VHPB  Country meeting

Prevention and control of Viral Hepatitis in Albania and the neighbouring countries: lessons learnt and the way forward

TIRANA, ALBANIA

27-28 OCTOBER 2016
Content

This pre-meeting document contains general background information of the countries and the reported current hepatitis situation. Furthermore a list of selected abstracts/references from a Pubmed MEDLINE search on different search terms. The references are ranged by publication year (most recent first) and for each year in alphabetical order of the first author’s name.

This document should guide you in the preparation of the meeting, it should not be considered as complete literature review, but hopefully it will give an overview of what has been published on the topics of the meeting.

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1. Albania

1.1. General background

Albania officially the Republic of Albania is a country (28,748 sq km) in Southeast Europe, bordered by Montenegro to the northwest, Kosovo to the northeast, the Republic of Macedonia to the east, and Greece to the south and southeast. It has a coast on the Adriatic Sea to the west and on the Ionian Sea to the southwest. It is less than 72 km from Italy, across the Strait of Otranto which connects the Adriatic Sea to the Ionian Sea.

<table>
<thead>
<tr>
<th>Demographics data</th>
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<tbody>
<tr>
<td>Population</td>
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<td>GDP (PPP) per capita</td>
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<td>GDP</td>
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<td>Unemployment rate</td>
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<td>Population growth</td>
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<td>Birth rate:</td>
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<td>Death rate:</td>
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<td>Net migration rate</td>
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<tr>
<td>Health expenditures</td>
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<tr>
<td>Physicians density:</td>
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<tr>
<td>Life expectancy at birth</td>
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</tbody>
</table>
1.2. Hepatitis

1.2.1. VHPB survey

VHPB survey on prevention and control of viral hepatitis in 53 European countries in 2014 – November 2014

1.2.2  WHO data
(http://www.who.int/gho/countries/alb.pdf?ua=1)
Albania: WHO statistical profile

Distribution of causes of deaths in children under-5, 2013

- Congenital anomalies: 28%
- Other causes: 21%
- Prematurity: 20%
- Acute respiratory infections: 10%
- Injuries: 9%
- Birth asphyxia: 7%
- Neonatal sepsis: 6%
- Diarrhoea: 4%
- Measles: <1%
- HIV/AIDS: 0%
- Malaria: 0%

DTP3 immunization among 1-year-olds

- Percentage of children aged under-5 stunted

Source: Country statistics and global health estimates by WHO and UN partners. For more information visit the Global Health Observatory (http://www.who.int/gho/)

Last updated: January 2015

Utilisation of health services

- Contraceptive prevalence:
  - Country: 59%
  - WHO region: 67%

- Antenatal care (4+ visits):
  - Country: 82%
  - WHO region: 67%

- Babies attended by skilled health personnel:
  - Country: 82%
  - WHO region: 75%

- Measles immunization (1-yr-olds):
  - Country: 88%
  - WHO region: 82%

- smear-positive TB treatment success:
  - Country: 75%
  - WHO region: 75%

Per capita total expenditure on health

- Data not available or applicable

Adult risk factors

- Raised blood glucose (aged 25+), 2008
  - Male: 10.3%
  - Female: 9.0%
- Raised blood pressure (aged 25+), 2008
  - Male: 23.1%
  - Female: 25.7%
- Obesity (aged 25+), 2008
  - Male: 28.4%
  - Female: 24.1%
- Tobacco use (aged 15+), 2011
  - Male: 46%
  - Female: 38%

Population using improved water and sanitation

- Improved drinking-water sources
- Improved sanitation facilities
Top 10 causes of death

Ischaemic heart disease was the leading cause of death, killing 7.5 thousand people in 2012.

<table>
<thead>
<tr>
<th>Causes</th>
<th>No of deaths (000's) 2012</th>
<th>Crude death rate 2000-2012</th>
<th>Change in rank 2000-2012</th>
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</thead>
<tbody>
<tr>
<td>Ischaemic heart disease (75.4%)</td>
<td>7.5</td>
<td>7.6</td>
<td>Increased</td>
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<tr>
<td>Stroke (19.2%)</td>
<td>7.4</td>
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<tr>
<td>Trachea, bronchus, lung cancers (3.3%)</td>
<td>1.0</td>
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<td>Lower respiratory infections (3.7%)</td>
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<td>Chronic obstructive pulmonary disease (2.9%)</td>
<td>0.9</td>
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<td>Increased</td>
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<td>Stomach cancer (2.4%)</td>
<td>0.7</td>
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<tr>
<td>Hypertensive heart disease (1.8%)</td>
<td>0.5</td>
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<td>Increased</td>
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<td>Kidney disease (1.6%)</td>
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<td>Cardiomyopathy, myocardial infarction (1.4%)</td>
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<td>Road injury (1.4%)</td>
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Burden of disease, 2012

Disability-adjusted life years (DALYs) are the sum of years of life lost due to premature mortality (YLL) and years of healthy life lost due to disability (YLD).

DALYs, YLL and YLD (thousands) by broad cause group

Cardiovascular diseases and diabetes
- Neuro-degenerative disorders
- Cancer (including other NCDs)
- Intentional injuries
- Maternal, neonatal, nutritional
- Chronic respiratory diseases
- Asthma, chronic obstructive pulmonary disease
- Other respiratory diseases
- Other infectious diseases
- HIV, TB, malaria

Deaths by broad cause group

Probability of dying, 2012

Probability of dying between relevant exact ages, for a person experiencing the 2012 age-specific mortality rates throughout their life.

- Before age 15, all causes
  - Male: 0%
  - Female: 7%
- Before age 70, all causes
  - Male: 40%
  - Female: 30%
- Between ages 15 and 49, from maternal causes
  - Female: 0%
- Between ages 15 and 70, from 4 major noncommunicable diseases (NCDs) –
  - Diabetes: 18%
- Source: Country statistics and global health estimates by WHO and UN partners
- For more information, visit the Global Health Observatory (http://www.who.int/gho/health-burden/diseases)
- Last updated: January 2015
WHO CISID database info (http://data.euro.who.int/cisid/?TabID=399572)

**Hepatitis A**

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**Hepatitis B Incidence (cases per 100 000 population)**

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**Hepatitis B chronic - Incidence (cases per 100 000 population)**

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**Hepatitis C Incidence (Cases per 100 000 population)**

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**Hepatitis C chronic - Number of cases**

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1.3 Presentation related Pubmed abstracts

Pubmed MEDLINE search on {(Hepatitis ) AND (Albani*) } in all fields
and filter: ‘last 10 years’ on was performed.
The references were manually sorted in the different subject in an EndNote database.
The references are listed by publication year (recent first).

1.3.1 Surveillance, epidemiology or viral hepatitis in Albania (session 3)

Hepatitis A


Hepatitis A disease is endemic in Albania even though records from the Medical Authority show outbreaks involving only limited numbers of people. In the city of Lac, 200 people became ill following an outbreak of hepatitis A started on November 2002. The age distribution of the cases shows a peak in the age group 5-9 (43.5%) followed by the age group 10-14 (28%) and the age group 1-4 (18%). No cases were recorded in the age group 0-1. Drinking water and sewage samples were collected, using electropositive cartridges, during the outbreak. Rotavirus was identified by RT-PCR in two out of five drinking water samples; however, all the samples tested negative for HAV and astrovirus. Rotavirus was also identified in three out of five sewage samples from which four were HAV positive. HAV-RNA was identified in 28 (62.2%) out of 45 IgM anti-HAV positive sera collected during the outbreak. Genotype IA was expressed from all the amplified samples. Sequence analysis of the overlapping VP1-2A region shows 97-99% homology with three Italian strains IT-SCH-00, IT-ZAM-01, and IT-CAP-00 and one Spanish strain (Sa 30/06/95), whereas the phylogenetic tree built from the 168 bp sequence of the VP1-2A shows four clusters, one including 24 out of 28 RT-PCR positive sera. Considering the deduced amino acid sequence, only one substitution was identified and reported previously for genotype IB.

Presentation related references
Epidemiology and outbreaks of hepatitis A in Albania
Provided by speaker: Elona Kureta


Three different studies are reported concerning the environmental pollution caused by viruses in Albania. The first study describes an outbreak of gastroenteritis in the capital city, involving 2,722 children attending the Paediatric Unit of Tirana Hospital. The age group with the highest morbidity was 0-5 years, with 89.5%; no fatalities were recorded during the outbreak. Rotavirus was detected in 26/28 faecal samples by RT-PCR, although astrovirus, adenovirus and calcivirus were also present. The second study describes an outbreak of hepatitis A virus involving the city of Lac. Two hundred cases were recorded, with the highest incidence in the age-group 5-9 years. Phylogenetic analysis of the VP1/2A region showed the presence of a unique sequence: genotype IA. Rotavirus was identified in drinking-water samples collected during the outbreak. The third study describes the prevalence of HAV and HEV in 202 sera randomly collected from 12 different cities in Albania.
HAV showed a high incidence (66.2%), whereas none was positive for HEV. The genomic analysis of the VP1/2A junction revealed the presence of only one genotype (IA) with few point mutations and just two amino acid substitutions at codons 22 and 34. Additionally, two potential antigenic variants were detected, the first at position 46 of VP3 and the second at position 23 of VP1.


Hepatitis A is a common disease in developing countries and Albania has a high prevalence of this disease associated with young age. In spite of the occurrence of a unique serotype there are different genotypes classified from I to VII. Genotype characterisation of HAV isolates circulating in Albania has been undertaken, as well as the study of the occurrence of antigenic variants in the proteins VP3 and VP1. To evaluate the genetic variability of the Albanian hepatitis A virus (HAV) isolates, samples were collected from 12 different cities, and the VP1/2A junction amplified and sequenced. These sequences were aligned and a phylogenetic analysis performed. Additionally, the amino acid sequence of the protein VP3 and the complete sequence of the VP1 was determined. Anti-HAV IgM were present in 66.2% of all sera. Fifty HAV isolates were amplified, and the analysis revealed that all the isolates were sub-genotype IA with only limited mutations. When the deduced amino acid sequences were obtained, the alignment showed only two amino acid substitutions at positions 22 and 34 of the 2A protein. A higher genomic stability of the VP1/2A region, in contrast with what occurs in other parts of the world, could be observed, indicating high endemicity of HAV in Albania. In addition, two potential antigenic variants were detected. The first at position 46 of VP3 in seven isolates and the second at position 23 of VP1 in six isolates.


Hepatitis A disease is endemic in Albania even though records from the Medical Authority show outbreaks involving only limited numbers of people. In the city of Lac, 200 people became ill following an outbreak of hepatitis A that started on November 2002. The age distribution of the cases shows a peak in the age group 5-9 (43.5%) followed by the age group 10-14 (28%) and the age group 1-4 (18%). No cases were recorded in the age group 0-1. Drinking water and sewage samples were collected, using electropositive cartridges, during the outbreak. Rotavirus was identified by RT-PCR in two out of five drinking water samples; however, all the samples tested negative for HAV and astrovirus. Rotavirus was also identified in three out of five sewage samples from which four were HAV positive. HAV-RNA was identified in 28 (62.2%) out of 45 IgM anti-HAV positive sera collected during the outbreak. Genotype IA was expressed from all the amplified samples. Sequence analysis of the overlapping VP1-2A region shows 97-99% homology with three Italian strains IT-SCH-00, IT-ZAM-01, and IT-CAP-00 and one Spanish strain (Sa 30/06/95), whereas the phylogenetic tree built from the 168 bp sequence of the VP1-2A shows four clusters, one including 24 out of 28 RT-PCR positive sera. Considering the deduced amino acid sequence, only one substitution was identified and reported previously for genotype IB.


A sample of 393 Albanian refugees, including both children and adults, was tested for serological HAV, HBV, HDV and HCV markers. A high prevalence of infection with both the hepatitis A and B viruses was found, while HDV and HCV infections were uncommon. The overall prevalence of anti-HAV was 96%; it was very high in children 0-10 years, suggesting that HAV infection is largely acquired during childhood and that poor ambiental conditions influence the spreading of this viral infection. One or more serological markers of HBV infection were found in 295 Albanians (75%), confirming the endemic nature of this virus in the Albanian community. The overall prevalence of HBsAg was 19%, and the carrier rate was higher in males than in females. The high HBsAg prevalence among children suggests that HBV infection is usually acquired in early
childhood. The serological data obtained in the Albanian sample examined clearly indicate the urgent need for measures to reduce the incidence of HAV and HBV infections and to avoid the further spread of HDV and HCV infections. Finally, the high prevalence of type B hepatitis indicates the necessity of vaccination against HBV for all risk groups and for all children at birth

**Hepatitis B&D**


The natural history of hepatitis B virus infection is not uniform and affected from several factors including, HBV genotype. Genotype D is a widely distributed genotype. Among genotype D, several subgenotypes differentiate epidemiologically and probably clinically. D1 is predominant in Middle East and North Africa, and characterized by early HBeAg seroconversion and low viral load. D2 is seen in Albania, Turkey, Brazil, western India, Lebanon, and Serbia. D3 was reported from Serbia, western India, and Indonesia. It is a predominant subgenotype in injection drug use-related acute HBV infections in Europe and Canada. D4 is relatively rare and reported from Haiti, Russia and Baltic region, Brazil, Kenya, Morocco and Rwanda. Subgenotype D5 seems to be common in Eastern India. D6 has been reported as a rare subgenotype from Indonesia, Kenya, Russia and Baltic region. D7 is the main genotype in Morocco and Tunisia. D8 and D9 are recently described subgenotypes and reported from Niger and India, respectively. Subgenotypes of genotype D may have clinical and/or viral differences. More subgenotype studies are required to conclude on subgenotype and its clinical/viral characteristics.


Despite a recent decrease in the prevalence of HBsAg in the general population, Albania is still highly endemic for HBV infection. Genotype D is the most prevalent HBV strain in the Mediterranean area. We studied the prevalence and distribution of HBV genotypes and subgenotypes in a total of 73 HBsAg-positive patients living in Albania, and reconstructed the epidemiological history of the most prevalent HBV D subgenotype using a "phylodynamic" framework. A time-scaled genealogy of the Albanian patients' and reference P gene sequences with known sampling dates was reconstructed using an MCMC Bayesian approach that allows population growth to be estimated on the basis of coalescent theory. All of the Albanian subjects were infected with the HBV D genotype, and a percentage varying from 44.4% to 100% (depending on the ethnic or risk group) were infected with subgenotype D2, the most prevalent in the study population (72.4%). The other subgenotypes present in a minority of subjects were D1 (13.8%) and D3 (13.8%). The Bayesian skyline plot population dynamics analysis showed that genotype D2 entered the Albanian population in the late 1960s, and that the effective number of infections grew gradually until the second half of the 1980s and more rapidly until the mid-1990s, when it reached a plateau that still persists today. Our data suggest that political and socio-economic factors played an important role in determining the rapid spread of HBV infection in Albania.


Hepatitis B virus genotype D can be found in many parts of the world and is the most prevalent strain in south-eastern Europe, the Mediterranean Basin, the Middle East, and the Indian subcontinent. The epidemiological history of the D genotype and its subgenotypes is still obscure because of the scarcity of appropriate studies. We retrieved from public databases a total of 312 gene P sequences of HBV genotype D isolated in various countries throughout the world, and reconstructed the spatio-temporal evolutionary dynamics of the HBV-D epidemic using a bayesian framework. The phylogeographical analysis showed that India had the highest
posterior probability of being the location of the tree root, whereas central Asia was the most probable location of the common ancestor of subgenotypes D1-D3. HBV-D5 (identified in native Indian populations) diverged from the tree root earlier than D1-D3. The time of the most recent common ancestor (tMRCA) of the tree root was 128 years ago, which suggests that the common ancestor of the currently circulating subgenotypes existed in the second half of the XIX century. On the basis of our phylogeographic reconstruction, it seems that HBV-D reached the Mediterranean area in the middle of the XX century by means of at least two routes: the first pathway (mainly due to the spread of subgenotype D1) crossing the Middle East and reaching north Africa and the eastern Mediterranean, and the second pathway (closely associated with D2) that crossed the former Soviet Union and reached eastern Europe and the Mediterranean through Albania. We hypothesise that the main route of dispersion of genotype D was the unsafe use of injections and drug addiction.


OBJECTIVE AND METHODS: The prevalence of viral hepatitis markers and of alcohol intake was evaluated in 106 and 99 Albanian patients with the diagnosis of viral and/or alcoholic chronic liver disease who were consecutively admitted to the University Hospital Center of Tirana, during 1995 and 2005, respectively. RESULTS: A slight decrease in HBsAg (78 vs. 70%) and HBeAg (18 vs. 12%) prevalences were observed in patients admitted to the hospital during 2005 compared with those admitted during 1995, respectively. In both periods of time, hepatitis B virus (HBV) DNA (genotype D) tested positive in all HBsAg-positive patients and in 36% of HBsAg-negative patients. Anti-hepatitis C virus (HCV) prevalence (mainly observed after 30 years of age) was 14 versus 11%; anti-hepatitis Delta virus (HDV) prevalence (more frequently present in young age group patients) was 9 versus 7% during 1995 and 2005, respectively. Among patients who reported alcohol intake, alcoholic liver disease (HBsAg and anti-HCV negative) was diagnosed in 35 and in 57% of patients admitted during 1995 and 2005, respectively (P = 0.05). CONCLUSION: In Albanian patients with chronic liver disease, we have found that: (i) HBV remained the most important aetiologic factor of chronic liver disease; HDV and HCV prevalences were still low, (ii) in HBsAg-positive patients, HBeAg-negative chronic hepatitis prevailed, (iii) in HBsAg-negative patients, HBV DNA prevalence was high, (iv) during the last decade, an increased prevalence of alcohol intake in the aetiology of chronic liver disease was observed.


