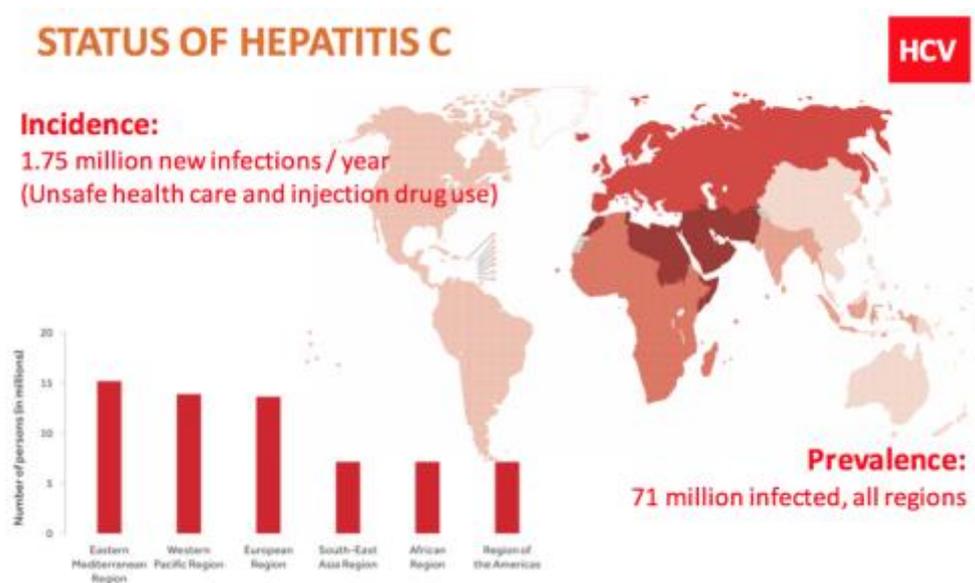


Hepatitis C in children: treatment of a lifelong infection and prevention of transmission

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To what extent children contribute hepatitis C morbidity ?

It is estimated that 11 millions children < 15 years are infected by hepatitis C virus, of whom 5 millions are viraemic. This means that around 6% of the total HCV infected population are children, and these patients are most likely to develop chronic liver disease and remain the long term reservoir of the virus.



WHO, Global Hepatitis Report, 2017

What is the dominant risk factor of the infection?

Mother to child transmission is the main source of contamination in children, being responsible of about two third of the cases. Four to 10% of children born to HCV infected mothers become contaminated, and between 80% to 90% will remain chronically infected, with the highest risk of transmission in infants from HIV - HCV co-infected

mothers. Spontaneous viral clearance is mainly associated to genotype 3 infections. The prevalence of hepatitis C in children is higher in lower socio-economic conditions, lower income countries and is linked with precarious condition of life, drug abuse and trading sex in parents. (1-4)

Is hepatitis C progressive in children?

Most children infected by HCV are asymptomatic. In a large European cohort of 224 infant and children infected by HCV, the mean fibrosis score was however significantly higher in the group of children above 15 years as compared with the younger cohort, and an average Metavir score progression of 0,142 /year, suggesting that the liver damage is indeed progressing with time in this population (5). In another cohort of Italian children, the rate of progression to decompensated cirrhosis in childhood was found

to be 1.8%, being related to genotype 1a, vertical transmission, maternal drug abuse and persistent transaminase elevation. Three quarters of chronically infected children had elevated (41%) or fluctuant (35%) elevation of transaminases (3). The slow disease progression in children may be linked with the lack of co-existing known risk factors of disease progression, such as alcohol and drug consumption, iron overload, and unfrequent co-morbidities.

How to prevent hepatitis C in the infantile population?

Increasing the safety of injection procedures and devices is a major goal to prevent contamination of infants and adults, as 5% of health care injections remain unsafe, being responsible for an estimated 1.75 millions new hepatitis C infections in 2015 (6). Additional measures include the detection and treatment of HCV in child bearing potential women, and the prevention of infection and reinfection in adolescents with an history of injection drug use. (7,8) Now that safe and efficient therapies are becoming available for

children, the systematic screening of pregnant women becomes justified. At this stage, DAAs remain contra indicated during pregnancy. For hepatitis B, antiviral treatment are now proposed to prevent mother to child HBV transmission during the last trimester of pregnancy. This may not be justified to the same extent for hepatitis C, as treatment can thereafter be applied safely and with definitive cure to the possibly contaminated children.

Are effective treatments for hepatitis C in children in place?

