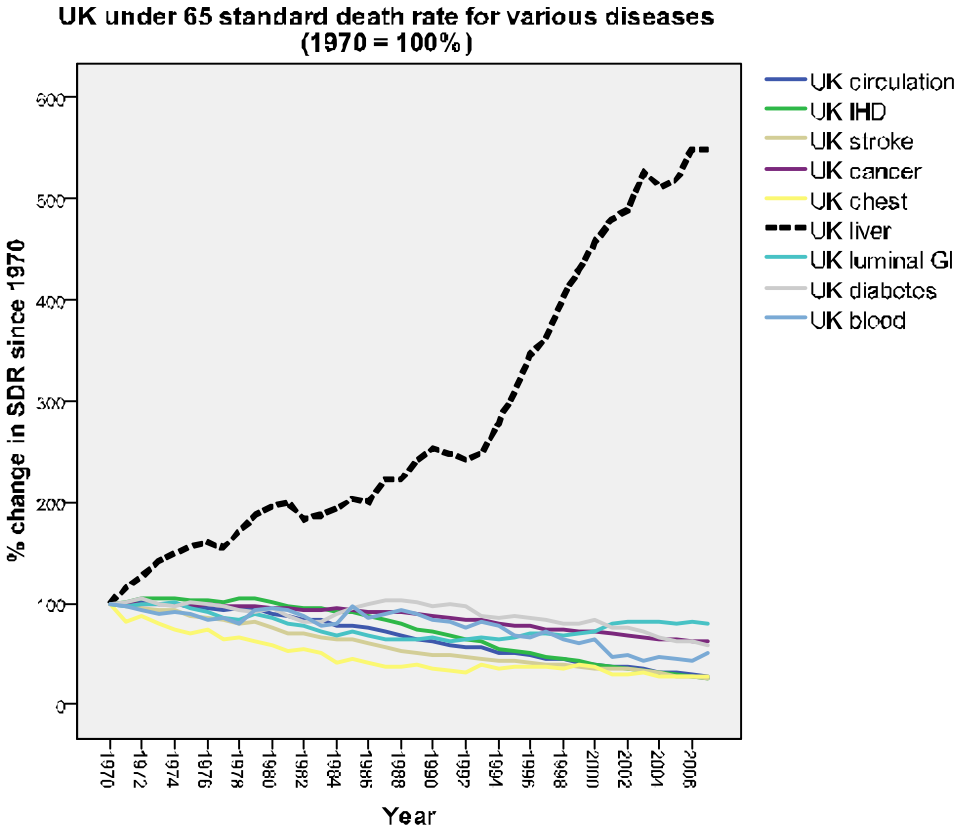
A TIME TO ACT:

IMPROVING LIVER HEALTH

AND OUTCOMES IN LIVER DISEASE



Prepared by the:

British Association for the Study of the Liver (BASL)

British Society of Gastroenterology (BSG) (Liver Section)

Executive Summary

Key facts

- Liver disease is the 5th largest cause of death in the U.K. The average age of death from liver disease is **59 years**, compared to 82-84 years for heart & lung disease or stroke.
- Liver disease morbidity and mortality are largely **preventable**.
- The UK is one of few developed nations with an upward trend in mortality.
- Patients are presenting and dying with liver disease at an earlier age, with a 5-fold increase in the development of cirrhosis in 35-55 year olds over the last 10 years
- The majority of treatable liver disease is undiagnosed and untreated. Early diagnosis and treatment requires engagement of primary care.
- Effective prevention strategies or treatments are available for the three main causes of liver disease – alcohol, viral hepatitis and obesity. These decrease the risk of developing cirrhosis, liver cancer and their associated mortality.
- The prevalence of chronic hepatitis B in the UK is increasing dramatically as a result of migration. The UK is in a minority by not providing universal vaccination against hepatitis B. Identification of patients with hepatitis B within high prevalence groups is suboptimal.
- With appropriate action, the associated disease burden for both hepatitis B and hepatitis C could be largely eliminated by 2030 and 2040 respectively.
- Secondary care of liver disease is currently poorly organized and services could be radically improved at relatively little cost.
- Liver disease represents one of the few diseases where the inequalities gap is increasing.

The aim of this document is:-

- To advise the DH on ways to improve outcomes of liver disease in the UK.
- To recommend a framework which ensures equal access to high quality and cost effective management of liver disease throughout the UK, and to outline ways to optimize the current configuration of Liver services, including paediatric hepatology.
- To recommend the setting of clinical standards, quality metrics and guidelines against which local services should be monitored and assessed.
- To demonstrate that **high quality** liver services lead to **cost savings** and improved health.
- To promote the concept that there should be a trained clinical hepatologist in every district general hospital, and establish a training framework for clinical hepatology with the goal of improving outcomes.
- To highlight the radical change in the profile of liver disease in the UK that is achievable through long term strategic planning in chronic viral hepatitis.

Key Recommendations

1. The provision of liver services in the UK needs to be reviewed and re-structured.

Liver disease and liver deaths have increased 6-fold over the last 35 years but the training and the structure of hepatology has not evolved to meet this challenge.

There needs to be a review of current liver services across the U.K, with the ultimate aim of embedding trained hepatologists throughout existing district general hospitals. This review will enable the Ministers and commissioners to identify areas of good and poor service provision as well as defining standards of care to be provided by liver services. Further, it will enable the testing of quality metrics on liver services throughout the UK.

2. There should be a national strategy to address and prevent the development of the three main causes of liver disease:

Low levels of public awareness of the liver and causes of liver disease need to be tackled with a comprehensive public education strategy to reduce the public's risk of developing alcohol, viral-related liver disease and obesity. Specifically:-

a. ***Reduction of alcohol induced liver injury*** *requires implementation of a properly funded programme of detection, intervention and treatment of harmful drinking and dependency, in addition to measures needed to reduce overall alcohol consumption at a population level.*

b. ***Reduction of transmission of viral hepatitis*** *requires identification of infected patients by testing of at risk groups. Hepatitis B and hepatitis C are treatable. The prevalence of chronic hepatitis C infection will double by 2020 unless we identify and treat the silent majority of undiagnosed cases and decrease the reservoir of infection, and thus deaths from cirrhosis or liver cancer. This requires the introduction of a national surveillance programme of patients at risk. The DH should reconsider implementation of a universal vaccination programme for hepatitis B. It is plausible to think that with effective utilization of existing technology and therapy, hepatitis B and C, and their associated disease burdens can be largely eliminated by 2030 and 2040, respectively.*

c. ***Decreasing obesity*** *would have a major impact on the development of obesity related diseases including cirrhosis. The UK still has an opportunity to prevent this potential epidemic of liver disease emerging.*

3. Primary Care Services need to be involved in the early detection, intervention and management of liver disease.

Early detection leads to early treatment and has a major impact on prognosis and outcome. There should be a national strategy to promote the early detection of patients with liver disease. QOF points should be allocated for obtaining specific information about the risk factors influencing the development of liver disease (e.g. drinking habits, history of IV drug use, immigration from high risk areas) as well as undertaking strategies to detect early liver disease (liver function testing).

National guidelines for the assessment of patients with abnormal liver biochemistry in primary care are required to enable devolution of routine investigation and management of liver disease from secondary to primary care.

4. A comprehensive Alcohol Liaison Service across the U.K. should be developed

Since alcohol related liver disease is such an important cause of increasing mortality, it is vital that alcohol liaison services should be developed as detailed in recent reports from the All Party Parliamentary Report on Alcohol and NICE. Brief interventions, (which are very cost effective and consistently produce reductions in alcohol consumption) should be adopted as standard practice in all components of the health service... The advice on alcohol consumption should evolve from simplistic 'safe levels' in a way that more effectively engages the 36% of men and 22% of women who are currently considered to drink alcohol to excess.

5. Research into liver disease should be promoted and encouraged in the U.K.

The DH should encourage specific calls for proposals on Liver Disease research including prevention and early detection through the Medical Research Council and the National Institute for Health Research (NIHR). Ultimately a clinical research network, focusing on liver conditions, should be superimposed on the service networks as part of the NIHR.

6. A National Clinical Director should be appointed to oversee the development of liver services across the UK.

There will need to be a clear system to oversee the implementation of the recommendations below, and this is best done by a National Clinical Director of Liver Services working closely with the DH and the professional bodies and patient groups who are stakeholders in liver disease.

Will implementation of these recommendations improve patient outcomes?

Implementation of these recommendations will

- Enhance access to **good quality healthcare** delivery for patients with liver disease, and lead to **equity of service delivery.**
- Enable patients with liver disease to be identified and treated early. This will prevent the development of cirrhosis and decrease the burden of liver cancer and liver failure.
- Provide PCTs and commissioners with nationally agreed standards of healthcare delivery that can be monitored and compared with other centres i.e. quality metrics in liver disease.
- Provide data on the clinical and cost effectiveness of treatments offered.
- Lead to a higher quality of liver service delivery, cost savings and improved liver health of the nation.
- Provide a structure to enable services to develop in hepatology centres where there is a local need, and enable effective planning of liver related services.

Section 1: Introduction

Liver disease mortality in the UK is increasing at a time when liver death rates are dropping practically everywhere else in Europe. Over the last 30 years liver disease mortality in young and middle-aged people in the UK has increased at least six-fold and liver admissions and liver deaths are both rising at between 8-10% per year. The contrast is striking when one compares the standardised rate of death from liver disease in those under the age of 65 years compared to other diseases, (figure 1) [1].

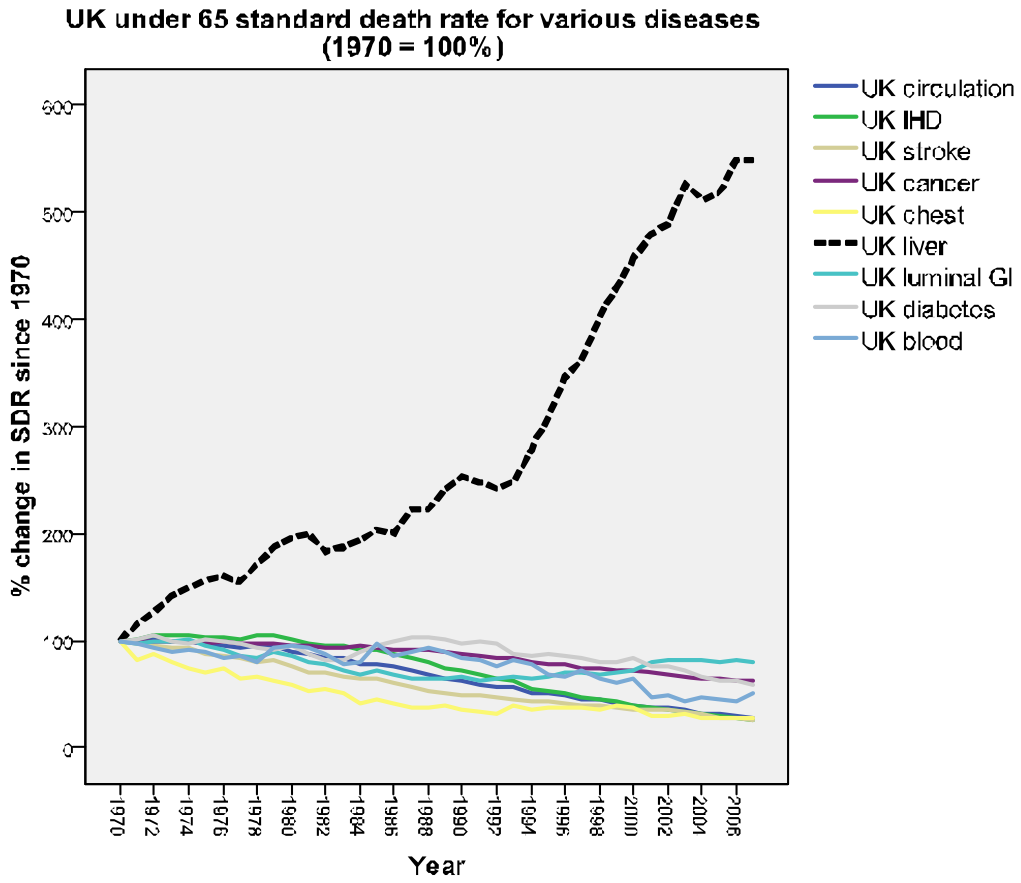


Figure 1: Rate of liver related deaths under 65 years of age compared to other causes related to base rates in 1970.

Alcohol: The key driver for the increase in liver deaths is alcoholic liver disease. According to death certification data, alcohol is responsible for 84% of liver deaths in the UK, and this figure is likely to be an underestimate [2]. There is a direct relationship between levels of liver deaths and overall alcohol consumption within the population (figure 2) [3].