AIM: To assess the prevalence and socio-demographic distribution of hepatitis B virus (HBV) infection in Albania. METHODS: Blood samples from 410 unselected schoolboys, 666 students, 500 military personnel, 1286 casual blood donors, 378 voluntary blood donors and 640 pregnant women (total 3880 non-vaccinated residents of rural and metropolitan areas from all over Albania; 2354 (60.7%) male and 1526 (39.3%) female; mean age of 26.3 years) were tested during 2004-2006 for hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B virus (anti-HBs) by ELISA. RESULTS: The HBsAg and anti-HBs prevalence were 9.5% and 28.7%, respectively. The highest HBsAg prevalence was evident in the younger age group, such as in schoolchildren (11.8%) and the military (10.6%). Consequently, the anti-HBs prevalence increased with age, from 21.2% in schoolchildren (mean age: 15.7 years), to 36.3% in pregnant women (mean age: 26.3 years) and 29.7% in voluntary blood donors (mean age: 40.1 years). There were no significant differences between males and females. CONCLUSION: Despite the estimated two-fold reduction of HBsAg prevalence in the general population from about 18%-19% to 9.5%, Albania remains a highly endemic country (i.e. over 8% of HBsAg prevalence rate).

**Katsanos, K. H., Christodoulou, D. K., Zervou, E., Babameto, A., Kraja, B., Hyphantis, H., Karetos, V.,"**

OBJECTIVE OF THE STUDY: To report on the results of two projects on chronic hepatitis B in Western Balkans lead by Ioannina, Northwest Greece and Tirana, Albania. METHODS: In two prospective projects, HEPAGA I and HEPAGA II which lasted 4 years. In HEPAGA I, serum samples from 410 Albanians were tested for HBV. In HEPAGA II, health care consumption was recorded in hospitalized patients with chronic hepatitis B. RESULTS: HEPAGA I showed that 11.89% of the Albanians was HBsAg(+) and only 21.19% had HBV immunoprotection. HEPAGA II study included 101 patients. There was a significant difference in hospitalization costs per patient between centers. The Greek patients were significantly older (p=0.027) and there was a significant correlation between age >50 years and hospitalization costs (p=0.035). In Greece, hospitalization costs, number of patients admitted and number of hospitalization days per patient were in a remarkable position compared to other causes of hospitalization. CONCLUSIONS: The HEPAGA I study showed a decrease in the prevalence of chronic HBV infection in Albania compared to that of the previous decade. The HEPAGA II study demonstrated that health care consumption due to HBV infection is still an important determinant of the overall health consumption in Western Balkans.

Hepatitis C


OBJECTIVE AND METHODS: The prevalence of viral hepatitis markers and of alcohol intake was evaluated in 106 and 99 Albanian patients with the diagnosis of viral and/or alcoholic chronic liver disease who were consecutively admitted to the University Hospital Center of Tirana, during 1995 and 2005, respectively. RESULTS: A slight decrease in HBsAg (78 vs. 70%) and HBeAg (18 vs. 12%) prevalences were observed in patients admitted to the hospital during 2005 compared with those admitted during 1995, respectively. In both periods of time, hepatitis B virus (HBV) DNA (genotype D) tested positive in all HBsAg-positive patients and in 36% of HBsAg-negative patients. Anti-hepatitis C virus (HCV) prevalence (mainly observed after 30 years of age) was 14 versus 11%, anti-hepatitis Delta virus (HDV) prevalence (more frequently present in young age group patients) was 9 versus 7% during 1995 and 2005, respectively. Among patients who reported alcohol intake, alcoholic liver disease (HBsAg and anti-HCV negative) was diagnosed in 35 and in 57% of patients admitted during 1995 and 2005, respectively (P = 0.05). CONCLUSION: In Albanian patients with chronic liver disease, we have found that: (i) HBV remained the most important aetiologic factor of chronic liver disease; HDV and HCV prevalences were still low, (ii) in HBsAg-positive patients, HBeAg-negative chronic hepatitis prevailed, (iii) in HBsAg-negative patients, HCV DNA prevalence was high, (iv) during the last decade, an increased prevalence of alcohol intake in the aetiology of chronic liver disease was observed.


Hepatitis C virus (HCV) infection is a worldwide concern. Knowledge of the HCV genotype is clinically important because it predicts the rate of response to therapy and guides the treatment duration. Moreover, it allows molecular epidemiology to be performed. To our knowledge, the prevalence of HCV genotypes has been assessed only once in Albania, using a line probe genotyping assay. We determined HCV genotypes by population sequencing of HCV-infected patients in Tirana, Albania. HCV genotype and sequence analyses were performed for serum samples collected from January 2011 through May 2012 from 61 HCV-seropositive patients using population sequencing of the NS3 protease gene and alternatively the NS5b gene and the 5'
untranslated region (UTR). HCV RNA was retrieved from the blood samples of 50 patients. The HCV NS3 protease gene was sequenced for 28 patients and NS5b and/or 5'UTR fragments were sequenced for an additional 22 patients. The predominant genotype was 1b in 25 patients (50%), followed by genotypes 2c, 4a, 3a, and 1a in 18%, 14%, 8%, and 6% of cases, respectively. Best matches for these HCV RNAs in GenBank were obtained in different countries worldwide. One NS3 protease naturally harbored an amino acid conferring minor drug resistance to newly available HCV protease inhibitors. In conclusion, HCV-1b was predominant in the present Albanian population, as in southeastern Europe.

Hepatitis E


A case-control study involving 109 in-patients with chronic liver disease and 190 in-patients with no apparent liver disease was conducted to evaluate the seroprevalence of anti-HEV antibodies and the possible association with chronic liver disease. Among cases, the anti-HEV prevalence was 36.6% which increased significantly by age; among controls, the prevalence was 12.1% (P<0.05) and was similar among age groups <60 years. Among cases, aged >50 years (OR 4.0, 95% CI 1.4-11) and the presence of end stage liver disease (ESLD) (OR 4.3, 95% CI 1.4-12.8) were associated independently with anti-HEV positivity. The mean optical density, determined by anti-HEV immunoenzymatic test, was significantly higher among patients with ESLD, compared to the other patients. These results indicate that there is a high seroprevalence of anti-HEV in patients with chronic liver disease and a possible association between HEV infection and/or anti-HEV production and advanced stage chronic liver disease.

1.3.2 Hepatitis in different risk groups (session 4)


The paper presents the results of the research and a comparative analysis of findings on key indicators for the study population. The study instrument was a standardized behavior study questionnaire provided in the Family Health International published manual (Family Health International, 2000). The target group was female sex workers working in Tirana. The prevalence of biological infections was low. HIV was detected in one case. Syphilis and Hepatitis B rates resulted to be respectively 6.5% and 7.6%. The median age of the study participants is 28 years. Almost 38% of the participants were illiterate, and more than half belong to the Roma community. Almost 50% of the respondents had received money in exchange of sex for the first time 18 years earlier. Almost 65% of respondents reported two or more different sex partners in the last seven days, while almost 30% referred five or more. Condom use at last sex with a paying client was reported by almost 68%. Consistent condom use with paying clients in the last month was reported by almost 35% of the respondents.


BACKGROUND: Hepatitis B virus (HBV) was among the first virus known to be transmitted by blood and blood productions. The objective of this study is to determine the trend of hepatitis B virus in blood donors. MATERIALS AND METHODS: In this study 79274 blood donors were retrospectively evaluated for HBsAg. The donors were selected using personal questionnaire, physical examination and testing blood before donation. Blood banks records are used as source of information. The blood donors samples were analyzed for the presence of hepatitis B
surface antigen (HBsAg) by commercial available kits ELISA method, third generation (from Abbott laboratory, Germany). A sample was considered as HBsAg positive when found twice repeatedly reactive. Reactive samples were not confirmed with addition tests. RESULTS: In the evaluation data, we found out that from 79274 of the total healthy blood donors, 15983 were voluntary donors, 52876 were family replacement donors and 10424 commercial blood donors. The prevalence of HBsAg in blood donors was 7.9%. It was increased steadily from 5.9% in 1999 to 9.1% in 2006 and decreased in 7.9% in 2009. According to blood donors status the HBsAg prevalence was 10.5% in commercial blood donors, 8.1% in voluntary donors and 8.6% in family replacement donors. The prevalence of anti-HBc in blood donors was 59.1%. CONCLUSION: The prevalence of HBsAg was lower in voluntary non remunerate blood donors than commercial donors and family replacement blood donors. In FDs the prevalence was higher than VDs but lower than CDs. So, it is important to encourage the voluntary blood donors to become regularly blood donors.


BACKGROUND: The objective of this study is to determine the trend of transfusion transmitted infection in blood donors. METHODS: In this study 52727 blood donors were retrospectively evaluated for markers of hepatitis B, C, HIV(1/2), and syphilis. To screen the blood donors for HIV(1/2)(HIV(1/2) Ag/Ab COMBO, ABBOTT Laboratory, Delkenheim, Germany), the microparticle enzyme immunoassay (MEIA) method was used. For HBsAg and anti-HCV third generation MEIA kits (ABBOTT Laboratory, Delkenheim, Germany) were used and for the syphilis RPR test the Biokit SA (Barcelona, Spain) was used. RESULTS: A total of 52,727 donors were tested within the five year period, of which 15 (0.03%), 3531 (6.7%), 323 (0.6%), and 35 (0.07%) were positive for HIV, HBV, HCV, and syphilis, respectively. The prevalence of TTI in blood donors was 7.4%. It increased steadily from 5.1% in 2004 to 8.3% in 2006, stayed in same level in 2007, and decreased to 8.1% in 2008. Distribution of transfusion-transmissible infection (TTI) based on donor status was 13.8% in first time commercial remunerated blood donors, 9.4% in first time voluntary blood donors, and 9.7% in family replacement blood donors. CONCLUSIONS: Our results in this study showed that family replacement donors are more likely to transmit transfusion-transmissible infections (TTIs) than voluntary donors, but are safer than commercial blood donors. So blood transfusion services should work on replacement of family blood donors with voluntary non-remunerated blood donors.


BACKGROUND: Health care workers (HCW) have an elevated risk of acquiring and transmitting parenteral infections. The aim of this study was to evaluate the prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) markers with the final goal to encourage HBV vaccination of the non-immune Albanian HCW. METHODS: Among 480 HCW enrolled, 92 were physicians, 246 were nurses/techniques, 120 were auxiliary workers and 22 were office workers. RESULTS: The HBsAg, anti-HBc and anti-HCV prevalence were 8.1%, 70% and 0.6%, respectively. The highest (11.4%) HBsAg prevalence was observed in the youngest age group (20-30 years of age). High HBsAg prevalence (7.2-7.5%) was detected also in age groups above 30 years. The highest HBsAg prevalence (12.6%) was found in the auxiliaries. The anti-HBc prevalence increased significantly with age from 59% in HCWs younger than 39 years to 87% among those older than 50 years. After adjustments for different job categories, age older than 40 years remained independently associated with anti-HBc positivity (OR = 2.9; 95% CI 1.9-4.6) and inversely associated with the lack of HBV immunity or infection markers (OR = 0.4; 95% CI 0.2-0.7). Of 142 HBsAg negative and/or anti-HBc Ab negative sera, 28 (20%) tested positive for anti-HBs. The 114 remaining individuals with no HBV infection or immunity markers were vaccinated against HBV infection. CONCLUSIONS: A high HBV infection rate and low HBV vaccination coverage were found in Albanian HCW. Albania is a Mediterranean country still highly endemic for HBV infection and new strategies to promote HBV vaccination are to be adopted.

BACKGROUND: Hepatitis C virus (HCV) is the main causative agent of post-transfusion hepatitis. The virus is distributed worldwide with varying prevalence in different countries, which could easily lead to chronic infections, cirrhosis, and even hepatocellular carcinoma. The aim of this study was to investigate prevalence of HCV infection and its trend in Iranian blood donors. MATERIALS AND METHODS: Literatures on the HCV prevalence among blood donors in Iran were acquired through searching PubMed, Magiran, IranMedex, Scientific Information Databank, and Google databases. All the potentially relevant papers were reviewed independently by two investigators by assessing the eligibility of each paper and abstracting data. Prevalence was calculated using random effects model for meta-analysis. RESULTS: Forty-eight studies with total samples of 10,739,221 persons from 1996 to 2011 were combined and meta-analyzed, the pooled prevalence of HCV infection among blood donors in Iran provinces and cities was 0.5% (95% CI: 0.4-0.6%). Trend of HCV infection was decreasing in recent years. CONCLUSION: This study provides a comprehensive and reliable data on the prevalence and trend of HCV infection among blood donors and may be helpful in providing insight into disease burden and opportunities for prevention. In comparison with countries in this geographic region, Iran has the lowest rate of HCV infection. Zou S, Dorsey KA, Notari EP, Foster GA, Krysztof DE, Musavi F, et al. Prevalence, incidence, and residual risk of human immunodeficiency virus and hepatitis C virus infections among United States blood donors since the introduction of nucleic acid testing. Transfusion. 2010; 50:1495–504. (PMID: 20345570).


Donor notification and counselling transforms the legal and ethical requirement of disclosure of transfusion transmissible infection (TTI) in a blood donor into practice. The present study was done to assess the response to the disclosure of TTI reactivity results in blood donors, assess the risk factors in blood donors and follow the compliance of the disclosure and clinical referral in a population of blood donors who are difficult to convince that they may be harbouring infections apparently in a healthy state today but with possible clinical disease consequences in the future. A retrospective study was conducted from April 2011 to November 2012. Screening was done using third generation ELISA kits used according to the manufacturer's directions; these kits were approved for use in blood banks by the Drug Controller General of India. Those testing repeat reactive were referred for further confirmation and management. The total number of TTI reactive donors was 787 (0.93 %, N = 83,865). The observed response rate in the present study is 21.6 % (167, N = 787). The risk factors for acquiring infections in TTI reactive donors were statistically significant history of high risk behaviour (20.3 %) for human immunodeficiency virus infection.
and history of jaundice in themselves, family or close contacts (16.1%) for hepatitis B virus infection. One hundred and ten (65.8%) of the referred donors were on outpatient clinical care when post-referral follow up was conducted. The study emphasises on continuing sensitization of blood donation camp organisers to the need of privacy during blood donor selection. The study also stresses the need to strengthen the pre-donation counselling at outdoor blood donation at the same time raise awareness amongst blood donors about the importance of post-donation counselling and follow up.


Background. Transfusion safety begins with healthy donors. A fundamental part of preventing transfusion transmitted infections (TTIs) is to notify and counsel reactive donors. Donor notification and counselling protect the health of the donor and prevent secondary transmission of infectious diseases. Methods. 113,014 donations were screened for TTIs, namely, HIV, HBV, HCV, and syphilis, by serology and nucleic acid testing. All reactive donors were retested (wherever possible) and notified of their status by telephone or letter. All initial reactive screens were followed over six months. Results. We evaluated 2,838 (2.51%) cases with reactive screening test results (1.38% HBV, 0.54% HCV, 0.27% HIV, and 0.32% syphilis). Only 23.3% of donors (662) responded to notification. The response among voluntary donors was better as compared to the replacement donors (43.6% versus 21.2%). Only 373 (56.3%) responsive donors followed their first attendance at referral specialties. Over six months, only 176 of 662 (26.6%) reactive donors received treatment. Conclusion. Our study shed light on the importance of proper donor counselling and notification of TTI status to all reactive donors who opt to receive this information. There is also an urgent need to formulate the nationally acceptable guidelines for notification and follow-up of reactive donors. (http://dx.doi.org/10.1155/2014/412105).

**Albanian migrants in Greece**


BACKGROUND: Greece is a place of settlement for a large number of immigrants, particularly from Albania, which constitute special community groups for public health policies. OBJECTIVES: This study was designed to assess the seroprevalence of serological markers for Hepatitis B and C among juvenile immigrants from Albania settled in Greece. METHODS: The study population included 504 subjects, 418 males and 86 females, aged 10-23 years old who have emigrated from Albania to Pogoniani-Greece and participated voluntarily in vaccination programmes against Hepatitis B. The serum samples were examined with enzyme immune assays for the immunological markers HBsAg, anti-HBc, anti-HBs and anti-HCV. HBsAg positive samples were further tested for IgM anti-HBc, HBeAg and anti-HBe. RESULTS: Among the examined subjects, 40.5% were found positive for anti-HBc, indicating an HBV contamination. Specifically, 11.7% were carriers of HBsAg, whereas 28.8% were negative for HBsAg but positive for anti-HBc. Only 6.5% was positive exclusively for anti-HBs. The rest (53.0%) presented no positive serological markers. Among the HBsAg positive patients, 8.5% were found positive for HBeAg, while 5.1% was positive for IgM anti-HBc. Finally, only 0.6% of the sample presented antibodies against HCV. CONCLUSION: The examined migratory population is described by a high prevalence of Hepatitis B. Therefore, specific public health measures are necessary. However, no data was found that indicate potential public health dangers regarding hepatitis C.

SUMMARY: Hepatitis B virus infection (HBV) has been recognized as a major health problem worldwide. Greece belongs to the intermediate endemiity countries with a trend of decreasing prevalence of HBV infection during the last decade. However, the recent massive immigration to our country may have led to alterations of HBV epidemiology. In this study, we evaluated the epidemiological features of HBV infection in a sample of 3480 patients followed up during the years 1997-2006. Immigrants mainly from Albania represented the 18.6% of the total study population and 56.6% of children. The majority of the patients had no family history of HBV infection (67.3%) or of acute hepatitis (95.4%), no known source of infection (64.6%), with intrafamilial spread accounting for 16.9% of the HBV transmission in adults and 33.9% in children. HBeAg(-) hepatitis B was the predominant form of hepatitis (92.1%) among the Greek patients in contrast to the immigrants where 16.6% were HBeAg(+). Liver cirrhosis was diagnosed in 8.8% of the total population and 0.9% had hepatocellular carcinoma. A high proportion of children were HBeAg(+) (62%), 55% from immigrant families, 25.2% were infected in the perinatal period and had no evidence of disease complications. In conclusion our results showed (a) a changing pattern in the epidemiology of HBV infection in Greece due to the significant number of HBeAg(+) patients, especially among children and (b) a considerable number of patients although aware of their infection, present with advanced disease.