Peginterferon and Ribavirin are currently approved in EU and in the US to treat children from three years of age, with an overall better sustained virological response in genotypes 2&3 (87 & 89% respectively, 24 weeks of treatment) as compared to genotypes 1 &4 (61% & 52%) (9,10) . However, direct acting agents have now replaced IFN containing regimen in adults, and a number of clinical trials are currently ongoing in children. The combination of Sofosbuvir 400 mg/day and Ribavirin (15mg/kg/day) for 12 or 24 weeks led to 97% SVR in genotype 2 and to 100% in genotype 3 adolescents (12-17yo) respectively (11), and this combination is now approved by FDA. Ongoing studies using combination in children include Sofosbuvir/ Ledipasvir +/- Ribavirin

(genotypes 1,4,5,6); ombitasvir/paritaprevir /ritonavir +/- dasabuvir +/- Ribavirin(gen1,4) ; sofosbuvir/ledispavir(gen1,4); sofosbuvir /velpatasvir(gne 1-6) and glecaprevir/pibrentasvir (gen1-6). Reduce doses and powder regimens are under study.

Hence, as these DAAs combinations will soon be approved for children, and in view of the mild disease activity and slow progression in the majority of children, treatment can be delayed until approval; the previously approved IFN containing treatments are becoming obsolete and were in the last years reserved to children with active progressing disease who had no access to approved or in investigation DAA regimen.

What it is needed to scale up access of adolescents to anti HCV therapy?

The final aim being the eradication of hepatitis C, continuous efforts to reduce the cost of direct acting agents in high endemicity/ poor income countries must be supported. License agreements between pharmaceutical companies and local generic producers in countries like Egypt or India have already allowed to treat at reduced cost large number of patients. For high-income countries, the cost of treatment remains prohibitive and prevents wide access to treatment as this would impact significantly the total health budget

of these countries (12). The longevity of children gives them time to develop severe HCV disease related complications. A basic concept of pediatric art is that the long lifespan and the future health hazards of adult life require bringing children in young adult life with the most healthy organs and body. Hence, despite budgetary restrictions, the small number of HCV infected children must have access to treatment on the basis of persistent viraemia, whatever is the stage of the parenchymal damage.

References

1. Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis. . WHO :
2. 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.
3. Bortolotti F, Verucchi G, Cammà C, Cabibbo G, Zancan L, Indolfi G, et al. Long-term course of chronic hepatitis C in children: From viral clearance to end-stage liver disease. *Gastroenterology* 2008, Jun;134(7):1900-7.
4. Aebi-Popp K, Duppenhaler A, Rauch A, De Gottardi A, Kahlert C. Vertical transmission of hepatitis C: Towards universal antenatal screening in the era of new direct acting antivirals (daas)? Short review and analysis of the situation in switzerland. *J Virus Erad* 2016, Jan 1;2(1):52-4.
5. Jara P, Resti M, Hierro L, Giacchino R, Barbera C, Zancan L, et al. Chronic hepatitis C virus infection in childhood: Clinical patterns and evolution in 224 white children. *Clin Infect Dis* 2003, Feb 1;36(3):275-80.
6. Global hepatitis report, 2017. World health organization (WHO) :
7. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu. EASL recommendations on treatment of hepatitis C 2016. *J Hepatol* 2017, Jan;66(1):153-94.
8. Islam N, Krajden M, Shoveller J, Gustafson P, Gilbert M, Buxton JA, et al. Incidence, risk factors, and prevention of hepatitis C reinfection: A population-based cohort study. *Lancet Gastroenterol Hepatol* 2017, Mar;2(3):200-10.
9. Druyts E, Thorlund K, Wu P, Kanters S, Yaya S, Cooper CL, Mills EJ. Efficacy and safety of pegylated interferon alfa-2a or alfa-2b plus ribavirin for the treatment of chronic hepatitis C in children and adolescents: A systematic review and meta-analysis. *Clin Infect Dis* 2013, Apr;56(7):961-7.
10. Sokal EM, Bourgois A, Stéphenne X, Silveira T, Porta G, Gardovska D, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in children and adolescents. *J Hepatol* 2010, Jun;52(6):827-31.
11. Wirth S, Rosenthal P, Gonzalez-Peralta RP, Jonas MM, Balistreri WF, Chuan-Hao L, et al. Sofosbuvir and ribavirin in adolescents 12 to 17 years old with hepatitis C virus genotype 2 or 3 infection. *Hepatology* 2017, May 22.
12. Sokal E, Nannini P. Hepatitis C virus in children: The global picture. *Arch Dis Child* 2017, May 4