Hepatitis B

Stakeholder workshop

25th May 2011
NICE, Level 1A, City Tower, Piccadilly Plaza, Manchester, M1 4BD

Summary notes

The stakeholder scoping workshop is held in addition to the formal consultation on the scope which is taking place from the 14th of June until the 5th of July 2011.

The objectives of the scoping workshop were to:

- obtain feedback on the specified population and key clinical issues included in the first draft of the scope
- seek views on the composition of the Guideline Development Group (GDG)
- encourage applications for GDG membership

The scoping group (Technical Team, NICE and GDG Chair) presented a summary of the guideline development process, the role and importance of patient representatives, the process for GDG recruitment and proposed constituency for this group, and the scope. The stakeholders were then divided into three groups which included a facilitator and a scribe and each group had a structured discussion based around pre-defined questions relating to the draft scope. Comments received from each discussion group have been combined and summarised below.

Scope Section	Comments
Title	• It was suggested to include ‘chronic’ in title and replace ‘adolescents’ with ‘young people’
2.1 a **Epidemiology**	• Migrants, MSM and injecting drug users should not be aggregated together • ‘Injecting’ was considered a more appropriate term than ‘intravenous’ • HPA figures do not distinguish between acute and chronic – no-one actually knows the prevalence of CHB
2.2 a **Current Practice**	• The group advised not to use brand names in this section (pegasys and truvada) • The stakeholders noted that more needs to be learnt about future drug resistance
3.1 **Population**	• It was suggested that HIV patients should be taken out as there are competing guidelines being developed for these group of patients. • A question was raised as to why children under 5 years are excluded from the scope: a 5-yr cut-off point just doesn’t feel right. This is more so when one considers the increasing incidence of vaccine failures in infants. It was also argued why pregnant women should be included in the scope but not their babies. The treatment choices for pregnant/lactating women will affect the treatment choices for babies. It was suggested that children should be included from birth.

	• Another point raised, was how to identify intravenous drug users and men who have sex with men. Typically physicians can ask ad hoc questions that may help identify these groups but it will be better to widen this group to commercial sex workers and those with multiple sexual partners. • It was also suggested that anybody at risk of suffering from a blood-borne virus should be screened for hepatitis B.
3.1.1 **Groups that will be covered** **Children over 5 years, young people and adults with chronic hepatitis B including:** **a. First generation migrants from endemic areas** **b. Intravenous drug users (IDU)** **c. Men who have sex with men (MSM)** **d. HIV Patients** **e. Pregnant and lactating women**	• It was suggested that the groups covered should be as follows: Children, young people and adults with chronic hepatitis B (viraemia and hepatic inflammation for more than 6 months following HBV infection). Within this group, particular consideration is required in respect of: a) Patients co-infected with HIV, hepatitis C or hepatitis delta (D) b) Immuno-compromised patients (such as those undergoing cancer treatments, and incl. prophylactic group) who are carriers or have been previously serologically active, to whom prophylactic treatment might be beneficial c) Pregnant and lactating women d) Cirrhotic patients e) Decompensated patients • The needs of particular at-risk groups will also be recognised within the guideline. These groups include: migrants from endemic areas, injecting drug users, men who have sex with men (MSM) and people with multiple sexual partners (MSM should not be singled out in the sexually active group) • The group felt that it is important to acknowledge the at-risk groups/subgroups within the guideline; but in terms of diagnosis and management, it's the same and therefore should take them out of the scope. Another reason is that there is fair amount of overlap between the groups, e.g. MSM are often IV drug users. • The stakeholders noted the need to be aware that Hep B is prevalent in prisons.
3.1.2	• Remove transplantation and ADD

Groups that will not be covered **a. Children, young people and adults having undergone liver transplantation**	• Those with acute hepatitis B – those who have undergone liver transplantation are treated the same as CHB patients
3.2 **Healthcare settings** **a. Primary, secondary, tertiary and community care setting**	• This was considered appropriate. No specific comments made.
3.3 **Management**	• It was suggested the paragraph title should be: 'Diagnosis and management'
3.3.1a **Key issues that will be covered** **a. Laboratory tests** – **Enzyme immunoassay (EIA) HBsAg** – **Monolisa HBe Ag-Ab PLUS assay quantitative HBV DNA assays** – **Liver function tests (LFTs)** – **Liver biopsy** – **Non invasive methods of assessing liver fibrosis (fibroscan,**	• The group stated that all the tests mentioned are the right ones. However, consideration should be given HbsAg quantitative assay as a cheaper alternative to HBV DNA assay. The problem is evidence on the clinical utility of HbsAg quantitative assays are scattered in conference abstracts and rarely come up from searched published literature. • It was mentioned that it is advisable to test for all markers, i.e., include hepatitis A, C and E. That is a patient is diagnosed with hepatitis B, it is advisable to check for A, C and E although this would not affect the chosen treatment pathway for hepatitis B. In relation to this, a question was raised as to the how cost-effective is genotype testing. • It was suggested to add 'and assessment' after Early diagnosis • Group argued that this section should be split into three: 1. Diagnostic testing in primary care:

