriptor] OR alcohol*) AND (liver OR liver/diseases[Descriptors] OR liver[Text Word])

AND

economics OR cost[Descriptors] OR cost of illness OR burden of illness OR cost OR costs OR economic*[Text Words]

**Internet**
Freetext internet searching, using the Google search engine and the following combination of terms
Alcohol* AND liver*

AND

cost of illness OR burden of illness OR cost OR costs OR economic*)
Appendix IV

ACRONYMS

AIH – Autoimmune hepatitis

ALD – Alcoholic liver disease

ALT – Alaine aminotranserase, a liver enzyme that enters the blood following liver damage. An ALT test is used to monitor and assess the degree of liver damage in patients with chronic HBV.

ANARP - Alcohol Needs Assessment Research Project

CCA - Cholangiocarcinoma, cancer of the bile ducts

CF - Cystic Fibrosis

CFRD – Cystic Fibrosis Related Disease

CFTR - Cystic fibrosis transmembrane conductance regulator

CHD - Coronary heart disease

COPD – Chronic obstructive pulmonary disease

CSP - Comprehensive service provider

CVD - Coronary vascular disease

DM – Diabetes mellitus

ELISA - Enzyme Linked Immunosorbent Assays

ERCP - Endoscopic Retrograde Cholangiopancreatography

FCE - finished consultant episode

GHS - General Household Survey

GI - Gastroenterology

GUM - Genito-Urinary Medicine

HAV – Hepatitis A Virus

HBV – Hepatitis B virus

HCC – Hepatocellular carcinoma, also called hepatoma. With biliary tree cancer, HCC is one of the two main types of primary liver cancer.
HCV – Hepatitis C virus

HES - Hospital Episode Statistics

HIV – Human Immunodeficiency Virus

IDU – Injecting drug user

ID – Infectious disease

NAFLD – Non-Alcoholic Fatty Liver Disease

NASH – Non-Alcoholic Steatohepatitis

NICE - National Institute for Health and Clinical Excellence

PBC – Primary Biliary Cirrhosis

NSF – National Service Framework

PSA - Public Service Agreement

PSC – Primary Schlerosing Cholangitis

QALY - Quality adjusted life year

RUCAM - The Rousssel - Uclaf causality assessment method

URSO - Ursodexoycholic acid
Appendix V

The International classification of diseases, 10th revision (ICD-10) codes used to for diseases of the liver. Chronic liver disease is specified by the codes K70, K73-K74.

<table>
<thead>
<tr>
<th>Description</th>
<th>ICD-10 code</th>
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<tbody>
<tr>
<td>Alcoholic liver disease</td>
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<tr>
<td>Toxic liver disease</td>
<td>K71</td>
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<tr>
<td>Hepatic failure, not elsewhere classified</td>
<td>K72</td>
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<tr>
<td>Chronic hepatitis, not elsewhere classified</td>
<td>K73</td>
</tr>
<tr>
<td>Fibrosis and cirrhosis of liver</td>
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<td>Other inflammatory liver diseases</td>
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<tr>
<td>Other diseases of liver</td>
<td>K76</td>
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<tr>
<td>Liver cell carcinoma</td>
<td>C22</td>
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Appendix VI

Other Hepatitis Viruses A,D&E

Hepatitis A.

Hepatitis A and E are spread through faeces, usually when they have contaminated food or water i.e. poor sewage or through oral and anal sex. The way hepatitis A works in the body is not well understood but the infection does not typically have a chronic stage and does not cause permanent liver damage as virtually all people get better on their own. However, the symptoms from the virus can be severe, even deadly: high liver enzymes, high fever, loss of appetite, nausea, vomiting, and jaundice, which is caused by the increased liver enzymes. The symptoms usually last 1 to 4 weeks. The virus can only be contracted once as the immune system makes antibodies against the hepatitis A virus that confer immunity against future infection.

At present there is no antiviral treatment for hepatitis A virus once it is contracted so the emphasis is on raising awareness of the precautions that individuals need to take and prevention through administering the vaccine, which can be given in combination with the vaccine for hepatitis B.