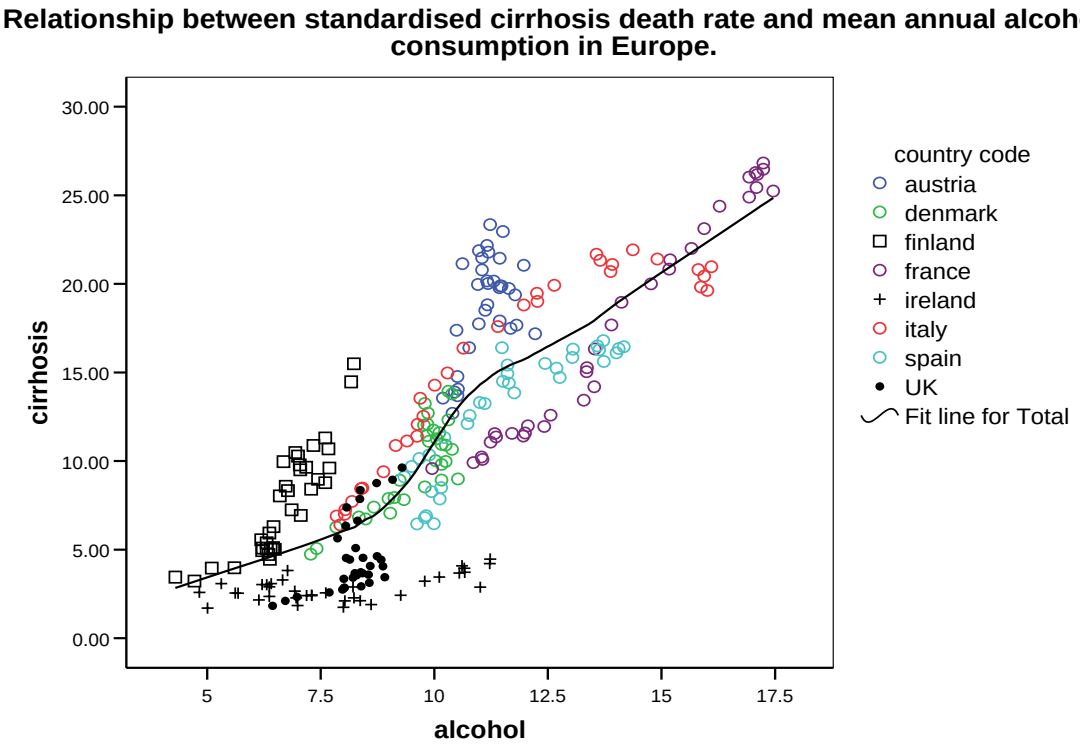


Figure 2: Relationship between liver deaths and mean alcohol consumption by country.

In addition to the direct effect of alcohol there is good evidence that it acts as a co-factor in both the causation and severity of liver disease from other causes. Deprivation is the most important co-factor with liver mortality increased threefold in lower income compared with higher income groups.

Hepatitis C: The prevalence of chronic viral hepatitis C is estimated at 0.5-0.7% (i.e. 250-350000 persons in the UK) and up to 70% of these subjects remain unaware of the infection [4]. This silent pool of HCV infection, if left unidentified and untreated, will deliver a significant burden of severe liver disease over the next two to three decades. It is estimated that 15-20% of

patients will develop cirrhosis after 20 years and as much as 30% after 30 years. Given the relatively young age of the population infected with hepatitis C, these time intervals are clinically relevant. Currently, up to 20% of patients have cirrhosis or hepatocellular carcinoma at the point of diagnosis [5].

The Health Protection Agency predicts that the number of individuals in England developing HCV related cirrhosis will double between 2005 and 2015 with a parallel increase in decompensated liver disease and liver cancer [6]. This increase in liver disease burden is **largely preventable** since currently available NICE approved treatment is available for HCV infection with cure rates of 40-80% (mainly determined by genotype of virus and severity of pre-existing live disease) [7]. Emerging new drugs, STAT-C molecules, are expected to further improve cure rates within about 3 years. It is a realistic ambition to largely eradicate hepatitis C infection and the associated burden of liver disesase in the UK by 2040. This will require an active testing and screening programme with the objective of identifying and treating at least 90% of infected patients. The risk profiles for patients at risk are fairly well understood and include patients with any intravenous drug use (no matter how remote), some immigrant populations and the prison population. This is logistically possible, as demonstrated in France, although the lesson to be learned from that initiative is the importance of matching detection rates with adequate resources to evaluate and treat these patients

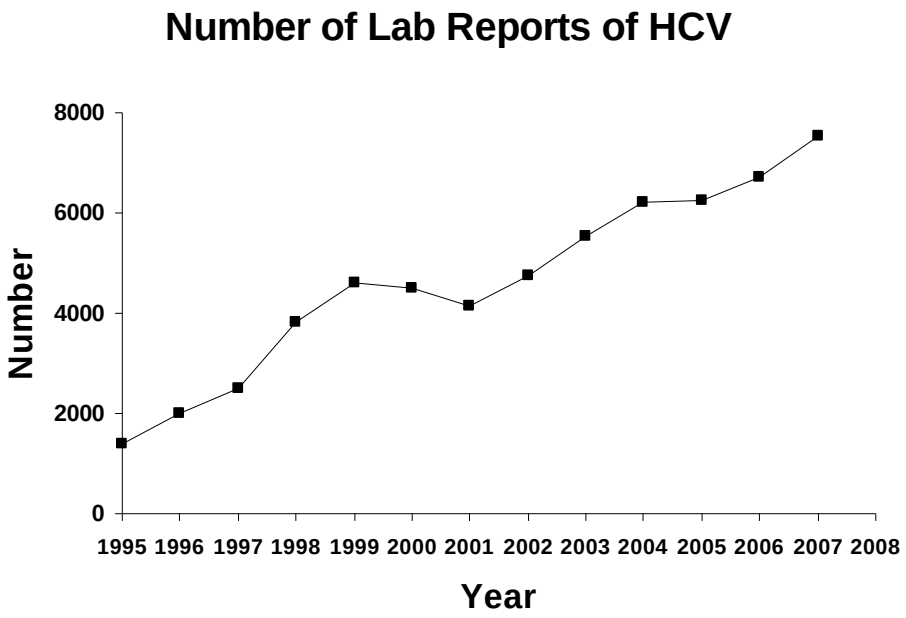


Figure 3 shows the number of new cases of hepatitis C diagnosed each year (HPA).

Hepatitis B: Chronic hepatitis B also leads to the development of cirrhosis or liver cancer. Unlike hepatitis C, the risk of hepatocellular carcinoma is increased in patients without cirrhosis, and even in those with previous exposure to hepatitis B but without ongoing infection. The prevalence of chronic hepatitis B has increased dramatically from 150 000 to an estimated 325 000 persons, with a significant contribution from immigration from areas of high endemnicity like Eastern Europe and Africa in the last 5 years. Data from the HPA show a progressive increase in notifications up to 2003, and single centre experience from a large unit in Birmingham suggests that trend continues (Figure 4). Although some of the increase in numbers in Birmingham might reflect organisational and referral changes, it is likely that the most significant contributor to growth is epidemiological. Current migration figures suggest that the number of chronically HBV infected cases in the UK will rise by 6000-7000 every year [8]. Most existing and newly arriving cases remain undiagnosed. It is estimated that about 10% of patients have cirrhosis or liver cancer at presentation.

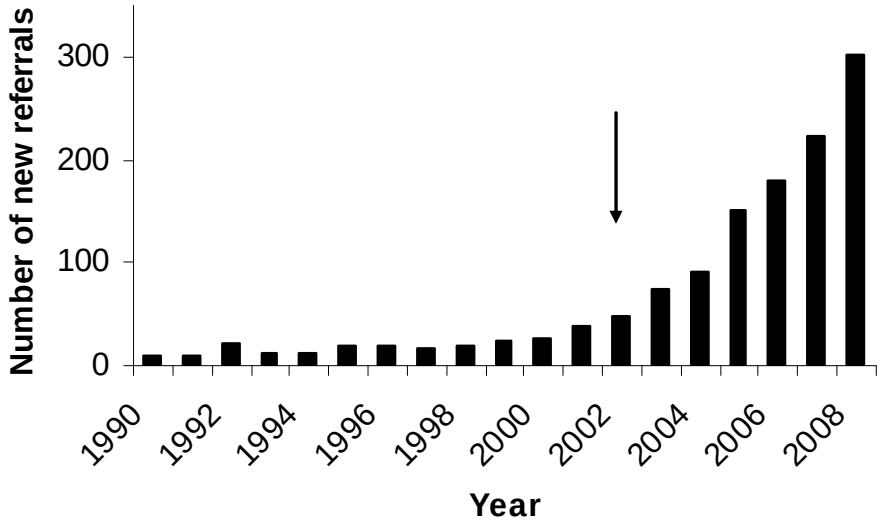


Figure 4: The data above shows the number of referrals with chronic hepatitis B to the QE Hospital, Birmingham. The number of referrals has increased 6 fold since 2003 (arrow) when the last set of HPA data became available (*D. Mutimer, Birmingham, personal communication*).

Transmission of HBV infection occurs at birth by vertical transmission or is acquired later in life, principally by sexual contact although other modes of transmission exist (e.g. contact with blood, close social contact). Hepatitis B is relatively easy to acquire (much easier than HIV when risk factors are common to the two viruses) and sexual transmission provides the potential for rapid transmission. These characteristics mean that there are fundamental differences between

hepatitis B and hepatitis C with respect to how the pool of infection can be controlled and eliminated.

Management strategies for hepatitis B combine vaccination of neonates, vaccination of cohorts at risk of acquisition and antiviral therapy for established infection. HBV infection is a preventable disease with an extremely safe and effective (95%) vaccine. Recent WHO figures show that 88.5% of countries across the world have adopted a universal vaccination policy for new born children (see below). The UK is **not** yet amongst them. Treatment of HBV infection is now highly effective with several NICE approved drugs generating treatment regimens with low probability of viral resistance. This is a very important step forward and detailed guidelines have emerged from both European and US liver associations on the use of these agents [9,10] As with hepatitis C, effective screening is an absolute requirement to allow effective containment and elimination strategies. However, there is the potential for more rapid progress than with hepatitis C and it is not unrealistic to aim to eliminate hepatitis B infection and associated liver disease burden by 2030.

Obesity: In the US, the epidemic of liver disease linked to obesity is visible and rising rapidly. Estimates suggest that as many as 20-25% of the US population have blood test or ultrasound abnormalities consistent with non-alcohol-related fatty liver disease (NAFLD) [11]. Although largely linked to obesity, there is an additional contribution from patients with diabetes or the metabolic syndrome. NAFLD predisposed to more severe liver disease and a number of recent, but small studies, suggest the risk of developing fibrosis is up to 40% and of developing cirrhosis or liver failure about 15% [12,13].

The incidence of obesity is rising in the UK [14]. At present this has a relatively small impact on the overall burden of cirrhosis, but if we follow trends in the US this will increase dramatically in future years. At present, there is no screening process in place for NAFLD and patients with fatty liver disease are typically diagnosed with cirrhosis (previously characterised as cryptogenic) in their 50's and onwards. The UK still has an opportunity to largely prevent the emergence of the epidemic of liver disease that is inevitable if the trend to obesity worsens.

Miscellaneous Causes of Liver Disease: There are other causes of liver disease which account for the remaining but smaller proportion of chronic liver disease and liver deaths. Some of these diseases, for example auto-immune hepatitis or haemochromatosis, are also treatable and benefit from early diagnosis. Consistent delivery of training in hepatology within the gastroenterology curriculum will lead to improved diagnostic and treatment strategies for these less common diseases.

Hepatocellular Carcinoma: Cirrhosis of any cause and hepatitis B are responsible for the overwhelming majority of cases of hepatocellular carcinoma in the UK. An increase in the incidence of cirrhosis will be paralleled by an increase in the incidence of hepatocellular carcinoma a few years later. The risk of developing hepatocellular carcinoma is influenced by the aetiology of liver disease and gender, but most patients have an annual risk of developing hepatocellular carcinoma in the range of 1-3%. Patients with hepatitis B without cirrhosis also have an increased incidence of hepatocellular carcinoma and the identified risks include ethnicity, male gender and viral replicative state (which is amenable to therapy). At present, 22% of patients referred to King's College Hospital are offered potentially curative therapy *(J. O'Grady. Personal communication)*. Effective surveillance strategies and earlier diagnosis in the pre-symptomatic state should at least double the number being managed with the expectation of cure.

What is the impact of liver disease to the National Health Service?

Hospital episodes (Figure 5) for liver disease have increased by 8.3% each year from 1998-2008. In 2005 there were 43,694 episodes coded with liver disease as the primary diagnosis, and 6,798 deaths – a huge mortality rate of 15.5% per episode reflecting the severity of liver disease when these patients present to hospital. Unlike most general medical conditions, 66% of these admissions were under the age of 60, so in terms of years of life lost, liver disease compares with smoking related diseases as a public health issue of vital importance (see figure 1). It is estimated that the cost of each admission to hospital with decompensated liver disease is £3400.

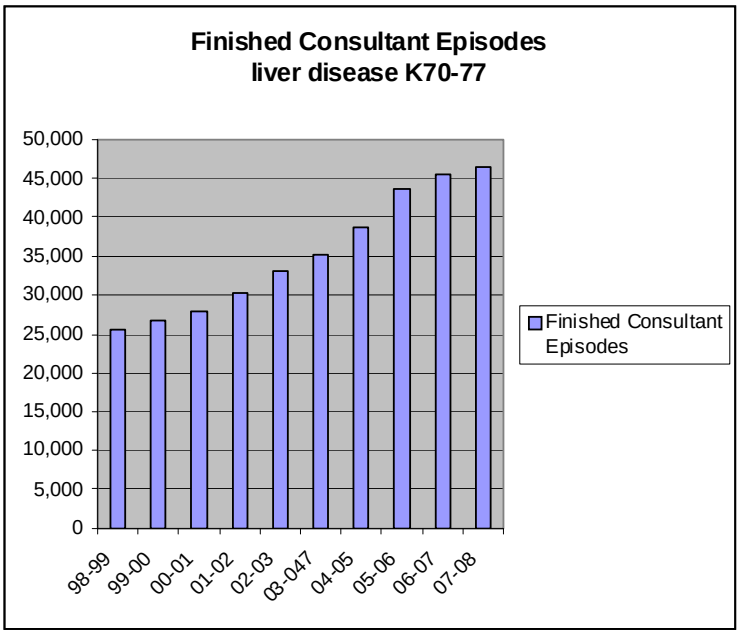


Figure 5: This shows the number of finished consultant episodes (all ages) for liver disease in England from 1998- 2007. Data extracted using ICD-10 codes K70-77 from HES online http://www.hesonline.nhs.uk [15].

