HEPATITIS C: AN UPDATE ON PREVALENCE AND TREATMENT OPTIONS

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I have nothing to disclose

Objectives

• Hepatitis C Prevalence
  - Worldwide and nationwide prevalence
  - Prevalence in New Mexico
• Hepatitis C Genotypes
  - Review the various genotypes and clinical significance of each
• Proper testing for hepatitis C in children
  - The use of PCR testing – roles and limitations
  - Antibody testing – still the gold standard
• Treatment options
  - Updated information for treatment options

Hepatitis C Overview

• WHO estimates prevalence ~2% of the world population
  - 150-180 million people
• Countries with the highest prevalence rates: Africa and Asia
• Industrialized nations have the lowest prevalence rates
• Highest reported seroprevalence rate is Egypt: 22% of 73 million

<table>
<thead>
<tr>
<th>Country</th>
<th>Estimated 2004 Total Population (millions)</th>
<th>Estimated HCV seroprevalence (%)</th>
<th>Population studied</th>
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<td>Nationally representative sample (n=68000)</td>
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<td>Community-based, West Bengal (n=5979)</td>
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<td>USA</td>
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<td>Indonesia</td>
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<td>Volunteer blood donors (n=79572)</td>
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<tr>
<td>Brazil</td>
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<td>Pakistan</td>
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<td>4.0</td>
<td>Volunteer blood donors (n=10285)</td>
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Hepatitis C Infection in New Mexico

- Between 30,000 and 45,000 people living with chronic hepatitis C virus infection
- Chronic liver disease is in the top 10 leading causes of death in New Mexico
- Over 40% of people coming into the prison system in New Mexico test positive for Hepatitis C antibodies
  - This prevalence is double that of the next leading state
- New Mexico Hepatitis C Virus Coalition:
  - New Mexico will prioritize the prevention, testing and treatment of infection with hepatitis C virus in order to reduce the number of new infections as well as cure the infection in those currently living with HCV, thereby reducing the negative health impacts of this disease.

Hepatitis C Overview

- The most common chronic bloodborne infection in the US
- Hepatitis C Virus (HCV): single-stranded RNA virus in the Flaviviridae family discovered in 1989
- 6 genotypes; over 50 subtypes
  - Genotypes 1-3 are the most common in the United States

There are mutations that occur during viral replication that leads to substantial heterogeneity

- The RNA polymerase is greatly prone to error
  - This results in many variant viruses which confer a survival advantage to HCV
- Antibodies elicited by one virus type do not recognize other virus types
  - (i.e. previous infection does not protect against reinfection with the same or different genotype)
Hepatitis C Overview

• Incubation period averages 6-7 weeks
  • Has a range of 2 weeks – 6 months
• The leading cause of liver transplantation in developed countries
• Estimated that by 2020, 1 million Americans will have HCV-related cirrhosis
• Acute infection: Typically the first 6 months of illness and asymptomatic
• Chronic infection: Long term illness that causes organ damage


Hepatitis C Genotypes

• Genotype 1
  • Most common genotype in children
  • In Britain, 63% of infected children had genotype 1 (only 3% had genotype 2)
• Genotype 2
• Genotype 3
  • Spontaneous clearance of HCV in vertically infected children has been associated with genotype 3 and with transaminase flare in the first year of life


Hepatitis C Risk Factors

• Injection drug use
  • Primary mode of transmission for HCV infection in the developed world
  • Prevalence of HCV infection among long-term injection drug users: 64-94% among those with duration of injecting ≥ 6 years

Hepatitis C Risk Factors

• Unsafe therapeutic injections and Health-care-related procedures
  • In developing countries the supply of sterile syringes may be inadequate
  • Egypt: transmission attributed to contaminated glass syringes used in nationwide schistosomiasis treatment campaigns from 1960 to 1987
  • WHO has the Safe Injection Global Network (SIGN) – coalition to advocate for safer injections practices worldwide
  • WHO estimates ~2 million new HCV infections in 2000 from unsafe injections


Hepatitis C Risk Factors

• Blood transfusions from unscreened donors
  • In US, more than threefold drop in the incidence of post-transfusion non-A, non-B hepatitis observed in a veterans' hospital after changing to all volunteer blood donations
  • Many countries do not screen appropriately:
    • In India, HCV screening is mandated by law but not usually done due to financial constraints
    • Of 12 Latin American countries, half screened all blood products for HCV