Hepatitis D

Main spread hepatitis D is contact with infected blood. However, hepatitis D is considered to be a subviral satellite because it can only develop in those already infected with hepatitis B. Co-infection with hepatitis D results in more severe complications compared to infection with hepatitis B alone. These complications include a greater likelihood of experiencing liver failure in acute infections and a greater likelihood of developing liver cancer in chronic infections. In combination with hepatitis B virus, hepatitis D has the highest mortality rate of all the hepatitis infections of 20%.
Hepatitis E

Hepatitis E is prevalent in most developing countries, and not uncommon in any country with a hot climate. It is widespread in Southeast Asia, northern and central Africa, India, and Central America. It is spread mainly through fecal contamination of water supplies or food; person-to-person transmission is uncommon. However, domestic animals have been reported to act as a reservoir for the hepatitis E virus, with some surveys showing infection rates exceeding 95% among domestic pigs. Outbreaks of epidemic hepatitis E most commonly occur after heavy rainfalls and monsoons because of their disruption of water supplies. The incidence of hepatitis E is highest in adults between the ages of 15 and 40. Though children often contract this infection as well, they less frequently become symptomatic. Mortality rates are generally low, for hepatitis E is a “self-limiting” disease, in that it usually goes away by itself and the patient recovers, the duration of the infection is typically a few weeks.

A recent study conducted with Nepalese male army recruits has indicated that the first vaccine against hepatitis E, which is yet to be named, is highly effective in protecting people from the disease. These are encouraging developments, however it must be noted that these are preliminary findings and work must be carried out with women and children.
## Appendix VII

### Synopsis of published Cochrane Collaboration Reviews

<table>
<thead>
<tr>
<th>Reference</th>
<th>Prevention or Treatment</th>
<th>Review or Protocol</th>
<th>Conclusion</th>
<th>Number of Duplicate entries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu JP, Gluud LL, Als-Nielsen B, Gluud C. Artificial and bioartificial support systems for liver failure. <em>Cochrane Database of Systematic Reviews</em> 2004, Issue 1.</td>
<td>Treatment</td>
<td>Review</td>
<td>INCONCLUSIVE – more work needed before any support systems may be recommended for routine use. Artificial support systems may reduce mortality in acute-on-chronic liver failure. Artificial and bioartificial support systems did not appear to affect mortality in acute liver failure. This Review indicates that artificial support systems may reduce mortality in acute-on-chronic liver failure.</td>
<td>11</td>
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<tr>
<td>Gurusamy KS, Kumar Y, Davidson BR. Ischaemic preconditioning versus no ischaemic preconditioning for liver transplantation. (Protocol) <em>Cochrane Database of Systematic Reviews</em></td>
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<td>5</td>
<td>Chen W, Gluud C.</td>
<td>Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No</td>
<td>Prevention Review EFFECTIVE – plasma-derived vaccines (PDV) significantly prevents hepatitis B events. Recombinant vaccines (RV) seems to be able to elicit similar protective anti-HBs levels.</td>
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<td>Oberdorfer A, Oberdorfer AL, Tran DT.</td>
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<td>9</td>
<td>Milk thistle for alcoholic and/or hepatitis B or C virus liver diseases.</td>
<td>Treatment Review</td>
<td>INCONCLUSIVE</td>
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<td>Bile acids for viral hepatitis.</td>
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<td>12</td>
<td>He Q, Chen XY, He L. Tiopronin for chronic hepatitis B. (Protocol) Cochrane Database of Systematic Reviews 2006, Issue 4.</td>
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<td>15</td>
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<td>Manheimer E, Tsutani K, Gluud C. Medicinal herbs for hepatitis C virus</td>
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<td>- Still awaiting evidence on efficacy of medicinal herbs for viral</td>
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<td>infection. <em>Cochrane Database of Systematic Reviews</em> 2001, Issue 4.</td>
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<td>Gurusamy KS, Kumar Y, Sharma D, Davidson BR. Methods of vascular</td>
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<td>occlusion for elective liver resections. *Cochrane Database of Systematic</td>
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<td>vascular occlusion is safe in liver resection, but it does not</td>
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<td>seem to reduce mortality.</td>
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<td>infections in cirrhotic patients with ascites. (Protocol) *Cochrane</td>
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<td>Rambaldi A, Gluud C. Anabolic-androgenic steroids for alcoholic liver</td>
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<td>NOT EFFECTIVE - No evidence to support anabolic-androgenic steroids</td>
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<td>disease. <em>Cochrane Database of Systematic Reviews</em> 2006, Issue 4</td>
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<td>Rambaldi A, Gluud C. Colchicine for</td>
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alcoholic and non-alcoholic liver fibrosis and cirrhosis. *Cochrane Database of Systematic Reviews* 2005, Issue 2.