Liver disease develops silently with no signs or symptoms, until presenting with potentially fatal complications of cirrhosis such as variceal haemorrhage, acute on chronic liver failure, alcoholic hepatitis, hepatorenal syndrome or ascites. A typical survival duration from this point is up to 3 years if the patient does not succumb during the initial illness. However, dramatically improved survival is seen in patients who stop consuming alcohol and patients with hepatitis B who receive anti-viral therapy. These groups may have survival rates of up to 80% from the point of diagnosis. Data from 100 consecutive admissions for alcohol related cirrhosis in Southampton showed that 50% of patients who continued to drink alcohol died within 4 years while 75% of those who stopped drinking fulfilled the anticipated 10 year survival rate (Figure 6) [16]. This amazing potential for re-compensation of the liver is one of the least well appreciated characteristics of cirrhosis.

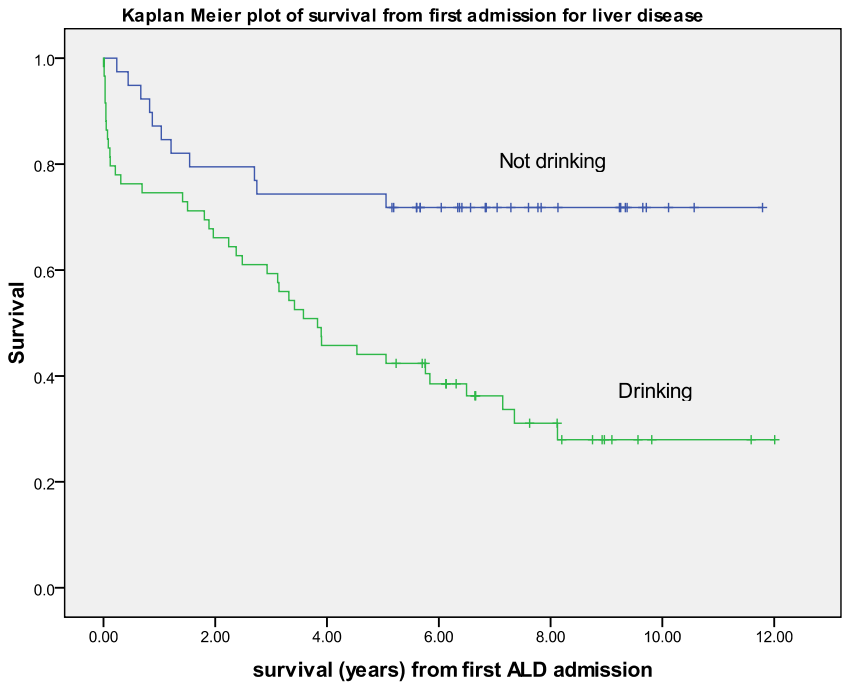


Figure 6: These data show the effect of abstinence from alcohol on survival in patients presenting with alcoholic cirrhosis, from [16].

How can the Government or the NHS decrease the incidence of liver deaths?

There are evidence based strategies that can reduce the risk of death from cirrhosis [17,18]. Each of the 3 main disease categories leading to cirrhosis is amenable to risk reduction through life-style modification – alcohol, chronic viral hepatitis (sexual behaviour, intravenous drug use, needle-sharing) and obesity - that can be promoted through public awareness. Early identification of disease offers real opportunities to modify the natural history and reduce or eliminate the risk of developing cirrhosis. Aggressive vaccination programmes will contribute to the elimination of hepatitis B.

Alcohol: Liver disease is of course only one aspect of the health burden caused by alcohol abuse. Measures to moderate alcohol consumption are part of the solution to alcohol-related liver disease and management of alcohol-related liver disease is an integral part of the overall strategy to deal with the consequences of alcohol. Three timely reports this year give perspective to the issues involved – the All Party Parliamentary Report on Alcohol and the two NICE reviews (report on clinical management currently in consultation phase). The aim of this report is to be fully synergistic with the most ambitious and challenging targets defined in these documents.

Patterns of alcohol consumption: Binge drinking receives a higher visibility and consequently more attention than longer term regular excessive alcohol consumption. However, both patterns are relevant to liver disease and both can potentially be changed. Binge drinking by young people will for some prove to be the gateway to prolonged alcohol abuse later in life. A prolonged binge also has the capability to be immediately life-threatening because of acute alcoholic hepatitis or alcohol related non-liver deaths. Recent anecdotal cases profiled in the media make the point that this disease is now presenting in the very young. Chronic excessive alcohol consumption can cause cirrhosis in the absence of alcohol dependency syndromes or any social, domestic, medical or forensic indicators of alcohol abuse.

There is a case for a more sophisticated and multi-pronged approach to modify alcohol consumption patterns within the population that lead to liver disease and other harmful manifestations of alcohol abuse. **The most** effective strategy will be to increase the price of alcohol through direct taxation, thus reducing affordability (figure 7, [19-22])

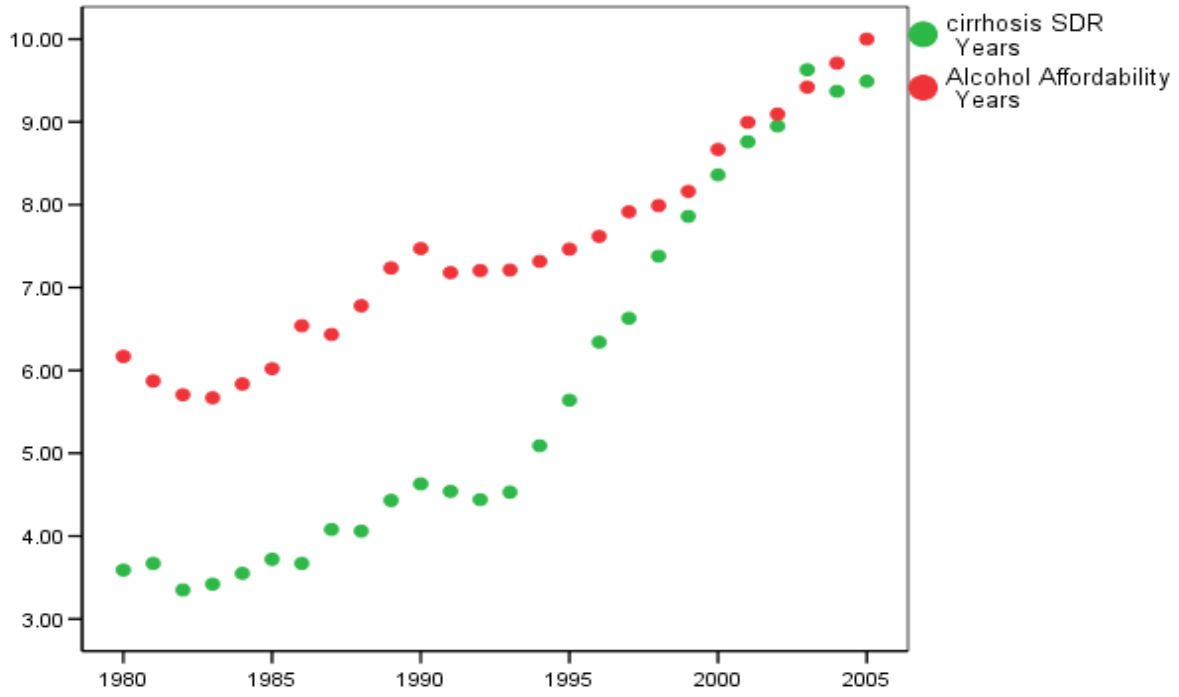


Figure 7: The strength of association between UK liver death rates and the affordability of alcohol is striking – a spearman rank correlation of 0.98 – which reflects the fact that you generally need to drink a lot of alcohol over a long period of time to get liver disease, and that this prolonged element risk is price sensitive [18].

Whilst we are aware of the political arguments which are sensitive to the public opinion that non-offenders should not be penalised, the Government should consider the following. In the UK, 75% of all alcohol is consumed by 25% of the adult population and tax rises will have limited impact on the majority of moderate drinkers. An independent review commissioned by the DH found that if the government were to legislate for a minimum price per unit of alcohol of 50p, the cost to an average drinker would be a mere £14 per year, but over 3000 deaths and nearly 100,000 hospital admission would be prevented [22]. Increasing the cost of alcohol will have the most impact on very heavy regular drinkers, and on the young binge drinkers who spend a high proportion of their income on alcohol [19-22].

Advice on safe alcohol consumption is currently limited to rigid limits on weekly consumption levels. These are ignored by 35% of men and 22% of women, partly because they lack credibility

amongst much of the general population. Additional strategies to modify consistent patterns of alcohol consumption that otherwise go undetected are required. Information on the benefits to be derived from regular periods of abstinence from alcohol consumption (e.g. at least two alcohol-free days per week) is more likely to be accepted by the population at risk. Acceptance of this message is also likely to reduce overall alcohol consumption. Awareness of the alcohol content of different drinks is also important given the relatively recent availability of more potent beverages by volume.

Screening and intervention: Despite alcohol being a major factor in the increasing incidence of liver disease, **no QOF points** are available for questioning or ascertaining the amount of alcohol each patient drinks in primary care. This is a potential instrument to improve screening for excessive alcohol consumption.

Numerous studies of so-called brief interventions have shown that early detection and intervention of alcohol abuse is cost effective [23]. The All Party Parliamentary Report on Alcohol identified a reluctance to use brief interventions systematically [24]. The key issue with the more widespread introduction of alcohol interventions in the UK is lack of targeted funding.

Hepatitis B: Hepatitis B is a readily preventable disease. Given the very rapid escalation of hepatitis B in the UK, it is difficult to justify failure to introduce universal Hepatitis B vaccination in the UK, since this disease is transmitted sexually. Universal vaccination against hepatitis B at birth is recommended. In the adult population, effective screening of all at risk groups should be promoted and supplemented with rapid access to assessment and treatment.

Hepatitis C: An effective programme to screen and treat the very significant cohort of patients (possibly around 200,000-250,000 people) **currently unaware** of their infection is central to the strategy to eliminate hepatitis C and its associated disease burden. With regard to new infections, the reduction in transmission of Hepatitis C relies on identical strategies to those used to reduce HIV transmission in injecting drug users. Needle exchanges and adequate treatment of drug users with methadone and other substitution programs remains the mainstay of Hepatitis C and HIV prevention, and both are highly effective when properly implemented [25,26]. Once identified delivery of treatment for this population has proven difficult and more research is required to integrate treatment of the hepatitis with management of the injecting drug use. A primary health care focused approach to identification of first generation migrants with hepatitis C, alongside hepatitis B, is also required and is currently being developed by DH.

.

Obesity and Metabolic Syndrome. The DH strategy to tackle obesity was outlined in the white paper Choosing Health (Department of Health). Hepatology should be seen as a major stakeholder in this process and the profile of potential liver disease in this process should be enhanced.

Hepatocellular Carcinoma Surveillance. Cirrhosis and the associated risk of hepatocellular carcinoma easily fulfil the requirements of a population at risk and a level of adverse event to justify surveillance. A screening modality is available using a combination of ultrasound and alpha-fetoprotein estimation at 6 month intervals. Surveillance has been shown to significantly increase the proportion of new cases of hepatocellular carcinoma that can be offered curative treatment [22]. More recent economic evaluations have demonstrated the cost-effectiveness of surveillance. Surveillance for hepatocellular carcinoma in defined at risk groups (all patients with cirrhosis and some additional patients with hepatitis B infection) has been recommended in guidelines from UK, Europe and US. Despite all the evidence, the UK does not have a robust surveillance programme.

Enabling actions would include the formal recognition within the cancer policy groups of surveillance for hepatocellular carcinoma. The challenge for the profession is then to design and implement a programme that is effective and fulfils the standards required for accuracy, patient recall and rigor of audit.

Primary care and screening for the early detection of liver disease

All strategies to significantly decrease the burden of liver disease must include the all important role of primary care. Since liver disease is usually asymptomatic in the early phases and patients have few clinical signs, there is a requirement for a more proactive approach to the detection of risk factors and appropriate screening. It is recognized that at present there are no incentives for general practitioners to undertake this role and this would need to be addressed. The hospital based services will also have to respond to the increased detection rates of liver disease by offering prompt access to diagnostic and treatment services for the cases that cannot be managed in primary care.

How should early detection and screening be implemented?

All new patients registered at a general practice should undergo health screening for liver disease. The current cardio-vascular checks include a check of ALT which could easily be expanded with a simple questionnaire for risk factors for the transmission of viral hepatitis, and a validated alcohol use questionnaire. We envisage these being done by a practice nurse.

These should include the following:-

1. Assess alcohol intake (AUDIT, an alcohol questionnaire)
2. Assess risk of chronic viral hepatitis (race, travel, intravenous drug use, family history)
3. Assess BMI, and presence of diabetes as risk factors for fatty liver.
4. Measure liver function tests (ALT or AST or gamma-GT) as part of screening.