aspartate aminotransferase/platelet ration index (APRI)) – **Serum fibrosis markers (fibrotest)**	• EIA for HBsAg • Monolisa HBe Ag-Ab • HBV DNA (there was a particular emphasis on the need for this in primary care) • Tests for coinfection (HIV, Hepatitis C and delta) 2. Threshold criteria for referral to specialist services, and maintenance of contact/monitoring with those who do not require immediate treatment 3. Assessment by specialist services – Liver biopsy – Non-invasive assessment of fibrosis (APRI, elastography) – Serum fibrosis marker test – Genotyping (important for decision on treatment with peginterferon • It was suggested to– remove 'early' (Diagnosis of chronic hepatitis B) • It was suggested that we need to look at the infrastructure – where and when the different tests are offered • Patients with decompensated liver disease – priority group to put on treatment and they usually show good response; but it's only a very small population. • Important to detect previous exposure to hep B, in those who are immune compromised (when the virus can become reactiviated).
3.3.1 b **Key issues that will be covered** **b. Pharmacological treatment of chronic Hepatitis B (sequential and combination therapy for specified subgroups)**	• The group suggested that although pharmacologic treatment of decompensated liver disease could possibly lead to a reversion of disease progression, there is lack of both evidence and experience of managing decompensated liver disease. (Currently, tenofovir and entecavir cannot be used in decompensated liver disease.) • It was mentioned that combination therapies are often used for the pharmacologic treatment of hepatitis B although the evidence in support of this is mostly based on cohort studies. It was indicated that there is new clinical evidence emerging on the effectiveness of tenofovir with pegylated interferon as well as pegylated interferon with entecavir.

– **Tenofovir** – **Entecavir** – **Pegylated interferon (2a and 2b)** – **Lamivudine** – **Adefovir** – **telbivudine**	• Increasingly the preferred clinical choice is to treat HIV patients with hepatitis B with TRUVADA® (tenofovir and emtricitabine/FTC) combination therapy. The group suggested the scope should look an any combination of drugs and TRUVADA. • Treatment of pregnant women is important to reduce the infectivity of babies. Currently treatment of pregnant women is usually with lamivudine: 3 months before and 3 months after delivery (treatment period of 6 months) although there is currently variation in clinical practice • It was suggested that the scope should not differentiate between 2a and 2b Pegylated interferon • The group raised the issue that many of the drugs are not licensed for Hep B in children and we should be aware of it.
3.3.1 c **Key issues that will be covered** **c. Monitoring stages of condition (timing and frequency of quantitative HBV DNA assays and resistance genotyping)**	• The group mentioned that there is specific problem of renal toxicity associated with the use of tenofovir and the specific details will be found in the BNF. It was again mentioned that the HbsAg quantitative assay will be worth considering for monitoring. It was stated that monitoring is particularly important • The group suggested this section should be split into four bullet points: 1 Surveillance (timing and frequency of quantitative DNA assays and resistance genotyping) 2 Renal monitoring and detection of other side effects 3 Case finding for hepatocellular carcinoma (HCC) 4 Duration of therapy (stopping points for treatment according to serology) • The group suggested that “Case finding for Hepatocellular carcinoma by APEIA and ultrasound” should be removed from the scope – the group felt that it will be a huge amount of work (patients with advanced/early liver disease can develop HCC and the risk varies according to genotype and ethnic groups.)

3.3.1 d **Key issues that will be covered** **d. Patient information**	• The group considered patient information an important issue and it was suggested that this could be done via family screening and counselling. There is the need to encourage the provision of information on maternal to infant transmission (which could be done by specialist nurse services) and adherence to treatments. Consideration must be given transition between services as a lot of patients get lost to follow-up. • The group suggested we cover the following in terms of patient information – long term nature of illness – Compliance issue (especially with the NAs) – Language barrier – for both diagnosis and management – Support group for the family
3.3.2 **Key issues that will not be covered** **a. Primary prevention of Hepatitis B including vaccinations and case finding** **b. Signs and symptoms of Hepatitis B** **c. Access issues related to case finding** **d. Non pharmacological management of chronic hepatitis B** **e. Coinfection of chronic hepatitis B with hepatitis viruses A,C,D or E** **f. Guidance on working practices for infected**	• The group noted that it might be necessary to make a trade off between hepatitis B patients co-infected with HIV and hepatitis B patients co-infected with hepatitis D (delta). The latter group of patients should be included as one of the groups that will be covered by the guideline (as the incidence of hepatitis D is always associated with hepatitis B). • It was suggested that ‘Co-infection with hep A,C,D or E’ should be replaced with ‘acute hepatitis B’