Epidemiological data on the prevalence of serological markers of hepatitis B virus (HBV) infection in pregnant women in Greece are limited. We evaluated the prevalence of HBV serological markers in a multinational population of pregnant women in Athens, Greece. The overall prevalence of hepatitis B surface antigen (HbsAg) was 4.1% with the highest rates among Albanian immigrants (12%). Relatively low vaccination-induced protection rates (32.5%) were observed, a finding suggesting that surveillance and immunisation programmes targeted at pregnant women are necessary.


OBJECTIVE: Seroprevalence of HBsAg in 26,746 women at reproductive age in Greece and evaluation of HBeAg/anti-HBe serological status as well as serum HBV-DNA levels in a subgroup of HBsAg(+) women at labor. STUDY DESIGN: Serological markers were detected using enzyme immunoassays. Serum HBV-DNA was calculated using a sensitive quantitative PCR assay, with a lower limit of quantification of 200 copies/ml. RESULTS: Overall, 1.53% of women were HBsAg(+) and the majority of them (64.96%) were Albanian. Among Albanian women the mean prevalence of HBsAg was 4.9%, 5.57% among Asian women, and 1.29% among women from Eastern European countries. The prevalence of HBsAg among African (0.29%) and Greek women (0.57%) was very low and significantly lower in comparison with the mean value of the studied population. Only 2.67% of HBsAg(+), women were HBeAg(+). Of a subgroup of women in labor with available serum samples 28.6% had undetectable levels of viremia (<200 copies/ml) and 15.9% had extremely low levels of viral replication (<400 copies/ml). Only 12.7% of pregnant women evaluated at labor exhibited extremely high serum HBV-DNA levels (>10,000,000 copies/ml) whereas 42.8% of them exhibited HBV-DNA levels between 1500 and 40,000 copies/ml. CONCLUSIONS: The overall prevalence of HBsAg is relatively low among women at reproductive age in Greece but is higher among specific ethnic populations (Asian, Albanian). The HBeAg(-)/antiHBe(+) serological status is a finding observed
in the vast majority of HBsAg(+) women of our study population, and a significant percentage of them (approximately 44.5%) exhibit extremely low or even undetectable levels of viral replication at labor, suggesting possibly that only a proportion of HBsAg(+) women in Greece exhibit an extremely high risk of vertical transmission of the infection.

1.3.3 Hepatitis Burden of disease (session 5)


Hepatitis B virus (HBV) is the infectious agent of both acute and chronic hepatitis. HBV exists in multiple genotypic variants that differ in their capacity to become persistent chronic infections and in their clinical manifestations, including hepatocellular carcinoma. The 8 genotypes (A-H) of HBV show a specific worldwide geographic distribution and are correlated with different disease course, severity, and response to therapy. We isolated DNA from 75 HBV-positive blood donors, chosen randomly from the database of the National Blood Bank in Tirana, to specifically analyze the UGT1A1 polymorphism to determine its correlations with bilirubin levels and liver function. The large number of subjects who were HBV-positive carriers of heterozygosis or homozygosis for the UGT1A1*28 (TA)7 polymorphism suggests that these individuals may be more susceptible to cancer and should follow a strict regime of prevention.


OBJECTIVE AND METHODS: The prevalence of viral hepatitis markers and of alcohol intake was evaluated in 106 and 99 Albanian patients with the diagnosis of viral and/or alcoholic chronic liver disease who were consecutively admitted to the University Hospital Center of Tirana, during 1995 and 2005, respectively. RESULTS: A slight decrease in HBsAg (78 vs. 70%) and HBeAg (18 vs. 12%) prevalences were observed in patients admitted to the hospital during 2005 compared with those admitted during 1995, respectively. In both periods of time, hepatitis B virus (HBV) DNA (genotype D) tested positive in all HBsAg-positive patients and in 36% of HBsAg-negative patients. Anti-hepatitis C virus (HCV) prevalence (mainly observed after 30 years of age) was 14 versus 11%; anti-hepatitis Delta virus (HDV) prevalence (more frequently present in young age group patients) was 9 versus 7% during 1995 and 2005, respectively. Among patients who reported alcohol intake, alcoholic liver disease (HBsAg and anti-HCV negative) was diagnosed in 35 and in 57% of patients admitted during 1995 and 2005, respectively (P = 0.05). CONCLUSION: In Albanian patients with chronic liver disease, we have found that: (i) HBV remained the most important aetiologic factor of chronic liver disease; HDV and HCV prevalences were still low, (ii) in HBsAg-positive patients, HBeAg-negative chronic hepatitis prevailed, (iii) in HBsAg-negative patients, HBV DNA prevalence was high, (iv) during the last decade, an increased prevalence of alcohol intake in the aetiology of chronic liver disease was observed.


OBJECTIVE: To determine whether chronic hepatitis B virus (HBV) infection, as evidenced by serum levels of HBsAg and HBV DNA, is a risk factor for spontaneous preterm birth (SPB). METHOD: The prevalence of HBV infection and the SPB rate were prospectively investigated among 1826 pregnant women, 30.89% Albanian and the remainder of other European origins. RESULTS: Overall, 70 (3.8%) of the women were chronically infected with HBV. HBsAg status was
strongly linked to SPB, which incurred to 5 (7.3%) of 64 women with circulating HBsAg compared with 28 (1.6%) of 1703 without current HBV infection (odds ratio, 5.2; P=0.007). SPB, however, was linked neither to HBsAg levels, nor to HBV DNA levels, nor to the presence or absence of viremia. CONCLUSION: Pregnant women were found to be at higher risk for SPB if they had circulating HBsAg, and the risk did not seem to be influenced by the levels of HBsAg or HBV DNA.


OBJECTIVE OF THE STUDY: To report on the results of two projects on chronic hepatitis B in Western Balkans lead by Ioannina, Northwest Greece and Tirana, Albania. METHODS: In two prospective projects, HEPAGA I and HEPAGA II which lasted 4 years. In HEPAGA I, serum samples from 410 Albanians were tested for HBV. In HEPAGA II, health care consumption was recorded in hospitalized patients with chronic hepatitis B. RESULTS: HEPAGA I showed that 11.89% of the Albanians was HBsAg(+) and only 21.19% had HBV immunoprotection. HEPAGA II study included 101 patients. There was a significant difference in hospitalization costs per patient

1.3.4 Screening, Prevention and Treatment of viral hepatitis in Albania (session 9)

Treatment


The prevalence and management of chronic hepatitis B virus (HBV) infection differ among European countries. The availability and reimbursement of diagnostics and drugs may also vary, determining distinct treatment outcomes. Herein, we analyse differences in medical facilities for the care of patients with chronic HBV infection across Europe. A survey was sent to the members of the ESCMID Study Group for Viral Hepatitis, all of whom are experts in chronic HBV infection management. The comprehensive survey asked questions regarding hepatitis B surface antigen (HBsAg) prevalence, the availability of diagnostics and drugs marketed, and distinct clinical practice behaviours in the management of chronic HBV infection. World Bank data were used to assess the economic status of the countries. With 16 expert physicians responding (69%), the HBsAg prevalence rates were <1% in France, Hungary, Italy, The Netherlands, Portugal, Spain, and the UK, intermediate (1-5%) in Turkey, Romania, and Serbia, and high (>5%) in Albania and Iran. Regarding the availability and reimbursement of HBV diagnostics (HBV DNA and liver stiffness measurement), HBV drugs (interferon, lamivudine, tenofovir, and entecavir), HBV prophylaxis, and duration of HBeAg-positive and HBeAg-negative HBV infection, the majority of high-income and middle-income countries had no restrictions; Albania, Iran and Serbia had several restrictions in diagnostics and HBV drugs. The countries in the high-income group were also the ones with no restrictions in medical facilities, whereas the upper-middle-income countries had some restrictions. The prevalence of chronic HBV infection is much higher in southern and eastern than in western European countries. Despite the availability of European guidelines, policies for diagnostics and treatment vary significantly across European countries.

BACKGROUND: Treatment of Hepatitis C in children has a better outcome than in adults, and for this reason the treatment had different views. However, in pediatric age hepatitis C is seen to have an evolution towards chronicity. Today is a normal option to treat chronic hepatitis C as early as possible according to certain criteria. The aim of this study is to show the results of treatment with interferon and ribavirin and the follow-up of children diagnosed with chronic hepatitis C in our service. PATIENTS AND METHODS: This is a prospective study which has included children 3 up to 15 years old (13 boys and 4 girls) diagnosed with chronic hepatitis C. All patients underwent a certain protocol, including liver biopsy prior to treatment. Treatment consisted in use for 48 weeks of INF alpha-2b, 3 MIU/m2 three times a week s/c and ribavirin 15 mg/kg orally divided bid. Two patients were treated with PEGINF alpha-2b with dose 1.5 mcg/kg once a week s/c and ribavirin 15 mg/kg. After the treatment all patients have stayed under our control for an average period of 24 weeks. RESULTS: At the end of the treatment we detected a patient with HCV-RNA positive. End Treatment Viral Response was 94%. Six months later we found three patients who showed relapse of disease. Sustained Viral Response was approximately 83% CONCLUSION: The combination therapy of interferon with ribavirin in treatment of children with chronic hepatitis C provides a higher SVR when treatment is initiated at the earliest stages of hepatic changes. Side effects of therapy are insignificant in comparison with results obtained.

Research on vaccination – adverse events


BACKGROUND: Vasculitides have been reported as adverse events following immunization (AEFI) following various vaccines. We describe reports of vasculitis to three international spontaneous reporting systems. METHODS: All spontaneous reports of vasculitis following immunization between January 2003 and June 2014 were retrieved from Eudravigilance (EV), the Vaccine Adverse Event Reporting System (VAERS), and VigiBase(R). A Standard MedDRA Query (SMQ) for vasculitis was used and vaccine types were categorized using the Anatomical Therapeutic Chemical classification system. We performed a descriptive analysis by source, sex, age, country, time to onset, vaccine, and type of vasculitis. RESULTS: We retrieved 1797 reports of vasculitis in EV, 1171 in VAERS, and 2606 in VigiBase(R). Vasculitis was predominantly reported in children aged 1-17 years, and less frequently in the elderly (>65 years). The generic term "vasculitis" was the most frequently reported AEFI in this category across the three databases (range 21.9% to 27.5% of all reported vasculitis for vaccines). For the more specific terms, Henoch-Schoenlein Purpura (HSP) was most frequently reported, (19.1% on average), followed by Kawasaki disease (KD) (16.1% on average) and polymyalgia rheumatica (PMR) (9.2% on average). Less frequently reported subtypes were cutaneous vasculitis (CuV), vasculitis of the central nervous system (CNS-V), and Behcet’s syndrome (BS). HSP, PMR and CuV were more frequently reported with influenza vaccines: on average in 29.3% for HSP reports, 61.5% for PMR reports and in 39.2% for CuV reports. KD was reported with pneumococcal vaccines in 32.0% of KD reports and with rotavirus vaccines in more than 20% of KD reports. BS was most frequently reported after hepatitis and HPV vaccines and CNS-V after HPV vaccines. CONCLUSION: Similar reporting patterns of vasculitides were observed in different databases. Implementation of standardized case definitions for specific vasculitides could improve overall data quality and comparability of reports.
2. Neighbouring countries (with presentation at the meeting)

2.1 Kosovo

2.1.1 Background info

Wikipedia: Kosovo is a disputed territory and partially recognised state in Southeast Europe that declared independence from Serbia in February 2008 as the Republic of Kosovo. While Serbia recognises administration of the territory by Kosovo's elected government, it still continues to claim it as its own Autonomous Province of Kosovo and Metohija.

Kosovo is landlocked in the central Balkan Peninsula. Its capital and largest city is Pristina. It is bordered by the Republic of Macedonia and Albania to the south, Montenegro to the west, and the uncontested territory of Serbia to the north and east.


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2.1.2 Country related hepatitis publications


**AIM OF STUDY:** is the estimation of prevalence of HCV infection in fourteen Central and Eastern European countries (CEEC). **MATERIAL AND METHODS:** This review describes the comparative data of persons possessing anti-HCV antibodies and persons with HCV viremia (% of population and number) in fourteen Central and Eastern European countries (CEEC). The study was performed according to data on the >/=15 years of age populations obtained from the Statistical Offices of the countries. **RESULTS:** The prevalence of anti-HCV in populations varied between 0.27 and 3.5%. The lowest values were reported from Kosovo, Hungary, Germany and the Czech Republic; 0.3-0.6%. The highest values of anti-HCV antibodies were noted in Latvia, Lithuania and Romania; 2.4, 2.85 and 3.5%, respectively. From eight countries the percentages of persons with HCV viremia were available (0.2-3.5%). **CONCLUSIONS:** The paper gives an estimate of the number of people infected with HCV in the general population of 8 countries from the CSEE region. This number is approximately ~1.16 million.


**BACKGROUND:** A cross-sectional study was carried out in Velika Hoca and Orahovac, two rural communities in Kosovo and Metohia, with the aim of assessing the prevalence of chronic diseases and associated risk factors. **METHODS:** The study involved 423 (180 male) adult inhabitants aged 51 +/- 16 years and included an interview, medical documentation, physical, ultrasound, laboratory examinations and ECG. **RESULTS:** Hyperlipidemia was the most frequent (70%) risk factor followed by alcohol consumption (47%), hypertension (42%), smoking (36%) and obesity (32%). Ischemic heart disease was diagnosed in 25 patients, hypertensive cardiomyopathy in 17, other cardiomyopathies in 5 and arrhythmia in 20 patients. Nine persons had chronic obstructive pulmonary disease. Previously diagnosed liver cirrhosis occurred in 5 and chronic hepatitis in 8 subjects, while liver steatosis with elevated serum transaminases (22 persons), elevated transaminases with normal ultrasound (20 persons), tumor or suspected tumor (7 persons) were detected in the survey. Gastrointestinal symptoms were the most prevalent but peptic ulcer and gastritis had been previously diagnosed in 64 and 47 patients. Kidney and urinary tract diseases were known for 52 patients (12 with chronic renal failure and 4 on hemodialysis) and 46 more were detected in the study. Among them in 22 patients with markers of kidney disease and unclear diagnosis 12 had a positive family history, 8 low-grade proteinuria, 14 tubular dysfunctions and 7 eGFR (estimated glomerular filtration rate) below 60 ml/min/1.73 m2. **CONCLUSION:** In the Serbian enclave of Velika HoEa and Orahovac the prevalence of cardiovascular diseases was similar to that of gastrointestinal, liver and kidney diseases. This differs from other parts of Serbia where cardiovascular disorders are the leading cause of disease burden.


One of the largest therapeutic problem during the continuous treatment of the patients with Hemophilia A and B, are viral infections as Hepatitis B and C, and HIV, and the other infective diseases, which can be transmitted by the transfusion of blood products. The aim of this study is to analyze the complications of the hemophiliacs in Kosovo which have been treated with fresh frozen plasma, cryoprecipitate and concentrated products of FVIII and FIX. We have tested 75 patients with hemophilia A or B and there were used enzyme immunoassay test-Elisa method for the following: anti-HCV, HBsAg, HIV and TPHA. The serological data showed that HCV infection was positive in 29 cases or 38.7%, whereas infection with HBV and HIV were present in a smaller percentage of the patients (2.7% HBV and 1.4% for HIV). HCV infection was...
present only in 9.5% of the cases of the age group under 18 years. Infected hemophiliacs with one or two infective agents were found in 34.7%, respectively 4%. Infection with T. pallidum was present at none of the examined patients with hemophilia. HCV infection was higher in severe forms of hemophilia B (44.4%), compared with severe form of hemophilia A (30%). Based on our results, despite the infrequent application of FVIII and FIX concentrates, and other anti-hemophilic preparations used in treating hemophilia patients, the number of infected hemophiliacs with blood-transmittable infectious agents was substantially high, especially with hepatitis C virus.


The serological status of hepatitis viruses and other infectious diseases in the 66 dialysed patients of one haemodialysis unit in Kosovo were studied, comparing the data with a large group of blood donors and out-patients. All dialysed patients were hepatitis A virus (HAV) positive. Prevalence of hepatitis B surface antigen (HBsAg), hepatitis B surface antibodies (anti-HBs), and hepatitis B core antibodies (anti-HBc) was 14 of 66, 21% (95% confidence interval (CI): 12-33%), 5 of 66, 8% (95%CI: 5-22%), and 50 of 66, 76% (95%CI: 64-85%), respectively. Antibodies to hepatitis C virus (anti-HCV) prevalence was 57 of 66, 86% (95%CI: 76-94%). No human immunodeficiency virus (HIV) positive case was found. Prevalence of past herpes simplex virus type 2 (HSV-2) infection was 29% (95%CI: 18-41%). Two patients (3%, 95%CI: 0-10%) were positive for Treponema pallidum and 18% (95%CI: 10-30%) were human herpesvirus 8 (HHV-8) antibody positive. Four hundred and fifty-two subjects were recruited for comparison. Markers of past HAV infection was associated with haemodialysis (Fisher s exact test p-value=0.037). Dialysed patients were at a higher risk of being HBsAg positive than others: the sex- and age-adjusted odds ratio (OR) was 5.18 (95%CI: 1.87-14.32). Anti-HBc positivity was strongly associated with haemodialysis: the sex- and age-adjusted OR was 6.43 (95%CI: 3.22-12-85). Anti-HCV positivity was 86% and 1% in presence and absence of haemodialysis, respectively. The Fisher s exact test for association proved a strong association between haemodialysis and HCV (p-value<0.0001). The OR for association between haemodialysis and HSV-2 positivity was 3.20 (95%CI: 1.46-7.00). Significant associations were also observed between haemodialysis status and antibodies to Treponema pallidum (Fisher s exact test p-value=0.044). In Kosovo, the prevalence of viral hepatitis infection and other viral infections and Treponema pallidum among dialysed patients is high, indicating major ongoing nosocomial transmission.


