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TOPIC HIGHLIGHT

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Burden of pediatric hepatitis C

Mortada Hassan El-Shabrawi, Naglaa Mohamed Kamal

Mortada Hassan El-Shabrawi, Naglaa Mohamed Kamal, Pediatrics and Pediatric Hepatology, Faculty of Medicine, Cairo University, Giza 12411, Egypt
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Correspondence to: Mortada Hassan El-Shabrawi, MD, Professor of Pediatrics and Pediatric Hepatology, Faculty of Medicine, Cairo University, 3 Nablos Street, Off Shehab Street, Mohandesseen, Giza 12411,
Egypt. melshabrawi@medicine.cu.edu.eg
Telephone: +20-1-223133705 Fax: +20-2-37619012
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Abstract

Hepatitis C virus (HCV) is a major health burden infecting 170-210 million people worldwide. Additional 3-4 millions are newly-infected annually. Prevalence of pediatric infection varies from 0.05%-0.36% in the United States and Europe; up to 1.8%-5.8% in some developing countries. The highest prevalence occurs in Egypt, sub-Saharan Africa, Amazon basin and Mongolia. HCV has been present in some populations for several centuries, notably genotypes 1 and 2 in West Africa. Parenteral anti-schistosomal therapy practiced in the 1960s until the early 1980s had spread HCV infection throughout Egypt. Parenteral acquisition of HCV remains a major route for infection among Egyptian children. Insufficient screening of transfusions, unsterilized injection equipment and re-used needles and syringes continue to be major routes of HCV transmission in developing countries, whereas vertical transmission and adolescent high-risk behaviors (*e.g.*, injection drug abuse) are the major routes in developed countries. The risk of vertical transmission from an infected mother to her unborn/newborn infant is approximately 5%. Early stages of HCV infection in children do not lead to marked impairment in the quality of life nor to cognitive, behavioral or emotional dysfunction; however, caregiver stress and family system strain may occur. HCV slowly progresses to serious complications as cirrhosis (1%-2%) and hepatocellular carcinoma (HCC) especially in the presence of risk factors as hemolytic anemias, obesity, treated malignancy, and concomitant human immune deficiency and/or hepatitis B virus co-infection. HCV vaccine remains elusive to date. Understanding the immune mechanisms in patients who successfully cleared the infection is essential for vaccine development. The pediatric standard of care treatment consists of pegylated interferon-α 2a or b plus ribavirin for 24-48 wk. The new oral direct acting antivirals, approved for adults, need further evaluation in children. Sustained virologic response varies depending on the viral load, genotype, duration of infection, degree of aminotransferase elevation, adiposity and single nucleotide polymorphisms of interleukin (IL)-28B locus. The goals of treatment in individual patients are virus eradication, prevention of cirrhosis and HCC, and removing stigmatization; meanwhile the overall goal is decreasing the global burden of HCV. *IL-28B* polymorphisms have been also associated with spontaneous clearance of vertically acquired HCV infection. The worldwide economic burden of HCV for children, families and countries is estimated to be hundreds of millions of US dollars per year. The United States, alone, is estimated to spend 199-336 million dollars in screening, monitoring and treatment during one decade. The emotional burden of having an HCV infected child in a family is more difficult to estimate.

Key words: Hepatitis C virus; Burden; Genotypes; Cost; Pediatrics

Core tip: Hepatitis C virus (HCV) is a worldwide health burden infecting up to 5.8% of children in some developing countries with thousands of annual new

infections. HCV vaccine is illusive, but understanding immune mechanisms in patients who cleared infection may be crucial. The pediatric standard of care treatment is pegylated interferon-α2 plus ribavirin for 24-48 wk. The new oral direct acting antivirals need further evaluation in children. Interleukin-28B polymorphisms have been associated with treatment response and spontaneous clearance of vertical HCV infection. The worldwide economic burden of HCV is estimated to be hundreds of millions United States dollars/year. The emotional burden is difficult to estimate.