healthcare workers **g. Liver transplantation as a clinical strategy**	
3.4 **Main outcomes** **a. Disappearance of serum HBV DNA by the most sensitive available quantitative assay (currently 12IU/ML) at the end of treatment and at yearly intervals during post treatment follow up (absence of drug resistance)** **b. Normalisation of liver enzyme ALT at the end of treatment and at yearly intervals during post treatment follow up** **c. Histological response to treatment (fibrosis measured by fibrotest, API, fibroscan) over 3 years post treatment follow up** **d. Clearance of HBsAg and HBeAg during treatment and at yearly intervals during post treatment follow up** **e. Absence of long term**	• It was suggested that all the health outcomes specified are ok. However, by considering pregnant women, it might be good to add hepatitis B transmission to infants. Typically, serology tests are conducted for HbsAg, core antibody and surface antibody. • Some of the discussants questioned the relevance of the outcome “absence of long-term complications and hepatocellular carcinoma”. It was argued that rarely do clinicians come across cases of hepatocellular carcinoma (HCC). However, no specific conclusions were reached on this point. • It was suggested that the intro line: ‘for both HBeAg (+) patients and HBeAg (-) patientsshould be removed • The group suggested the section could be split into oral and injectable treatment. • The group suggested the following potential outcomes: – Time taken to achieve disappearance of serum HBV DNA – Monitoring and maintained disappearance of serum DNA within a defined time interval (Absence of viral resistance) – Histological response to treatment (fibrosis levels) – Time taken to achieve seroconversion – Reversal of liver decompensation, absence of hepatocellular carcinoma (HCC) and increased survival – Improved quality of life (SF-36 and liver-specific questionnaires) – Absence of experience of adverse effects (renal toxicity) • The group felt that the patients should not have liver biopsy after treatment.

complications of liver decompensation and Hepatocellular carcinoma (HCC) **f. Improving Quality of life: using a validated general instrument (such as SF-36) or a validated liver disease-specific instrument (e.g. the Chronic Liver Disease Questionnaire (CLDQ))** **g. Increased survival** **h. Absence of experience of adverse effects (renal toxicity)**	
3.5 **Economic Aspects**	• It was put forward that apparently in current clinical practice, it is common to do just surface antigen test (core testing is not necessarily done). The group suggested that the scope could look at the cost in adding in another test
4.1.1 **Quality Standards – Areas of care from the guideline that will be considered** **a. Early diagnosis: referral to diagnostic services, access to correct diagnostic tests** **b. Management: access to treatments and specialist services,**	The following points were highlighted with regards to quality standards: • Referral to specialist services • Access to specialist nurses • Information provision • Testing for other blood-borne viruses whenever hepatitis B is diagnosed. • Early diagnostic assessment • Early decision on who requires treatment • Frequent testing for maintenance of HBV-DNA negativity • Continued engagement with those who do not require immediate treatment • Effective treatment follow-up

treatments for specific populations **c. Long term management: referral to specialist services, monitoring of stages of condition (timing and frequency of tests)** **d. Patient information**	• Equity of access to services (distance to travel, account taken for language problems, special environments such as prison) • Infants that are born to HBeAg-positive mothers should be tested (antigen testing) at 12 months
GDG composition – **Hepatologist** – **Virologist** – **GP with special interest in hepatology** – **GP/PCT commissioner** – **Anti viral nurse specialist** – **2 x patient reps (one parent, one adult)** – **Community/outreach nurse with interest in migrant health** – **Pharmacist** – **Paediatrician** – **Obstetrician** – **HIV Specialist**	• The group suggested the following inclusions to the proposed GDG composition: • Specialist midwife with expertise in infectious diseases • Infectious disease physician • Patient/carer from a migrant population • Hepatologist with specific interest in antenatal medicine) • Oncologist (co-optee) • Pharmacist (co-optee) • Nurse – should be public health specialist • Paediatrician – should have an interest in Hep B • Radiologist – as a co-optee

The meeting was closed by a brief summary of the 3 key points discussed at each table. Attendees were informed of the scope consultation dates and process and that GDG recruitment would happen simultaneously. Further comments on the scope and applications for GDG membership were encouraged.