Hepatitis is disease of the liver caused by the infectious and non-infectious agents. The aim of study was to analyze the prevalence of HBV and HCV among voluntary blood donors in Kosovo, during 2000-2003. The data from National Center for Blood Transfusion of Kosovo were collected and analyzed through descriptive and comparative epidemiological method of retrospective study. All samples were tested by ELISA test. Out of 70348 samples of the blood donors, 3145 were positive. From overall positive samples, 2939 were HBV positive, 192 HCV positive while 14 samples were positive for both viruses. The HBV prevalence among the blood donors of Kosovo is 4.2%, which range Kosovo to the second zone according to the CDC classification of the geographical spread of the HBV infection. The HCV prevalence among the blood donors in Kosovo is 0.3%. Compared to the other European countries this level of prevalence is relatively low. Age group 30-39 years old was presented with 34.8% of cases. The higher number was among the workers, 842 or 26.8%. Based on the results we can conclude that Kosovo have the similar prevalence for HBV and HCV infections as other South East European countries.

The prevalence of hepatitis infection among the Kosovarian population is largely unknown. The aim of the study was to evaluate the prevalence and risk factors of hepatitis A, B, C, and D (HAV, HBV, HCV, HDV) infection among the general population and in a group of health care workers in the Kosovo region. Overall, 1,287 participants were recruited, 460 males (36%) and 827 females (64%). Health care workers accounted for 253 individuals (20%), 301 were blood donor candidates (23%), 334 were pregnant women (26%), and 399 (31%) were subjects who had been examined in two clinics for routine laboratory testing. The prevalence of total anti-HAV was 88.6% (95% CI: 86.69-90.25). Prevalence of anti-HAV among children up to 10 years was 40.5% (95% CI: 29.6-53.15), reaching 70% (95% CI: 62.25-77.10) in the 11-20 age group. Age, living in rural areas and unemployment were factors associated with higher risk of HAV infection. HBsAg was detected in 2.4% (95% CI: 1.57-3.38%) of the study sample, with a significant age trend (P-value:0.0110). Positivity for total anti-HBc was detected in 18.4% (95% CI = 16.27-20.59) of the subjects. Ninety-three subjects (7.2%) were positive for anti-HBs alone. An association between age, HSV-2 positivity, working nurses and HBV infection has been observed. One patient was HDV positive. The prevalence for HCV was 0.5% (95% CI: 0.22-1.12%). HAV infection seems to be high-intermediate, while HBV shows an intermediate endemicity. It is necessary to highlight the importance of an immunization strategy against HAV and HBV in reducing the incidence of the infection. The prevalence for HCV was very low.
2.2 Montenegro

Wikipedia (https://en.wikipedia.org/wiki/Montenegro) meaning “Black Mountain”) is a sovereign state in Southeastern Europe. It has a coast on the Adriatic Sea to the south-west and is bordered by Croatia to the west, Bosnia and Herzegovina to the northwest, Serbia to the northeast, Kosovo[a] to the east and Albania to the south-east. Its capital and largest city is Podgorica, while Cetinje is designated as the Prijestonica, meaning the former Royal Capital City.
2.2.1 Background info
(http://www.who.int/gho/countries/mne.pdf?ua=1)

### Montenegro: WHO statistical profile

<table>
<thead>
<tr>
<th>Basic statistics</th>
<th>Life expectancy (years), 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Indicators</td>
</tr>
<tr>
<td>Population</td>
<td>621</td>
</tr>
<tr>
<td>Population aged under 50 (%)</td>
<td>18</td>
</tr>
<tr>
<td>Population aged over 60 (%)</td>
<td>10</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>37</td>
</tr>
<tr>
<td>Population living in urban areas (%)</td>
<td>64</td>
</tr>
<tr>
<td>Total fertility rate (per woman)</td>
<td>1.7</td>
</tr>
<tr>
<td>Number of live births (thousands)</td>
<td>7.3</td>
</tr>
<tr>
<td>Number of deaths (thousands)</td>
<td>5.9</td>
</tr>
<tr>
<td>Birth registration coverage (%)</td>
<td>&gt;90</td>
</tr>
<tr>
<td>Cause-of-death registration coverage (%)</td>
<td>100</td>
</tr>
<tr>
<td>Gross national income per capita (PPP Int $)</td>
<td>14500</td>
</tr>
<tr>
<td>WHO region</td>
<td>European</td>
</tr>
<tr>
<td>World Bank income classification</td>
<td>Upper middle</td>
</tr>
</tbody>
</table>

**Life expectancy at birth for both sexes increased by 1 year(s) over the period of 2009-2012; the WHO region average increased by 4 year(s) in the same period.**

In 2012, healthy expectancy at birth was 60 years lower than overall life expectancy at birth. This last healthy life expectancy represents 30 equivalent years of full health lost through years lived with morbidity and disability.

### Millennium Development Goals (MDGs)

<table>
<thead>
<tr>
<th>Indicators</th>
<th>Statistics</th>
<th>Baseline*</th>
<th>Latest**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under-5 mortality rate (per 1000 live births)</td>
<td>17</td>
<td>6</td>
<td></td>
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<tr>
<td>Maternal mortality ratio (per 100,000 live births)</td>
<td>80</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Deaths due to HIV/AIDS (per 100,000 population)</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Deaths due to malaria (per 100,000 population)</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Deaths due to tuberculosis among HIV-positive people (per 100,000 population)</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
</tr>
</tbody>
</table>

*2000 for under-5 mortality and maternal mortality, 2005 for other indicators
**2015 for deaths due to HIV/AIDS and malaria, 2013 for other indicators
Montenegro: WHO statistical profile

Top 10 causes of death

Ischaemic heart disease was the leading cause of death, killing 12 thousand people in 2012.

<table>
<thead>
<tr>
<th>Cause</th>
<th>No. of deaths (000s) 2012</th>
<th>Crude death rate 2000-2012</th>
<th>Change in rank 2000-2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic heart disease</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke (13.7%)</td>
<td>1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy, myocarditis (10.1%)</td>
<td>0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trachea, bronchus, lung cancers (5.8%)</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon and rectum cancers (2.7%)</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (5%)</td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis (2%)</td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Road injury (1.8%)</td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer (1.7%)</td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach cancer (1.3%)</td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Burden of disease, 2012

Disability-adjusted life years (DALYs) are the sum of years of life lost due to premature mortality (YLL) and years of healthy life lost due to disability (YLD).

DALYs, YLL and YLD (thousands) by broad cause group

- Cardiovascular diseases and diabetes
- Cancers
- Neuro-psychiatric conditions
- Other NCDs
- Unintentional injuries
- Musculoskeletal diseases
- Maternal, neonatal, nutritional
- Suicide, homicide and conflict
- Chronic respiratory diseases
- Acute respiratory infections
- Other infectious diseases
- HIV, TB, malaria

Probability of dying, 2012

Probability of dying between relevant exact ages, for a person experiencing the 2012 age-specific mortality risks throughout their life.

- Before age 15, all causes
  - Male: 3%
  - Female: 3%
- Before age 70, all causes
  - Male: 49%
  - Female: 31%
- Between ages 15 and 49, from maternal causes
  - Female: 0%
- Between ages 50 and 70, from major noncommunicable diseases (NCDs)
  - Both: 35%

Source: Country statistics and global health estimates by WHO and UN partners
For more information visit the Global Health Observatory
Last updated: January 2013

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WHO CISID database (http://data.euro.who.int/cisid/?TabID=399805)

### Table: Hepatitis Incidence

<table>
<thead>
<tr>
<th>Year</th>
<th>Montenegro</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>7.01</td>
</tr>
<tr>
<td>2006</td>
<td>9.55</td>
</tr>
<tr>
<td>2007</td>
<td>8.26</td>
</tr>
<tr>
<td>2008</td>
<td>5.7</td>
</tr>
<tr>
<td>2009</td>
<td>3.83</td>
</tr>
<tr>
<td>2010</td>
<td>3.18</td>
</tr>
<tr>
<td>2011</td>
<td>3.81</td>
</tr>
<tr>
<td>2012</td>
<td>2.38</td>
</tr>
<tr>
<td>2013</td>
<td>2.85</td>
</tr>
<tr>
<td>2014</td>
<td>3.95</td>
</tr>
<tr>
<td>2015</td>
<td>1.9</td>
</tr>
</tbody>
</table>

2.2.2 Country related hepatitis publications


The Mediterranean area and the Balkans in particular show the highest level of genetic heterogeneity of HBV in Europe. Data about the circulation of HBV genotypes in Montenegro are lacking. It was studied the prevalence and distribution of HBV genotypes/subgenotypes in a total of 150 HBV infected patients living in Montenegro. Phylogenetic analysis of 136 successfully amplified P sequences showed a high degree of genetic heterogeneity of HBV in Montenegro. Subgenotype D2 (36.8%) and D3 (32.3%) were the most prevalent, followed by genotype A (subgenotype A2 in all of the cases-19.8%). Eight patients were infected with recombinant strains. HBV-D1 which is the most spread HBV subgenotype in the south-eastern Mediterranean countries, seems to be relatively rare in Montenegro, suggesting a penetration of HBV more probably from North-East or West than from Eastern Mediterranean countries. The relatively different prevalence of D3 and A2 among subjects infected through sexual route, seems to confirm the association of these subgenotypes with different route of transmissions (mainly parenteral for D3 and mainly sexual for A2) even in Montenegro. The low prevalence of D2 among children and its absence in perinatal transmission, suggests that this subgenotype circulated prevalently in the past. If this is due to changes in the most prevalent way of transmission and in the recent different contacts of Montenegro with other European countries, it remains to be established by other larger studies.


BACKGROUND: People who inject drugs (PWID) have significantly higher rates of blood borne and sexually transmitted infections due to unsafe injecting practices and risky sexual behaviors. METHODS: We carried out an HIV bio-behavioral survey using respondent-driven sampling
(RDS) in people who use drugs (PWID) in Podgorica, Montenegro in 2013 in order to determine the prevalence of HIV, hepatitis C (HCV), hepatitis B surface antigen (HBsAg) and risk behaviors. Data were analyzed using RDS Analyst and SPSS 12.0 to obtain prevalence estimates of key bio-behavioral indicators and assess correlates of needle and syringe sharing using multivariate logistic regression. RESULTS: A total of 402 PWID were recruited. HIV prevalence was 1.1%, while the prevalence of HCV and HBsAg was 53.0% and 1.4%, respectively. In the multivariate analysis, significant correlates of needle and syringe sharing in the past month were being older than 26 years, female, injecting drugs more than once per day, injecting in parks or on streets, not being able to obtaining free-of-charge sterile needles and syringes and reporting more than four partners in the past 12 months. CONCLUSIONS: The results indicate that the HIV epidemic in PWID in Montenegro might still be at a low level, though the HCV epidemic is well-established.


More than 20 million hepatitis C virus (HCV) carriers live in the countries of the Eastern Mediterranean. We determined HCV genotype distribution among chronically infected patients in Montenegro and investigated the phylodynamics and phylogeography of the most represented HCV subtypes. The HCV-NS5b sequences of the Montenegrin patients were compared with sequences isolated in different known localities of the Mediterranean area, Europe and Asia. A Bayesian approach was used in order to allow the simultaneous estimate of the evolutionary rate, time-scaled phylogeny, demography and ancestral spatial status. The most frequent HCV subtypes among the Montenegrin patients, were 1b (34.7%) and 3a (24.7%), but there was also a significant prevalence of 1a and 4d (19.5%). Subtype 3a was significantly more frequent among younger patients and intravenous drug users (IDUs), whereas subtype 1b was more frequently associated with iatrogenic exposure and older ages. The spatio-temporal analysis of the epidemic suggested that HCV-1b penetrated Europe at the beginning of the XX century, probably through Greece and Cyprus and in the 1920s reached Montenegro, where there was an exponential increase in the effective number of infections between the 1950s and 1970s. The phylogeographic and phylodynamic analysis of HCV 3a showed that its most probable origin was in the Indian sub-continent (Pakistan in our reconstruction) about 300 years ago. The evolutionary dynamics analysis showed that HCV-3a reached Montenegro more recently in the late 1970s and underwent multi-phasic growth still persisting. Our data suggest multiple introduction of HCV subtypes in the area, supported by different causes of dispersion: adverse social conditions and unsafe medical practices for HCV-1b and i.v. drug use for HCV-3a.


BACKGROUND: In Southeastern Europe, similar to other postsocialist regions on the continent, injection drug users (IDU) are exposed to a high risk of blood-borne infections. In this paper, we report the prevalence of HIV, hepatitis C (HCV) and hepatitis B (HBV) among IDUs in Montenegro. We also examine the risk factors associated with HCV diagnosis. METHODS: In 2008, 322 IDUs in Montenegro participated in a respondent-driven sampling survey. Blood specimens were collected and tested for HIV, HCV and HBV. Behavioral data were collected with self-administered questionnaires. RESULTS: In comparison to 2005, HCV prevalence had increased from an estimated 22 to 53.7%. Only one HIV and no HBV cases were detected. Anti-HCV positivity was associated with the region of origin, income, sharing injection equipment and frequency of injecting drugs. CONCLUSION: The increasing HCV prevalence among IDUs in Montenegro calls for increased and better designed programs to prevent its further spread and a potential HIV outbreak.

Terzic, D., Mijovic, G., Dupanovic, B., Draskovic, N. and Svrljih, N. "[Comparison of clinical and laboratory characteristics of viral hepatitis A and E in Montenegro]." Med Pregl 2010 63(3-4): 31
INTRODUCTION: Hepatitis E has many similarities with hepatitis A concerning clinical picture, route of transmission and nonexistence of chronicity. Comparison of clinical and laboratory parameters of patients with hepatitis A and E to estimate characteristics of these diseases.

MATERIAL AND METHODS: Total of 54 patients divided into two groups was investigated: 27 had hepatitis A, others had hepatitis E. Detailed history past, clinical examination, liver function tests and ultrasonography of the upper abdomen, were done in all patients. Aetiology of viral hepatitis was investigated serologically by enzyme immunoassay (ELISA) using commercial kits for following viruses: Hepatitis A-E viruses, cytomegalovirus, and Epstein-Barr virus. RESULTS: Asymptomatic infections (29.6%) and clinical forms without jaundice (59.3%) were more frequent in patients with hepatitis E. Splenomegaly was found more frequent in patients with hepatitis A than in hepatitis E (66.7% vs. 33.3%). Patients with hepatitis E had significantly lower activity of aminotransferases than patients with hepatitis A. A significant increase of γ-glutamyltransferase was found in patients with hepatitis E (mean value: 120 IU/L).

DISCUSSION: Our results are in concordance with other reports that hepatitis E virus infection is more common asymptomatic disease than hepatitis A. In addition, hepatocyte necrosis in hepatitis E is less extensive than in hepatitis A measured by the activity of aminotransferases. Contrary to that the value of γ-glutamyltransferase is more increased in hepatitis E than in hepatitis A without exact explanation so far: CONCLUSION: Viral hepatitis E and A have differences in some clinical features and laboratory parameters although both diseases principally have resolved without consequences after 6-8 weeks.


OBJECTIVE: To evaluate the incidence, demographic, clinical and laboratory characteristics of patients with acute viral hepatitis E in Montenegro. MATERIAL AND METHODS: A total of 400 patients with acute viral hepatitis from January 1st, 2000 to December 31st, 2007 were enrolled in the study. Serological tests for hepatitis A, B, C, D, and E viruses, Epstein-Barr virus, cytomegalovirus, and herpes simplex viruses were performed. Standard laboratory tests for liver function were analyzed. The results are presented as absolute numbers, mean +/- SD, range of values, and percent. A P value < 0.05 was considered significant. RESULTS: Twenty-four (6%) patients had clinically and/or serologically confirmed acute hepatitis E. The mean age of the patients was 25 +/- 6 years; 62.5% were males. The majority of the patients (66%) belonged to the 20 to 40 yrs age group (P < 0.05). Seven patients were asymptomatic. Foremost symptoms were loss of appetite (100%), fatigue (94%) and vomiting (75%). The most frequent clinical sign was mild to moderate liver enlargement (94%). Jaundice had 12/17 symptomatic patients. Elevation of alanine aminotransferase was found in 19 patients including two patients without symptoms. The enzyme, γ-glutamyltransferase was increased in all patients.

CONCLUSION: Acute hepatitis E in Montenegro emerges as an autochthonous infection with a low incidence. Sub-clinical and anicteric infections may occur. Elevation of γ-glutamyltransferase is an important parameter of the biochemical profile of the disease.


