GUIDELINES FOR IMMIGRANT HEALTH

Appendix 7: Screening for hepatitis C infection: evidence review for newly arriving immigrants and refugees

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ABSTRACT

Background: Immigrant populations have increased mortality from chronic viral hepatitis and from hepatocellular carcinoma compared to the Canadian born population. A large proportion is likely attributable to undetected and untreated chronic hepatitis C infection, most often acquired through unsafe injections or medical procedures in their countries of origin. Despite this, there are no systematic targeted screening programs in Canada for chronic hepatitis C infection in the immigrant population. We conducted an evidence review to determine the burden of hepatitis C infection in the immigrant population and to assess the effectiveness of screening and treatment programs for chronic hepatitis C infection.

Methods: Systematic search for evidence on the burden of hepatitis C infection in the immigrant population and the benefits and harms, applicability, clinical considerations and implementation issues of screening and treatment programs for chronic hepatitis C infection in the general and the immigrant populations. The quality of this evidence was assessed and ranked using the GRADE approach.

Results: Immigrants have a higher prevalence of chronic hepatitis C (HCV) infection (~3% versus ~ 0.8%) as compared to the Canadian born population. They are also at increased risk of mortality from the complications of cirrhosis including hepatocellular carcinoma, a third of which is likely due to chronic hepatitis C. Given a similar mode of transmission some immigrants are at increased risk for infections with chronic HCV, chronic hepatitis B, and HIV. Co-infection with one of these other infections increases the risk of chronic HCV associated liver fibrosis. Treatment of chronic HCV in those with cirrhosis eliminates the risk of liver failure and reduces rates of hepatocellular carcinoma and mortality from chronic liver disease.

Interpretation: Immigrants to Canada bear a disproportional burden from chronic HCV. Many may also be co-infected with chronic hepatitis B infection or HIV which puts them at even greater risk for advanced liver disease. Immigrants would

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The cases

Tatiana is a 60 year old female from Romania and has been living in Canada for 15 years. At age 17 she was in a car accident, was hospitalized, and had several intramuscular injections and blood transfusions. She is now admitted to hospital with a one month history of abdominal swelling and is diagnosed with cirrhosis secondary to chronic hepatitis C. What type of screening could she have benefited from when she arrived in Canada?

Ashraf is a 49 year old male from Egypt living in Canada for 25 years who has been recently diagnosed with cirrhosis and hepatocellular carcinoma. He is found to be co-infected with both chronic hepatitis C and chronic hepatitis B. What type of screening could he have benefited from when he arrived in Canada?

Introduction

Chronic hepatitis C (HCV) infection is an important health problem worldwide with an estimated 170 million prevalent cases, 3-4 million newly infected cases each year and a mean global seroprevalence of 2.2-3.0%. [1,2] Approximately 70% (50-85%) of those with acute infection develop chronic HCV infection and 20% of these individuals develop cirrhosis and 1-5% develop hepatocellular carcinoma (HCC) during the two decades following initial infection.[1,2] Persons with chronic HCV are asymptomatic and only come to clinical attention when they develop complications of advanced liver disease a situation that could have been prevented with early screening and appropriately timed treatment. Canada is a low hepatitis C burden country with an estimated seroprevalence of ~0.8%.[3] The majority of chronic HCV infections in Canada occur in individuals who are previous or current injection drug users (IDU) however, it is estimated that ~20% of cases occur in immigrants.[3] Chronic hepatitis C infection is likely an unrecognized health burden in the immigrant population given the fact that they have increased mortality from chronic viral hepatitis (2-4 fold) and hepatocellular carcinoma (2-5 fold) as compared to the Canadian population, a large proportion of which is likely due to chronic HCV infection.[4,5] There is no effective vaccination to prevent against transmission of HCV. Chronic hepatitis C infection however, can easily be detected through widely available screening blood tests and standard treatment regimens (PEG-interferon and Ribivirin) are moderately successfully (50% overall) in achieving sustained viral response (SVR) which in those with cirrhosis decreases disease progression to liver failure and HCC.

Standard treatment however, is long (24-48 weeks) and is often difficult to tolerate.[6,7] Recent data on combination therapies with protease inhibitors have shown substantially improved efficacy (70% vs 50%) in those with genotype 1 with shorter duration of treatments and may change the standard of therapy in the near future, making screening and appropriately timed treatment for chronic HCV infection an important strategy to control the burden of chronic HCV.[8] We conducted an evidence review to determine the need to screen for Hepatitis C in the immigrant population. CCIRH recommendations on screening for Hepatitis C are outlined in Box 1.

Box 1: Recommendations on Hepatitis C from the Canadian Collaboration for Immigrant and Refugee Health

Screen for Hepatitis C antibody in all immigrants and refugees originating from countries with an expected prevalence of disease of ≥ 3%. Refer if positive to a colleague with expertise in managing patients with Hepatitis C infection.