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<tr>
<td>20 Rambaldi A, Gluud C. Propylthiouracil for alcoholic liver disease. <em>Cochrane Database of Systematic Reviews</em> 2005, Issue 4.</td>
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<td>INCONCLUSIVE - Evidence supporting or refuting propylthiouracil for alcoholic liver disease was not found</td>
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<td>23 Saab S, Nieto JM. Surgical versus medical treatment of refractory ascites. (Protocol) <em>Cochrane Database of Systematic Reviews</em></td>
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<td><strong>25</strong> Efsen E, Gluud LL, Schlichting P. Immunosuppressive drugs for autoimmune hepatitis. (Protocol) Cochrane Database of Systematic Reviews 2004, Issue 1</td>
<td>Treatment Protocol ONGOING 1</td>
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<td><strong>27</strong> Wun YT, Dickinson JA. Alpha-fetoprotein and/or liver ultrasonography for liver cancer screening in patients with</td>
<td>Treatment Review INCONCLUSIVE - Inadequate evidence on screening with alpha-fetoprotein and/or ultrasound of the liver for patients with 2</td>
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<td>Schroth RJ, Hitchon CA, Uhanova J, Noreddin A, Taback SP, Moffatt MEK, Zacharias JM. Hepatitis B vaccination for patients with chronic renal failure. Cochrane Database of Systematic Reviews 2004, Issue 3.</td>
<td>Prevention Review</td>
<td>INCONCLUSIVE - Hepatitis B vaccines achieve antibody production in patients with chronic renal failure, but we do not know if the vaccines are protective</td>
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<td>30</td>
<td>Katz LHAIM, Fraser A, Leibovici L, Turkaspa R. Lamivudine for preventing reactivation of hepatitis B infection in patients planned to undergo</td>
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<td>Study</td>
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<td>34 Wu T, Roger H, Xie L, Liu G, Hao B. Bicyclol for chronic hepatitis B. Cochrane Database of Systematic Reviews</td>
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<td>Review</td>
<td>INCONCLUSIVE - Evidence on beneficial or harmful effects of bicyclol for chronic hepatitis</td>
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<td>Liu JP, Lin H, Gluud C. Comparison of medicinal herbs for chronic hepatitis B virus infection. (Protocol) <em>Cochrane Database of Systematic Reviews</em></td>
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<td>Davidson BR. Antiviral prophylactic intervention for hepatitis C virus in patients undergoing liver transplantation. (Protocol) Cochrane Database of Systematic Reviews 2007, Issue 3.</td>
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<td>INCONCLUSIVE - No evidence to support or refute glucocorticosteroids for viral hepatitis C</td>
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<td>Brok J, Mellerup MT, Krogsgaard K, Gluud C. Glucocorticosteroids for viral hepatitis C. Cochrane Database of Systematic Reviews 2004, Issue 2.</td>
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<td>EFFECTIVE - It is effective in interferon naive patients with chronic hepatitis C but the efficacy in patients with normal aminotransferases is unproven.</td>
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<td>previous nonresponse to or relapse following interferon therapy</td>
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<td>51 Brok J, Gluud LL, Gluud C. Ribavirin plus interferon versus interferon for chronic hepatitis C. <em>Cochrane Database of Systematic Reviews</em> 2005, Issue 2.</td>
<td>Treatment Review EFFECTIVE - Adding ribavirin to interferon increases the number that clear hepatitis C virus but also increases the risk of several adverse events</td>
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<td>54 Brok J, Gluud L, Gluud C. Ribavirin monotherapy for chronic hepatitis C. <em>Cochrane Database of Systematic Reviews</em> 2005,</td>
<td>Treatment Review NOT EFFECTIVE - Ribavirin monotherapy seems without beneficial effects for patients with chronic hepatitis C</td>
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<td>Yang XY, Zhuo Q, Wu TX, Liu GJ. Bicyclol for chronic hepatitis C. Cochrane Database of Systematic Reviews 2007, Issue 1</td>
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<td>Soares-Weiser K, Brezis M, Tur-Kaspa R, Leibovici L. Antibiotic prophylaxis for cirrhotic patients with gastrointestinal</td>
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<td>Ioannou G, Doust J, Rockey DC.</td>
<td>Terlipressin for acute esophageal variceal hemorrhage.</td>
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<td>Khan S, Tudur Smith C, Williamson P, Sutton R.</td>
<td>Portosystemic shunts versus endoscopic therapy for variceal rebleeding in patients with cirrhosis. <em>Cochrane Database of Systematic Reviews</em> 2006, Issue 4.</td>
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<td>Khan SA, Williamson P, Sutton R, Tudur C.</td>
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<td>Saab S, Nieto JM, Lewis SK, Runyon BA. TIPS versus paracentesis for cirrhotic patients with refractory ascites. <em>Cochrane Database of Systematic Reviews</em> 1998, Issue 1.</td>
<td>- The meta-analysis supports that TIPS was more effective at removing ascites as compared with paracentesis without a significant difference in mortality, gastrointestinal bleeding, infection, and acute renal failure. However, TIPS patients develop hepatic encephalopathy significantly more often.</td>
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<td>Wang RT, Koretz RL, Yee HF. Weight reduction for non-alcoholic fatty liver. <em>Cochrane Database of Systematic Reviews</em> 2002, Issue 1</td>
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<td>Lirussi F, Azzalini L, Orando S, Orlando R, Angelico F. Antioxidant supplements for non-alcoholic fatty liver disease</td>
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<td>Orlando R, Azzalini L, Orando S, Lirussi F. Bile acids for non-alcoholic fatty liver disease and/or steatohepatitis. Cochrane Database of Systematic Reviews 2007, Issue 1.</td>
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<td>Angelico F, Burattin M, Alessandri C, Del Ben M, Lirussi F. Drugs improving insulin resistance for non-alcoholic fatty liver disease and/or non-alcoholic steatohepatitis. Cochrane Database of Systematic Reviews 2007, Issue 1.</td>
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<td>Lirussi F, Mastropasqua E, Orando S, Orlando R. Probiotics for non-alcoholic fatty liver disease and/or steatohepatitis. Cochrane Database of Systematic Reviews 2007, Issue 1.</td>
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<td>Brok J, Buckley N, Gluud C. Interventions for paracetamol (acetaminophen) overdose. Cochrane Database of Systematic Reviews 2006, Issue 2.</td>
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# Appendix VIII