BACKGROUND: Little is known about the prevalence of HIV or HCV in injecting drug users (IDUs) in Serbia and Montenegro. We measured prevalence of antibodies to HIV (anti-HIV) and hepatitis C virus (anti-HCV), and risk factors for anti-HCV, in community-recruited IDUs in Belgrade and Podgorica, and determined the performance of a parallel rapid HIV testing algorithm. METHODS: Respondent driven sampling and audio-computer assisted survey interviewing (ACASI) methods were employed. Dried blood spots were collected for unlinked anonymous antibody testing. Belgrade IDUs were offered voluntary confidential rapid HIV testing using a parallel testing algorithm, the performance of which was compared with standard laboratory tests. Predictors of anti-HCV positivity and the diagnostic accuracy
of the rapid HIV test algorithm were calculated. RESULTS: Overall population prevalence of anti-HIV and anti-HCV in IDUs were 3% and 63% respectively in Belgrade (n = 433) and 0% and 22% in Podgorica (n = 328). Around a quarter of IDUs in each city had injected with used needles and syringes in the last four weeks. In both cities anti-HCV positivity was associated with increasing number of years injecting (eg Belgrade adjusted odds ratio (AOR) 5.6 (95% CI 3.2-9.7) and Podgorica AOR 2.5 (1.3-5.1) for >or= 10 years v 0-4 years), daily injecting (Belgrade AOR 1.6 (1.0-2.7), Podgorica AOR 2.1 (1.3-5.1)), and having ever shared used needles/syringes (Belgrade AOR 2.3 (1.0-5.4), Podgorica AOR 1.9 (1.4-2.6)). Half (47%) of Belgrade participants accepted rapid HIV testing, and there was complete concordance between rapid test results and subsequent confirmatory laboratory tests (sensitivity 100% (95%CI 59%-100%), specificity 100% (95%CI 98%-100%)). CONCLUSION: The combination of community recruitment, ACASI, rapid testing and a linked diagnostic accuracy study provide enhanced methods for conducting blood borne virus sero-prevalence studies in IDUs. The relatively high uptake of rapid testing suggests that introducing this method in community settings could increase the number of people tested in high risk populations. The high prevalence of HCV and relatively high prevalence of injecting risk behaviour indicate that further HIV transmission is likely in IDUs in both cities. Urgent scale up of HIV prevention interventions is needed.


BACKGROUND AND AIM: Liver disease is commonly present in human immunodeficiency virus (HIV) infection. The aim was to determine the frequency of liver enlargement and its association with opportunistic infections in patients with HIV infection. PATIENTS AND METHODS: A total of 400 HIV-infected patients were investigated. Commercial kits (Ortho EIA; BioRad, ELISA) were used for detection of serum specific antibodies to HIV, hepatitis C virus, surface antigen of hepatitis B virus, and cytomegalovirus. Liver tissues were stained for various microorganisms. The electronic data base SPSS for Windows (version 10.0) was used for statistical analysis. A p <0.05 was considered significant. RESULTS: Ultrasonographic screening revealed liver enlargement in 63.75% of HIV patients. In 40.7% the right lobe size varied from 140 mm to 160 mm. Of those with hepatomegaly, 60.7% had AIDS. Hepatitis C and B viruses and Mycobacterium tuberculosis were detected in 50%, 29% and 18% of patients, respectively. Histological changes were mostly non-specific. Liver pathology depended on the degree of cellular immune deficiency, particularly in patients with HBV co-infection. In a minority of patients (32.5%), the histology revealed granulomatous hepatitis. Liver function tests were abnormal in 46%. CONCLUSION: Liver enlargement is common in HIV-infected patients mostly in association with hepatitis C and B viruses and Mycobacterium tuberculosis.


AIM: To investigate the prevalence of hepatitis C virus (HCV) genotypes in Serbia and Montenegro and their influence on some clinical characteristics in patients with chronic HCV infection. METHODS: A total of 164 patients was investigated. Complete history, route of infection, assessment of alcohol consumption, an abdominal ultrasound, standard biochemical tests and liver biopsy were done. Gene sequencing of 5’ NTR type-specific PCR or commercial kits was performed for HCV genotyping and subtyping. The SPSS for Windows (version 10.0) was used for univariate regression analysis with further multivariate analysis. RESULTS: The genotypes 1, 2, 3, 4, 1b3a and 1b4 were present in 57.9%, 3.7%, 23.2%, 6.7%, 6.7% and 1.8% of the patients, respectively. The genotype 1 (mainly the subtype 1b) was found to be independent of age in subjects older than 40 years, high viral load, more severe necro-inflammatory activity, advanced stage of fibrosis, and absence of intravenous drug abuse. The genotype 3a was associated with intravenous drug abuse and the age below 40. Multivariate
analysis demonstrated age over 40 and intravenous drug abuse as the positive predictive factors for the genotypes 1b and 3a, respectively. CONCLUSION: In Serbia and Montenegro, the genotypes 1b and 3a predominate in patients with chronic HCV infection. The subtype 1b is characteristic of older patients, while the genotype 3a is common in drug abusers. Association of the subtype 1b with advanced liver disease, higher viral load and histological activity suggests earlier infection with this genotype and eventually its increased pathogenicity.
2.3 Serbia

Wikipedia: officially the Republic of Serbia is a sovereign state situated at the crossroads between Central and Southeast Europe, covering the southern part of the Pannonian Plain and the central Balkans. Relative to its small territory, it is a diverse country distinguished by a transitional character, situated along cultural, geographic, climatic and other boundaries. Serbia is landlocked and borders Hungary to the north; Romania and Bulgaria to the east; Macedonia to the south; and Croatia, Bosnia-Herzegovina, and Montenegro to the west; it also claims a border with Albania through the disputed territory of Kosovo. Serbia numbers around 7 million residents, and its capital, Belgrade, ranks among the largest cities in Southeast Europe.
2.3.1 Background info

PREVENTION AND CONTROL OF VIRAL HEPATITIS IN EUROPE IN 2014: THE CASE OF SERBIA

Country profile

- Gross national income per capita (Int $) (year): 12 020 (2013)*
- Most recent EEV prevalence data:
  - General population
    - Blood donors (first time): 4.2 % (2000-2003)*
    - Pregnant women
  - Risk groups
    - Injecting drug users
    - Men having sex with men
    - Sex workers

Vaccination programs

<table>
<thead>
<tr>
<th>Hepatitis</th>
<th>Target</th>
<th>Since/period</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Universal</td>
<td>No</td>
</tr>
<tr>
<td>B</td>
<td>Universal</td>
<td>Yes</td>
</tr>
<tr>
<td>Risk group</td>
<td>Catch-up</td>
<td>7</td>
</tr>
</tbody>
</table>

Screening

- Recommended for following groups:
  - Blood and organ donors
  - Pregnant women
  - Injecting drug users
  - STI clinic patients
  - Haemodialysis patients
  - Health care workers
  - Men having sex with men
  - Prison population
  - Migrants
  - Others

National plan

There is no written national strategy or plan that focuses exclusively or primarily on the prevention and control of viral hepatitis.

Impact

Figure 1: Hepatitis B vaccination coverage and impact on hepatitis B incidence

Specific issues and future challenges

A comprehensive mandatory reporting system for HBV and HCV cases (acute and chronic cases are reported by physician). And a passive case based surveillance system, epidemiologists investigate all reported cases (suspected or laboratory-confirmed) and follow up with the patient and his direct contacts, are in place in Serbia. Asymptomatic infections are often not included in the national surveillance system.

Note: There is a wide variety in reported data since hepatitis C is often asymptomatic and no clear diagnostic criteria are available to differentiate between acute and chronic cases.

Country contact: Goranka Loncarevic, MD, epidemiologist, Head of Department for surveillance, VPD and Immunisation, IPH of Serbia. d Libyanelva.org.rs and Dunja Simic, MD (Head of department for HIV/AIDS, TBC, sexual transmitted diseases and hepatitis in IPH of Serbia)
WHO data (http://www.who.int/gho/countries/srb.pdf?ua=1)
WHO CISID (http://data.euro.who.int/cisid/?TabID=399811)

2.3.2 Country related hepatitis publications

**Epidemiology**


BACKGROUND: Members of armed forces worldwide are considered to be very susceptible to sexually transmitted infections, thus falling into a high-risk group of blood donors regarding transfusion-transmissible infections. In the Serbian Military Medical Academy a significant number (44% for the period 2005-2013) of blood donations were from members of the Serbian Army. The aim of this study was to determine the significance of military blood donors for the safety of blood transfusion. MATERIAL AND METHODS: Between January 2005 and December 2013, a total of 155,479 blood donations were tested for hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) and syphilis using serological assays (enzyme immunoassays, chemiluminescent microparticle immunoassay and western blot) and molecular testing (polymerase chain reaction analysis). RESULTS: The percentage of blood donations positive for transfusion-transmissible infections in the estimated period was 0.38%, and the percentage of HBV, HCV, HIV and syphilis positive blood donations was 0.20%, 0.12%, 0.005% and 0.06%, respectively. During that period, the percentage of all transfusion-transmissible infections, and in particular of HBV and HCV, declined significantly. In contrast, the percentage of HIV and syphilis positive blood donations remained unchanged. Higher rates of positivity for transfusion-transmissible infections in blood donations from members of the Serbian Army were not found, especially after mandatory military service was abolished in 2009. DISCUSSION: The reported rate of positivity for transfusion-transmissible infections in blood donations from the Military Medical Academy was considered low. This information is of great significance for further implementation of public health measures.

Mitrovic, N., Delic, D., Markovic-Denic, L., Jovicic, M., Popovic, N., Bojovic, K., Simonovic Babic, J. and Svirtih, N. "Seroprevalence and risk factors for hepatitis C virus infection among blood

BACKGROUND: The epidemiological characteristics of hepatitis C virus (HCV) infection have not yet been described in Serbia. AIMS: To determine the prevalence of anti-HCV-positive individuals among first-time blood donors and the risk factors for hepatitis C transmission. METHODS: A multicentre case-control study nested within a prospective cohort study was conducted at 10 main transfusion centres in Serbia in 2013 and 27,160 blood donors who gave blood for the first time were included. Blood donors with confirmed anti-HCV positivity and seronegative controls were enrolled to determine the risk factors. RESULTS: Of 27,160 blood donors 52 were anti-HCV-positive; seroprevalence was 0.19%. By univariate analysis, marital status, educational level, drug use, previous transfusion, tattooing, non-use of condoms and number of sexual partners, were risk factors for hepatitis C. In the final multivariate analysis, three factors remained independently predictive: drug use, tattooing and previous blood transfusion. In total, 87.5% of cases had at least one of the risk factors for HCV transmission; 20.9% presumed that they knew when the infection occurred. CONCLUSION: HCV seroprevalence in Serbia is higher than in developed European countries. Preventive measures need to be directed towards drug use and tattooing facilities. The admission questionnaire for blood donors should be improved.


INTRODUCTION: Hepatitis E virus (HEV) infection is rarely reported in industrialized countries, but recent studies have revealed quite variable seroprevalence rates among European populations, including blood donors. In Serbia, very limited data about HEV seroprevalence are available. This study aimed to determine the prevalence of anti-HEV IgG antibodies and HEV RNA in the sera of volunteer blood donors in Serbia. METHODOLOGY: Serum samples from 200 volunteer blood donors were tested for the presence of anti-HEV IgG by enzyme-linked immunosorbent assay (ELISA) using ORF-2 HEV genotype 3 recombinant proteins as antigen, and for the presence of HEV RNA by nested reverse transcriptase polymerase chain reaction (RT-PCR). RESULTS: In total, 15% of the volunteer blood donors were seropositive. The prevalence increased with age; 21.5%, 14.2%, and 5.4% HEV seroprevalence rates were found in individuals older than 51 years, between 31 and 50 years, and in those younger than 30 years of age, respectively. However, no HEV RNA was detected in any of the individuals analyzed. CONCLUSIONS: The prevalence of anti-HEV IgG among blood donors as representatives of the general population is quite high in Serbia compared to data from many European countries. One of the reasons for this could be the high prevalence of HEV among Serbian pigs and the traditional consumption of piglet meat in the country. The relatively high HEV seroprevalence found among Serbian blood donors indicates the need for further investigation.


BACKGROUND/AIMS: Acute viral hepatitis is complicated rarely with severe liver failure due to many factors associated with the etiology, patient age, and time of development of hepatic encephalopathy, etc. The aim of this study was to identify some of the clinical and laboratory features associated with a fatal outcome in patients dying from acute viral hepatitis in Serbia. METHODS: Clinical and laboratory data from 47 patients hospitalized from January 1989 December 2006 were reviewed retrospectively. Serological tests for hepatitis A, B, C, D, and E viruses, herpes simplex viruses, cytomegalovirus, and Epstein-Barr virus were done. Histological features were assessed from 35 liver tissues. The electronic base, SPSS for Windows (version 11.0), was used for statistical analysis. RESULTS: The majority of the patients had alanine aminotransferase (ALT) >20x the normal value, serum bilirubin >300 mumol/L, prothrombin time >25 seconds (s), and white blood cell count >12 x 10(9)/L. Regression analysis revealed activity of alanine aminotransferase >20x the normal value to be associated with fulminant (p=0.015) and serum bilirubin concentration with subfulminant hepatitis (p=0.008). Hepatitis B
virus was the most commonly detected virus (70%). Massive hepatocyte necrosis vs. submassive with bridging necrosis were found to be independent of clinical presentation.

CONCLUSIONS: Hepatitis B virus infection, severe impairment of liver function tests, and confluent hepatocyte necrosis and infection characterize patients dying from acute viral hepatitis in Serbia. High activity of alanine aminotransferase reflects rapid and extensive acute viral liver injury, while deep jaundice is more common in a protracted course of the disease.


AIMS AND BACKGROUND: The objective of this case-control study was to test the existing hypotheses about factors related to the occurrence of hepatocellular carcinoma in the population of Belgrade (Serbia). METHODS AND STUDY DESIGN: The investigation was conducted between 2004 and 2007 and consisted of 45 newly diagnosed, histologically confirmed hepatocellular carcinoma patients and 90 individually gender- and age-matched hospital controls. Conditional univariate and multivariate logistic regression analyses were applied. RESULTS: A highly statistically significant association (P = 0.001) was demonstrated between hepatocellular carcinoma and HBsAg positivity and the presence of hepatitis C virus antibodies. Diabetes mellitus was significantly (P = 0.018) associated with an increased risk of hepatocellular carcinoma. A statistically significant inverse association was shown between low parity and the risk of hepatocellular carcinoma (P = 0.033). The risk increased significantly with a longer history of cigarette smoking (P = 0.044), as well as the daily consumption of hard liquor (P = 0.049). A weekly intake of fish (P = 0.003) and yogurt (P = 0.003) and daily intake of boiled vegetables (P = 0.001) were reported more frequently by controls than hepatocellular carcinoma cases. In the current study, a high intake of salty food also significantly increased the risk of hepatocellular carcinoma (P = 0.027). Based on multivariate analysis, the presence of hepatitis C virus antibodies (OR = 24.6, P = 0.001) and duration of smoking > or =25 years (OR = 3.8, P = 0.020) were significantly related to hepatocellular carcinoma, whereas the daily consumption of boiled vegetables (OR = 0.1, P = 0.011) was inversely associated with the risk of hepatocellular carcinoma. CONCLUSIONS: The findings obtained in the current study support the hypotheses that non-viral factors, such as lifestyle factors, reproductive factors, and a history of diabetes, might be involved in the etiology of hepatocellular carcinoma.


BACKGROUND/AIM: Acute non-A, non-B, non-C, non-D, non-E hepatitis (non-A-E AH) is an acute disease of the liver of unknown etiology for which one or more new, so far undetected, hepatotropic viruses may be responsible. The frequency of non-A-E AH ranges from 3.8% to 33.9%, and therefore it has a significant place within current infectology and hepatology. The aim of our study was to establish the frequency, clinical and biochemical characteristics, natural course and outcome of non-A-E AH and compare them with control groups affected by acute viral hepatitis A, B and C. METHODS: This descriptive-analytic prospective study included 31 patients with non-A-E AH treated at the Institute of Infectious and Tropical Diseases, Clinical Center of Serbia, Belgrade, from 2003 to 2008. They were followed up during the period not less than 6 months. The controls involved randomly selected patients, treated at the same time with a definite diagnosis of acute viral hepatitis A, B and C. Statistical data analysis used Mann-Whitney U-test, Student’s t-test and variance analysis. The value of p < 0.05 was considered statistically significant. RESULTS: The frequency of non-A-E AH was 7.6%. Almost no difference was found between sexes (male/female ratio was 1:1.07); it was developed in all age groups, with the highest incidence in the middle age (mean age was 38.32 +/- 15.3 years). It appeared equally throughout the whole year. Out of risk factors, inoculation risk was predominant (before all, dental interventions), mostly involving urban population living in comfortable conditions. The duration of incubation varied much ranging from 20 to 180 days (median 60 days). By clinical course, moderate and icteric forms were most common, mostly corresponding to acute hepatitis A and C. On the other hand, by duration of the disease (mean duration was 67.1 +/-
and chronic transformation, non-A-E AH resembled to acute hepatitis B. Progression to chronicity was recorded in 9.68% of the patients. There was no fulminant neither cholestatic form of the disease. CONCLUSION: Based on the results obtained in this study, it is probable that there are some so far undetected primary hepatotropic viruses in our environment.

**Treatment**


INTRODUCTION: Seroprevlence of chronic hepatitis C viral infection in correctional facilities ranges from 16% to 49%. However, there are only very limited data available on the course of hepatitis C viral infection and outcomes of treatment with pegylated interferon plus ribavirin in correctional settings. The aim of this study was to assess the feasibility and effectiveness of use of pegylated interferon plus ribavirin treatment in the Serbian correctional setting. MATERIAL AND METHODS: The study sample consisted of the patients with hepatitis C hospitalized in the Special Hospital for Prisoners in Belgrade (Serbia) during 2007-2013. Health authorities approved treatment for 32 patients out of 76 treatment-naive patients referred to this institution. The patients (N=32) received 180 mcg pegylated interferon alfa-2a once a week plus oral ribavirin in dosage of 800 mg or 1000/1200 mg/day for 24 or 48-week treatment. All patients who completed therapy were assessed at the end of an additional 24-week treatment-free period for a sustained virological response. RESULTS: Sustained virological response was achieved in 53.8% of hepatitis C viral infection genotype I patients and in 73.3% and 66.6% of patients with hepatitis C viral infection genotype 3 and 4, respectively. One patient with mixed genotype (1, 2) did not achieve sustained virological response. The overall safety profile of the treatment regimen was very good. The incidence of influenza-like symptoms and depression were low. A serious adverse event was recorded only in 6.4% of patients. CONCLUSION: The results showed that pegylated interferon alfa-2a plus ribavirin given once a week was well tolerated among prisoners and the regimen had the same adherence and effectiveness as in general population.