Basis of Recommendation

- **Balance of benefits and harms:** Immigrants have a higher prevalence of chronic hepatitis C infection (~3% versus ~0.8%) as compared to the Canadian born population. They are also at increased risk of mortality from chronic viral hepatitis and hepatocellular carcinoma, a third of which is likely due to chronic hepatitis C infection. Treatment with PEG-interferon and ribavirin (standard of care) achieves a higher sustained viral response (SVR) compared to interferon plus ribavirin (SVR 50% versus 38%; RR 0.80 CI 0.74-0.88). Persons with cirrhosis due to chronic HCV infection who did not achieve SVR had higher rates of hepatocellular carcinoma (HR 2.59 95% CI 1.13-5.97) and liver-related mortality (HR 6.97 95% CI 1.71-28.42) compared to those who achieved SVR. Harms include multiple adverse effects of treatments.
- **Quality of evidence:** Moderate
- **Values and preferences:** The committee attributed more value to the diagnoses and prevention of serious complications from hepatitis than to the cost and risk of multiple adverse effects of treatments.

Methods

We used the 14-step method developed by the Canadian Collaboration for Immigrant and Refugee Health.[9] A clinician summary table was used to highlight the population of interest, the epidemiology of disease, population-specific considerations and potential clinical

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actions (Appendix 2). The first search was done to identify relevant systematic reviews (including those that might be contained in guideline documents) to address the effectiveness of screening for Hepatitis C and the efficacy of Hepatitis C treatment in the immigrant population. For this search 5 electronic databases MEDLINE (Ovid), MEDLINE InProcess, EMBASE, CINAHL, and Cochrane Database of Systematic Reviews from 1950- Jan 28, 2010 were searched. The terms immigrant or refugee AND Hepatitis C were used and restricted to guidelines and systematic reviews. A similar search for systematic reviews and guidelines for Hepatitis C with the same objectives in the general population for the same 5 databases was performed but the search dates were restricted to Jan 1, 1996-January 28, 2010. Any eligible systematic reviews were assessed for their application of a consistent and comprehensive approach, transparency (clarity about the process involved), quality of methods (appropriate methods and analysis) and relevance. A web based search up until September 14, 2010 for other guidelines pertaining to Hepatitis C was done in the CMA Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guideline Clearing House (http://www.guideline.gov/. The websites of official organization that produce guidelines was also searched and included: the Canadian Task Force on Preventative Health Care (CTFPHC), the Public Health Agency of Canada (PHAC), Canadian Association for the Study of the Liver (CASL), the Association of Medical Microbiology and Infectious Diseases (AMMI) Canada, the U.S. Preventative Task Force (USPTF), Centre for Disease Control and Prevention (CDC), American Society for the Study of Liver Disease (AASLD), Infectious Disease Society of America (IDSA), National Institute of Clinical Excellence (NICE), and the World Health Organization (WHO).

A separate search for Hepatitis C and the immigrant population to address population specific concerns classified as; 1) baseline risk or prevalence in comparison to the Canadian born population; 2) risk of clinically important outcomes; 3) genetic and cultural factors (e.g. preferences values, knowledge); and 4) compliance variation (including at the primary care to search for population specific burden) was also performed. We searched the terms Hepatitis C AND immigrants or refugees in 5 electronic databases MEDLINE, MEDLINE InProcress, CINAHL, Embase and Cochrane Database of Systematic Reviews from 1950 to January 28, 2010.

Synthesis of evidence and values

The evidence from systematic reviews and pertinent cohort studies and clinical trials was synthesized using the GRADE summary of findings tables which assesses both relative and absolute effects of interventions (relative risk and absolute event rate). The quality of each outcome was also appraised using the GRADE quality assessment tool which assesses study limitations, directness, precision, consistency, and publication bias across all studies (Box 2). In the search and synthesis of data on clinical considerations we identified both clinically relevant considerations and implementation issues relevant to our population. Finally, we identified gaps in the research and evidence base

Results

In the search for systematic reviews and guidelines for immigrants and Hepatitis C, 31 records were identified, but none met eligibility criteria. The search for systematic reviews and guidelines involving the general population and Hepatitis C, 4714 articles were identified and 243 full-text articles were assessed for eligibility. A total of 21 met eligibility criteria (were systematic reviews or guidelines) and covered the topics of cost-effectiveness,[10-13] diagnosis,[14-16] epidemiology[2,17], HCC,[18] knowledge and compliance,[19,20] screening,[21] and treatment.[6,7,22-27] A total of 15 were included (relevant and recent) in the summary of findings table and in the discussion of effectiveness of screening and treatment to decrease hepatitis C associated morbidity and mortality. In addition, a search for immigrant and Hepatitis C identified 250 articles of which 50 were relevant and addressed the following areas; epidemiology, and knowledge and compliance with screening treatment in the immigrant population (Appendix 1).

What is the burden of hepatitis C in the immigrant population?