## Economic evaluations - Hepatocellular carcinoma (HCC)

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<th>Reference</th>
<th>Intervention</th>
<th>Decision Model</th>
<th>Patient Characteristics</th>
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<tr>
<td>243</td>
<td>Performing ultrasound and alpha-fetoprotein (AFP) every six month v seeking tumours only if clinically suspected.</td>
<td>Yes</td>
<td>Child-Pugh A cirrhosis patients.</td>
<td>Switzerland</td>
<td>1994</td>
<td>Costs and future life years by 5%.</td>
<td>Health Care system</td>
<td>Best case scenario $26,000-$55,000/life year gained. Intermediate case scenario $48,000-$284,000/life year gained.</td>
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<td>244</td>
<td>Screening using AFP and ultrasound approximately every 6 months v diagnosis</td>
<td>280 patients with cirrhosis of various causes</td>
<td>Italy</td>
<td>Not given</td>
<td>Not given</td>
<td>Health Care system</td>
<td>Mean cost per life year saved $9,152.</td>
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<td></td>
<td>because of other symptoms.</td>
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<td>245</td>
<td>Screening with AFP and US every 6 months vs. diagnosis of HCC by other symptoms.</td>
<td>313 patients with liver cirrhosis less than 60 years old if Child-Pugh C.</td>
<td>Italy</td>
<td>Not given</td>
<td>Health Care system</td>
<td>$113,534 per life year saved.</td>
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<tr>
<td>246</td>
<td>Screening using AFP and ultrasound every six month vs. no screening</td>
<td>174 patients with proven HCC. Mean age 58.9.</td>
<td>Mexico</td>
<td>Not given</td>
<td>Health Care system</td>
<td>$309 - $346 per correct diagnosis</td>
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<tr>
<td>247</td>
<td>Six strategies were compared against no screening: 1) Annual screening using AFP 2) Annual screening using ultrasound 3) Annual screening using AFP and ultrasound 4) 6 monthly screening using</td>
<td>People with cirrhosis up to age 70. All causes of cirrhosis</td>
<td>Try to use UK data or those from countries with similar disease epidemiology</td>
<td>2004</td>
<td>Health care system</td>
<td>£20,700 per QALY for AFP annual vs. no screening \n£22,900 per QALY for 6 months vs. no screening \n£27,900 per QALY for AFP 6month + ultrasound</td>
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<tr>
<td>Time</td>
<td>Intervention 1</td>
<td>Intervention 2</td>
<td>Country</td>
<td>Effectiveness</td>
<td>Cost per Life Year Saved</td>
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<tr>
<td>5 months</td>
<td>6 monthly screening using ultrasound</td>
<td>6) six monthly screening using AFP and ultrasound</td>
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<tr>
<td>6 months</td>
<td>OLTx vs. no treatment</td>
<td>Surgery vs. no treatment</td>
<td>Italy</td>
<td>Not given</td>
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<td></td>
<td>Percutaneous ethanol injection (PEI) vs. no treatment</td>
<td>Transcatheter lipiodol-mediated arterial chemoembolization (TACE) vs. no treatment</td>
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<td></td>
<td>Patients with small single HCC. Mean age of over 60, Child-Pugh A and B.</td>
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<td>Health Care system</td>
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<td></td>
<td></td>
<td>OLTx £21,664/life year saved. Surgery, $1,959/life year saved. PEI $1,233/life year saved. TACE $4,009/life year saved</td>
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<tr>
<td>249</td>
<td>standard management as adjuvant therapy for HCC during the waiting list for OLT.</td>
<td>single tumour&lt;5cm on the waiting list for OLT.</td>
<td>3%</td>
<td>system saved (12 month waiting list)</td>
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<tr>
<td>PEI v standard management as adjuvant therapy for HCC during the waiting list for OLT.</td>
<td>Yes</td>
<td>Child-Pugh B patients with a single tumour &lt;5cm or with three tumours &lt;3cm on the waiting list for OLT.</td>
<td>Spain</td>
<td>1999 $US</td>
<td>Costs and benefit at 3%</td>
<td>Health Care system</td>
<td>$12,489/year of life saved (12 month waiting list)</td>
<td></td>
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</tbody>
</table>
## Appendix IX