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INTRODUCTION AND EPIDEMIOLOGY

Hepatitis C virus (HCV) is a small, enveloped, positive-sense, single-stranded RNA virus of the *Flaviviridae* family[1]. HCV was first cloned in 1989 after more than 6 years of work to extract the virus from infected patients by a group of scientists from California in the United States[2]. HCV infection is recognized nowadays as a disease of global importance[3]. It is considered a major health and economic burden in adults as well as children in both developing and developed countries[3,4].

Viral hepatitis is the most common cause of liver disease in the world. Acute infections with their sequelae are responsible for 1-2 million deaths/year. Of them 54000 deaths are due to acute HCV infection[4]. After acute infection with HCV, as many as 50%-85% of patients fail to clear the virus resulting in chronic infection with 350000 deaths/year and 955000 disability due to related complications such as cirrhosis and liver cancer[5].

A recent systematic review found that globally between 1990 and 2005, the prevalence of people with anti-HCV has increased from 2.3% to 2.8%[4]. It is estimated that approximately 210 million individuals, *i.e.*, approximately 3% of the world population, are chronically infected with HCV[3,6] and 3-4 millions are newly infected each year[3]. Available data indicate that infection with HCV varies considerably by country and region, and the true burden of disease is not well known in many countries, because the capacity is often limited for collecting epidemiologic data[7]. The prevalence may vary markedly from one geographic area to another and even within the population assessed[8]. The highest prevalence of HCV is in Sub-Saharan Africa (5.3%), followed by the Eastern Mediterranean (4.6%), Western Pacific (3.9%) and South-Eastern Asia (2.15%) regions. Europe is thought to have the lowest prevalence of HCV (1.03%). In North America, prevalence is also low and estimated at 1.6% in the United States and 0.8% in Canada[9].

The study carried out by Uhanova *et al*[9] on the epidemiology of HCV in a North American population from the Canadian province of Manitoba, revealed several important findings: First, the diagnosis of HCV appears to have peaked in 1998 and has been relatively stable thereafter; second, the prevalence of HCV continued to increase amongst both men and women (4.6-fold during the 12-year period of the study). Overall, 84% of all subjects diagnosed since 1991 were alive in 2002, supporting the evidence of the growing burden of HCV; third, with the exception of young adults, males were 1.7 times more often infected than females; fourth, HCV infections were more common in urban centers.

Egypt has the highest worldwide prevalence with 9% countrywide rate; and up to 50% rates in certain rural areas due to specific modes of infection[10]. Prevalence in healthy Egyptian children is reported, by our group and others, to range from 1.4% to 5.8%[11,12]. Parenteral antischistosomal therapy, practiced in the 1960s until the early 1980s, had had a major role in the spread of HCV throughout Egypt[13].

GLOBAL HCV GENOTYPE DISTRIBUTION

By phylogenetic analysis, 6 distinct genotypes of HCV (denoted 1 to 6) and more than 100 subtypes (denoted 1a, 2c, 3d, 6f, *etc.*) have been described. Each genotype differs in its amino acid sequence by 31%-34%[14]. Genotypes 1-3 have a worldwide distribution, whereas 4 is found principally in Egypt, the Middle East and black Africa, 5 in South Africa, and 6 in Asia[15].

Genotype 1 (subtypes 1a and 1b) is by far the most prevalent genotype worldwide, with a higher prevalence of 1b in Europe and 1a in the United States. Genotype 3a is highly prevalent in European intravenous drug abusers[16]. This group is currently experiencing an increasing incidence and prevalence of infections related to HCV genotype 4 as well. Genotype 2 is found in clusters in the Mediterranean region[17]. Molecular clock analyses suggest that HCV strains have been present in some populations in their respective geographical regions for at least several centuries, notably genotypes 1 and 2 in West Africa and genotype 6 in Southeast Asia[18].