Canada is a low prevalence country for chronic HCV infection (seroprevalence ~0.8%) however, mortality from non-A, non-B hepatitis (the majority of which is presumed to be due to chronic HCV infection) has increased 3.4 fold (0.12/100,000 to 0.41/100,000) in Canada over the past 30 years (1979 to 1997) with a 2.2 fold increase in incidence of HCC during the same time period.[3,28,29] This is thought to be due to the uncontrolled epidemic in injection drug users and importation of the virus due to changing patterns of migration. Over the past 40 years the majority of new immigrants have originated from countries with a higher seroprevalence hepatitis C than that in Canada.[3] The

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Table 1: Hepatitis C, prevalence rates by country/area in 1999 [34]					
Country/area	Rates (%)	Country/area	Rates (%)	Country/area	Rates (%)
Algeria	0.2	Guatemala	0.7	Portugal	0.5
Angola	1.0	Guinea	10.7	Puerto Rico	1.9
Argentina	0.6	Haiti	2.0	Qatar	2.8
Australia	0.3	Honduras	0.1	Republic of Korea	1.7
Austria	0.2	Hong Kong Special Administrative Region of China	0.5	Republic of Moldova	4.9
Bangladesh	2.4	Hungary	0.9	Réunion	0.8
Belarus	1.4	Iceland	0.1	Romania	4.5
Belgium	0.9	India	1.8	Russian Federation	2.0
Belize	0.1	Indonesia	2.1	Rwanda	17.0
Benin	1.5	Iraq	0.5	Saudi Arabia	1.8
Bhutan	1.3	Ireland	0.1	Senegal	2.9
Bolivia	11.2	Israel	0.4	Seychelles	0.8
Botswana	0.0	Italy	0.5	Sierra Leone	2.0
Brazil	2.6	Jamaica	0.3	Singapore	0.5
Bulgaria	1.1	Japan	2.3	Slovakia	0.4
Burundi	11.1	Jordan	2.1	Solomon Islands	0.9
Cambodia	4.0	Kenya	0.9	Somalia	0.9
Cameroon	12.5	Kiribati	4.8	South Africa	1.7
Canada	0.1	Kuwait	3.3	Spain	0.7
Central African Republic	4.5	Libyan Arab Jamahiriya	7.9	Sudan	3.2
Chad	4.8	Luxembourg	0.5	Suriname	5.5
Chile	0.9	Madagascar	3.3	Swaziland	1.5
China	3.0	Malaysia	3.0	Sweden	0.003
Colombia	1.0	Mauritania	1.1	Switzerland	0.2
Costa Rica	0.3	Mauritius	2.1	Thailand	5.6
Croatia	1.4	Mexico	0.7	Togo	3.3
Cuba	0.8	Micronesia (Federated States of)	1.5	Trinidad and Tobago	4.9
Cyprus	0.1	Mongolia	10.7	Tunisia	0.7
Czech Republic	0.2	Morocco	1.1	Turkey	1.5
Democratic Republic of Congo	6.4	Mozambique	2.1	Uganda	1.2
Denmark	0.2	Nepal	0.6	Ukraine	1.2
Dominican Republic	2.4	Netherlands	0.1	United Republic of Tanzania	0.7
Ecuador	0.7	New Zealand	0.3	United Arab Emirates	0.8
Egypt	18.1	Nicaragua	0.6	United Kingdom	0.02
El Salvador	0.2	Niger	2.5	United States of America	1.8
Ethiopia	0.8	Nigeria	1.4	Uruguay	0.5
Finland	0.02	Norway	0.1	Vanuatu	0.9
France	1.1	Oman	0.9	Venezuela	0.9
French Guiana	1.5	Pakistan*	2.4	Viet Nam	6.1
Gabon	6.5	Panama	0.1	West Bank and Gaza Strip	2.2
Germany	0.1	Papua New Guinea	0.6	Yemen	2.6
Ghana	2.8	Paraguay	0.3	Zambia	0.0
Greece	1.5	Peru	1.6	Zimbabwe	7.7
Grenada	1.1	Philippines	3.6		
Guadeloupe	0.8	Poland	1.4		

*Rates in Pakistan have been reported to be as high as 4.9% - 6.0%[1,72]
The estimated prevalences in this table are based on published reports complied by the WHO in 1999[34] except for those listed below
Hepatitis C prevalence data available from other publications
Africa: Cote d'Ivoire (3.3%), Burkino Faso (4.9%) Tanzania (3.2%)[73] Asia: Myanmar (3.9%)[1]

seroprevalence of chronic HCV infection in the immigrant population is estimated to be ~3% (range 0.1-18% for different global regions of origin)[30-33] and likely reflects rates in their country of origin (Table 1, Table 2 and Figure 2).[34] In a recent Canadian study, immigrants had a 1.8-3.8 fold increased mortality from viral hepatitis and 2.2-4.9 fold increased mortality from hepatocellular carcinomas (HCC) as compared to the Canadian population.[4] It is unclear what proportion of chronic

Table 2: Hepatitis C, estimated prevalence rate and number infected, by WHO region (1999)[34]				
WHO Region	Population (millions)	Estimated Prevalence	Infected Population (millions)	No Data Available
Africa	602	5.3	31.9	12
Americas	785	1.7	13.1	7
Eastern Mediterranean	466	4.6	21.3	5
Europe	858	1.03	8.9	19
South-East Asia	1 500	2.15	32.3	3
Western Pacific	1 600	3.9	62.2	11