Once flagged as at risk for liver disease, patients will undergo a stepped intervention program which may range from brief intervention with specialist alcohol services, enrollment into a needle exchange or methadone program to prevent transmission or development of viral hepatitis, or referral to the local specialist liver centre for further investigation and treatment, or advice on diet and exercise. The protocols will be simple with escalation through medical pathways to the GP in those who need further specialist input (figure 8 below).

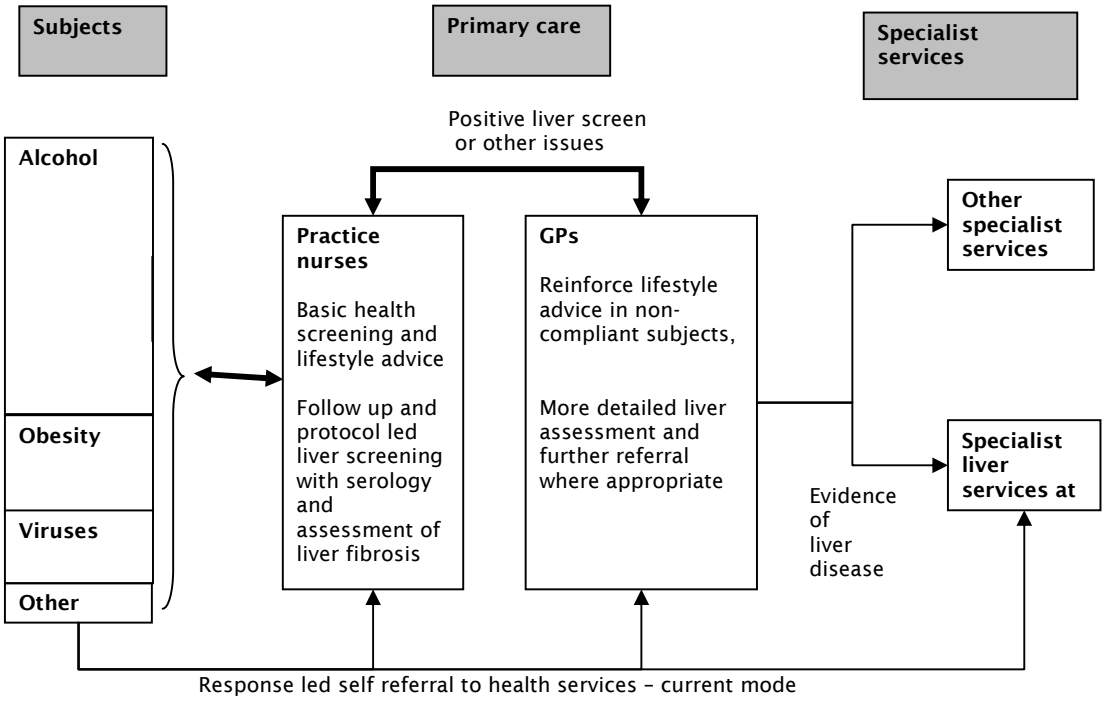


Figure 8: Screening, management and referral for liver disease in Primary Care

GPs or specialist GPs within polyclinics will continue to perform a similar role to that which they perform now but with more detailed and specific investigation and management guidelines. The compliance of patients to health advice increases when individual health risks are identified [Depending on the outcome of the GP assessment, patients will be managed in primary care or referred to a liver specialist. For example if there is no evidence of serious liver disease (i.e. no evidence of cirrhosis on ultrasound scan, no evidence of chronic viral hepatitis B or C, normal serum markers of fibrosis or Fibroscan©) then patients may continue with regular follow up in primary care. On the other hand, if GP examination and investigation suggests that the patient has significant liver disease, then these patients would be referred to hospital or a specialist in a polyclinic. For an example of how this would work see appendix 5 and figure 9.

Quality and resources

Practice Nurses should be trained in the use of simple, easy to follow, screening programmes to allow rapid assessment of patients in primary care. Furthermore, clear thresholds for escalating the level of intervention need to be defined.

Adult Liver Services

History and current status of UK liver services: Currently, the need for liver services and the provision thereof are not in harmony. The fact that hepatology is not widely considered to be an independent specialty and the historical development of hepatology services have contributed to this imbalance. Hepatology is a sub-specialty within gastroenterology, with all hepatologists being primarily on the specialist register as gastroenterologists. Historically, liver disease was managed by gastroenterologists and for the majority of these it was a secondary interest. Specialist liver disease was developed in three centres (Queen Elizabeth Hospital Birmingham, King's College Hospital, London and the Royal Free Hospital, London). This network widened through the development of liver transplantation services in seven centres (Kings College, Royal Free, Cambridge, Birmingham, Leeds, Newcastle and Edinburgh), as well as a number centres with a critical mass of clinicians with a primary interest in liver disease (e.g. Southampton, Liverpool, Manchester, Nottingham, Plymouth, Derby, Sheffield, Bristol). To date, service provision has rarely been primarily designed or commissioned based on clinical need.

Similarly the gastroenterology and hepatology SpR training programmes were largely developed to service the needs of endoscopy focussed DGH luminal gastroenterologists, and have been less focussed on training clinical hepatologists.

As of September 2008 there were 990 Consultant Gastroenterologists in the UK. Only a fraction specialise in liver disease, the exact number remains unknown at this time, but is estimated as being 10%. Almost half (43%) of gastroenterology consultants have not spent any dedicated time training in hepatology as a sub-specialist subject (i.e. training delivered in a hepatology centre). There are currently 762 trainees in gastroenterology, and in one survey 42% of these expressed interest in being trained in hepatology, with 12% of SpR trainees expressing an interest in a career post in Hepatology. Recently a number of specialist Hepatology SPR training posts have been established – totalling 16 out of the total of 762 gastroenterology trainees in UK. On the whole these additional posts have not been allocated central Deanery funding and are dependent on local trust funding. There is a need for more detailed workforce data collection to dissect out hepatology from within gastroenterology. This would allow appropriate planning for the needed expansion within the sub specialty.

On a positive note, these issues are now being addressed. The national curriculum in gastroenterology and hepatology is being revised at the time of writing. The proposed curriculum is detailed includes sections on competencies for basic and advanced hepatology. The immediate challenge of the hepatology profession is to match these aspirations with

provision of appropriate training. The British Association for the Study of the Liver is starting to look at manpower issues and trainee flow to develop insight into needs and likely solutions.

Effective delivery of liver services will require appropriate support services. A survey of support services in District General Hospitals in 2005 effectively makes the point that at present the infrastructure in this setting falls well short of optimal service provision.

Table 1 shows the support facilities available to consultants (UK DGHs).

	2005
Nurse Specialist	23%
Hepatobiliary radiologist	11%
Gastrointestinal pathologist	46%
Liver pathologist	17%
Alcohol support team	33%
Psychiatrist with interest in alcohol	21%
Multidisciplinary team – liver	13%
Multidisciplinary team – alcohol	8%
Multidisciplinary team – hepatitis C	11%

Of note, 21% of consultants commented that their local intensive care unit (ICU) was often reluctant to accept liver patients, since many ICUs have a perceived poor outcome in liver disease. The majority (~90%) felt that access to transplant units was good.

A recent Opinion Leader liver workshop held by the DH concluded that – "The shortage of adequately trained health professionals, at every level, was highlighted as a barrier to effective diagnosis and treatment. Importantly, stakeholders believed the shortage of trained clinicians was not necessarily due to a lack of desire from doctors and nurses to specialise in liver disease, but rather to a shortage of posts. As such, posts should be created and clinicians trained to adequate standards to fill them. e.g. providing opportunities for training and places so that every District General Hospital has a trained liver specialist.'

Service Development in adult liver disease

Currently three categories of hospital provide liver services in the UK:

- **District general** and **university-associated hospitals** that usually have a gastroenterologist with a primary interest in liver disease (District hospitals).
- **Hospitals with a major interest in liver disease** that do not undertake liver transplantation (**Hepatology centres**). These hospitals provide both hepatology and HPB services. Some of these hospitals are predominantly HPB centres.
- **Liver transplant centres** (Transplant centres.

To ensure uniformity of definition and delivery of care all levels should be assessed and subjected to regular accreditation visits akin to the endoscopy JAG system meeting agreed criteria formulated by BASL and the BSG (see appendix 2). Quality Metrics of healthcare delivery will be developed to ensure that we deliver what patients want and expect, and to the best standards of health care available (see appendix 3). All units will follow national or international guidelines as far as possible. All units will need to have the basic facilities outlined in the appendices order to qualify and maintain designation as a specialized liver or HB Surgery Unit.

Proposed Director of Liver Services

If we are to ensure the development of a high quality service of liver healthcare delivery with equal access to all, there needs to be coordination from within the DH. We believe this is best organized by the appointment of a Clinical Director of Liver Services, ideally of an individual with experience in liver services, and whose remit is to ensure that all hospitals develop existing liver services to a nationally acceptable standard, and to ensure that there is equity of hepatology services throughout the UK. There has been involvement with representation from Scotland to the current proposals.

Patient involvement and patient information

It is clear from the involvement of patients in the NIHR research programme, and the design of clinical studies, that we need to involve patients much more in designing clinical services. The proposed director of clinical liver services should engage patient groups and patients in the development of services so that we can deliver what patients want and expect. All clinicians should spend some time explaining the implications of the patient's diagnosis, and patients should be provided with information leaflets and referral to local patient support groups.

Configuration and competencies of the workforce

Specific criteria are outlined below for designation as a Hepatology or HPB Centre. Integral to these recommendations is the establishment of managed clinical networks including systems for the monitoring of clinical outcomes and effectiveness in an auditable format for the National Specialised Commissioning Group. This will provide an effective Clinical Governance Network for the provision and improvement of patient care. Thus:-

Each District General Hospital should be able to provide the following services:

- Assessment of abnormal liver function tests.
- Investigation of chronic liver disease.
- Evaluation and basic management of complications of cirrhosis (variceal bleeding, ascites etc).
- Basic investigation of a focal lesion (ultrasound and CT).
- Assessment of acute liver disease (acute viral hepatitis, acute alcoholic hepatitis).

Each Hepatology Centre should be able to provide the following services:

- Advice for district general hospitals on the management of complex liver disease.
- Admission, diagnosis and management of rare or complex liver diseases.
- Coordination and delivery of anti-viral therapy for chronic viral liver disease including advice on the management of anti-viral resistance.
- Admission, diagnosis and management of hepatocellular carcinoma & cholangio-carcinoma.
- Basic work-up and advice for patients who may need a liver transplant.
- Admission and management of patients with recurrent variceal haemorrhage.
- The placement of a transjugular intra-hepatic portosystemic shunt (TIPSS) if indicated for variceal haemorrhage, diuretic resistant ascites or hepatic hydrothorax.
- Renal support if indicated for patients with the hepatorenal syndrome.
- Provide intensive care facilities that are able to admit at least 80-90% of referred patients within a 24 hour window.
- Advice and support to patients through a liver support group or clinical nurse specialist.
- Advice and support for patients with substance misuse problems

Each Hepatobiliary Centre should be able to provide the following:-

Each centre should serve a population of 2 to 4 million, and operate within the guidelines of the Cancer Networks, and work closely with hepatology colleagues to provide the above services as well as those outlined below. The configuration of these centres will include activity which is not covered in this plan including liver resection in non-cirrhotic patients, and pancreatic surgery.

Liver Cancers

Management of hepatocellular carcinoma: The management of hepatocellular carcinoma usually involves the parallel management of two diseases – the underling cirrhosis and the malignant disease. Consequently, it does not follow the traditional model of oncological care. The other characteristic of hepatocellular carcinoma is that there is a range of established and therapeutic options including resection, liver transplantation, loco-regional therapies (chemoembolisation and ablative techniques) and novel drugs. Patients should be managed in centres that offer all options or have appropriate relationships to cover local efficiencies. Hepatologists must remain central to the multi-disciplinary team

Surgery in cirrhosis: Surgery for portal hypertension is rarely performed; interventional radiological procedures (TIPPS) have replaced this procedure in most centres. It is rare to find surgeons with expertise in porto-systemic shunt procedures and the number of patients who require this surgery is relatively small; therefore these procedures should be performed in liver transplant centres.

Developing Managed Clinical Networks (MCNs)

It is important that all patients, regardless of geography, are offered good and equal access to liver healthcare, and that we can demonstrate improvements of service delivery. Although we think it is important to establish a database for each network which captures activity and outcomes, we also propose that there are several areas where managed clinical networks can be used to develop strategy for future care models. This might include managed clinical networks in chronic viral hepatitis, variceal bleeding, ascites, hepatocellular carcinoma, and even rarer conditions such as autoimmune hepatitis or Wilson's disease. If all networks are established along similar lines, then we can later create large databases to assess treatments and outcomes. For example, we are not required to record the number of patients treated with hepatitis C or their outcomes

Why do we need specialized centres?

There are good data to show that treatment in a liver centre improves outcome [29]. Patients with advanced liver disease need specialized care if they are to have improved survival during intercurrent complications and to be able to be treated with liver transplantation if indicated. This has implications not only for improving patient care but for decreasing litigation against NHS Trusts who fail to provide what many would consider basic care of the liver patient.