BACKGROUND: European guidelines recommend treatment of chronic hepatitis B virus infection (CHB) with the nucleos(t)ide analogs (NAs) entecavir or tenofovir. However, many European CHB patients have been exposed to other NAs, which are associated with therapy failure and resistance. The CAPRE study was performed to gain insight in prevalence and characteristics of NA resistance in Europe. METHODS: A survey was performed on genotypic resistance testing results acquired during routine monitoring of CHB patients with detectable serum hepatitis B virus DNA in European tertiary referral centers. RESULTS: Data from 1568 patients were included. The majority (73.8%) were exposed to lamivudine monotherapy. Drug-resistant strains were detected in 52.7%. The most frequently encountered primary mutation was M204V/I (48.7%), followed by A181T/V (3.8%) and N236T (2.6%). In patients exposed to entecavir (n = 102), full resistance was present in 35.3%. Independent risk factors for resistance were age, viral load, and lamivudine exposure (P < .001). CONCLUSIONS: These findings support resistance testing in cases of apparent NA therapy failure. This survey highlights the impact of exposure to lamivudine and adefovir on development of drug resistance and cross-resistance. Continued use of these NAs needs to be reconsidered at a pan-European level.

BACKGROUND AND AIMS: Long-term treatment with tenofovir disoproxil fumarate (TDF) alone, or in combination with emtricitabine (FTC) is associated with sustained viral suppression in patients with lamivudine resistant (LAM-R) chronic hepatitis B (CHB). METHODS: LAM-R CHB patients were randomised 1:1 to receive TDF 300 mg or FTC 200 mg and TDF 300 mg once daily in a prospective, double-blind, study. The proportion of patients with plasma hepatitis B virus (HBV) DNA <69 IU/mL (<400 copies/mL) at Week 96 (primary efficacy endpoint) was reported previously. Here we present Week 240 follow-up data. RESULTS: Overall, 280 patients were randomised to receive TDF (n=141) or FTC/TDF (n=139), and 85.4% completed 240 weeks of treatment. At Week 240, 83.0% of patients in the TDF arm, and 82.7% of patients in the FTC/TDF treatment arm had HBV DNA <69 IU/mL (P=0.96). Rates of normal alanine aminotransferase (ALT) and normalised ALT were similar between groups (P=0.41, P=0.97, respectively). Hepatitis B e antigen loss and seroconversion at Week 240 were similar between groups, (P=0.41, P=0.67, respectively). Overall, six patients achieved hepatitis B surface antigen (HBsAg) loss and one patient (FTC/TDF arm) had HBsAg seroconversion by Week 240. No TDF resistance was observed up to Week 240. Treatment was generally well tolerated, and renal events were mild and infrequent (approximately 8.6%). The mean change in bone mineral density at Week 240 was -0.98% and -2.54% at the spine and hip, respectively. CONCLUSIONS: TDF monotherapy was effective and well tolerated in LAM-R CHB patients for up to 240 weeks.

LAY SUMMARY: The goal of oral antiviral treatment for chronic hepatitis B (CHB) is to achieve and maintain undetectable HBV DNA levels. Treatment options with enhanced potency, and low risk of resistance development for patients infected with lamivudine resistant (LAM-R) HBV are required. Tenofovir disoproxil fumarate (TDF) monotherapy was effective and well tolerated without TDF resistance development in CHB patients with LAM-R, for up to 240 weeks.


Hepatocellular carcinoma (HCC) is one of the major malignant diseases in many healthcare systems. The growing number of new cases diagnosed each year is nearly equal to the number of deaths from this cancer. Worldwide, HCC is a leading cause of cancer-related deaths, as it is the fifth most common cancer and the third most important cause of cancer related death in men. Among various risk factors the two are prevailing: viral hepatitis, namely chronic hepatitis C virus is a well-established risk factor contributing to the rising incidence of HCC. The epidemic of obesity and the metabolic syndrome, not only in the United States but also in Asia, tend to become the leading cause of the long-term rise in the HCC incidence. Today, the diagnosis of HCC is established within the national surveillance programs in developed countries while the diagnosis of symptomatic, advanced stage disease still remains the characteristic of underdeveloped countries. Although many different staging systems have been developed and evaluated the Barcelona-Clinic Liver Cancer staging system has emerged as the most useful to guide HCC treatment. Treatment allocation should be decided by a multidisciplinary board involving hepatologists, pathologists, radiologists, liver surgeons and oncologists guided by personalized -based medicine. This approach is important not only to balance between different oncologic treatments strategies but also due to the complexity of the disease (chronic liver disease and the cancer) and due to the large number of potentially efficient therapies. Careful patient selection and a tailored treatment modality for every patient, either potentially curative (surgical treatment and tumor ablation) or palliative (transarterial therapy, radioembolization and medical treatment, i.e., sorafenib) is mandatory to achieve the best treatment outcome.


INTRODUCTION: The triple therapy which consists of one of the protease inhibitor plus pegylated interferon and ribavirin (P/R) is the standard of care for the treatment of chronic hepatitis C virus (HCV) genotype 1 (G1) infection both in treatment-naive and experienced
patients. OBJECTIVE: The aim of this study was to analyze the efficacy and tolerability of this regime in hospital practice in Serbia. METHODS: From July 2012 to October 2012, 20 previously treated patients with advanced fibrosis and HCV G1 infection were included in the triple antiviral regimen in six referral centers in Serbia. All patients were treated with response guide therapy (RGT) regime according to the boceprevir treatment protocol. During the 4-week lead-in period all patients received peginterferon plus ribavirin. After the lead-in period boceprevir was added in the dosage of 800 mg three times a day orally. The subsequent treatment varied according to virologic response and fibrosis. During the therapy HCV RNA level was measured at week 4, 8, 12, 24 of the treatment for the assessment of virologic response profile. All patients who completed therapy were assessed at the end of the treatment and at the end of an additional 24-week treatment-free period for a sustained virologic response (SVR). RESULTS: The total of 20 patients with advanced fibrosis was treated. Among patients with an undetectable HCV RNA level at week 8 the rate of SVR was 100%. No patient with decrease in the HCV RNA level < 1 log 10 IU/ml at treatment week 4 achieved SVR. The overall rate of SVR was 55%. The safety profile of the treatment regimen was good. Anemia was reported in 25% of patients. There was no life-threatening treatment adverse event. CONCLUSION: Boceprevir in combination with P/R achieved fairly good SVR rates in patients that were "most difficult to treat" who failed on dual therapy and was effective among patients with cirrhosis.


INTRODUCTION: Dual antiviral therapy with pegylated interferon alfa-2a and ribavirin leads to sustained elimination of hepatitis C virus infection in over 50% patients with genotypes 1 and 4 and in over 80% with genotypes 2 and 3. In addition to genotype, for predicting success of therapy, important factors are baseline HCV RNA level, age, sex, stage of fibrosis, insulin resistance, degree of fat in liver, and patient's weight and genetics. Also, adherence to therapy could be a very important factor associated with success of therapy. OBJECTIVE: The aim of this study was to assess importance of therapy adherence and reduced doses of pegylated interferon alfa-2a and ribavirin on sustained virological response. METHODS: One hundred and sixteen patients with chronic hepatitis C were analyzed. Sustained virological response was analyzed in relation to whether the patients received a full cumulative dose of pegylated interferon alfa-2a, a full cumulative dose of pegylated interferon alfa-2a and ribavirin, and a full cumulative dose of pegylated interferon alfa-2a and at least 60% of cumulative dose of ribavirin. RESULTS: At the end of the follow-up period, sustained virological response was achieved in 26 (96.3%) patients who received full cumulative dose of pegylated interferon alfa-2a and in 66 (74.2%) who did not (p < 0.05). Sustained virological response was achieved in 18 (94.7%) patients who received full cumulative dose of pegylated interferon alfa-2a and ribavirin, and in 73 (76%) who did not (p < 0.05). Sustained virological response was achieved in 25 (96.2%) patients who received full cumulative dose of pegylated interferon alfa-2a and at least 60% of cumulative dose of ribavirin and in 66 (74.2%) who did not (p < 0.05). CONCLUSION: These findings indicate that adherence to therapy for chronic hepatitis C is a very important factor for achieving sustained virological response.


BACKGROUND: Hepatitis B virus (HBV) genotypes influence disease progression and treatment outcome. OBJECTIVES: To determine natural history and treatment outcome in patient chronically infected with HBV. STUDY DESIGN: A cohort study included 162 treatment naive patients with chronic HBV infection in order to analyze factors influencing natural history of infection and survival. RESULTS: Genotype A was far less prevalent, detected in 14.2%. The prevalence of HBeAg+ serology of 60.8% among patients infected with genotype A was significantly higher then 30.9% recorded among those with genotype D (P=0.02). Even though patients from two genotypes subgroups had significantly different prevalence of HBeAg
serology, their viral loads were similar at the time of diagnosis (2.90 log10 and 3.31 log10 HBV DNA IU/ml plasma, for genotypes A and D, respectively). The analyses of viral loads across three serologic patterns of chronic HBV infection were: for HBeAg+/HBeAb-, HBeAg-/HBAb+, and both "e" antigen and antibodies negative: 4.24, 2.67 and 2.69 log10 IU/ml of HBV DNA IU/ml, respectively (P=0.01). Mean time to liver cirrhosis was 23.2+/−3.4 years and 15.1+/−8.4 years, for genotypes A and D, respectively (P=0.02). The overall estimated mean survival of patients with chronic HBV infection was 28.4 years, and was influenced by the stage of liver disease, but not by gender, age above 40, viral genotype and lamivudine therapy.

CONCLUSIONS: Patients infected with genotype D had more rapid progression to ESLD regardless of levels of viral replication. All clinical and laboratory differences between genotypes did not affect survival of patients with chronic hepatitis B, regardless of lamivudine therapy.


BACKGROUND: Three single nucleotide polymorphisms (SNPs) near IL28B gene were shown to be highly predictive of sustained virological response (SVR) in patients with chronic hepatitis C virus (HCV) infection. OBJECTIVES: This study attempted to demonstrate the role of single and combined IL28B polymorphisms (rs8099917, rs12979860 and rs12980275) and other host and viral factors in predicting response to treatment, in Caucasian patients infected with HCV genotype 1. STUDY DESIGN: The IL28B genotypes at 3 SNPs were determined in 106 patients who underwent standard 48-week therapy and out of which 55.7% achieved SVR. RESULTS: Patients carrying genotypes CCrs12979860 or AArs12980275 were 3.5 and 3 times more likely to achieve SVR, respectively. Genotypes GGrs8099917 and TTrs12979860 were identified as predictors of treatment failure. The presence of IL28B profiles including at least one of the favourable genotypes was identified as the most important factor associated with SVR, followed by younger age and lower grade of histological activity. Of all patients who achieved SVR, 88.1% was carrying one of these IL28B profiles. The strongest PPV of single SNPs for achieving SVR was observed for CCrs12979860 (76.9%). The presence of GGrs8099917 showed the strongest NPV of 85.7%. The correlation of SNPs with other host and viral factors revealed association of TTrs8099917 and lower AST levels. CONCLUSIONS: Results of this study confirm that all investigated IL28B polymorphisms are associated with treatment response and that presence of any of the favourable IL28B genotypes can be considered independent pretreatment determinant of the effectiveness of therapy.


Despite the fact that the majority of prevalent and incident cases of HCV are associated with intravenous drug use (IVDU), these patients have largely been excluded from HCV care. The aim of this study was to examine the treatment outcome of chronic hepatitis C in IVDUs compared to non-IVDUs. PATIENTS AND METHODS: Patients with chronic hepatitis C (CHC) who initiated and completed combination antiviral therapy with peglated interferon and ribavirin, at the Hepatology Department of the University Hospital for Infectious and Tropical Diseases in Belgrade, were retrospectively analyzed. The study included a series of 254 patients of which 100 (39.4%) were former IVDU. RESULTS: Sustained virological response (SVR) was recorded in a total of 172 patients (67.7%). The analyses of the favorable treatment outcome, regarding particular viral genotypes, revealed that among those with genotype 1 and/or 4, including patients with genotype 1 recombinants with genotype 3, SVR was achieved in 114 (63.3%), while it was almost equally distributed between subgroups of former IVDU and all others (P=0.079). Among patients infected with HCV genotypes 2 and/or 3 the SVR rate was as high as 86.6%. CONCLUSION: IVDU with CHC infection should be treated with standard combination antiviral therapy for CHC, since the success rate is equal or even better than in non-IVDU patients.

INTRODUCTION: Chronic hepatitis C virus (HCV) infection can progress to liver cirrhosis that causes bleeding from the gastrointestinal tract, liver failure and primary hepatocellular carcinoma. Use of standard therapeutic option consists of recombinant pegylated interferon alpha 2a/b with ribavirin in order to eradicate virus and prevent complications. OBJECTIVE: The aim of investigation was to evaluate efficiency of combination therapy (pegylated interferon alpha 2a/b plus ribavirin) in patients with chronic HCV infection and to estimate predictive factors for successful treatment. METHODS: A total of 387 patients with confirmed diagnosis of hepatitis C were evaluated (aged 18-65 years of both genders). Patients were treated with pegylated interferon alpha 2a/b and ribavirin according to a standard regimen lasting 24 or 48 weeks, dependent on virus genotype. RESULTS: Negative HCV RNA (PCR assay) was recorded in 79.7% of patients at the end of treatment. Six months after completed therapy, negative HCV RNA, i.e. stained virologic response (SVR) was assessed in 70.5% of patients. Statistical summary of our results concerning SVR confirmed better efficiency of combination therapy for the following parameters compared to other investigated variables: age < or = 40 (84.3% vs. 59.1%; p < 0.0005), absence of cirrhosis (75.6% vs. 58.3%; p = 0.003), lack of genotype 1 (86.6% vs. 61.8%; p < 0.0005), and in patients who received full doses of pegylated interferon alpha 2a (78.3% vs. 63.3%; p = 0.002). CONCLUSION: Combination therapy of recombinant pegylated interferon alpha 2a with ribavirin leads to SVR in the majority of treated patients (70.5%).


INTRODUCTION: Reactivation of chronic hepatitis B virus (HBV) infection often occurs in hepatitis B surface antigen (HBsAg) positive patients undergoing immunosuppressive or chemotherapy, but can also occur in HBsAg negative, anti-HB core positive patients. Treatment of HBV reactivation with lamivudin results in favourable outcome in the majority of patients. The aim of the authors was to show the effect of lamivudin therapy to HBV reactivation caused by immunosuppressive therapy. OUTLINE OF CASES: The first patient was a 35-year-old woman with chronic hepatitis B virus infection who underwent prednisolone therapy for pulmonal sarcoidosis. Four months after the beginning of the therapy she presented with jaundice and a significant increase in serum aminotransferase level. Liver biopsy showed chronic viral B hepatitis of strong activity in the stage of rapidly developed cirrhosis. The patient was treated with lamivudine with slow reduction of prednisolone doses, which resulted in full clinical and biochemical recovery. The second patient was a 40-year-old HBsAg negative female with a previous history of resolved acute B hepatitis who received chemotherapy for non-Hodgkin lymphoma. After the third cycle of chemotherapy a significant increase in aminotransferase level occurred, chemotherapy was discontinued, but aminotransferase level still increased. At that moment she was found to be HBsAg positive, and PCR analysis detected a high viral load. Lamivudine treatment resulted in the patient’s recovery and allowed further chemotherapy. CONCLUSION: In case of the reactivation of chronic HBV infection during immunosuppressive therapy, it should be stopped and antiviral therapy should be immediately initiated. The use of lamivudine results in rapid suppression of serum HBV DNA, improves the outcome and enables the continuation of immunosuppressive and chemotherapy.


OBJECTIVE: To prospectively evaluate depressive symptoms and risk factors for depression in
patients with chronic hepatitis C (CHC) treated with pegylated interferon alpha therapy combined with oral ribavirin (PEG-IFN-alpha+RBV) and to analyze self-rating scale for depression in comparison to observer-based scale in the given population. SUBJECTS AND METHODS: The Hamilton Depression Rating Scale and Zung Self Rating Depression Scale were used to screen for depressive symptoms in 74 subjects with CHC before PEG-IFN-alpha (mean dose 152.6 +/- 25.6 mcg), and in the follow-up visits (4, 12 and 24 week). RESULTS: Incidence of depressive symptoms in patients (mean age 39.9 +/- 13.4 years; equal sex distribution p=0.225) treated by PEG-IFN-alpha was the highest on 12th week of the treatment, when more than a 20% of our sample had moderate/severe symptoms of depression, and about 30% had minor depressive symptoms. For the screening of depression during PEG-IFN-alpha self-assessment scale was equally reliable as observer-based assessment of depressive symptoms. Common clinical parameters- subject related risk factors (age (p=0.955), sex (p=0.008), lifetime psychiatric disorder (p=0.656)), illness related risk factors (duration of CHC (p=0.267), i.v drug aplication as way of transmission (p=0.292)) and therapy-related risk factors (recommended duration of PEG-IFN-alpha (p=0.993) and dose of PEG-IFN-alpha (p=0.841)) were not significantly associated with depressive symptoms on PEG-IFN-alpha. CONCLUSIONS: Liaison-consultation services should collaborate with hepatologists in creating screening programmes, supplemented by objective criteria and guidelines, for early recognition and treatment of interferon-induced depression.