METHODS OF TRANSMISSION

Prior to the 1990s, the principal routes of HCV infection were via blood transfusion, unsafe injection procedures, and intravenous drug abuse. These modes of acquisition are estimated to account for approximately 70% of cases in industrialized countries. Epidemiological evidence shows that a wave of HCV infection occurred in the 1945-1965 period (baby boomers) in Western countries, as there was an increase in the use of injections, blood products and illicit drugs following World War II[1]. Screening of blood products for HCV by means of enzyme immunoassays and now, in an increasing number of countries, by nucleic acid testing (NAT) has virtually eradicated transfusion-transmitted HCV. Currently, new HCV infections are primarily due to intravenous or nasal drug abuse, and to a lesser degree to unsafe medical or

surgical procedures. Parenteral transmission via tattooing or acupuncture with unsafe materials is also implicated in occasional transmissions[8]. The risk of heterosexual transmission is low, while recent data indicate that promiscuous male homosexual activity is related to HCV infection[19].

In developing countries, insufficient screening of blood, blood products and parenteral exposure, continue to be the major causes of HCV transmission and are still reported among Egyptian children[20]. Unsafe use and re-use of injection equipment in hospitals is still a threat in many parts of Africa[21]. Intra-familial transmission may occur, but specific immune responses may be protective against house-hold infection in some children[22].

At present the vertical, maternal-neonatal or perinatal transmission is the most common route of pediatric HCV infection[23]. Worldwide, it has been estimated that 60000 HCV-infected infants are born yearly[24]. Mother-to-infant vertical transmission of HCV is reported to occur in approximately 5% of cases (with a range of 3%-10%), mostly in the late intrauterine period, at delivery or in the peri-natal period[1,24]. Many factors have been reported to influence the transmission rate[25], including maternal high viral load[26-28], labor duration, newborn gender, HCV genotype[29], human immuno-deficiency virus (HIV) co-infection[24], amniocentesis[30,31], fetal scalp monitoring[32], prolonged rupture of membranes[32,33] and fetal anoxia around the time of delivery[28].

The role of elective cesarean section to reduce mother-to-infant transmission rates is debated and controversial[33] and the guidelines of the European Association for the Study of the Liver (EASL) do not recommend cesarean section to prevent HCV vertical transmission[8]. Breast feeding is not considered to be contraindicated in women who are infected with HCV[34,35]. In spite that the majority of HCV-infected women do not transmit the virus to their offsprings, maternal uncertainty and guilt always surround possible transmission. Cost-effectiveness analysis based on available epidemiologic data indicates that screening of all pregnant mothers for HCV infection is not cost-effective[36]; however high risk mothers should be screened[25].

NATURAL HISTORY OF INFECTION

In some patients, HCV infection is a self-limited disease and HCV RNA becomes undetectable in most of these cases within 3 to 4 mo after the onset of acute infection[37]. Symptoms and signs following acute HCV infection are mild and usually non-specific; and fulminant HCV has not been reported in childhood[38].

Unfortunately spontaneous clearance of HCV occurs only in a minority of cases as 54%-86% of adult patients establish a chronic infection[39]. Many chronically infected patients do not know that they have been infected with HCV because infection is largely asymptomatic[40]. In the approximately 86% of infected patients who develop a chronic infection, HCV progresses insidiously with 10%-20% progressing to cirrhosis and approximately 7% of cirrhotic patients developing HCC[41].

Little is known about the characteristics of chronic HCV infection in children. Children rarely require liver transplantation for HCV infection. In the United States, only 133 children were transplanted for chronic HCV infection between 1988 and 2009[25]. To date, HCC is extremely uncommon in children with HCV infection[25]. Only 2 cases have been reported in children[42] and two further cases who had acquired chronic infection in childhood presented as young adults[43], however other unreported cases may exist. HCC complicating HCV infection may develop in the absence of cirrhosis[44,45], a finding of potential importance to pediatric patients[25]. Progression of liver affection depends on the viral load, serum aminotransferase levels, gender, ethnicity, obesity, toxins, environmental factors and co-morbid risk factors such as hemolytic anemias, treated malignancy, immunosuppression, and concomitant HIV or hepatitis B virus infection, or genetic factors *e.g.*, single-nucleotide polymorphisms (SNPs) of interleukin (IL)-28B gene locus[46].