### Economic evaluation - variceal bleeding (VB)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Intervention</th>
<th>Decision model</th>
<th>Patient Characteristics</th>
<th>Country</th>
<th>Year of Cost estimation</th>
<th>Discount Rate for costs and effects</th>
<th>View Point</th>
<th>CU/CE ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>No screening/no prophylaxis vs. universal screening</td>
<td>Yes</td>
<td>Two cohorts of 50 yr old patients (compensated Child-Pugh A and decompensated Child-Pugh B or C).</td>
<td>Hypothetical cohort (study based in US)</td>
<td>2000 $US</td>
<td>3% for both</td>
<td>Health Care Purchaser</td>
<td>Compensated Universal screening US$3,771/life year saved. Universal prophylaxis compared to universal screening $66,000/life year saved Decompensated Universal prophylaxis compared to universal screening $1,154/life year saved</td>
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1 Endoscopic Variceal Ligation
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<tbody>
<tr>
<td>252</td>
<td>Propranolol v observation Sclerotherapy v observation Surgery v observation. Yes Hypothetical cohort stratified by bleeding risk.</td>
<td>US</td>
<td>Not stated (year of study 1997)</td>
<td>Not given</td>
<td>Health care purchaser</td>
<td>Propranolol $1,277-5,110/cost of prolonging QALE by 1 year. Results not given for sclerotherapy or surgery.</td>
<td></td>
</tr>
<tr>
<td>253</td>
<td>Universal prophylaxis with $\beta$ blockers vs. no prophylaxis Screen all with upper endoscopy Yes Hypothetical cohort of patients with cirrhosis with no history of oesophageal</td>
<td>Not specified</td>
<td>2000 Varied between 0-7%</td>
<td>Health care provider</td>
<td>Universal prophylaxis dominated but only CE ratio presented is $800 per QALY for endoscopy + $^2$ Patients divided into high and low risk. High risks scoped, those found with large esophageal varices treated with $\beta$ blockers and nitrates.</td>
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<tr>
<td>5 strategies vs. do nothing:</td>
<td>Hypothetical cohort of patients with compensated cirrhosis with no prior evaluation for varices. Newly diagnosed with Child-Pugh A or B cirrhosis. 50 year old.</td>
<td>Not states</td>
<td>2001</td>
<td>No cost discounting due to short time frame of model</td>
<td>3rd party payer</td>
<td>$12,408 per additional VB prevented for Universal β blockers vs. do nothing</td>
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<td>+ β blockers if large varices vs. no prophylaxis</td>
<td>variceal bleeding</td>
<td>206</td>
<td>β blockers if large varices vs. no prophylaxis</td>
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<tr>
<td>β blockers vs. EVL as primary prophylaxis</td>
<td>Yes</td>
<td>Patients with Child-Pugh A or B cirrhosis. Medium to large varices</td>
<td>Not given</td>
<td>Not given</td>
<td>3%</td>
<td>Health care provider</td>
<td>£ 25,548 per QALY for EVL vs. β blockers</td>
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<tr>
<td>1) β blockers vs β blockers + Hepatic venous gradient (HVPG) measurement 4 weeks after initial β blockers.</td>
<td>Yes</td>
<td>Hypothetical cohort of patients with non-bleeding, high risk varices.</td>
<td>Not given</td>
<td>2001</td>
<td>3% costs and effects</td>
<td>Health care provider</td>
<td>$108,185 per VB episode prevented for β blockers + HVPG 4 weeks late vs. β blockers</td>
