A Consensus Conference was convened by the Italian National Institute of Health on May 5–6, 2005, to address the issue of the screening for hepatitis C virus infection in adults in Italy.

It was concluded that a mass screening for hepatitis C virus infection is inappropriate. It was recommended that the following high-risk groups be tested for hepatitis C virus infection, particularly if they are potentially eligible for antiviral treatment: subjects with history of intravenous drug use; haemodialysis patients; subjects who received blood coagulation factors before 1987; subjects who received blood transfusions or organ transplantation before 1992; households of hepatitis C virus-infected individuals; subjects with multiple sexual partners which have or have had a sexually transmitted disease. A screening for hepatitis C virus infection was considered unjustified for persons who are scheduled for an invasive procedure (e.g. surgery, endoscopy) and during pregnancy.

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Keywords: Hepatitis C virus; Italy; Screening

1. Preamble

In 1997, a first Consensus Conference on screening for hepatitis C virus (HCV) infection in Italy was convened by the Istituto Superiore di Sanità (ISS, Italian National Institute of Health) [1]. In 2004, in view of the new evidence attained on epidemiology, natural history and treatment of HCV-related chronic liver disease, the Clinical Epidemiology and Guidelines Unit of the ISS (hereafter referred to as the Organising Committee) decided to rediscuss this issue and promoted a second Conference which was held on May 5–6, 2005. The Conference was aimed at screening asymptomatic people. Accordingly, diagnosis of HCV infection in patients with a clinical indication specifically requiring HCV infection assessment (e.g. those with: altered liver enzymes or other clinical/biochemical/instrumental evidence of liver disease; extraprotective manifestations of HCV infection such as mixed cryoglobulinaemia) was beyond the scope of the Conference and was not addressed. The issue of viral hepatitis testing in healthcare workers had been previously addressed in an ad hoc Consensus Conference [2] and so it was not rediscussed.

The Organising Committee evaluated a range of processes in current use for making consensus recommendations, selecting among them a two-stage procedure, largely based upon the National Institutes of Health guidelines [3].

First stage: Groups of experts (hereafter called Expert Group (see Appendix A)) were first convened over several months by the Organising Committee to review the relevant medical literature subcategorised into specific sub-topics, namely:

- Prevalence and incidence of HCV infection in the Italian general population; sub-groups at higher risk.
- Characteristics of the diagnostic tests for HCV infection.

See Appendix A for the list of members.
- Natural history of chronic HCV infection.
- Therapy: work-up of potential candidates for antiviral therapy; eligibility for treatment of HCV-infected subjects identified through screening.
- Therapy: side effects; impact on laboratory parameters (viraemia, aminotransferases, liver histology); predictors of viral clearance.
- Therapy: impact on clinical endpoints (progression to cirrhosis, hepatic decompensation, development of hepatocellular carcinoma (HCC), mortality).
- Impact of the counselling (reduction of alcohol consumption, diet, anti-hepatitis A and B vaccinations, information on routes of HCV transmission) on disease progression and on HCV spread.

The following methods were employed by the Expert Group:

Searched databases: Medline, Embase, Cochrane Controlled Trials Register, Cochrane Library. The strategies were developed according to the database to be searched. Relevant consensus documents and guidelines were also consulted.

Search strategy: (hepatitis c or hepavirus or hcv or hepatitis c antibodies) and (Italy and (prevalence or incidence)) or (mass screening or (sensitivity and specificity) or (predictive value of tests or (antibody testing))) or ((biopsy and liver/pathology) or ‘liver biopsy’) or (natural history or fibrosis or diagnostic accuracy or performance of ultrasound or hepatitis c/therapy or predictors of response or predictive factors) or (mass screening and (antiviral agents/therapeutic use or interferons/therapeutic use or ribavirin/therapeutic use)) or (antiviral agents/adverse effects or interferons/adverse effects or ribavirin/adverse effects) or (long-term or longterm) or ((hepatitis a or hepatitis b) and (vaccination or vaccines)) or hepatitis c or hepatitis c virus) and (hepatitis a vaccines or hepatitis b vaccines) or ((diet or diet therapy or diet, vegetarian or weight-loss or anti-obesity agents) and (fatty liver/pathology or liver/pathology or liver cirrhosis or liver diseases or steatosis)) or (patient education or counselling or patient counselling or family counselling or parent counselling or genetic counselling or alcohol abuse or alcoholism).

The Expert Group, once completed the literature search, compiled evidence-based review papers (available at www.enlg.it), which were presented to the Conference Panel (see Appendix A) prior to the Conference. The Panel was assembled as an independent, multidisciplinary group of experts from various disciplines (including epidemiologists, health services researchers, health educators, clinical pharmacologists, general practitioners, infectious diseases clinicians, hepatogastroenterologists and patient advocates from two Italian patient associations involved in viral hepatitis—EpaC and COPEV) to make its recommendations about detection of asymptomatic adults with chronic HCV infection in the Italian population.