Chronic HCV infection in children is associated with a variety of histological patterns of liver disease, generally not as severe as in adults. Indeed in many children, liver biopsy may disclose no obvious histological changes or only mild inflammation and fibrosis. Nevertheless, significant fibrosis or cirrhosis may occur[47]. Reports on the histological features and progression of hepatitis C in children are scarce but are generally milder than in adults[48]. In 1997, Kage *et al*[49] reported, in a cohort of Japanese children with chronic HCV infection, that liver histopathology presents the same lesions as in adults such as lymphoid aggregates, sinusoidal lymphocytosis and steatosis[48]. The stage of fibrosis in this cohort was mild, with only a 3.6% prevalence of bridging fibrosis with architectural distortion, and no cases of cirrhosis[48]. This seemingly mild course is in contrast with the findings in some of the earlier clinical reports in which the prevalence of cirrhosis was found to be up to 14%[50-52]. In a North American study carried out by Badizadegan *et al*[48], the characteristic histopathological lesions occurred with approximately the same frequencies in children as have been reported in adults. Necroinflammatory activity was generally mild. Portal fibrosis was present in 78% of the specimens, including fibrous portal expansion (26%), bridging fibrosis (22%), bridging fibrosis with architectural distortion (22%), and cirrhosis (8%). Centrilobular pericellular fibrosis, which has not been previously reported in the context of chronic HCV infection in adults or children, was also a prominent feature in their series, occurring with a similar frequency as steatosis or portal lymphoid aggregates/follicles. They suggested that in spite of mild histological necroinflammatory activity in general, the stage of fibrosis in children can be severe in spite of relatively short duration of infection[48].

EXTRAHEPATIC MANIFESTATIONS OF HCV

Chronic HCV infection may cause numerous extrahepat-

ic manifestations. Up to 40%-74% of patients with HCV infection develop at least one extrahepatic manifestation during their life time. The disorder with strongest link to HCV infection in adults is mixed cryoglobulinemia[46]. Other common symptoms are peripheral polyneuropathy, Raynaud's syndrome and sicca-like symptoms. Seven and a half to 10% of the patients develop a B-cell lymphoma at some point[53-55]. The clinically most relevant manifestation of mixed cryoglobulinemia is membrano-proliferative glomerulonephritis, which appears in 30%-36% of the cases and significantly increases mortality[54,55]. Membrano-proliferative glomerulonephritis may occur in children with chronic HCV infection, but unlike in adults, neither cryoglobulinemia nor lymphoma has yet been reported in children[25].

Another important extrahepatic manifestation of HCV infection is the involvement of the central nervous system. About 20%-80% of the patients with chronic HCV infection develop fatigue at some point independent from the severity of hepatitis. Fatigue often is the predominant complaint of the patients and might reduce the quality of life to a large extent. Patients may also develop depression or a general cognitive impairment irrespective of the stage of liver disease[56] which may be linked to HCV-induced neuro-inflammation and brain dysfunction[57]. These observations raise the issue of learning impairment in children with chronic HCV[25].

Impaired quality of life, potentially severe enough to have a negative effect on learning, has been reported in children with chronic HCV infection including developmental delay, learning disorders, and cognitive deficits less severe than those of attention deficit hyperactivity disorder but still reflecting decreased executive function[58,59].

COSTS OF INFECTION

Vietri *et al*[40] studied the burden of HCV in Europe and found that HCV patients compared to healthy controls have more impairment in work and non-work activities, and more annual physician visits per patient. Work-productivity impairment due to HCV costs over €7500 per employed patient per year[40]. Health-related quality of life was lower among HCV patients. Treatment-naïve HCV patients reported higher work impairment and more frequent physician visits. Each treatment-naïve HCV infected patient incurred €934 in direct costs. Employed treatment-naïve patients reported higher productivity loss per year[40]. In comparison, in the United States, Menzin and his group estimated that it costs $4956/patient in the year following the diagnosis of advanced liver disease secondary to HCV which were largely driven by inpatient costs[60].

There are no precise estimates of the true costs of HCV for a child and family. In one country like the United States, it is likely that several thousand children per year need treatment costing several thousand dollars/child; and it is estimated that in one decade, 26 million dollars will be spent in screening, 117-206 million dollars in monitoring, 56-104 millions dollars in treatment and the total cost would be about 199-336 million. Worldwide, global costs would be millions of dollars/year[61].