In particular good intensive care has a major impact on patients with liver disease survival, and yet patients with cirrhosis and portal hypertension are often denied admission to intensive care, even when there is a reasonable chance of survival. This is because there is often a misplaced perception of an inevitably poor prognosis. The prognosis of patients with decompensated cirrhosis is relatively good when they are managed in a hepatology centre with a **survival of ~50%** (table 2, and figure 9), and is increasing year on year in hepatology centres. Ideally all patients with decompensated liver disease needing intensive care support should be managed by a hepatologist and an intensive care physician to improve survival, so that realistic assessment of survival and outcome can be made using tools that have recently been developed (e.g. SOFA scores). The prognosis for a patient who has been deteriorating inexorably and who is poorly nourished is very different from that of a patient with an acute deterioration and associated organ dysfunction (e.g. triggered by variceal bleeding or sepsis).

The fact that the survival of patients with decompensated liver disease admitted to specialized units is increasing justifies the provision of these resources. Importantly, one can use the experience of these units to improve outcomes in other parts of the UK. Studies from Kings College (table 2) and the Royal Free Hospital (Figure 9) have shown that ITU mortality has decreased over the last decade. Also both groups have shown there has been a reduction in admission APACHE II and SOFA scores suggesting that these patients were being offered admission to critical care areas earlier.

Table 2

Category	**2000-4**	**2004-7**	**p value**
Number	263 patients	300 patients	0.009
Survival	89 (34%)	139 (46%)	0.003
MELD	25	25	0.86
SOFA	11	10	0.009
Apache II	23	20	0.003

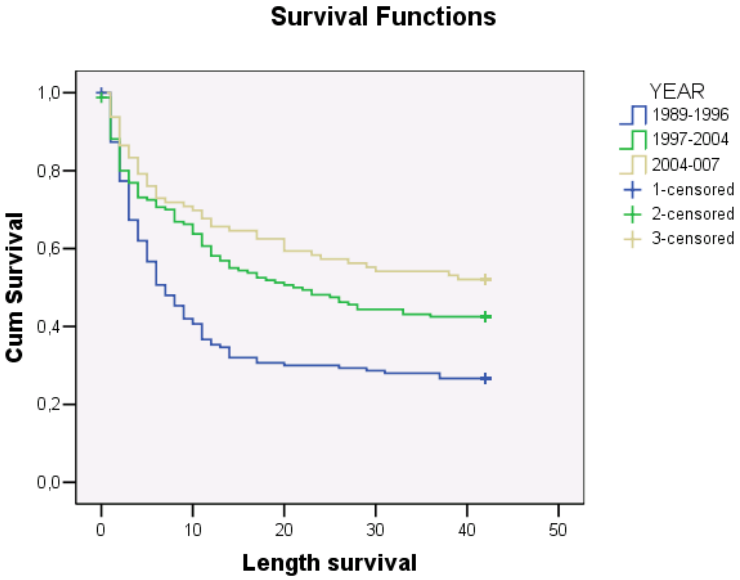


Figure 9. Change in mortality over time at Royal Free Hampstead NHS Trust. Kaplan Meier plot of survival from admission to ITU over time (days, n=412). *These data show that the survival of patients with severe liver disease and good intensive care are improving [29].*

Acute Liver Failure (ALF): In general, this area of clinical activity is well organised in the UK. Referral criteria are well developed and widely disseminated, and prioritisation for access to ITU is accepted practice. To a significant degree this has developed around the need for access to emergency liver transplantation. It is very important that all patients with acute liver failure are discussed with the regional liver transplant centre and transferred as rapidly and safely as appropriate.

Liver Transplantation: Liver transplantation is an integral component of the management of acute liver failure, end-stage chronic liver disease and selected patients with hepatocellular carcinoma. In addition to these broad patients categories there are a number of less common indications. The criteria for listing patients for liver transplantation are agreed, and the minimal listing criteria and agreed exceptional categories now mean that patients listed for liver transplantation should have comparable levels of disease severity across all transplant centres [30]. This delivers equity of access to liver transplantation once patients have been referred for assessment for transplantation. It is less clear if equity of access is established at the earlier stage of consideration of referral for assessment.

There are ~650 liver transplants carried out in the UK and Scotland each year, including a re-transplant rate of 8-10%. This activity figure has been largely flat over the past decade. From a position of historic leadership in liver transplantation, the UK has now fallen to 13th place in Europe in terms of number of liver transplants performed per million population (Table 3).

Belgium and the Iberian Peninsula countries have liver transplant rates that are more than twice the UK level (25.2, 25.1 and 24.6 versus 10.7). The Council of Europe data indicate that in the UK in 2007, 644 liver transplants were performed but there were 255 deaths on the waiting list and there were 316 patients awaiting transplantation at year end [25], and the numbers patients listed for liver transplantation is increasing yearly. A robust audit and quality assurance process is in place monitoring outcomes after liver transplantation.

Table 3

Liver transplant rates per million population in 2007

Belgium	25.2	Germany	14.0
Portugal	25.1	Switzerland	11.5
Spain	24.6	Switzerland	11.5
Italy	18.4	Czech Republic	11.2
France	16.8	**UK**	**10.7**
Norway	15.3	Finland	10.0
Sweden	14.8	Holland	9.1
Austria	14.3	Denmark	7.9
Ireland	14.0	Turkey	6.3

The UK Organ Donation Task Force has set a target of a 50% increase in organ donation within 5 years, which is clearly long overdue given that ~25% of patients die on the waiting list. However, it is not known if there is capacity within the existing service provision to deliver this increase.

Since the existing centres have evolved historically rather than by prospective planning there is an imbalance between the geographical location of liver transplant centres and local need. Thus, there is no liver transplant programme in the densely populated North-West centred around Liverpool and Manchester. There are also arguments in favour of locating liver transplant centres in the South-West Peninsula and Wales. If donor rates increased and there was an expansion in liver transplant activity, this would provide an opportunity to address these issues.

Liver Trauma

Liver trauma has various associated risk factors depending cause and the pattern of associated injuries (e.g. cardiac contusions, lung contusions, pancreatic and small bowel injuries). Liver injuries may be associated with early arterial bleeding requiring surgery or angiographic intervention and venous bleeding requiring packing. Many of these injuries are associated with injury to the biliary system and associated peritonitis with sepsis later in their clinical course. Many of these complications are preventable with early intervention by a specialist team. Bleeding following a liver biopsy requires surgical support and care dependant on the severity of live injury and underlying liver disease.

Section 4: Paediatric liver disease

Organisation and referral

Paediatric hepatology is organised differently to adult hepatology. This is due to the smaller number of patients. This has resulted in the creation of three NCG-funded centres, in which workload, and the necessary services and skills have been concentrated. These 3 NCG-funded centres also provide care to patients from Scotland and Northern Ireland.

Paediatric liver disease has two modes of presentation. Approximately 50% of patients present in the same way as adults, with either acute or chronic liver disease. The exact causes vary with age, but show considerable overlap with most adult diseases. There is however a quite separate group of patients that present in the first few months of life. The presentation of neonates or infants with liver disease follows the physical separation from the mother (i.e. birth). Most liver conditions do not manifest *in utero* since placental and maternal functions compensate for foetal liver abnormalities. Once birth occurs the infant has to maintain its own hepatic function. The various diseases that present at this stage do so through development of jaundice or other signs.

Referral pathways vary depending on the type of presentation and geography. Much work has been done to improve both referral and subsequent management through the establishment of Managed Clinical Networks, and which have largely bridged the gaps between tertiary centres and secondary referrers. In addition the tertiary centres provide a considerable number of outreach clinics, mainly in centres with Paediatric Gastroenterology. The majority of patients are referred to tertiary care from General Paediatricians in secondary care, although a few patients are extensively investigated prior to referral by Paediatric Gastroenterologists.

In general most patients presenting as neonates are first seen by General Practitioners or Health Visitors, whose experience of paediatric liver disease is very limited. Even at secondary care level, the babies with genuine liver disease are vastly outnumbered by the many babies with unconjugated jaundice, and late referral still occurs. Improving prompt referral at this level is a continuing challenge.

The majority of paediatric liver disease requires investigation and management by a tertiary centres. However the long term care of most patients requires considerable input from primary and secondary care. The conditions and presentation for which referral to a tertiary centre are required are listed in Appendix 4.

The major organisational issue that requires further work is the development of services for the management of adolescent patients and the ***transition of their care to adult services***. There is no single model for this, and it is important that mechanisms are in place to allow transition to occur at different times and at different speeds depending on the disease, the individual and the geography. It will be necessary for some patients to be managed in the same tertiary centre for their whole life. This could be due to particular complexities of the individual or due to the rarity of the condition from which they suffer. There are still many conditions, with which patients are emerging from paediatric care, that are largely unknown to adult services. In due course this will slowly change, but in the meantime there will be patients with similar needs to those adults with congenital heart disease.

Key priority areas affecting children's liver health

The British Society of Paediatric Gastroenterology, Hepatology and Nutrition, through its Liver Steering Group, is the main representative of the providers of paediatric hepatology services. The Children's Liver Disease Foundation is the only charity that, amongst its other roles, represents the users of these services. Between them they had no difficulty recognising the key areas requiring urgent attention, in order to maximise the long term liver-health of the paediatric and soon-to-be adult populations.

Non alcoholic fatty liver disease (NAFLD)

With the increasing prevalence of obesity in children there is an associated increase in the incidence of NAFLD [31-34]. It is major concern that we are recognising so much of this liver disease in childhood. At present it is difficult to predict how many of these children will end up needing a liver transplant in adulthood. Indeed some of these children have already developed cirrhosis in childhood. Clinical studies on the management of these young patients are needed. Funding has so far been elusive.

Universal vaccination for Hepatitis B

The number of children referred to Tertiary Paediatric Liver Centres with chronic hepatitis B is increasing year on year. Most of these children are from immigrant families but others are infected within the UK. Targeted vaccination of high risk groups and screening of all pregnant mothers has clearly failed to prevent this increase. New referrals with hepatitis B are decreasing in young people and adults in the rest of Europe because in most countries universal hepatitis B vaccination has been implemented. Drug treatment for hepatitis B in children has limited success and some patients need liver transplantation, usually as adults.

Autoimmune hepatitis

Preliminary data from King's College Hospital, London, suggests an increase in paediatric autoimmune liver disease [35]. This needs to be confirmed in other centres and consideration given to the possible aetiological factors, and implications for health service providers.

Hepatitis C

The incidence of hepatitis C in adults is increasing, and we are identifying more children with chronic hepatitis C, despite a relatively low risk of transmission of hepatitis C from mother to child. However, this is a relatively minor problem in paediatric hepatology, but the increasing incidence needs to be considered in any forward planning.

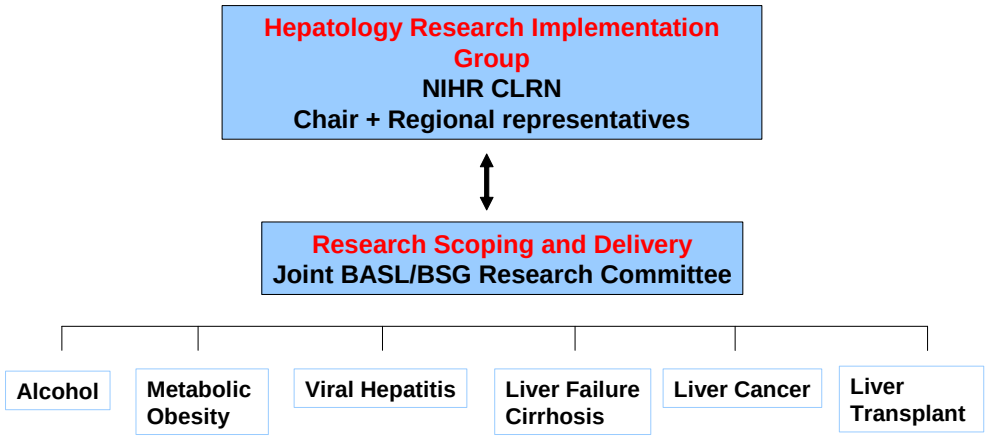
Adolescent/transition services

Adolescents with chronic liver disease or following a liver transplant are a high risk group. Puberty may affect the control of their liver disease per se, but the biggest problem is lack of adherence with treatment. The incidence of graft loss in adolescents with a liver transplant transitioning to adult services is unacceptably high. Paediatricians and Adult Liver Services need to work together to improve this transition process and study strategies to aid adherence.

Section 5: *Liver Related Research*

The UK has had a great tradition for providing the world with leadership in Hepatology research with substantial contributions to the development of several fields in Hepatology which include, use of liver biopsy in clinical practice and its interpretation, steroid usage in autoimmune liver disease, defining prognostic criteria and management algorithms of liver failure, development of liver transplantation, viral hepatitis classification and treatment, studies into the use of liver support and novel ideas about management of complications of cirrhosis. These clinical advances have been associated with a plethora of high impact and ground breaking advances in basic Hepatology research. These have happened despite a lack of cohesion between units and a fragmented clinical service.

The recent establishment of the NIHR CLRN network to facilitate the delivery of clinical research within the UK provides the framework to further develop research networks on the background of the proposed clinical pathway (see case study Appendix 7). Of the 26 networks, thus far, eight have identified Hepatology as a research priority and there are several more coming on-line. There is the potential for other areas to prioritise research via co-adoption (infectious diseases or gastroenterology). The British Society of Gastroenterology and BASL have met to discuss and describe a model for developing a research strategy which will integrate with the clinical service deliver framework. The structure that is under development is summarized in the flow diagram below (figure 10).