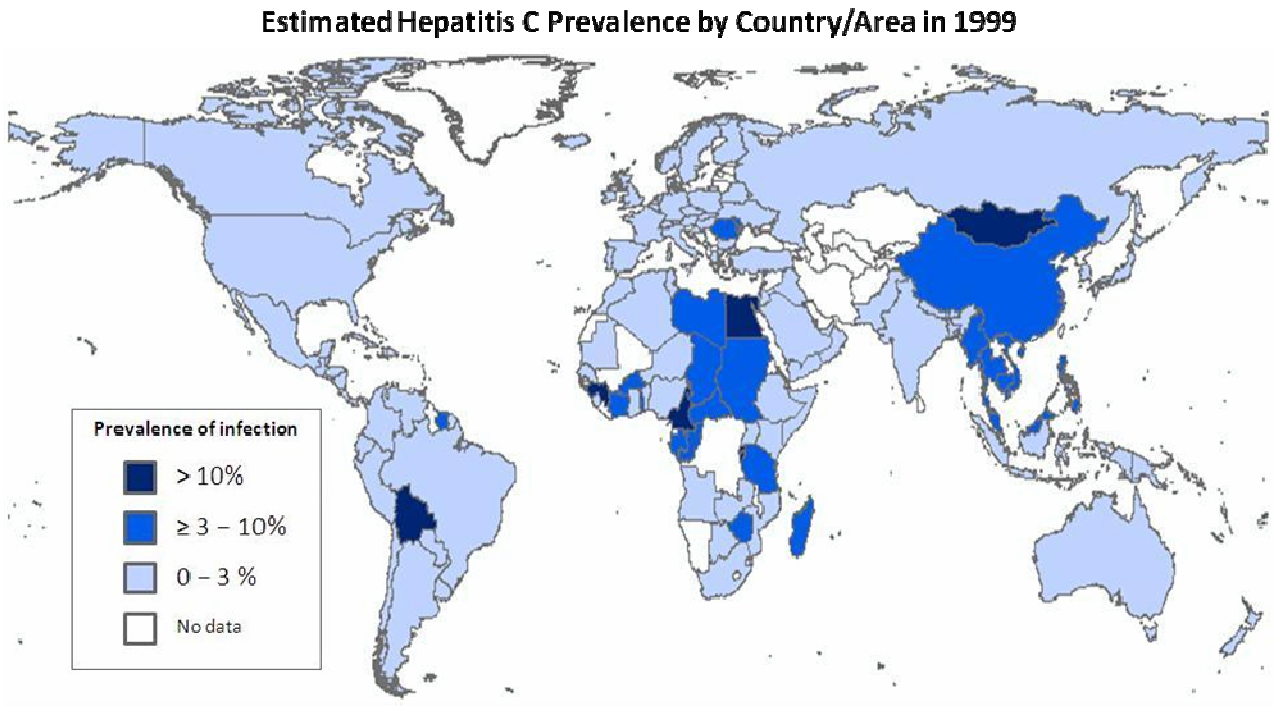

Figure 2: Estimated Hepatitis C Prevalence by County/Area in 1999

*Rates in Pakistan have been reported to be as high as 4.9% - 6.0%[1,72]
The estimated prevalences in this map are based on published reports complied by the WHO in 1999[34] except for those listed below
Hepatitis C prevalence data available from other publications
Africa: Cote d'Ivoire (3.3%), Burkino Faso (4.9%) Tanzania (3.2%)[73] Asia: Myanmar (3.9%)[1]

viral hepatitis and HCC mortality are attributable to chronic HCV infection in the immigrant population but this may be up to 31%. This is extrapolated from the fact that Hepatitis B and C account for 80-90% of all HCC worldwide and that 31% is attributable to chronic HCV infection.[5,18]

The primary mode of transmission of HCV is percutaneous and is much less frequently transmitted sexually or perinatally. As a result the group at greatest risk for HCV in Canada are former or current injection drug users (IDU). Immigrants are probably also an important unrecognized risk group for chronic HCV infection in Canada but unlike IDU are more likely to have acquired their infection through unsafe health care related injections, or other medical equipment,

unscreened blood products or surgical procedures in their countries of origin. It is estimated that up to 40% of chronic HCV infections globally are acquired through unsafe injections or medical procedures.[35,36] The proportion of immigrants ineligible for treatment due to co-morbidities such as psychiatric illness, current IDU or medical conditions is lower as compared to those who acquired their infection in Canada. In a recent study of persons with chronic HCV infection, immigrants were less likely to have a history of mental health illness (26% vs 54%, p=<0.001) and were less likely to have a history of IDU (20% vs 67%, p=<0.001) as compared to those born in Canada.[37]

There are 6 HCV genotypes and many subtypes (a, b, c etc.). Genotypes 1 to 3 are widely distributed globally, with the remaining genotypes have a more regional distribution (see Table 3)[1,2]. More than 70% of the chronic HCV infections in North America are due to genotype 1 whereas in certain countries other genotypes may predominant (ie Egypt genotype 4 and Pakistan genotype 3). Certain ethnic groups (such as South East Asians) have a better response to therapy as compared to other ethnic groups.[38]

Does screening and treating hepatitis C decrease associated morbidity and mortality?