Treatment of a child which results in virus eradication is highly cost-effective because of the higher costs of the long-term consequences of untreated HCV cirrhosis and/or HCC. The small numbers of liver transplants for children with HCV performed each year cost several million dollars. The emotional costs of having an HCV infected child are more difficult to estimate for the child and family; but are real[61].

PREVENTION

The reduction of global morbidity and mortality related to chronic HCV infection should be a concern to public health authorities, and primary, secondary and tertiary prevention activities should be implemented and monitored in each country, with precise targets set to be reached. A working group was created to assist the World Health Organization in estimating the global burden of disease associated with HCV infection[3]. Public awareness of the transmission and prevention of HCV is crucial in decreasing the incidence and prevalence of the disease. Public and physician education in various forms is therefore extremely important. There is a need for implementing evidence-based international guidelines for preventing and managing hepatitis C in children worldwide[62].

One of the major hurdles in the eradication/reduction of the burden of HCV is the lack of hepatitis C vaccine. An effective HCV vaccine remains elusive to date. HCV has been difficult to target with a vaccine because it has many different strains. In addition, HCV mutates rapidly and exists as a complex family of mutated viruses within each infected individual (quasispecies) allowing the infecting virus to escape control by the immune system. This makes it difficult to identify which part of the virus should be targeted for developing a vaccine[62].

Viral and host specific factors contribute to viral evasion and present important impediments to vaccine development. Both, innate and adaptive immune responses are of major importance for the control of HCV infection. However, HCV has evolved ways of evading the host's immune response in order to establish persistent infection. For example, HCV inhibits intracellular interferon (IFN) signaling pathways, impairs the activation of dendritic cells, $CD8^+$ and $CD4^+$ T cell responses, induces a state of T-cell exhaustion and selects escape variants with mutations $CD8^+$ T cell epitopes[63]. An effective vaccine will need to produce strong and broadly cross-reactive $CD4^+$, $CD8^+$ T cell and neutralizing antibody (NAb) responses to be successful in preventing or clearing HCV. Vaccines in clinical trials now include recombinant proteins, synthetic peptides, virosome based vaccines, tarmogens, modified vaccinia Ankara based vaccines, and DNA based vaccines. Several pre-clinical vaccine strategies are also under development and include recombinant adenoviral vaccines, virus-like particles, and synthetic peptide

vaccines. Moreover, vaccines may also be used in the future in combination with the recent direct acting antiviral (DAA) drugs enabling IFN-free treatment regimens[63]. Indeed understanding the immune mechanisms, particularly HCV-specific cell mediated immune response, of patients who have successfully cleared the infection is essential to design and develop a vaccine[64].

Because there is no vaccine and no post-exposure prophylaxis for HCV, the focus of primary prevention efforts should be safer blood supply in the developing world, safe injection practices in health care and other settings, and decreasing the number of people who initiate injection drug abuse[6]. People with known HCV infection should be counseled regarding ways to reduce the risk of transmitting HCV to others, and means of minimizing their risk for HCV-related complications. As part of secondary prevention efforts, HCV-infected people should be referred for medical evaluation and antiviral treatment consideration, and programs ensuring access to these services should be in place[6].

Health education is also essential to reduce the HCV burden, and specific programs should be provided to increase public awareness on transmission and prevention of infection[62].

TREATMENT

HCV is a potentially curable disease[65] with a good percentage of treated patients getting a sustained virologic response (SVR) defined as undetectable serum HCV RNA 24 wk after the end of therapy (and now at 12 wk after the end of therapy[8]). Although the available standard of care (SOC) therapy has led to significant improvements in treatment response rates, less than 50% of HCV-infected persons are aware of their diagnosis[66], and among them, only 1%-30% receive treatment. The true rate-limiting factor in achieving better outcomes may turn out to be access to diagnosis and treatment[66].

Multiple barriers may impede the delivery of HCV therapy[67]. To increase cure rates, the psychological (psychiatric illness, attitudes and coping skills), lifestyle (alcohol consumption, diet, and exercise), social (income, education, social class, poverty), and other different barriers to treatment adherence and completion must be identified and overcome[68].