The combined BASL/BSG research committee will be chaired by an elected member of the societies. The 6-main areas of research will be divided into sub-committees which will be formed of 2-3 key investigators. It is envisaged that recommendations of the scoping committee will be fed through to the NIHR-CLRN implementation group who will prioritize suggestions and in an iterative manner discuss with the funding bodies.

As is clear from Appendix 7, one of the main thrusts of the programme will be to engage the Primary and Secondary care sectors more closely which will serve to enhance not only the research agenda but also allow improvement in the quality of care across the whole network.

Research re-organization and co-operation has already started with a recent large grant from the NIHR which will involve several centres around the UK and bring to fruition the largest ever study in patients with alcoholic hepatitis and aims to recruit 1200 patients. There are discussions which are involving those in secondary and primary care for patient recruitment and follow up. Most importantly we could establish research networks in hepatology across the UK that will focus on **preventative strategies** or new ways at delivering liver health care in a more cost effective manner. It is good for the patients, it is good for the researchers, and it is good for the NHS. The provision of a rational clinical structure would allow delivery of the collective research aims by access to patients across the pathway as outlined in Appendix 7. The key research priorities have been identified and could be delivered in the new structure. These are summarized below:

- Alcohol and Obesity
- Viral Hepatitis
- Alcohol related liver disease
- Fatty liver disease
- Liver Failure and Extracorporeal Liver Support
- Complications of Cirrhosis
- Liver Transplantation
- Liver Cancer

Conclusions

Liver disease is largely preventable, and yet constitutes the 5th largest cause of death in the U.K with a marked increase in liver related mortality since 1970. Patients are presenting and dying with liver disease at an earlier age, with a 5-fold increase in the development of cirrhosis in 35-55 year olds over the last 10 years

Effective prevention strategies or treatments are available for the three main causes of liver disease – alcohol, viral hepatitis and obesity, and tackling these issues would decrease the risk of cirrhosis and liver cancer and their associated mortality.

This document outlines the professional aspirations of UK adult and paediatric hepatologists who wish to ensure that we develop high quality and cost effective management of liver disease throughout the UK with the aim of improving outcomes of liver disease. Ultimately we believe that high quality liver services lead to cost savings and improved health.

Appendix 1

Personnel and Facilities Requirements

To provide a comprehensive service in hepatology and hepato-pancreato-biliary (HPB) surgery services, a minimum set of criteria in terms of personnel, and local services are needed. It is recognized that not all of these services need to be in place at the same hospital, but local access is needed, with good liaison between hepatologists and HPB surgeons.

District general hospitals

Trained hepatologists: All district general hospitals will have at least one gastroenterologist formally trained in Hepatology by 2016. The basic needs for the provision of DGH Hepatology already exist, and these are defined on page 21above. Histopathology requirements are outline below.

Hepatology and HPB Centres

Beds: Designated beds for Hepatology or HPB surgery admissions should be allocated within each Hepatology centre, and there must be recognition by intensive care that beds must be made available to patients with liver disease when needed.

Medical Care: A sufficient complement of consultant hepatologists to provide continuous 24 hour cover throughout the year. Medical support from consultant hepatologists or gastroenterologists trained in hepatology. For distinction, a hepatologist is a gastroenterologist who only looks after liver patients, whereas a gastroenterologist trained in hepatology may look after both. The team will also include clinical nurse specialists (see below), as well as good access to expert radiology and histopathological diagnosis.

Surgical Care: A sufficient complement of HPB consultant surgeons able to provide continuous 24 hour cover throughout the year. The consultants should be supported by specialist registrars, as well as a nutrition team, oncologists with an interest in HPB related cancers, with regular multi-disciplinary team (MDT) meetings to discuss management of HPB cancers. The team will also include at least 2 clinical nurse specialists, as well as good access to expert radiology and histopathological diagnosis.

Nursing Care: Ward nurses should be trained in the care of hepatology or HPB surgical patients including the management of intravenous nutrition for HPB patients. Each centre will include a nurse consultant and clinical nurse specialists who deliver anti-viral therapy and other specialist

treatment or management services. Their role might also include drainage of ascites, early discharge follow up clinics, alcohol liaison services etc.

Oncology Care: Each managed clinical network should identify a lead oncologist who has an interest in the treatment of hepatobiliary malignancies. The oncology team, together with HPB surgeons, hepatologists, nurse specialists and palliative care professionals, will form a multidisciplinary team to provide high quality of care to patients with hepatobiliary cancer, and will liaise with local cancer networks. Specialist Nurse support will encompass patient queries, nurse led clinics, and nurse training. There should be active participation at local cancer network meetings.

Intensive Care: All centres (hepatology or HPB) should have at least one intensive care physician or anaesthetist with an interest in hepatology or HPB Surgery. There should be sufficient ITU beds to accommodate at least 95% of hepatology / hepatobiliary emergencies without needing to transfer patients to other centres.

Nutrition Care: A nutrition team should be available to provide competent nutritional support. This is particularly important for HPB services.

Palliative care: There should be access to a palliative care team with an emphasis of enabling the patient to die at the most appropriate location (normally home).

Pharmacy: A senior pharmacist with a specialist interest in liver disease should be attached to each Hepatology centre.

Radiology Services: Each hepatology centre should have access to at least 3 interventional radiologists for the diagnosis and management of complex liver disease (eg. biliary stents, TIPSS, angiography ± embolisation). Ideally this should be available 365 days per year. It is recognized that there are insufficient interventional radiologists to meet this demand. However, all centres should have access to an interventional radiologist during daylight hours, and should plan to develop these services within existing personnel to provide more extensive cover where possible. There should be readily accessible (7 days per week) high quality diagnostic imaging (US, CT, MRI). PET scanning should also be available during weekdays.

Pathology services: Each hospital, whether it is a Hepatology centre or a district general hospital should have direct or indirect access to a specialized liver pathologist. Ideally this would be on the site of the lead centre and would provide expertise and training for other local pathology departments within the managed clinical network. For the majority of patients with

chronic liver disease, (as for cancer) their future treatment and care is dependent on accurate histopathological diagnosis. Detailed information on requirements for liver histopathology service delivery are available in the RCPath Tissue Pathways [36]

Histopathologists working in District General Hospitals should have sufficient awareness of liver pathology to be able to provide accurate reports on biopsies reflecting common chronic liver diseases. They should also have the opportunity for regular communication with an appropriately qualified gastroenterologist/hepatologist. They should be able to recognise biopsies where unusual features merit referral for an expert review. If this level of support is not available from within the histopathology department, the hospital should contract to routinely send liver biopsies to the local hepatology centre. Either pattern of delivery needs to be supported by a formal funded arrangement within the network centre.

Histopathologists working in hepatology centres should have sufficient time and expertise to report the full range of medical liver disease specimens, including difficult biopsies from their own centre and surrounding primary hospitals. Where appropriate they should also have relevant expertise in hepatobiliary and pancreatic cancer, paediatric liver disease and liver transplant pathology. Use of appropriate minimum datasets devised by the Royal College of Pathologists is recommended [37]

Histopathologists working in hepatology centres should also be involved in teaching, training, audit and research at a local and national level. They should also have evidence of participation in an appropriate national external quality assurance (EQA) scheme. The National Liver EQA scheme has been in place for fifteen years and currently has 79 participants.

Microbiological services: Each centre should have access to good microbiological services.

Virology services: Each Hepatology Centre should have access to molecular virology facilities who can provide viral load, genotype and sequencing services within a reasonable time, these should include:

Hepatitis A: IgG and IgM anti-HAV

Hepatitis B: HBsAg (including confirmatory assay), Anti-HBs, HBeAg and anti-HBe, IgG anti-HBc & IgM anti-HBc, HBV DNA* (viral load) and HBV genotyping*
Resistance mutation analysis* to licensed nucleos(t)ide DNA polymerase inhibitors

Hepatitis C: Anti-HCV (including confirmatory assay), HCV RNA (qualitative and quantitative) and HCV RNA genotyping, Resistance mutation analysis to new small molecule antiviral agents**

Hepatitis D: IgG* and IgM* anti-HDV, HDV RNA* (viral load)

Hepatitis E: IgG* and IgM* anti-HEV

Other viral causes of acute hepatitis: EBV serology, including IgM and EBV DNA* assays
CMV serology, including IgM and CMV DNA* assays

* indicates assays which may be performed at reference laboratories
** this is a likely requirement for the future, as new agents become available for the treatment of HCV infection

Not all laboratories will have the full range of assays listed above available locally. Therefore arrangements should be in place to refer samples to appropriate reference laboratories and receive results in a timely manner. Tests which may be regarded as reference tests are asterisked. All laboratories should have the wherewithal to investigate a case of acute jaundice by testing for IgM anti-HAV, HBsAg and IgM anti-HBc, and anti-HCV within 24 hours of receipt of a sample, and HCV RNA within 48-72 hours.

Data Manager: A manager with primary responsibility for the collection and provision of auditable data should be employed by each network.

Endoscopy Facilities: Diagnostic and therapeutic endoscopy should be available 24 hours a day to deal with bleeding complications related to portal hypertension. ERCP should also be available.

HPB Theatres: Dedicated HPB theatres should be available with anaesthetic and nursing staff who regularly help in these operations. Apart from specialist instruments, operating theatres performing major hepatobiliary surgery should be appropriately equipped (eg: including CUSA (Cavitron Ultrasonic Aspirator) dissector, harmonic scalpel, intra-operative ultrasonography, argon beam coagulator, laparoscopic equipment, ablation treatment equipment, thromboelastography, near patient coagulation monitoring, level one rapid infusion system, etc) If the HPB surgeon is not trained in intra-operative ultrasound, a trained radiologist should be available during liver resections particularly for metastatic disease. There should be easy access to blood and blood products with good support from blood transfusion services.

Renal Facilities: Renal support on site for haemofiltration or dialysis

Operational Requirements

Regional Cover

Each unit should have the ability to accept Hepatology emergencies within a reasonable timeframe appropriate to the clinical needs.

Planned care and training:

Weekly planning multi-disciplinary team (MDT) meeting.

Clinical Trials:

Clinical trials facility and active research programme.

Data collection

All Liver centres should maintain a patient database. The data items should conform to a Nationally agreed minimum dataset. The database should be compliant with the Data Protection Act, and accessible to all clinicians involved in the managed clinical network.

Links with referring hospitals:

All Liver centres will have close links with local district general hospitals, who will manage and assess the majority of patients with uncomplicated HPB disease (e.g. gallstone disease, uncomplicated pancreatitis, initial workup of HPB surgical patients), and most of these patients will not require referral to HPB surgery centres.

Links with liver transplant centres:

Similarly HPB centres will liaise with a designated liver transplant centre regarding optimal management of patients with more complex HPB disease, especially those with parenchymal liver disease (usually liver cancers in the setting of liver cirrhosis, rare conditions like Budd Chiari syndrome), since this group of patients pose particular problems surgically, and may benefit from liver transplantation.

Appendix 2:

Training in Hepatology

To ensure a quality liver service throughout the UK it is recommended that BSG (liver section) and BASL develop a system to ensure the quality of service, standards for liver centres and training in hepatology something akin to JAG for Endoscopy.

Role of The Liver Advisory Group (LAG)

The Liver Advisory Group (the LAG) will assume an active and broad role in the quality assurance of hepatology training and services across the UK.

Our mission as an organisation will be to provide UK wide support for the whole of the hepatology workforce to ensure they have the skills, resources and motivation necessary to provide the highest quality, timely, patient-centred care.

We would aim:

To set standards for individual hepatologists
To set standards for training hepatology
To quality assure hepatology units for training
To quality assure hepatology training courses

The LAG Committee

The LAG Committee will be an executive board, responsible for agreeing and setting policy and strategy and advising its constituent bodies and other significant organisations (such as the GMC, DH, and NHS) on standards and quality.

The LAG Committee will provide a forum for gaining professional consensus and agreement on standards in hepatology. It will also advise on suitable processes and frameworks to quality assure and enhance those standards.

It will be largely self-sustaining, but retains firm links with the BASL, BSG, the Royal College of Physicians London, and its constituent bodies, and will liaise with and advise the proposed National Clinical Director of Liver Services.

The remit of LAG would focus in the following key areas:

- Validating assessment of competence of trainees
- Hepatology training courses – agreeing curricula and setting standards
- Appraisal and assessment of trainees –formalised, validation and documented processes
- Accreditation and re-accreditation of hepatology units – delivered through co-operative visits.
- The quality of trainers

Guidance from LAG will be divided into sections for Individuals in training, Consultants and other independent hepatologists and Hepatology units. The guidance will also cover the provision of courses, both LAG designed [LAG Compliant] and those organised by units and meeting LAG criteria [LAG Approved], as well as providing advice and documentation to assist educational supervisors with workplace assessment.

The LAG will maintain records of approved training units and individual practitioners in training from disciplines other than Gastroenterology and General Surgery (who are catered for by the relevant Specialist Advisory Committees [SACs] of the Medical & Surgical Royal Colleges). It is hoped that both SACs will fully subscribe to the standards and processes laid out in the Guidelines and all trainees are encouraged to utilise the portfolio when in hepatology training modules.

Formative & Summative Assessment in Hepatology

Direct Observation of Procedural Skills - DOPS

Background: This assessment method is now widely used, accepted, and in general validated, in the UK and elsewhere. This current suite of DOPS form is derived from work carried out previously by the JAG, the Royal College of Physicians of London, the network of endoscopy training centres, and the NHS Bowel Cancer Screening Programme. The appropriate DOPS forms can be used formatively throughout training and as an independent hepatologist, to guide development of skills and practice.