</tr>
<tr>
<td>2) β blockers vs. β blockers + HVPG prior to intervention and 4 weeks after.</td>
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<td>$202,796 per VB episode prevented for β blockers + HPVG before and 4 weeks after initial treatment vs. β blockers.</td>
</tr>
<tr>
<td>257</td>
<td>Hemodynamic monitoring of primary pharmacotherapy prophylaxis (β blockers) vs. no monitoring</td>
<td>Yes</td>
<td>Hypothetical cohort of Child –Pugh A or B cirrhosis patients with medium to large varices.</td>
<td>Not given</td>
<td>2001</td>
<td>3% costs and effects</td>
<td>Health care system</td>
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<tr>
<td>258</td>
<td>TIPS v Endoscopic sclerotherapy (ES)</td>
<td>RCT of 38 people (mainly men 27/38). With previous variceal bleeding</td>
<td>Italy</td>
<td>Not given (year of study 1999)</td>
<td>Not given</td>
<td>Health care purchase</td>
<td>TIPS IT2.26m/month free from re-bleeding. ES IT2.16m/month free from re-bleeding</td>
</tr>
<tr>
<td>259</td>
<td>TER-GTN v placebo. At home before endoscopic diagnosis of rupture of varices and admittance to ICU.</td>
<td>84 cases of home management.</td>
<td>France</td>
<td>1994</td>
<td>Not applicable</td>
<td>Health care purchaser</td>
<td>TER-GTN FF 25,000/death avoided.</td>
</tr>
<tr>
<td>261</td>
<td>TIPS v Surgical shunt</td>
<td>Good risk cirrhotics (i.e. Child-Pugh A or B). At least 1 prior episode of bleeding from portal hypertension.</td>
<td>US</td>
<td>Not given</td>
<td>Not given</td>
<td>Total cost of treatment + follow up. TIPS $111,573. PSS $61,934.</td>
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<tr>
<td>262</td>
<td>1) β blockers +nitrate therapy vs. endoscopic band ligation (EBL)</td>
<td>Yes</td>
<td>Hypothetical cohort of cirrhosis patients with previous variceal bleeding treated with EBL.</td>
<td>Not given</td>
<td>2001</td>
<td>No discounting due to short time horizon</td>
<td>Health care provider $5974 per recurrent bleed prevented for HVPG+ β blockers and nitrates vs. EBL.</td>
</tr>
<tr>
<td>263</td>
<td>4 interventions for secondary prophylaxis for variceal haemorrhage vs. observation alone: 1) medical therapy 2) TIPS 3) EBL 4) EBL + medical therapy</td>
<td>Yes</td>
<td>Hypothetical cohort of male patients with history of controlled bleeding varices. Child-Pugh B cirrhosis with average age of 50.</td>
<td>Not given</td>
<td>2001</td>
<td>3% costs and outcomes</td>
<td>Health care provider</td>
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<td>264</td>
<td>6 interventions for secondary prophylaxis of VB vs. combination therapy of β blockers + mononitrate with no haemodynamic screening:</td>
<td>Yes</td>
<td>Hypothetical cohort of patients with a Child-Pugh score of 8, average age of 55. Presenting with an initial episode of VB</td>
<td>Not given</td>
<td>2002</td>
<td>3% costs and effects</td>
<td>Not given</td>
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<tr>
<td>1)</td>
<td>( \beta ) blockers + no screening</td>
<td>2) EVL</td>
<td>3) ( \beta ) blockers +1 HPVG measurement taken 3 months after intervention</td>
<td>4) ( \beta ) blockers +_mononitrate and HVPG 3 months after intervention</td>
<td>5) ( \beta ) blockers +mononitrate and HVPG before intervention and 3 months after.</td>
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Appendix X

Map of Liver Services in England 2004