For adults, standard IFN has been approved for the treatment of HCV since 1991, Ribavirin (RBV) since 1998 and pegylated-IFN (peg-IFN) since 2002. Nine years had passed before the American Food and Drug Administration (FDA) approved a new drug to be added to the excising SOC, the DAA oral protease inhibitors, boceprevir and telaprevir[69]. New drugs under development include other protease inhibitors, the NS5B polymerase and NS5A inhibitors[70]. In the coming years, the number of the new drugs will multiply exponentially and pharmaceutical companies have begun to combine them in triple and quadruple regimens (with and without peg-IFN)[69].

In children 3-17 years old, treatment with peg-IFNα-2 a or b plus RBV for 24-48 wk is the SOC therapy[71,72], whereas the recently approved DAA still need evaluation in children.

In the United States and most European countries, the current first line therapy for infection with genotype-1 is a combination of peg-IFN alpha plus RBV plus either boceprevir or telaprevir. High SVR rates can be achieved even in those with evidence of fibrosis and cirrhosis, but response is poor in prior null responders, especially those with cirrhosis[73].

Preliminary data from investigational studies suggest the potential for cure rates of 80%-90% in genotype-1 infection using combinations of DAAs and RBV without peg-IFN, but larger studies will be needed to confirm these results across a wider range of populations[74-76].

Quadruple therapy with pegylated-IFN combines BI201335, a protease inhibitor, and BI207127, a non-nucleoside NS5B polymerase inhibitor, with peg-IFN and RBV[77]. The only quadruple peg-IFN-free study is the Gilead Sciences all-oral quad regimen[78]. It is a phase II study for genotype 1, treatment-naïve patients who are not cirrhotic. It combines GS-5885, GS-9451, tegobuvir, and RBV for 24 wk. The triple peg-IFN-free therapy combines mericitabine, a nucleoside NS5B polymerase inhibitor; danoprevir, a protease inhibitor; ritonavir, a booster for danoprevir; and RBV or placebo[79].

SVR varies considerably from 26%-80% depending on age, duration of infection, viral load, viral genotype, adiposity, hepatic fibrosis iron scores, aminotransferase elevation, compliance with therapy, SNPs of IL-28B gene locus. It was found that a single *IL28B* genotype SNP rs12979860 determination predicts treatment response in patients with chronic hepatitis C Genotype 1 virus[80,81]. IL-28B has been also reported to play a role in spontaneous clearance of HCV genotype 4 in Egypt/North Africa[82]. Regarding the HCV genotypes 2 and 3, the polymorphisms rs12979860 and rs8099917 showed significant associations. However, the strength of this association was almost three times lower than for genotypes 1 and 4[83]. In addition regarding genotype 2, it was found that the Asian population was solely responsible for this association in rs8099917[84]. The generally reduced association for patients with HCV genotypes 2/3 could be related to the high rate of SVR present in these IFN-sensitive genotypes[85].

SNPs of *IL-28B* gene received considerable interest also for their association with spontaneous clearance of HCV among vertically-infected children[86].

SNPs of *IL-28B* as well as *IL-10* are good predictors of response to IFN/RBV therapy in HCV genotype 4 infected Egyptian children[87].

The combination of serum level of IFN-gamma inducible protein and SNPs of IL-28B can identify patients with acute HCV who are most likely to undergo spontaneous clearance and those in need of early antiviral therapy[88].

SNPs of osteopontin gene were also reported as pre-

dictors for the efficacy of IFN therapy in chronic HCV Egyptian patients with genotype 4[89].

CONCLUSION

HCV infection is an increasing health and economic burden in adults as well as children, in both developing and developed countries. The natural history and histopathology of HCV-related liver disease in children are still conflicting and variable. Prevention of infection depends on screening of blood with the most sensitive tests, avoiding nosocomial infections, and avoiding injection drug abuse and unprotected sex in adolescents; as well as education. Development of a vaccine preventing HCV infection is of thorough public health importance. The SOC therapy is peg-IFN plus RBV. The SVR is variable (26%-80%) and depends on several viral and host factors. Eradication of HCV in a child (if possible) is cost-effective as it may prevent cirrhosis and HCC; and can have major family, public health and global benefits.

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