Second stage: The Panel began its deliberations by discussing and analysing the review papers prepared by the Expert Group, until a general agreement was reached on how to answer the key questions identified. After a 2-day general discussion, a subset of Panel members was appointed as the Writing Committee (see Appendix A), and worked on summaries and recommendations, then presenting proposals to the entire group in the form of a drafted document for further discussion and refinement. The Writing Committee modified the first statement according to the suggestions made during the discussion, and, in the days following the Conference, circulated a second draft among all Panel members for final approval.

The Panel judged that the Expert Group review documents cited most of the known evidence on the topics of interest, with adequate critical appraisal of evidence from the individual studies. In cases, explicit account was made to the fact that some of the studies were deficient by a methodological point of view. Therefore, the Panel elected to take a fundamentally conservative approach by making a limited number of statements and recommendations on issues that could be addressed with confidence even against the backdrop of an evidence base of varying and, in some cases, unknown quality. On the key question of recommending for or against HCV screening in adults in Italy, the Panel was especially conservative, finding that the standard of evidence for making a positive recommendation at this time was not met. On the other hand, on the question: ‘Are there subjects in the Italian adult population for whom the screening for HCV infection is warranted?’ specific comments and final statements were made.

The present recommendations are based on the scientific evidence provided by the Experts. The Organising Committee is willing to reconsider the matter and, if needed, convey a new Consensus Conference whenever clinically important evidence is provided by new studies on epidemiology, natural history, diagnosis and therapy of hepatitis C.

2. Summary of relevant data

2.1. Epidemiology

Chronic HCV infection is an important cause of morbidity and mortality in Italy. It is, likely, the leading cause of mortality from liver cirrhosis and HCC [4,5], and is the leading indication for liver transplantation [6].

In the general population (not belonging to the high-risk groups listed below) the prevalence of HCV RNA-positive subjects shows a cohort effect, and is:

- Higher than 3% among subjects born in the period 1940–1949, and higher than 5% among subjects born before 1940, with particularly high levels in some areas of South and major Islands.
- Lower than 1.5% among subjects born in the period 1950–1959 and it decreases further in younger generations, with no substantial differences by geographic areas [7–20].
The population sub-groups with a significantly higher prevalence (usually higher than 10%) compared to the general population include:

- Current or past intravenous drug users [21,22].
- Haemodialysis patients [23–25].
- Subjects who received blood coagulation factors before 1987 [26].
- Subjects who received blood transfusions or organ transplantation before 1992 [27].

Although not all studies are unequivocal, HCV prevalence is usually ≥3% in the following groups:

- Households of HCV-infected individuals [28–36].
- Subjects with multiple sexual partners which have or have had a sexually transmitted disease [38–40].
- Subjects who received blood coagulation factors before 1987 [26].

The population sub-groups with a significantly higher prevalence compared to controls [29,32,33]. Moreover, a case-control study found a significantly higher prevalence of HCV-related cirrhosis in families of HCV cirrhotics than in matched controls [37]. As a matter of fact, having a household with chronic liver disease was an independent predictor of HCV infection in the two largest population-based prevalence studies which collected this information [13,20]. In a case-control study in which the odds ratio (OR) of the association did not reach formal statistical significance, the confidence interval (CI) lay almost completely in the area favourable to the association (OR = 2, 95% CI = 0.9–4.6) [33].

- Subjects with multiple sexual partners which have or have had a sexually transmitted disease [38–40].
- Although sexual transmission of HCV is generally inefficient [41], in this group a high HCV incidence has been shown as well (1.14/100 person-years) [42]. Human immunodeficiency virus (HIV) and syphilis may possibly favour HCV infection [40,43].

Nowadays, the estimated annual incidence of new HCV infections in the general population is very low (4–6/100,000/year) [44,45].

2.2. Natural history, diagnosis, and treatment

The natural history of chronic hepatitis C is highly variable according to several factors, among which comorbidity (in particular hepatitis B virus and HIV co-infections), older age, male sex and alcohol abuse have a major role. It is usually slowly progressive with an average estimated probability of cirrhosis at 40 years since the infection in about 20% of subjects infected when younger than 40 years of age, and in 40% of those infected when older than this age, respectively [46,47]. The two largest studies conducted in patients with compensated cirrhosis found a cumulative incidence of decompensation or HCC of 16–25% at 5 years and of 43–53% at 10 years from diagnosis [48,49]. It is possible that these figures, based on patients enrolled and followed up in tertiary referral centres, are in excess because of a selection bias, progressively increasing in studies with a longer follow-up. Currently the aetiologic diagnosis of HCV-related hepatitis or cirrhosis is highly reliable. In fact, there is wide availability of diagnostic tests for HCV infection with sensitivity and specificity close to 100% [50,51].