Screening tests for hepatitis C

Widely available third generation EIA serologic tests to detect anti-HCV antibodies are highly sensitive (97%) and specific (99%). False positives occur in populations where the prevalence of hepatitis C is low and false negatives may occur in the setting of severe immunosuppression such as in those with HIV, solid organ transplants, hypo- or agammaglobulinemia or in patients on hemodialysis.[15,16] If positive a nucleic acid test to detect hepatitis C RNA (qualitative or quantitative) should be performed to confirm the presence of circulating virus.[14]

Efficacy of hepatitis C treatment

The current standard for HCV treatment is combination therapy with a pegylated interferon and ribavirin and achieves an overall sustained viral response (SVR) of about 50% in all patients.[7,22,24,25,39] SVR is associated with improved clinical outcomes. In those with cirrhosis due to chronic HCV infection who have not achieved SVR rates of hepatocellular carcinoma (HR 2.59 95% CI 1.13-5.97) and liver-related mortality (HR 6.97 CI 1.71-28.42) were higher as compared to those who did achieved SVR (Table 4).[40-42] The response rate, dosage of the medications and duration of treatment (ranges from 24-48 months) are determined by the HCV genotype. For genotype 1 infection the SVR ranges from 42% to 46% and requires 48 weeks of treatment. The SVR is better for those with genotype 2 (74%) and less for genotype 3 as compared to genotype 1 and are given for a shorter duration (usually 24 weeks).[7,22-25,43] For other genotypes (4, 5, 6) the results are less well defined, but appear better than for genotype 1 but not as good as for genotypes 2 and 3.[44,45] Treatment however, is associated with numerous side-effects and 10%-14% discontinue therapy due to an adverse event most commonly psychiatric symptoms or severe anemia.[7,46] Persons with advanced cirrhosis are less likely to achieve SVR, highlighting the importance of screening and initiating treatment prior to the presence of advanced liver disease.[47,48] Treatment options for HCV will change dramatically in the upcoming few years as there are several promising new agents at all stages of development.[8] Recent results of combination regimens with protease inhibitors and standard therapy have shown substantial improved efficacy (70% vs 50%) in those with genotype 1 and shorter duration of treatments.[8,49] These new combinations will likely change the standard of therapy in the near future making screening for and giving appropriately timed treatment for chronic HCV infection an important strategy to control the burden of chronic HCV. Management during therapy often requires a multidisciplinary approach and all patients found to be positive should be referred to a health professional with experience managing patients with hepatitis C infection.

Table 3: Distribution of HCV genotype by Region of Origin

Genotype	Region of Origin
1a	Northern Europe and North America
1b	Southern and Eastern Europe and Japan
2	Europe more than in North America
3	South Asia (especially Pakistan)
4	Middle East, Egypt, and central Africa
5	South Africa
6	South East Asia

*Genotypes 1 to 3 are the most widely distributed globally, with gentoypes 1a and 1b accounting for 60% of infections worldwide. Certain genotypes are predominantly found in certain geographic regions.

Cost effectiveness of screening for hepatitis C

Screening for hepatitis C in most studies has only been found to be cost-effective when the prevalence of hepatitis C is high (>10%) due to relatively poor efficacy of treatment (overall 50%), the high side-effect profile and the low proportion of persons eligible for treatment due to underlying co-morbidites such as substance abuse, psychiatric illness or medical diseases (37%).[13] In a study by Plunkett and Grobman, screening pregnant women was found not to be cost-effective. They assumed an 1% HCV seroprevalence and 48 weeks of PEG IFN and ribavirin treatment, but they only calculated direct costs.[50] The study by Singer and Younossi also found screening for HCV in the general US population not to be cost-effective. They assumed 3% HCV seroprevalence, that only 20% of positive individuals would be given treatment (due to underlying co-morbidities) that the response rate to (IFN and Ribavirin) in genotype 1 patients would be 37% and that 72% of all patients would be genotype 1.[51] In a sensitivity analysis however, they found that if 50% of HCV positive individuals started treatment then screening would be cost-effective at a seroprevalence of 3%.[50,51] We feel that it is justified to recommend screening the immigrant population when the estimated HCV seroprevalence is ≥3% given the increase in mortality from viral hepatitis and HCC in this population (30% of which is likely to be due to undetected chronic HCV), the fact that immigrants are more likely to be

Table 4. Summary of findings on pegylated interferon plus ribavirin compared to interferon plus ribavirin for chronic hepatitis C

Patient or population: Patients with chronic hepatitis C
Settings: Multiple countries (Italy, Egypt, Japan, Taiwan, Germany, Saudi Arabia, Belgium, etc.).
Intervention: Pegylated interferon plus ribavirin
Comparison: Interferon plus ribavirin
Source: Shepherd J et al. Pegylated interferon -2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation. *Health Technol Assess* 2004 Oct;8(39): iii-iv, 1-125.
Simin et al. Cochrane systematic review: pegylated interferon plus ribavirin vs. interferon plus ribavirin for chronic hepatitis C. *Aliment Pharmacol Ther* 2007 May 15;25(10):1153–62.