There will be 8 main DOPS forms, each with a formative and a summative version:

- Liver biopsy
- Management of ascites and its complications
- Management of variceal bleeding and its complications
- Management of transjugular intra-hepatic portosystemic shunts (TIPS) and its complications
- Management of viral hepatitis and its complications
- Management of cirrhosis,including the screening for HCC
- Management of biliary disease
- Liver transplantation, indications and management

Each main form comes will be a detailed set of descriptors of levels of skill expected at each of the four possible grades for a skill domain. Formative versions will have a "Learning objectives for next case" comments box at the foot of each form. The summative versions, used for accreditation in hepatology, will have a second page with a box for "Expert Global Evaluation" and a sign-off from the assessors. This will have several functions including:-

- Formatively assess hepatologists in training to aid development
- Assess hepatologists in training for accreditation as independent hepatologists
- Help maintain and develop skills in independent hepatologists following their initial successful accreditation

However, the DOPS is only part of a multi-method assessment strategy in all of these situations, and supplements the performance data of a practitioner. For trainees therefore, for each of the main procedures, these include eligibility criteria for provisional accreditation, and guidelines on further development leading to full accreditation.

Grading standards using the DOPS

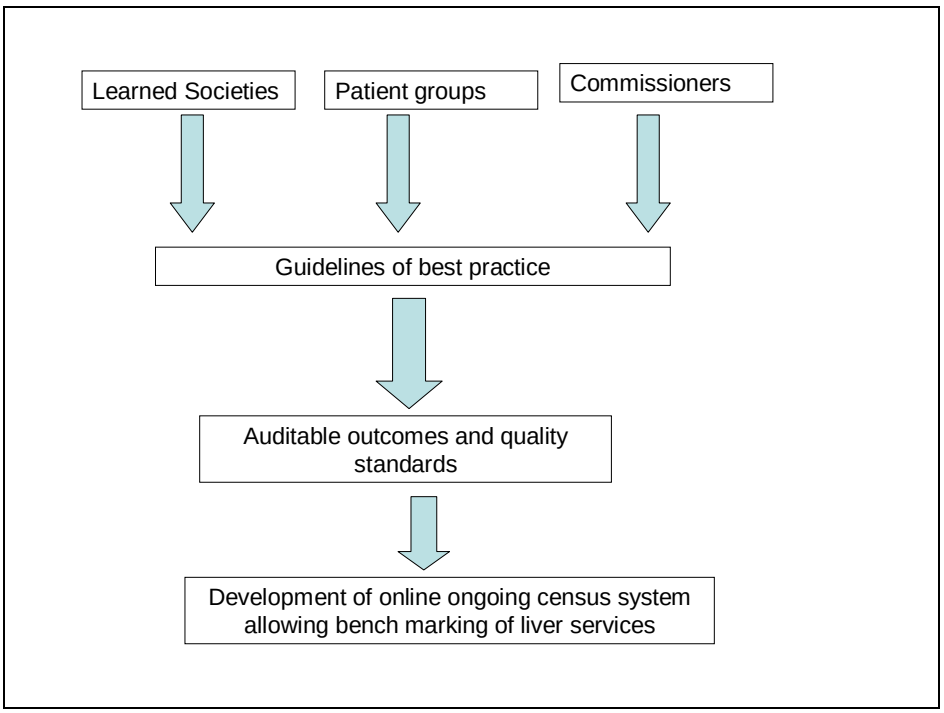
The standards as outlined are set at the high level necessary for independent, (safe & competent) hepatology. When used formatively, trainers should therefore be awarding grades 1 and 2 routinely to trainees, and trainees should expect this. Grade 3 is a high level of competence, and grade 4 implies mastery of the skill, which may never be attained by many.

Appendix 3

Quality of Care assessment in Liver Services

The process of defining and measuring the quality of care delivered to patients with a diagnosis of liver disease is being developed. There is already a robust scheme applied in liver transplantation where defined standards and structural, process and outcomes measures exist.

The ideal system would ensure that effective, efficacious and cost effective care is delivered in a humane and culturally appropriate way to all patients. How this might be achieved in patients with liver disease is outlined in Figure 12.



It is quite clear that the most robust assessments of quality of care are patient-centred. This provides direct evidence that the quality of service is high, and is familiar to most gastroenterologists and hepatologists as the Endoscopy Global Rating Scale. In this system there are twice yearly census periods in which all endoscopy units complete a series of questions on-line relating to the following dimensions which are subdivided further into items, descriptors and measures. Two examples of quality metrix for management of ascites or viral hepatitis are given below.

EXAMPLE OF QUALITY METRIX FOR MANAGEMENT OF CIRRHOTIC ASCITES

	QUALITY	SAFETY
STRUCTURE	• Avalibility of equipment to preform theraputic paracentesis • Access to TIPSS	• Availibilty of surgery for complications of paracentesis
PROCESS	• Documented agreed guidelines on the treatment of ascites and spontaneous bacterial peritonitis. • Written report in notes of all inpatients regarding recommendations on further management. • Written report in notes regrading consideration for liver transplantation	• Documented agreed guidelines on the monitoring and treatment of renal function and hyponatraemia during treatment of ascites. • Agreed policies regards fluid resuscitation with large volume paracentesis.
STAFFING	• Large volume paracentesis should only be undertaken by (or under the supervision of) experienced personel • Dietetic advice available	• Avalibility of personel experienced in monitoring patients undergoing large volume paracentesis.
AUDITABLE OUTCOMES	• Frequency of large volume paracentesis • Rates of Diurectic intolerance/diuretic resistance • Rates of LVP • Rates of TIPSS for ascites • Rates of SBP	• Rates of renal failure
QUALITY STANDARDS	• >99% rates of diagnostic paracentesis • Appropriate antibiotic and albumin use in SBP >95% • >95% rates for antibiotic prophylaxis post-SBP • >99% documented consideration for liver transplantation (does not require formal transplant assessment.	

An example of possible quality and safety indicators in the management of patients with ascites based on the BSG and international asciytes club guidelines is presented in Table 1.

EXAMPLE OF QUALITY METRIX FOR MANAGEMENT OF CHRONIC VIRAL HEPATITIS C

STRUCTURE	• Availability of high quality histopathology • Availability of diagnostic molecular virology services • Community service provision coordinated with drug and alcohol services and prisons	• CPA accredited pathology services • Facilities for day case liver biopsies • Viral results available within 1 week
	QUALITY	**SAFETY**
PROCESS	• Local guidelines for treatment initiation which comply with international recommendations • Audit and documentation of treatment decisions and alterations to therapy regimens	• consultant and nursing staff trained in the management of viral hepatitis • Agreed policies for management of cytopaenias • Agreed policy for use of anti-depressants
STAFFING	• Clinical nurse specialists with training in viral hepatitis • Consultant with training and experience in viral hepatitis • Links with local drug services and psychiatry	• Clinical cover for nurse when on leave • Designated clinician to manage complications of treatment • Link psychiatrist for treatment related or exacerbated problems
AUDITABLE OUTCOMES	• Proportion of referred patients who commence treatment • SVR rates for HCV • Treatment completion rates for HCV • Tailored short treatment courses for appropriate cases	• Early discontinuation of treatment • Number of cases requiring anti-depressant treatment • Use of rapid viral response to guide short treatment course decisions • Renal function measurement frequency for patients on Tenofovir
QUALITY STANDARDS	• SVR > 40% for HCV genotype I • SVR > 70% for HCV genotype 2/3 • Planned treatment completion rate > 90% • Number of patients stopping for viral non-response	• HCV RNA measured at treatment week 12 • Continuity of prescriptions for HBV treatment

Appendix 4: Paediatric Hepatology

Medical conditions requiring referral to Tertiary Paediatric Hepatology Centre

The list of conditions requiring referral to tertiary centres is widely accepted. It is for these conditions, and for liver transplant services, that the NCG-funded centres have been established.

Neonatal Hepatitis Syndrome

Jaundiced infants who present with alcoholic stools, hypoglycaemia, ascites (in utero or after birth), or severe failure to thrive and those with coagulopathy not corrected by intravenous vitamin K.

Neonatal hepatitis of unknown cause, which has not resolved completely with normal transaminases by 4 months of age.

Included in this group are diseases such as:

biliary atresia, Alagille syndrome, alpha-1-antitrypsin deficiency, lipid storage disorders, parenteral nutrition associated liver disease, progressive familial intrahepatic cholestasis syndromes, hypopituitarisim.

Chronic Liver Disease of Childhood

Children with clinical and/or biochemical evidence of cryptogenic chronic liver disease or when local facilities do not allow rapid diagnosis of treatable conditions like autoimmune hepatitis or Wilson disease (at least within two weeks from presentation).

Children with problematic complications of chronic liver disease such as cholangitis, intractable ascites, failure to thrive, malnutrition, pruritus, encephalopathy and recurrent gastrointestinal bleeding.

Children with recognised causes of chronic liver disease who do not respond satisfactorily to treatment (e.g. autoimmune hepatitis, Wilson disease)

Children with chronic hepatitis B or C to be considered for anti-viral treatment.

Children with unexplained abnormality of liver function tests to be referred: immediately in the presence of coagulopathy not responding to vitamin K and after no more than 3 month's observation in the presence of normal synthetic function (PT, INR, albumin)

Children with unexplained hepatomegaly

Children with chronic liver disease for consideration of liver transplantation

Diseases in this category include:

Biliary Atresia, Alagille syndrome, alpha-1-antitrypsin deficiency, auto-immune liver disease, hepatitis B / C, sclerosing cholangitis, cystic fibrosis, drug-induced liver disease, hereditary fibrocystic disorders, haemochromatosis, progressive familial intrahepatic cholestasis, tyrosinaemia type 1, Wilson disease, Budd-Chiari syndrome, non alcoholic steato-hepatitis.

Acute Liver Failure

All children with acute decompensation of chronic liver disease or with fulminant hepatic failure. These children may require transplantation and should be referred as soon as possible, without waiting for the onset of encephalopathy.

Underlying diseases in this group would be:

viral hepatitis (A,B,C,D,E), non A/non E hepatitis, drug-induced liver disease (overdose, idiosyncratic), Wilson disease, neonatal haemochromatosis, autoimmune hepatitis, Budd-Chiari syndrome, venoocclusive disease, tyrosinaemia, mitochondrial electron chain disease.

Metabolic conditions requiring consideration for liver transplantation

e.g. alpha-l-antitrypsin deficiency, Crigler Najjar syndrome type 1, glycogen storage disease, Tyrosinaemia, propionic Acidaemia, urea cycle defects etc

Multi-system conditions requiring consideration for liver and kidney, or liver and bone marrow transplantation

e.g. primary oxalosis, fibropolycystic disease, methylmalonic Acidaemia, primary immunodeficiencies

Surgical Paediatric Liver Disease

Biliary atresia: all suspected cases.

Choledochal cysts: diagnosed antenatally or within 6 months of life, as they may represent cystic biliary atresia, or with features of chronic liver disease (e.g. ascites, portal hypertension) or evidence of intrahepatic involvement, or with recurrent pancreatitis

Primary Liver Tumours (benign/malignant): central (segments I, IV, V, VIII), or multifocal where an extended partial hepatectomy may be required, or which may require evaluation for total hepatectomy and transplantation (typically hepatoblastoma), or rare tumours such as liver/bile duct rhabdomyosarcoma, or vascular tumour with complications (cardiac, mechanical, DIC), or undiagnosed liver masses

Portal Hypertension: variceal bleeding (unless specialist paediatric therapeutic endoscopy is available locally), or children requiring consideration for shunt surgery or transplantation, or children requiring consideration for prophylactic treatment (e.g. air travel, living in remote areas), or children with ectopic variceal bleeding (e.g. gastric varices), or Budd-Chiari syndrome

Congenital Vascular Anomalies (e.g. congenital porto-caval shunts): All cases will need specialist investigation (i.e. angiography) to determine relevant vascular anatomy. A proportion will require specialist surgical reconstruction.

Liver Trauma: children requiring urgent laparotomy and perihepatic packing should be referred as soon as they have stabilised, or any child with complications of liver trauma (e.g. haemobilia, abscess, biloma).

High risk liver biopsies requiring interventional radiology and surgical back up: e.g. in the presence of coagulopathy (PT>3 seconds prolonged, thrombocytopaenia $<70x10^9/1$), post liver transplant or biliary surgery, cystic disease, obesity, anatomical abnormalities

Appendix 5

Example of how primary care would enhance management of a patient with alcohol abuse

Example 1: A thirty year old man with a negative liver screen in terms of blood tests but who is drinking 40-50 units a week.

In this situation the Practice Nurse would provide a standard brief intervention. However, the key difference is that rather than discharging the patient back into the community with no follow-up, this patient would be flagged up with regard to alcohol risk and followed up by the Practice Nurse. If lifestyle risks are modified, for example the alcohol intake decreases, then no further action needs to be taken. If alcohol excess continues the patient is referred to the GP, and undergoes screening tests for liver disease, in this instance this would be either a blood test for serum fibrosis markers or a measure of liver elasticity. Patients with a negative liver screening test would have a GP led intervention, and followed up by the practice nurse to reinforce active lifestyle change. Patients with a positive liver screening test would be referred to hospital liver services for further evaluation. A parallel pathway would be to a specialised alcohol services for those patients with evidence of dependency, with a fast track for patients with evidence of severe dependency on the initial screening test at the Practice Nurse level.