INTRODUCTION: Hepatitis C Virus infection represents not just a medical, but also a socio-economic problem. It is estimated that among 170 million infected, 60% belongs to the category of intravenous drug users (IDUs). OBJECTIVE: The aim of this paper was to compare the response to the combined therapy of pegylated interferon alfa 2a and ribavirin, in the group of patients with HCV infection who were intravenous drug users (IDUs) and in patients who were identified in the other way of transmission of HCV. Also to identify the influence of the therapy on diseases of addiction, during the course of HCV infection and on the effects of the combined therapy of pegylated interferon alfa 2a and ribavirin. METHODS: We conducted a retrospective-prospective study, on 60 patients, treated with combined antiviral therapy--pegylated interferon alfa 2a and ribavirin. 30 patients were from the group of IDUs, and 30 patients from other epidemiological groups. RESULTS: There were significant differences between the age of the patients (30.2 +/- 7.1 vs. 39.3 +/- 11.2 years; p = 0.002), but no significant difference in the duration of the HCV infection between the two groups of patients (8.9 +/- 7.4 vs. 13.1 +/- 7.0 years; p > 0.05). A large number of the patients in the group of IDUs had a problem with the abstinence of the drug abuse. In this group, there was the influence of alcohol (30%) and other substances with potential hepatotoxicity: marihuana (23.3%) and psychoactive drugs (73.6%). Staging of the liver fibrosis was not influenced by those two parameters and was similar in both groups (p > 0.05). The genotype 3a was dominant in intravenous drug users (50.0%) and genotype 1b in the control group of the patients (76.6%). In both groups, SVR was achieved at a higher percentage (86% vs. 70.00%; p > 0.05), but among the intravenous drug users the relapses of HCV infection were at a lower percentage (3.3% vs. 20.0%; p = 0.044). Side effects were noticed in solitary cases in both of the examined groups, but severe side effects were found only in the control group of the patients. Relapse of drug abuse was noticed in 6.66% of cases. CONCLUSION: We have registered that the group of intravenous drug users has the same or even better response to the antiviral therapy than other epidemiological groups and that the use of drugs does not change the course of HCV infection.

Burden of disease

BACKGROUND: Chronic ethyl alcohol consuming is well known independent negative predictor of unfavorable natural course and therapy outcome of Chronic Hepatitis C (CHC) infection.

OBJECTIVE: The aim of the present study was to clarify the impact of alcohol consumption on fibrosis rate progression in patients with CHC and Sustained Virologic Response (SVR) rates in patients undergoing treatment with pegylated interferon and ribavirin. METHOD: This cross sectional retrospective study included 807 CHC patients underwent liver biopsy and hospitalized at Clinical center of Vojvodina, Novi Sad, Serbia. According to the alcohol consumption equal or greater than 50 g/day prior to liver biopsy, patients were divided into two groups. We compared demographic, clinical, virologic and histopathological markers of CHC, as well as response to antiviral therapy. RESULTS: We find statistically significant difference (p=0.001) in gender, but not in age (p=0.081), estimated duration of the CHC (p=0.470) and hepatitis C genotype (p=0.545) between two groups. Among patients with CHC who consume alcohol >/=50 g/day there were significantly higher incidence of intravenous drug users (p=0.000). Binary logistic regression showed that the only independent predictors of moderate to severe fibrosis (fibrosis >/=2) were age (p=0.000) and alcohol use (p=0.027). There was not statistically significant difference in SVR rate between two groups (p=0.810).

CONCLUSION: We believe that this good result in treatment outcome was the consequence of proper selection of patients based primarily on regulations of Republic of Serbia on the necessity of abstinence from the use of alcohol and psychoactive substances at least one year before starting antiviral therapy.


BACKGROUND/AIM: In recent years mental health of patients including those with chronic liver disease (CLD), has become interesting because its disturbance leads to reduced quality of life, that is associated with worsening of clinical outcome, reduced compliance and increased mortality. The aim of the study was to determine the frequency and severity of depression and frequency of anxiety in patients with CLD and to assess the contribution of selected socio-demographic, clinical and laboratory risk factors for depression and anxiety. METHODS: In this cross-sectional study, we used the Hamilton depression rating scale (HDRS) and Hamilton anxiety rating scale (HARS) in patients with CLD. RESULTS: The study included 54 male and 43 female patients. Depression was present in 62.9%, and anxiety in 13.4% of the patients. A higher HDRS was noted in the patients older than 50 years (p = 0.022) and unemployed patients (p = 0.043). The patients with at least one episode of gastrointestinal bleeding had a significantly higher frequency of anxiety than those without bleeding (p = 0.018). A higher HARS score was present in the women (p = 0.011), unemployed patients (p = 0.008) and those with non-alcoholic liver disease (p = 0.007). There was a significant correlation between the mean corpuscular volume (MCV) and the value of the HDRS score, and between serum potassium and sodium levels and HDRS score. CONCLUSION: Age and the mean corpuscular volume have significant influence on the HDRS score while unemployment, gastrointestinal bleeding, serum potassium and serum sodium have predictive value for HARS score.


INTRODUCTION: Health-related quality of life (HRQL) of chronic patients has been researched as the ultimate goal of modern treatment of chronic diseases to improve patients' quality of life.

OBJECTIVE: The objective was to assess the reliability of the Serbian version of the Sickness Impact Profile (SIP) questionnaire on the sample of patients with chronic viral hepatitis.

METHODS: The research covered 102 patients with chronic hepatitis (47 type B and 55 type C). The assessment of the reliability of the SIP questionnaire was performed by testing the internal consistency of the questions by calculating the Cronbach's alpha coefficient. The factor analysis was used to assess whether the grouping of the questions within dimensions matches the
distribution of the questions in the original English version of the questionnaire administered to U.S. patient population. RESULTS: The Cronbach’s alpha coefficient for the entire questionnaire is 0.925, 0.869 for the physical dimension, and 0.857 for the psychosocial dimension. After running a factor analysis of the psychosocial dimension, “emotional instability” was extracted as the key factor, confirming the results of previous research. Compared with the English version of the questionnaire, the Cronbach’s alpha coefficient of the Serbian version does not diverge significantly, whereas the factor analysis confirms the classification of the questionnaire into two dimensions. CONCLUSION: Our study has shown that the Serbian version of the SIP questionnaire is a reliable tool for assessing the HRQL of patients with chronic hepatitis B and C before starting treatment.


INTRODUCTION: Hepatitis C virus often causes chronic liver disease reducing physical, mental and social functions in these patients. OBJECTIVE: The aim of this investigation was analysis of the quality of life in chronic hepatitis C patients compared to patients with other chronic liver diseases and healthy population, as well as investigation of the influence of socio-demographic factors on the quality of life in patients with chronic hepatitis C. METHODS: A generic Short Form-36 (SF-36) questionnaire and Chronic Liver Diseases Questionnaire (CLDQ) were used in this prospective study for the investigation of the quality of life in 160 patients (100 patients with chronic hepatitis C, 30 patients with chronic hepatitis B, 30 patients with non-viral chronic liver diseases) and 50 healthy controls. RESULTS: Reduced quality of life was noted in patients with chronic hepatitis C patients in comparison with healthy controls (p = 0.00). Significant differences in SF-36 were found between patients with chronic hepatitis C and B regarding physical functions, activity, physical pain and emotional functions. Multivariate linear regression analysis revealed ages below 50 years as the most important positive variable in chronic hepatitis C patients for total score of the quality of life and physical component score (B = 14.5; SE = 5.16; p = 0.049; and B = 16.4; SE = 5.94; p = 0.003, respectively). The most important positive variable for the mental component of the quality of life was male gender (B = 15.3; SE = 5.81; p = 0.003). CONCLUSION: Quality of life is reduced in patients with chronic hepatitis C in comparison with healthy population. The quality of life in chronic hepatitis C patients is better than in patients with other non-viral chronic liver diseases. In comparison with patients with chronic hepatitis B, reduction in some domains of the quality of life is noted. Younger age is the most predictable group for the lowest damage of the total quality of life in patients with chronic hepatitis C patients among other sociodemographic characteristics of these patients.

Research


BACKGROUND: There is positive correlation between the number of activated hepatic stellate cells and necroinflammatory activity and/or the stage of liver fibrosis in viral hepatitis. No study has investigated such a relationship with regard to the activated hepatic cells within specified zones of liver tissue in chronic C hepatitis. The aim of the present study was to correlate the level of activated hepatic stellate cells within perivenular, intermediate, periportal, and portal tracts area and fibrous septa with stages of liver fibrosis and necroinflammatory activity in patients with chronic C hepatitis. METHODS: This retrospective study included 20 liver biopsy samples from patients with chronic C hepatitis and 10 normal liver biopsies. Biopsy specimens were processed routinely and stained with haematoxylin-eosin, periodic acid-Schiff, Masson’s trichrome, aldehyde fuchsin, reticulin and iron (Pearls). Activated hepatic stellate cells were identified immunohistochemically using antibody to alpha-smooth muscle actin. Assessment of
immunoreactivity was performed using a semiquantitative method. RESULTS: In chronic C hepatitis, a positive correlation between the stage of fibrosis and the number of activated hepatic stellate cells within portal spaces and fibrous septa was found. These cells were increased in number in other areas of liver tissue as well, but without statistical significance. There was no correlation between either the stage of fibrosis and necroinflammatory activity or the number of activated hepatic stellate cells and necroinflammatory activity. CONCLUSION: An increased number of activated hepatic stellate cells within portal spaces and fibrous septa may be a useful prognostic marker for the development of advanced fibrosis and cirrhosis in chronic C hepatitis.
different demographic and risk factors involved in the spread of these viruses. RESULTS: The prevalence of hepatitis B and hepatitis C viruses varied regionally across the country. The overall prevalence of hepatitis B was 2.2% (95% CI 2.1%-2.3%) and was higher among males than females (1.4:1.0). Hepatitis C virus (HCV) prevalence was 1.2% (95% CI 1.1-1.3) and it increased gradually after the age of 30 years (0.7-0.9% for < 30 years; 3.6% for >/= 60 years). Prevalence of HBsAg was 0.8-0.9% below the age of 10 years, and higher but similar in older age groups (2.3-2.7%). There was an association between literacy and prevalence of hepatitis, particularly for HCV. Hospital admission, surgical operation, blood transfusion, and intravenous drug use were the main risk factors, and they were associated independently with a higher prevalence rate of viral hepatitis. CONCLUSIONS: Libya may be considered an area of low-intermediate endemicity for hepatitis B virus infection, with lower rates in young age groups, and an area of low endemicity for hepatitis C. The prevalence of hepatitis B and C across Libya is not homogeneous, with indications of the effect of the higher rates in some neighbouring countries. Libya should adopt full coverage national plans and guidelines to face the future consequences of viral hepatitis, particularly hepatitis C virus.

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4. GBD (2013). Mortality and Causes of Death Collaborators. Global, regional, and national age-sex-specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015 Jan 10; 385(9963):117-71. BACKGROUND: Up-to-date evidence on levels and trends for age-sex-specific all-cause and cause-specific mortality is essential for the formation of global, regional, and national health policies. In the Global Burden of Disease Study 2013 (GBD 2013) we estimated yearly deaths for 188 countries between 1990, and 2013. We used the results to assess whether there is epidemiological convergence across countries. METHODS: We estimated age-sex-specific all-cause mortality using the GBD 2010 methods with some refinements to improve accuracy applied to an updated database of vital registration, survey, and census data. We generally estimated cause of death as in the GBD 2010. Key improvements included the addition of more recent vital registration data for 72 countries, an updated verbal autopsy literature review, two new and detailed data systems for China, and more detail for Mexico, UK, Turkey, and Russia. We improved statistical models for garbage code redistribution. We used six different modelling strategies across the 240 causes; cause of death ensemble modelling (CODEm) was the dominant strategy for causes with sufficient information. Trends for Alzheimer’s disease and other dementias were informed by meta-regression of prevalence studies. For pathogen-specific causes of diarrhoea and lower respiratory infections we used a counterfactual approach. We computed two measures of convergence (inequality) across countries: the average relative difference across all pairs of countries (Gini coefficient) and the average absolute difference across countries. To summarise broad findings, we used multiple
decrement life-tables to decompose probabilities of death from birth to exact age 15 years, from exact age 15 years to exact age 50 years, and from exact age 50 years to exact age 75 years, and life expectancy at birth into major causes. For all quantities reported, we computed 95% uncertainty intervals (UIs). We constrained cause-specific fractions within each age-sex-country-year group to sum to all-cause mortality based on draws from the uncertainty distributions. FINDINGS: Global life expectancy for both sexes increased from 65.3 years (UI 65.0-65.6) in 1990, to 71.5 years (UI 71.0-71.9) in 2013, while the number of deaths increased from 47.5 million (UI 46.8-48.2) to 54.9 million (UI 53.6-56.3) over the same interval. Global progress masked variation by age and sex: for children, average absolute differences between countries decreased but relative differences increased. For women aged 25-39 years and older than 75 years and for men aged 20-49 years and 65 years and older, both absolute and relative differences increased. Decomposition of global and regional life expectancy showed the prominent role of reductions in age-standardised death rates for cardiovascular diseases and cancers in high-income regions, and reductions in child deaths from diarrhoea, lower respiratory infections, and neonatal causes in low-income regions. HIV/AIDS reduced life expectancy in southern sub-Saharan Africa. For most communicable causes of death both numbers of deaths and age-standardised death rates fell whereas for most non-communicable causes, demographic shifts have increased numbers of deaths but decreased age-standardised death rates. Global deaths from injury increased by 10.7%, from 4.3 million deaths in 1990 to 4.8 million in 2013; but age-standardised rates declined over the same period by 21%. For some causes of more than 100,000 deaths per year in 2013, age-standardised death rates increased between 1990 and 2013, including HIV/AIDS, pancreatic cancer, atrial fibrillation and flutter, drug use disorders, diabetes, chronic kidney disease, and sickle-cell anemias. Diarrhoeal diseases, lower respiratory infections, neonatal causes, and malaria are still in the top five causes of death in children younger than 5 years. The most important pathogens are rotavirus for diarrhoea and pneumococcus for lower respiratory infections. Country-specific probabilities of death over three phases of life were substantially varied between and within regions. INTERPRETATION: For most countries, the general pattern of reductions in age-sex specific mortality has been associated with a progressive shift towards a larger share of the remaining deaths caused by non-communicable disease and injuries. Assessing epidemiological convergence across countries depends on whether an absolute or relative measure of inequality is used. Nevertheless, age-standardised death rates for seven substantial causes are increasing, suggesting the potential for reversals in some countries. Important gaps exist in the empirical data for cause of death estimates for some countries; for example, no national data for India are available for the past decade. FUNDING: Bill & Melinda Gates Foundation.

5. Bechini A, Levi M, Falla A, Ahmad A, Veldhuijzen I, Tiscione E, Bonanni P. The role of the general practitioner in the screening and clinical management of chronic viral hepatitis in six EU countries. J Prev Med Hyg. 2016;57(2):E51-60. INTRODUCTION: Chronic viral hepatitis is still a major public health concern in the EU. In order to halt the progression of the disease and to prevent onward transmission, timely recognition and accurate clinical management are crucial. The aim of the present study was to investigate the role of the general practitioner (GP) in the screening of persons at risk and in the clinical management of chronic viral hepatitis patients in six EU countries. METHODS: An online survey among GPs and secondary-care specialists was conducted in the UK, Germany, the Netherlands, Hungary, Italy and Spain. In the GP survey, we used a four-point Likert scale to find out how commonly risk groups are screened. In both surveys, we measured GPs involvement in monitoring clinical indicators in patients undergoing antiviral treatment, and explored whether patients in four clinical scenarios are referred back to primary care. RESULTS: Between five and 10 experts per professional group were surveyed, except for Spain (GPs: n = 2; Specialists: n = 4) and, in the case of the GP survey, Hungary (GPs: n = 1) and Germany (GPs: n = 4). Migrants are variably or not routinely screened for hepatitis B/C in the majority of cases. The majority of GPs reported that hepatitis B/C screening was routinely offered to people who inject drugs. In Hungary, Italy and in the Netherlands, screening sex workers is not a regular practice. As to whether GPs offer screening to men who have sex with men, responses varied; in Germany, the Netherlands and Italy,
screening was "variably" or "commonly" implemented, while in Hungary the practice seems to be sporadic. In the UK, screening for hepatitis B seems to be common practice among GPs, while hepatitis C testing is only occasionally offered to this risk group. Most GPs (> 44%) in all countries except Hungary reported that hepatitis B/C screening was very commonly offered to HIV patients. The role of GPs in monitoring hepatitis cases and the referral of cases back to GPs by specialists varied both within and between countries. GPs are unlikely to monitor clinical outcomes other than side effects in patients undergoing treatment. Patients who have had a sustained virological response are usually referred back to GPs, whereas patients undergoing antiviral treatment and those who do not respond to treatment are rarely referred back.

CONCLUSIONS: The GP's decision to offer screening to risk groups often seems to be an individual choice of the healthcare professional. Raising GPs' awareness of the disease, for example through the adoption of effective strategies for the dissemination and implementation of the existing guidelines for general practice, is strongly needed. The role of GPs and specialists involved in the management of chronically infected patients should also be clarified, as opinions sometimes differ markedly even within each professional group.
3.4 The Republic of Macedonia

3.4.1 Background info

Wikipedia The former Yugoslav Republic of Macedonia officially the Republic of Macedonia is a country in the Balkan peninsula in Southeast Europe. It is one of the successor states of the former Yugoslavia, from which it declared independence in 1991. It became a member of the United Nations in 1993, but, as a result of an ongoing dispute with Greece over the use of the name Macedonia, was admitted under the provisional description the former Yugoslav Republic of Macedonia (sometimes unofficially abbreviated as FYROM), a term that is also used by international organizations such as the European Union, the Council of Europe and NATO.