Outcomes	Absolute effect		Relative effect (95% CI)	No. of participants (studies)	GRADE quality of evidence	Comments
	Interferon plus ribavirin	Difference with pegylated interferon plus ribavirin (95% CI)				
Sustained virological response	489 per 1000	147 fewer per 1000 (181 to 108 fewer per 1000)	RR 0.70 (0.63 to 0.78)	1878 (2) §	High	NNT 7 (95% CI 6 to 10)
Sustained virological response	617 per 1000	123 fewer per 1000 (160 to 74 fewer per 1000)	RR 0.80 (0.74 to 0.88)	4659 (16) ¶	Low*†	NNT 9 (95% CI 7 to 14)
Dose reductions	290 per 1000	128 more per 1000 (41 to 238 more per 1000)	RR 1.44 (1.14 to 1.82)	Unknown (8) ‡¶	Moderate*	NNH 8 (95% CI 5 to 25)

Note: CI = confidence interval, GRADE = Grading of Recommendations Assessment, Development and Evaluation, NNT = number needed to treat, NNH = number needed to harm, RR = risk ratio.
* Lack of blinding; inadequate allocation concealment
† Significant heterogeity (I2 = 56%; p=0.003)
‡ Actual N unknown; only % and RR given
§ Shepherd J et al. Pegylated interferon -2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation. Health Technol Assess 2004 Oct;8(39): iii-iv, 1-125.
¶ Simin et al. Cochrane systematic review: pegylated interferon plus ribavirin vs. interferon plus ribavirin for chronic hepatitis C. Aliment Pharmacol Ther 2007 May 15;25(10):1153–62.

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eligible for treatment (due to lower underlying co-morbidities) and the improved response to treatment in the absence of cirrhosis supporting the practice of earlier detection and treatment.

Clinical considerations

Risk factors for hepatitis C: How they differ for the immigrant population

The most common risk factors for acquiring hepatitis C infection in Canada is through IDU (account for 56% of cases in Canada and IDUs have a prevalence of chronic HCV ranging from 40-80%) or older age through receipt of contaminated blood products prior to availability of serologic testing for hepatitis C.[3,6] In contrast, it is estimated that up to 40% of chronic HCV infections globally are acquired through unsafe injections or medical procedures and likely is a common mode of transmission in many immigrants.[35,36] In a recent Canadian study immigrants with chronic HCV were less likely to have a history of IDU (20% vs 67%, p=<0.001) as compared to those born in Canada.[37]

Important co-infections that may increase the risk of progressive fibrotic liver disease secondary to chronic hepatitis C.

There are several different factors such as male sex, older age at acquiring infection, an immunosuppressed state, an altered metabolic state (central obesity) and co-infection with certain infections all which increase the risk and rate of progression to liver fibrosis in those with chronic HCV infection.[52] Relative to patients with chronic HCV alone, several studies have reported increased inflammation and fibrosis in patients co-infected with chronic HCV and chronic hepatitis B, or HIV. In these patients treatment for HCV may modify the course of hepatitis C progression.[52,53] Due to shared routes of transmission co-infection with one or more of these viruses would not be unexpected. The prevalence of chronic HBV infection is ~4% (range 0.5%-15%) in the new immigrant population (see evidence review on hepatitis B).[54,55] Certain immigrant groups have a high prevalence of HIV infection >3-4% esp. refugees from Sub-Saharan Africa and immigrants from the Caribbean (see Evidence review on HIV).[56] The rapid progression of HCV infection in those co-infected with HIV is well described.[52]

Cultural and socioeconomic considerations

Knowledge of the importance of hepatitis C, its consequences and the risk factors for transmission is low in the immigrant population (30-60%), and was significantly lower than non-immigrants living in the same country.[57,58] Better knowledge of hepatitis C in the immigrant population however, was associated with a higher level of education, employment and being highly accultured.[58]

Several studies showed that more than half of primary care physicians feel they have little experience in treating HCV positive patients and have a poor understanding of the natural history of the disease.[20] Similarly, risk factors for acquiring the disease were incorrectly identified by health care professionals in many instances.[59-61] In a survey of primary care practitioners in the US 59% reported they routinely inquired about risk factors for hepatitis C and 70% indicated they tested all persons with risk factors.[62] A chart review of newly identified cases however, by the same group found very few newly identified cases of hepatitis C were tested because of physician-identified risk factors.[63] Of those who do identify higher risk patients, only 50- 75 % order the appropriate diagnostic tests and correctly interpreted the results.[59] Knowledge on treatment was also limited, with 48-63% of primary care physician surveyed aware of the optimal anti-viral therapies or of existing treatment protocols. Knowledge can be improved however, through different educational strategies tailored to the general practitioners' needs.[64,65]