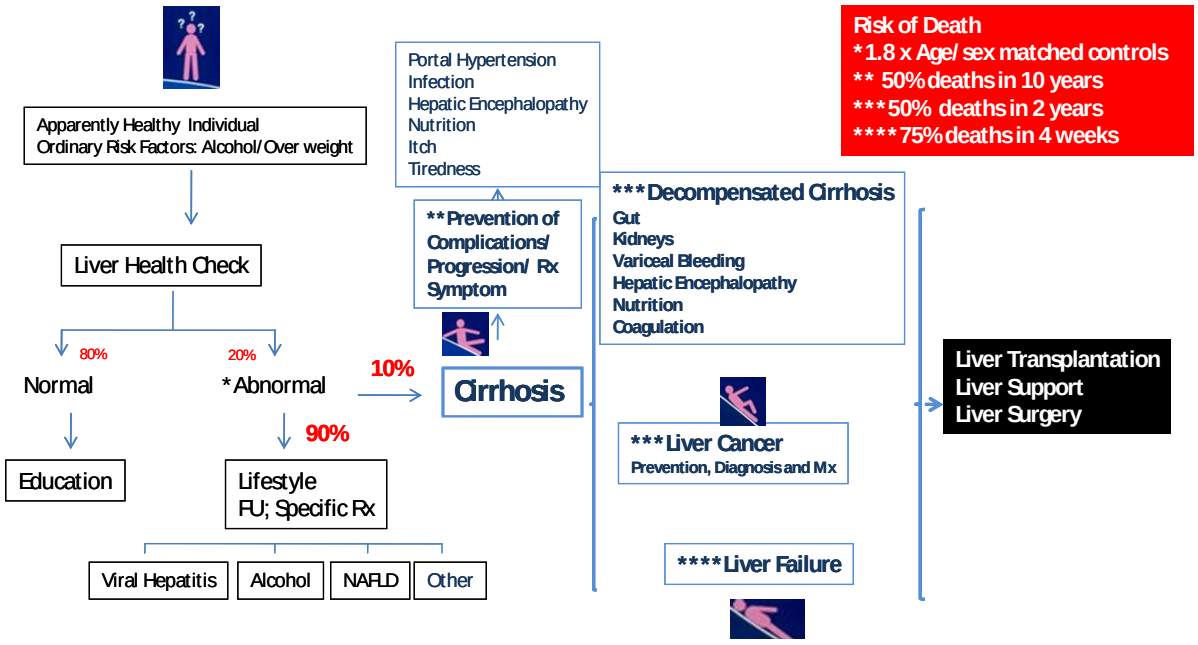
Similar stepped intervention protocols can be designed for patients with obesity or metabolic syndrome and for patients at risk of viral hepatitis (see figure 10).

Appendix 6: Understanding how liver disease develops

The basis for all liver disease, or indeed the majority of chronic disease is identical and involves chronic inflammation. In order to explain to patients the effect of excess fat on their liver there is a simple analogy that many patients can understand as the basis of their disease, and it is as follows. "If you prick your hand with a needle just once, every day for a week, your hand will be a bit sore, maybe a bit red in places, but so what? If you prick it everyday for a year, your hand will be red and sore, with some areas that are quite inflamed. If you prick your hand everyday for 20 years it will look a mess, with scar tissue, areas of redness, and areas where your skin is trying to re-grow and recover." This is what we do to our livers everyday when we drink to excess, or if we are obese, or if we have chronic viral hepatitis. The pathology is basically the same. Insult (alcohol, virus or fat) causes mild degrees of inflammation and repair. In the liver, t is only when it is sustained that we get the end result of excessive scarring and areas of regeneration or new growth of liver tissue (nodules).

Liver Insult → **Liver Inflammation** → **Liver Fibrosis** → **Cirrhosis**
(alcohol, fat, virus)

Appendix 7: Rationale for Staged Care for the delivery of Liver Health: Integration of clinical and research



Translational Research Programmes

Delivery at the GP surgery/ Community

Lifestyle diseases such as obesity and alcohol abuse account for about 80% of all liver disease. The presence of an abnormal liver blood test is found in up to 20% of the adult population [38] and is associated with a risk of death of about 1.3-1.8 times that of an age and sex matched population. *Interventions would allow prevention of progression of liver disease. Lifestyle intervention could be provided at the GP/Community Interface.*

Delivery at the Secondary Care Level

Of all the patients who have abnormal liver test, about 5-10% will have cirrhosis, the presence of which confers a risk of death of 50% in 10 years. Establishment of the cause of liver disease would allow treatment which would prevent progression to cirrhosis. *Treatments for specific liver diseases such as viral hepatitis and non-alcoholic hepatitis could be managed at the GP/Community level in close consultation with the Secondary Care environment.*

Delivery at the Tertiary/Quarternary Level Care

Within 2 years of diagnosis of cirrhosis ~30% patients will develop a complication of cirrhosis such as ascites, variceal bleeding or encephalopathy, which can be prevented in about 50% patients by established and/or emerging prophylactic measures. Following the occurrence of the 1st complication of cirrhosis the 5 year survival rates are reduced to 50%. *In the patients who develop complication, the management will be at the tertiary institution.*

Research dividend

Improved organisation will provide a framework for the development of a world-class translational research programme into liver disease in the UK, and put us back at the forefront of development of liver service development.

References

1. WHO. WHO European Health for All database. 2009.

2. Hansard. Response by Caroline Flint to a parliamentary question by Alex Salmond. ***Hansard 2006 Oct 9.***

3. Sheron N, Olsen N, Gilmore I. An evidence based alcohol policy. ***Gut 2008;57:1341-4.***

4. *HCV Ref for incidence of cirrhosis*

5. *20% have HCC at presentation ref*

6. Hepatitis C in England. The Health Protection Agency Annual Report 2007. http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1204100441645

7. McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, Nyberg LM, Lee WM, Ghalib RH, Schiff ER, Galati JS, Bacon BR, Davis MN, Mukhopadhyay P, Koury K, Noviello S, Pedicone LD, Brass CA, Albrecht JK, Sulkowski MS; IDEAL Study Team. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. ***N Engl J Med. 2009;361:580-93.***

8. *Estimates of increasing HBV through migration*

9. Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. ***Hepatology. 2009;49:1335-74***.

10. EASL Clinical Practice Guidelines: management of chronic hepatitis B. European Association For The Study Of The Liver. ***J Hepatol. 2009;50:227-42.***

11. Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. ***Gastroenterology 1999;116:1413-9.***

12. Ekstedt M, Franzen LE, Mathiesen UL, Thorelius L, Holmqvist M, Bodemar G, et al. Long-term follow-up of patients with NAFLD and elevated liver enzymes. ***Hepatology 2006;44:865-73.***

13. Gupte P, Amarapurkar D, Agal S, Baijal R, Kulshrestha P, Pramanik S, et al. Non-alcoholic steatohepatitis in type 2 diabetes mellitus. ***J Gastroenterol Hepatol 2004;19:854-8***

14. Department of Health. Choosing Health. 2004.

15. Department of Health. Hospital Episode Statistics - HES online. 2009

16. Verrill C, Markham H, Templeton A, Carr NJ, Sheron N. Alcohol-related cirrhosis--early abstinence is a key factor in prognosis, even in the most severe cases***. Addiction 2009;104:768-74.***

17. Harrison L, Gardiner E. Do the rich really die young? Alcohol-related mortality and social class in Great Britain, 1988-94. ***Addiction 1999;94:1871-80***

18. Regidor E, Calle ME, Navarro P, Dominguez V. The size of educational differences in mortality from specific causes of death in men and women. ***Eur J Epidemiol 2003;18(5):395-400***

19. Chisholm D, Doran C, Shibuya K, Rehm J. Comparative cost-effectiveness of policy instruments for reducing the global burden of alcohol, tobacco and illicit drug use. ***Drug Alcohol Rev 2006;25:553-65***

20. Chisholm D, Rehm J, Van OM, Monteiro M. Reducing the global burden of hazardous alcohol use: a comparative cost-effectiveness analysis. ***J Stud Alcohol 2004;65:782-93***

21. Academy of Medical Sciences. Calling time - The nation's drinking as a major health issue. ***Academy of Medical Sciences, London; 2004 Jan 3.***

22. Brennan A, Purshouse R, Taylor K, Rafia R, Booth A, O'Reilly D, et al. INDEPENDENT REVIEW OF THE EFFECTS OF ALCOHOL PRICING AND PROMOTION: Part B Modelling the Potential Impact of Pricing and Promotion Policies for Alcohol in England: ***Results from the Sheffield Alcohol Policy Model. School of Health and Related Research at the University of Sheffield (ScHARR); 2009.***

23. Kaner EF, Beyer F, Dickinson HO, Pienaar E, Campbell F, Schlesinger C, et al. Effectiveness of brief alcohol interventions in primary care populations. ***Cochrane Database Syst Rev 2007;(2):CD004148.***

24. http://www.cabinetoffice.gov.uk/media/cabinetoffice/strategy/assets/all.pdf

25. Hallinan R, Byrne A, Dore GJ. Harm reduction, hepatitis C and opioid pharmacotherapy: an opportunity for integrated hepatitis C virus-specific harm reduction. ***Drug Alcohol Rev 2007;26:437-43.***

26. Wright NM, Tompkins CN. A review of the evidence for the effectiveness of primary prevention interventions for hepatitis C among injecting drug users. ***Harm Reduct J 2006;3:27.***

27. HCC screening ref

28. Egede LE. Lifestyle modification to improve blood pressure control in individuals with diabetes: is physician advice effective? ***Diabetes Care 2003;26:602-7.***

29. Cholongitas E, Betrosian A, Senzolo M, Shaw S, Patch D, Manousou P, O'Beirne J, Burroughs AK. Prognostic models in cirrhotics admitted to intensive care units better predict outcome when assessed at 48 h after admission. ***J Gastroenterol Hepatol. 2008;23(8 Pt 1):1223-7.***

30. Neuberger J, Gimson A, Davies M, Akyol M, O'Grady J, Burroughs A, Hudson M; Liver Advisory Group; UK Blood and Transplant. Selection of patients for liver transplantation and allocation of donated livers in the UK. ***Gut. 2008;57:252-7.***

31. Marion AW, Baker AJ, Dhawan A. Fatty liver disease in children. ***Arch Dis Child 2004; 89:648-52.***

32. Ariel E Feldstein, Phunchai Charatcharoenwitthaya, Sombat Treeprasertsuk, Joanne T Benson, Felicity B Enders, and Paul Angulo. The natural history of nonalcoholic fatty liver disease in children: A follow-up study for up to 20-years. ***Gut 2009;;58:1538-44.***

33. Carter-Kent C, Yerian LM, Brunt EM, Angulo P, Kohli R, Ling SC, Xanthakos SA, Whitington PF, Charatcharoenwitthaya P, Yap J, Lopez R, McCullough AJ, Feldstein AE. Nonalcoholic steatohepatitis in children: a multicenter clinicopathological study. ***Hepatology. 2009;50:1113-20.***

34. Denzer C, Thiere D, Muche R, Koenig W, Mayer H, Kratzer W, Wabitsch M.Gender-specific prevalences of Fatty liver in obese children and adolescents: roles of body fat distribution, sex steroids, and insulin resistance. ***J Clin Endocrinol Metab 2009 94:3872-81.***

35. Mieli-Vergani G, Vergani D. Autoimmune hepatitis in children: what is different from adult AIH? ***Semin Liver Dis 2009; 29:297-306.***

36. http://www.rcpath.org/resources/pdf/g064tpliverandfocalmay08final.pdf

37. http://www.rcpath.org/resources/pdf/G050DatasetLiverSept07-AR.pdf

38. García-Romero D, Anastassiou J, Hart G, Mookerjee R, Jalan R. High prevalence of abnormal alanine and aspartate aminotransferases in a "worried-well" population in the United Kingdom: rationale for a liver screening program? ***Hepatology. 2008;48:1729-30.***

Contributors

Kevin Moore (Chair):	Professor of Hepatology, Centre for Hepatology, University College London.
Nick Sheron:	Head of Clinical Hepatology, University of Southampton
John O'Grady	Consultant Hepatologist, King's College Hospital, London
Jan Freeman	Consultant Hepatologist, Trent and Derby Hospitals
Richard Thompson	Consultant Paediatric Hepatologist, King's College Hospital, London
Ian Gilmore	President, Royal College of Physicians and Consultant Hepatologist
Matthew Cramp	Consultant Hepatologist, Derriford Hospital Hospital, Plymouth
Rajiv Jalan	Professor of Hepatology, Institute of Hepatology, University College London
Mark Thursz	Professor of Hepatology, Imperial College London
Stephen Ryder	Professor of Hepatology, University College London
James O'Beirne	Consultant Hepatologist, Royal Free Hospital, London
Ken Simpson	Consultant Hepatologist, Edinburgh
Stefan Hubscher	Professor of Hepatic Pathology, University of Birmingham
Judy Wyatt	Consultant Histopathologist, St James's University Hospital Leeds
Will Irving	Consultant Virolologist, Nottingham
Humphrey Hodgson	Professor of Hepatology, University College London
Howard Thomas	Professor of Hepatology, Imperial College London
Alison Rogers	CEO, British Liver Trust
Graham Foster	Professor of Hepatology, Royal London Hospital
Roger Williams	Director, Institute of Liver Studies, University College London
Kathryn Nash	Consultant Hepatologist, University of Southampton