A landlocked country, the Republic of Macedonia is bordered by Kosovo to the northwest, Serbia to the north, Bulgaria to the east, Greece to the south, and Albania to the west. It constitutes approximately the northwestern third of the larger geographical region of Macedonia, which also comprises the neighbouring parts of northern Greece and smaller portions of southwestern Bulgaria and southeastern Albania. The country's geography is defined primarily by mountains, valleys, and rivers. The capital and largest city is Skopje, which is home to roughly a quarter of the nation's 2.06 million inhabitants. The majority of the residents are ethnic Macedonians, a South Slavic people. Albanians form a significant minority at around 25 percent, followed by Turks, Romani, Serbs, and others.
WHO country profile (http://www.who.int/gho/countries/mkd.pdf?ua=1)
WHO Cisid data [http://data.euro.who.int/cisid/?TabID=399803]

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3.4.2 Country related hepatitis publications


In their review Domont et al. (1) reported that chronic hepatitis C virus (HCV) infection was associated with cardiovascular disease (CVD) increased risk and interferon-based therapy (IBT) revealed a beneficial impact on this risk (1). Apart from other infectious agents associated with CVD, mentioned by the authors (1), the widespread Helicobacter pylori infection (Hp-I) is strongly associated with chronic HCV liver disease in Europe and other ethnic populations and Hp eradication holds promise for the improvement of the long-term health condition of patients with chronic HCV infection (2-3). Moreover, a large body of evidence has linked Hp-I to CVD (2,4). In this regard, our series demonstrated that increased fibrinogen levels (a serum inflammatory marker mentioned by the authors (1) and an independent risk factor for CVD), are associated with Hp-I and can be significantly reduced by Hp eradication. Other relative follow-up studies also reported that Hp eradication is associated with modification of certain CVD clinical and biochemical parameters (2,4). This article is protected by copyright. All rights reserved.


BACKGROUND: It has been shown that single nucleotide polymorphisms (SNPs) near the interleukin 28B (IL28B) gene were associated with sustained virological response following standard antivirological treatment of chronic hepatitis C. OBJECTIVES: The aim of the study was to evaluate the association between SNPs near the IL28B gene and response to the treatment of chronic hepatitis C in hemodialysis patients. PATIENTS AND METHODS: The study group
included 24 hemodialysis patients with chronic hepatitis C routinely treated with pegylated interferon alpha-2a. HCV genotype 1 was the cause of chronic hepatitis C in all study participants. Sustained virological response was determined by an assay with a sensitivity of 20 IU/mL, 6 months after completion of the antiviral treatment. The genotyping of the three most widely studied IL28B gene polymorphisms (rs12979860, rs8099917, and rs12980275) was performed in all study participants. RESULTS: Sustained virological response was achieved in 50% of the treated patients. The treatment response was significantly associated with the CC genotype of rs12979860, TT genotype of rs8099917, and AA genotype of rs12980275 (p = 0.003, p = 0.009, and p = 0.012, respectively). CONCLUSIONS: The three most widely studied SNPs near the IL28B gene were associated with sustained virological response following antivirological treatment of chronic hepatitis C in hemodialysis patients.


The genome-wide association studies have identified a strong association between interleukin 28B (IL28B) gene polymorphisms and the response to treatment in patients with hepatitis C virus (HCV) infection. The aim of the study was to evaluate the association between three most widely studied IL28B gene polymorphisms and the response to antiviral treatment of chronic hepatitis C. We performed the genotyping of the three IL28B gene polymorphisms: rs12979860, rs8099917, and rs12980275 in 72 Caucasian patients with chronic hepatitis C, previously treated with the combination therapy of pegylated interferon alpha (PEGIFN alpha) and ribavirin (RBV). The patients included in the study had finished the treatment regimen at least 6 months before enrolling in the study. We used the sustained viral response (SVR) for the evaluation of the effectiveness of the antiviral treatment, and it was tested with an assay with a sensitivity of 20 IU/mL. An SVR was achieved in 59.7% (43/72) of the treated patients. The three IL28B gene polymorphisms (CC genotype of rs12979860, TT genotype of rs8099917, and AA genotype of rs12980275) were associated with the SVR (p = 0.029, p = 0.016, and p = 0.028, respectively) in the study patients with chronic hepatitis C treated with the combination therapy of PEGIFN alpha and RBV. The association of IL28B gene polymorphisms with the treatment response points to the possibility of personalized medicine for the treatment of HCV infection.


Occult hepatitis C virus (HCV) infection is characterized by the presence of HCV RNA in the liver cells or peripheral blood mononuclear cells of the patients whose serum samples test negative for HCV RNA, with or without presence of HCV antibodies. The present study reviews the existing literature on the persistence of occult hepatitis C virus infection, with description of the clinical characteristics and methods for identification of occult hepatitis C. Occult hepatitis C virus infection was detected in patients with abnormal results of liver function tests of unknown origin, with HCV antibodies and HCV RNA negativity in serum, and also in patients with spontaneous or treatment-induced recovery from hepatitis C. The viral replication in the liver cells and/or peripheral blood mononuclear cells was present in all clinical presentations of occult hepatitis C. The peripheral blood mononuclear cells represent an extra-hepatic site of HCV replication. The reason why HCV RNA was not detectable in the serum of patients with occult hepatitis C, could be the low number of circulating viral particles not detectable by the diagnostic tests with low sensitivity. It is uncertain whether occult hepatitis C is a different clinical entity or just a form of chronic hepatitis C virus infection. Data accumulated over the last decade demonstrated that an effective approach to the diagnosis of HCV infection would be the implementation of more sensitive HCV RNA diagnostic assays, and also, examination of the presence of viral particles in the cells of the immune system.

Davalieva, K., Kiprijanovska, S. and Plaseska-Karanfilska, D. "Fast, reliable and low cost user-
Early detection and genotyping of HCV infection is important for disease management. It is important to develop fast and cost-effective semi-automated techniques allowing an accurate and reproducible detection, quantification and genotyping of HCV. The proposed protocol includes a real-time RT-PCR assay for HCV detection/quantification and a type-specific one-tube RT-PCR assay for genotyping. Both assays detect genotypes 1-4 as intended. The limit of detection was 112IU/ml for the real-time assay and 600 +/- 278IU/ml (mean +/- SD) for the genotyping assay. Concordance between the real-time assay and AMPLICOR HCV v2.0 test was 100%. The real-time assay has wide linear dynamic range of detection and quantification and excellent reproducibility with 2% and 0.75% coefficients of variations, for inter- and intra-assays, respectively. The observed correlation with AMPLICOR HCV Monitor v2.0 kit was linear with the correlation coefficient of 0.988. The diagnostic specificity and sensitivity of the genotyping assay, tested on 102 samples, was 100% and 95%, respectively. The overall procedure of HCV diagnosis is completed within 6h in a closed system with minor contamination risk. In addition to being fast and cost-effective, this approach is reproducible and avoids post-PCR enzymatic and hybridization steps while detecting and genotyping HCV with high clinical sensitivity.


BACKGROUND AND OBJECTIVES: Emerging infections abroad pose a threat to the safety of blood, donated by travelling blood donors. In this study, the yield of donor deferral after travelling was evaluated, by comparing the estimated numbers of infected donors returning from various affected areas. METHODS: A deterministic model was applied to calculate the number of infected donors, returning from six areas affected by outbreaks: Greece - Macedonia (West Nile fever), Italy - Emilia Romagna (West Nile fever), Thailand (chikungunya), Latvia (hepatitis A), central Turkey (Sicilian sandfly fever) and Italy - Tuscany (Toscana sandfly fever).

RESULTS: The estimated number of infections among returning blood donors was surprisingly low, ranging from 0.32 West Nile virus-infected donors per year returning from Macedonia (Greece) to approximately 0.005 infected donors per year returning respectively from Tuscany (sandfly fever), Latvia (hepatitis A) and central Turkey (sandfly fever). CONCLUSION: The yield of the temporary exclusion of blood donors travelling to a specific, affected area is low, but the continuous monitoring of emerging infections and the timely assessment of new threats are laborious and imperfect. Safety measures may be instituted after the greatest threat of a new outbreak has passed. A general deferral of travelling donors may be more appropriate than targeted measures. It can be argued that all donors who stayed outside their country or continent of residency should be deferred for 4 weeks.


The prevalence of hepatitis C virus (HCV) genotypes depends on geographical location. HCV genotyping is important for epidemiological investigations and treatment management. The aim of this study was to determine the HCV genotype prevalence in the most prominent risk groups in the Republic of Macedonia in the last 5 years and to evaluate its association with patient’s age, gender, and mode of transmission. A total of 1,167 HCV positive patients, divided into three risk groups (intravenous drug use, chronic hemodialysis, and other risk factor), were genotyped using an in-house ASO hybridization method with genotype-specific oligonucleotide probes. The genotypes 1, 2, and 3 were present with 52.2%, 0.6%, and 47.0%, respectively. Genotype 1 was most prevalent in hemodialysis (89.0%) and other risk factor group (53.8%). It was found associated independently with hemodialysis, age </=40 and female gender. Genotype 3 predominated in intravenous drug users (64.0%) and was associated significantly also with age </=40 and male gender. Multivariable logistic regression analysis pointed out hemodialysis (P < 0.0001, Exp (B) = 12.0) as a positive predictor factor for genotype 1 and age </=40 (P = 0.021, Exp (B) = 1.8) and intravenous drug use (P < 0.0001, Exp (B) = 8.4)
as a positive predictor factors for genotype 3. In conclusion, the main transmission route of HCV infection in the Republic of Macedonia is intravenous drug use, followed by hemodialysis. HCV genotypes 1 and 3 dominate in these two most prominent risk groups in the Republic of Macedonia.


Ultrasound examination was performed in 80 hemodialysis (HD) patients with chronic hepatitis C in order to determine the ultrasound predictors of compensated liver cirrhosis. The ultrasound score (US) was calculated from the morphological parameters (liver size, morphology, surface, echogenicity and spleen volume) and the hemodynamic parameters (portal vein diameter and portal vein mean flow velocity). The US ranged from 0 to 200, with a cut-off value of 66, for discrimination between absence and presence of liver cirrhosis. A logistic regression model with stepwise variable selection was used to determine predictors of the progression of liver disease. According to the calculated US, patients were divided into two groups. The first group consisted of 37 (46.3%) patients with US greater than 66, indicating the presence of compensated liver cirrhosis. The second group included 43 (53.7%) patients without liver cirrhosis, with US equal to or less than 66. The value of liver morphology was significantly higher, but the portal vein flow velocity was significantly lower in patients with compensated liver cirrhosis compared with those without cirrhosis. Furthermore, rounded liver surfaces and increased liver echogenicity were significantly more frequent in patients with compensated liver cirrhosis compared with the non-compensated group. Logistic regression model with stepwise discriminant analysis identified liver morphology, liver echogenicity and portal vein mean flow velocity as independent ultrasound predictors of compensated liver cirrhosis in HD patients with chronic hepatitis C. Ultrasound examination could be used for non-invasive diagnosis of compensated liver cirrhosis, with accurate estimation of the disease severity in HD patients with chronic hepatitis C.


Hepatitis C virus (HCV) is a major public health problem. It is a leading cause of chronic liver disease and the most common indication for liver transplantation. The therapy for eradication of HCV infection is successful in only 50.0-80.0% of patients and is highly dependent on the HCV genotype. Molecular detection and characterization of HCV in the Republic of Macedonia started in 1990. Since then, more than 4000 samples have been analyzed at the Research Centre for Genetic Engineering and Biotechnology (RCGEB) "Georgi D. Efremov," Skopje, Republic of Macedonia. The prevalence of HCV infections in the healthy population of the Republic of Macedonia was found to be 0.4%, while it varies between 23.0 and 43.0% in different at-risk groups of patients. The prevalence of HCV genotypes, according to associated risk factors in HCV infected patients from the Republic of Macedonia, was analyzed. We found genotype 1 to be predominant in a group of hemodialysis patients, while genotype 3 was predominant in intravenous (IV) drug users. Association of six polymorphisms in the Oligoadenylate synthetase (OASL)-like interferon-stimulated gene with a sustained virological response was also analyzed. Our preliminary results suggest that non ancestral alleles in four of the six studies polymorphisms in OASL gene are associated with sustained virological response among HCV infected patients in R. Macedonia.


Primary immunization at 3, 4.5, and 6 months and boosting between 15 and 27 months of age with combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus (DTPa-HBV-IPV) vaccine was compared with separate administration of DTPa-HBV and IPV to healthy
children (trials DTPa-HBV-IPV-019/033). Antibody titres were measured before and 1 month after primary and booster courses. Solicited local and general symptoms were recorded using diary cards. One month after primary vaccination, all children in both groups developed antibody titres above the assay cut-off for all vaccine components. Significantly higher anti-diphtheria, anti-pertactin (PRN) and anti-polio GMTs were measured following DTPa-HBV-IPV than DTPa-HBV plus IPV. Prior to boosting similar seroprotection/seropositivity rates were recorded in both groups. After boosting all children had seroprotective levels of diphtheria, tetanus, polio and HBV. Criteria for pertussis vaccine response were fulfilled in most children. Significantly higher anti-PRN GMTs were measured following DTPa-HBV-IPV than DTPa-HBV plus IPV. There was no difference between groups in the incidence or intensity of local and general symptoms after primary or booster vaccination, except for fever which was more frequent after the booster dose in the combined vaccine group. Both vaccine regimens were well tolerated and immunogenic, however the combined administration has the advantage of being administered as a single injection.

Presentation related references

Republic of Macedonia Victoria Chalovska

2. Consensus for prevention, diagnostic, rationale for therapy and monitoring of patients with hepatitis B and C in the Republic of Macedonia. Ministry of Health of Republic of Macedonia, 2005
3. Patient organisation

Hepar Centar Bitola - Macedonia
https://www.facebook.com/hepar.centar

B18. Bosnia-Hezegovina
http://www.hepatitis.rs.ba/

HRONOS - Serbia
http://www.hronos.rs
4. **WHO Euro Action plan for the health sector response to viral hepatitis**

EUR/RC66/R10 Action plan for the health sector response to viral hepatitis in the WHO European Region

At the Sixty-sixth Session of the WHO Regional Committee for Europe (RC66), the 53 Members States of the WHO European Region have unanimously adopted the first ever “Action plan for the health sector response to Viral Hepatitis in the WHO European Region”, and endorsed the EUR/RC66/R10. Many Member States and WHO partners have voiced their support through strong statements of support at RC66.

[View Document](http://www.euro.who.int/__data/assets/pdf_file/0008/315917/66wd10e_HepatitisActionPlan_160555.pdf?ua=1)
5. Bibliography of the Speakers

List of publications achieved via speaker’s form, when this form was not available a Pubmed MEDLINE search was performed on Name of the speaker in [Author]-field. If more than 10 references were available only the most recent articles are shown.

**ALKETA HILA, Minstry of health of the republic of Albania**
From speaker’s form:

**ELONA KURETA** Institute of Public Health, Department of Infectious Diseases Control and Prevention
From speaker’s form:
MIMOZA BASHO, Institute of Public Health, Department of control of Infectious Diseases
From speaker's form:

VJOLLCA DURO, University Hospital "Mother Theresa", Faculty of Medicine, Laboratory department, Microbiology
From speaker's form:


EUGENA TOMINI, Institute of Public Health
From speaker’s form:


2. Eugena Erindi Tomini, Silvia Bino, Mimoza Basho, Shpetim Qyra, Artan Simaku Revista Challenges Review; “Biological Surveillance of infectious agents among multi blood transfusions persons in Albania. ISSN-2227-8134, No.1- 2013


4. Eugena Erindi Tomini, Silvia Bino, Mimoza Basho, Shpetim Qyra, Artan Simaku Medicus “Viral Hepatitis in Multi blood transfusions in Albania”., ISSN 1409-6366 UDC 61, Vol. XVIII(1), 2013


ROLAND BANI, Institute of Public Health, Epidemiology and Control of Infectious Diseases
From speaker’s form:
1. HIV Risky Behaviours of Men Who Have Sex with Men in Tirana, European Scientific Journal, Jul 2015

ADRIANA BABAMETO, University Hospital "Mother Theresa", Gastro Hepatology Department
From speaker’s form:


SILVIA BINO, Institute of Public Health
(10 most recent articles –from Pubmed search [Bino S [author])


MILAN MISKOVIKJ, Hepar Centar Bitola, patient organization
https://www.facebook.com/hepar.centar

ANTONS MOZALEVSKIS (World Health Organization Regional Office for Europe Focal Point for Viral Hepatitis)
www.euro.who.int/hepatitis
(recent articles –from Pubmed search [MOZALEVSKIS A [author])

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**LEPOSAVA GAROTIC**, Institute of Public Health of Belgrade, Center for Disease Control and Prevention

From speaker’s form


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**XHEVAT JAKUPI**, National Institute of Public Health of Kosovo, Microbiology

(recent articles –from Pubmed search [JAKUPI X [author]])


VICTORIA CHALOVSKA, University Clinic of Gastroenterohepatology, Medical Director
From speaker’s form

ERIDA NELAJ, Institute of Public Health, Department of Infectious Diseases Control and Prevention
(recent articles –from Pubmed search [NELAJ E[author])


JOVAN BASHO, University Hospital "Mother Theresa", Gastroenterology and Hepatology
(recent articles – from PubMed search [BASHO J [author]])


NAJADA COMO, University Hospital "Mother Theresa", Infectious Diseases Department
From speaker’s form


**PASKAL CULLUFI, University Hospital "Mother Theresa", Pediatric Department**

(Recent articles – from Pubmed search [CULLUFI P[author]])


**DAVID FITZSIMONS, rapporteur, Prévessin, France**