The current information regarding adherence comes from studies of injection drug users compared to patients who acquired HCV through other routes.[66-68] It is difficult to draw any conclusions on treatment adherence in immigrants based on the available data as these populations differ greatly. One study by Giordano and colleagues demonstrated that with the help of a multidisciplinary health care team, the rates of successful diagnosis of HCV and treatment initiation, as well as rates of sustained virological response, did not differ between foreign-born and Canadian-born.[37]

The majority of persons with chronic HCV infection (57-85%) experience stigma by family, friends and health care professionals[69] and this is associated with decreased health seeking behaviors and decreased disclosure practices.[70] This stigma stems primarily from the association of HCV infection with IDU.[71] It is unclear what role stigmatization may play a role as a barrier to seeking screening and therapy for HCV in immigrants as we could not find data addressing this issue.

Other recommendations

The US Preventative Task Force (USPTF) does not recommend screening for hepatitis C in the general US population (seroprevalence of ~1.8%) but rather

recommends screening high risk groups such as IDU.[21] Neither the recent Canadian or American Hepatitis C Management Guidelines identify immigrants as an at risk group that should be targeted for HCV screening.[6,7]

The cases revisited

Tatiana is not a former or present IDU and likely acquired hepatitis C infection through unsafe health care related injections, unscreened blood products or surgery during her hospitalization in Romania. Persons with chronic HCV infection and cirrhosis have a lower response rate to treatment. She therefore would have benefited from screening for HCV on arrival in Canada and could have been offered treatment prior to developing cirrhosis.

Ashraf is co-infected with HCV infection and chronic hepatitis B. Co-infected individuals have an increased risk of progression to HCV associated cirrhosis and hepatocellular carcinoma. The earlier these infections are detected, the fewer complications they will have and the easier they will be to treat, highlighting the importance of screening all immigrants at risk.

Conclusions and research needs

There is very little epidemiologic data on the prevalence or burden associated with chronic HCV infection in the immigrant population. Population based studies of the seroprevalence of chronic HCV, risk factors for acquisition and the proportion that are eligible for treatment as well as the overall response rate in this population are urgently needed. Cost-effectiveness studies that determine the threshold seroprevalence at which screening should be considered will be particularly important for practitioners and policy makers alike. This will become even more pertinent with the imminent availability of new more effective and shorter antiviral combination therapies. Primary care practitioners need to be made aware that immigrants and refugees are at increased risk for chronic HCV infection and increased attributable morbidity and mortality. Given the fact that chronic HCV is an easily detectable and treatable disease that if left untreated may cause significant morbidity and mortality, it is critical that that those immigrants at risk be screened and those found to be infected referred for further management.

Key points

- Immigrants have increased mortality from chronic viral hepatitis (2-4 fold) and hepatocellular carcinoma (2-5 fold) compared to the Canadian born population, a large proportion of which is likely due to chronic HCV infection.
- Approximately 3% of immigrants are chronically infected with HCV (up to 18% in certain populations).
- The majority of immigrants likely acquire HCV infection through unsafe injections or medical procedures in their countries of origin and not through injection drug use and therefore a large proportion of immigrants are eligible for treatment.
- Screening individuals for chronic HCV and offering treatment prior to development of cirrhosis is important because in the absence of cirrhosis SVR is higher and treatment is better tolerated.

Box 2: Grading of Recommendations Assessment, Development and Evaluation Working Group grades of evidence (www.gradeworkinggroup.org)
High quality: Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality**: Further research is likely to have an important impact on our confidence in the estimate of effect and could change the estimate. **Low quality**: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality**: We are very uncertain about the estimate.