At present, the best antiviral treatment includes pegylated interferon plus ribavirin. In clinical trials this combination induced a sustained virological response (SVR) in 42–52% of patients infected with genotype 1, and in 76–84% of patients infected with genotype 2 or 3 [52–54]. The probability of SVR is decreased in patients older than 40–50 years, in those with advanced liver fibrosis or cirrhosis and in overweight subjects. In prescribing the antiviral treatment, the frequent occurrence of side effects must be taken into account, since it can result in treatment discontinuation or dose reduction, with consequent decrease of efficacy [52–56].

The studies evaluating the impact of the SVR on clinical endpoints of the natural history of HCV infection (hepatic decompensation, HCC, mortality) have several methodological limitations [57,58]. However, the hypothesis that the SVR reduces morbidity and mortality events is highly plausible on a biological basis, and this enhances the a priori probability of the results of the studies conducted on this issue.

3. Final consensus statement

As a general principle, the participants in the Conference believe that the diagnostic test for HCV infection should be offered to asymptomatic persons only if an advantage is anticipated in case diagnosis of infection is made, although it should be available to any individual who requests it.

In particular, the primary goal of testing asymptomatic persons is the reduction of morbidity and mortality from HCV-related chronic liver disease, in the hypothesis that this can be achieved through virus eradication with antiviral therapy.

Other goals do not seem relevant in the decision-process leading to the development of recommendations for HCV screening. In fact, it cannot be excluded that the awareness of being HCV-infected may increase the compliance with a counselling aimed at reduction of liver damage cofactors (alcohol [59], liver steatosis [60], hepatitis A and B infection [61–64]) and of HCV transmission to other people. However, lifestyle changes that reduce alcohol consumption [65] and metabolic/vascular risk factors [66–68], and the adoption of measures for prevention of viral hepatitis transmission [45] improve the general health status in a population, and must be considered as universal recommendations, independently from presence or absence of HCV infection.

In the general population, Panelists believe that the following groups are not eligible for a mass screening:

- Subjects older than 65 years, because usually not eligible for antiviral therapy.
- Subjects born after 1950, since HCV prevalence is very low unless they belong to specific high-risk groups.
High prevalence of infection among those born from 1940 to 1949 would make this cohort potentially eligible for a mass screening. However, the following considerations should be put forth:

- Prevalence studies performed in several Italian regions found that an appreciable proportion of HCV-positive subjects were already aware of being infected (from 26 to 28% in the 1990s [12,16]), to more than 50% in more recent studies [20]).
- HCV-positive persons unaware of their infection and identified by screening are expected to present in high proportion persistently normal alanine aminotransferase (ALT) levels. In fact, in prevalence studies approximately 45% of subjects with HCV chronic infection showed persistently normal ALT [44,69]. In these individuals HCV-related liver disease would likely show a very slow progression and an uncertain impact on life expectancy [46,70–72].
- Comorbidity in this age group could further limit the eligibility to treatment, which usually does not exceed 30% of HCV-infected subjects seeking medical care [73,74].
- Treatment is likely to induce a SVR globally in no more than 40% of treated subjects older than 55 years [75].
- The infection awareness in asymptomatic subjects who are not eligible for or non-responders to the treatment might have a negative impact on their quality of life [76].

It is concluded that these limitations in eligibility for and effectiveness of treatment make a mass screening in this age group inappropriate, independently of cost-effectiveness evaluations which might discourage universal screening.

The Panelists recommend that the following groups be tested for HCV infection, particularly if they are potentially eligible for antiviral treatment:

- Subjects with history of intravenous drug use.
- Haemodialysis patients.
- Subjects who received blood coagulation factors before 1987.
- Subjects who received blood transfusions or organ transplantation before 1992.
- Households of HCV-infected individuals.
- Subjects with multiple sexual partners which have or have had a sexually transmitted disease.

Before being tested for HCV, persons should receive full information about the meaning of a positive test and about possible benefits and disadvantages of having a diagnosis of HCV infection while asymptomatic.

A screening for HCV infection is unjustified for:

- Persons scheduled for an invasive procedure (e.g. surgery, endoscopy), since the universal hygienic precautions on blood contamination must be applied at all times with maximal care, regardless of the viral status of patients.
- During pregnancy, since no means to reduce the risk of HCV vertical transmission are currently available [77].

The issue of HCV screening in immigrants from other countries was not addressed during the Conference, so that no specific recommendations can be formulated on this topic.

Note: Gardini Ivan, President of Epac Onlus association, attending the Consensus Conference, by decision of the Epac directors board, did not approve the present statement. Major points of dissent were as follows: (1) Epac would have appreciated a wider range of disciplines and institutions involved in the Conference. (2) Epac agrees that a mass screening in the general population is inappropriate. On the other hand it believes that, besides the groups reported in the consensus statement, HCV test should also be recommended for: those who received blood products before 1995, those who underwent a major surgical intervention; those scheduled for an invasive medical procedure. (3) Epac believes that a screening for HCV infection is justified independently of antiviral treatment, through a counselling aimed at reduction of liver damage cofactors and of HCV transmission to other people.

Conflict of interest statement
None declared.

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Appendix A

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