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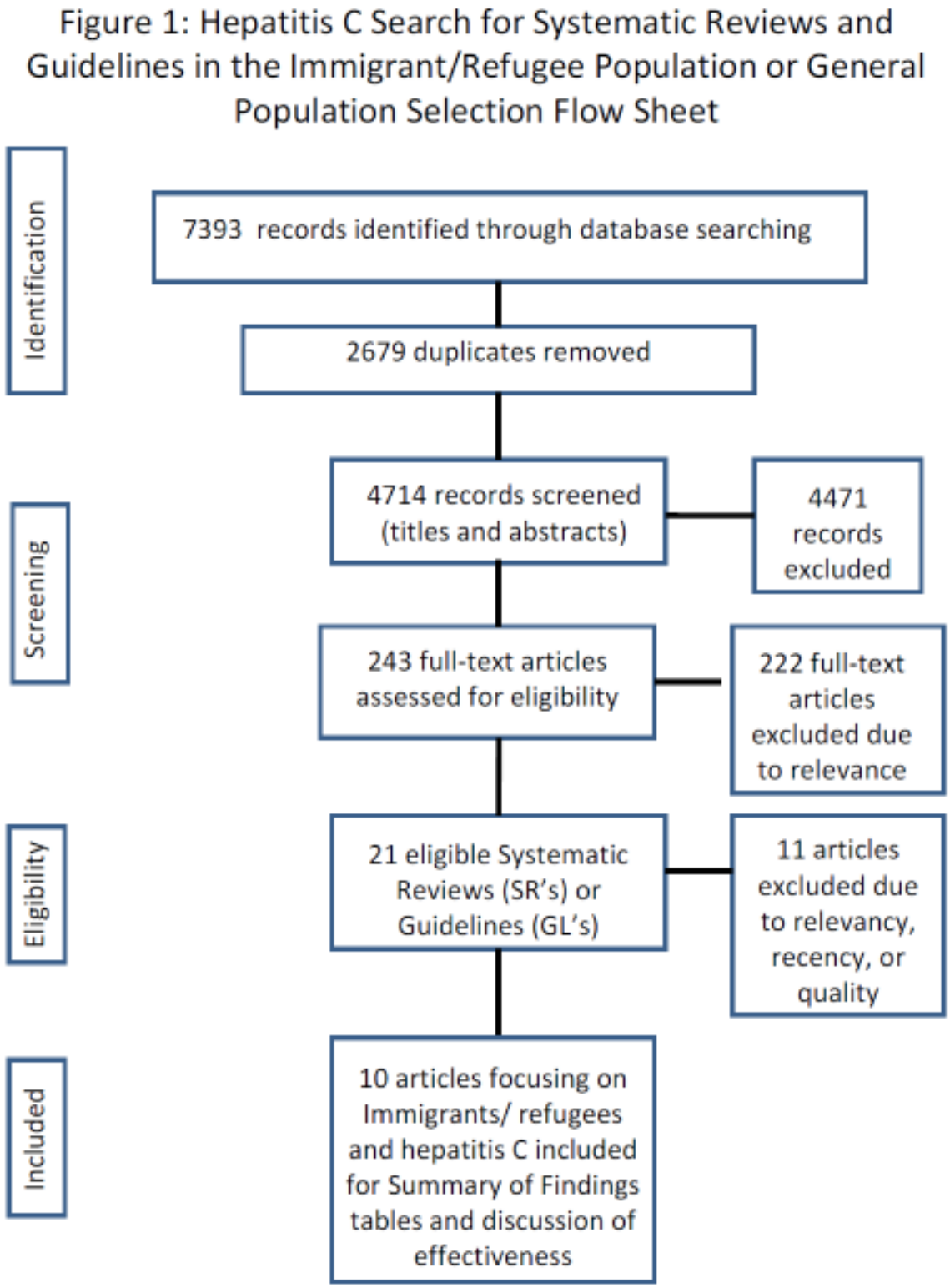
Clinical preventive guidelines for newly arrived immigrants and refugees

This document provides the review details for the CMAJ CCIRH Hepatitis C paper. The series was developed by the Canadian Collaboration for Immigrant and Refugee Health and published at www.cmaj.ca.

Appendix 1: Figure



Appendix 2: Hepatitis C Evidence Based Clinician Summary Table

Screen for Hepatitis C antibody in an immigrants and refugees originating from countries with an expected prevalence of disease of ≥ 2%. Refer if positive to a colleague with expertise in managing patients with Hepatitis C infection.

Prevalence: Up to 3% (range 0.5%-20%) of immigrants have chronic hepatitis C infection. The highest risk group are those from Sub-Sahara, North Africa (esp Egypt), Pakistan and certain countries in Eastern Europe.

Burden: Immigrant populations have increased mortality from chronic viral hepatitis (2-4 fold) and from hepatocellular carcinoma (2-5 fold) compared to the Canadian born population. A third of this burden is likely attributable to undetected chronic hepatitis C infection.

Access to Care: The immigrant populations' knowledge of the importance of hepatitis C, its consequences and the risk factors for transmission is likely to be quite limited, lower then those born in Canada, but may be increased by higher level of education, employment and being highly accultured. A large proportion of primary care practitioners have limited knowledge of risk factors, diagnostic test, and management of chronic hepatitis C infection, that can be improved through education. Primary care practitioners need to be made aware that newly arrived immigrants are a group at risk for chronic hepatitis C infection and that they would benefit from targeted screening.

Key Risk Factors for Hepatitis C: Traditional risk factors for acquiring hepatitis C in Canada are current or previous IDU or receipt of blood products prior to the 1990s before there were screening tests for hepatitis C. Immigrants are less likely than those born in Canada to be current or previous IDU (20% vs 67%) and are likely to have acquired their infection through unsafe health care related injections, unscreened blood products or surgical procedures in their countries of origin.

Screening Tests: Serologic tests to detect anti-HCV antibodies are highly sensitive (97%) and specific (99%) and are widely available. If positive a nucleic acid test to detect hepatitis C RNA (qualitative or quantitative) should be performed to confirm the presence of circulating virus.

Special Considerations: Many immigrants with chronic hepatitis C infection may also be co-infected with chronic hepatitis B infection or HIV which increases the risk and rate of progression to HCV associated liver fibrosis. Immigrants have a lower rate of traditional risk factors for chronic hepatitis C as compared to those born in Canada.

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