Hepatitis C Risk Factors

• Mixed opinions regarding tattoos, acupuncture, ear piercing
  • Cross-sectional prevalence studies in the UK and Australia found significant associations between anti-HCV seropositivity and a history of tattooing (p<0.00001)
  • A community-based cross-sectional seroprevalence study in Taiwan found a significant association with acupuncture (p<0.05) but not with tattooing

Hepatitis C Risk Factors

• Mother to child transmission is the major route of new infections in children
  • An average of 5% of infants born to HCV infected mothers acquire HCV from mother
  • Estimated to occur 2.7-8.4% of infants born to HCV infected mothers
  • Higher in infants born to HIV/HCV co-infected mothers
  • Study in Great Britain from 1991-2008 showed 49% of infections identified in children occurred via vertical transmission


Risk Factors for Mother to Child Transmission

• HIV co-infection
  • Study found that rate of transmission in HIV co-infected mothers was 25% compared to mother without HIV co-infection 3.8% (P<0.05)
  • Duration of membrane rupture
    • Membrane rupture ≥6 hours (95% CI, 1.5-179.7)
    • A separate study found labor of more than 4 hours was a risk factor
  • Internal fetal monitoring
    • (95% CI, 1.1-35.9)


Hepatitis C Risk Factors

• Meta-analysis showed vertical infection in children of HCV antibody-positive and RNA-positive women and HIV negative to be 5.8%
  • Increased to 10.8% in HIV-positive women
  • Mother-to-Child Transmission results in 60-90% of chronic hepatitis C infections in the pediatric population


Risk Factors for Mother to Child Transmission

• Maternal viremia
  • Among 41,856 women screened, 188 were HCV antibody positive
  • 61% had detectable HCV RNA
  • 34 Children contracted HCV
    • 10 to mothers with high viral load (36x10^6 IU/mL)
    • No child born to RNA-detectable but non-high viral load mothers were infected (p<0.001)


Hepatitis C Risk Factors

• Prevalence of HCV in pregnant women is not truly known due to current selective screening
  • HCV seroprevalence among women of child bearing age was estimated to be:
    • 1% for ages 20-29 years
    • 1.6% for ages 30-39 years
    • BUT excluded homeless and imprisoned women
    • Estimated to be ~8% in developing countries


Risk Factors for Mother to Child Transmission

• Sex of infant
  • Girls were twice as likely to be infected when compared to boys (n = 1787)
  • Possible different susceptibility to infection between the sexes
• IV drug abuse
  • Can be difficult to estimate – users may be reluctant to admit to use

Risk of Transmission Due to Inability to Treat

- The most important risk factor for transmission seems to be a high viral load in the mother during the perinatal period
  - Reduction of viral load is obtained via treatment
  - The use of pegylated interferon (PegIFN) is associated with an increased risk of miscarriage and low birth weight
  - Ribavirin is classified as category X because of its teratogenic effects
  - Standard therapy cannot be applied during pregnancy
  - Women who begin treatment before pregnancy should discontinue therapy immediately after confirmation of pregnancy

Screening for Hepatitis C

- Targeted approach to HCV screening is difficult
  - Likely many infected pregnant women not identified
  - 40-70% of HCV-infected pregnant women do not initially report major risk factors
  - An estimated 85-95% of HCV-infected children in the United States have not been identified
  - Vertical transmission is the leading cause of pediatric chronic HCV

NOT Risk Factors for Maternal to Child Transmission

- Breast-feeding does not promote HCV transmission from mother to infant
- Cesarean section does not appear to be protective
  - Very few studies have shown any difference in the mode of delivery
  - Those with differences usually have a low number of women studied

Timing of Transmission

- Timing of transmission is not known
- HCV RNA has been detected within a month of birth in non-breast fed infants delivered by cesarean section
  - Suggests that transmission may occur in utero
- HCV RNA has been detected in breast milk
  - The risk of HCV transmission is similar in breast-fed and bottle-fed babies
  - The CDC and the American Academy of Pediatrics support breast feeding

Impact of Pregnancy on HCV

- The immune changes of pregnancy and how it affects the course of acute HCV infection is not well understood
  - It is unknown if pregnancy alters the outcome of acute HCV infection
Impact of Pregnancy on HCV

• Some women have sharp decreases in viremia 1-3 months postpartum; some resolve chronic viremia in this period
• It is thought to be due to broader HCV-specific T-cell IFN-Ƴ-producing responses
• Would the postpartum time be a strategic time for maternal antiviral treatment??

Gonzalez-Peralta et al. JPGN. 2012.

Potential Protection for Neonate?

• Proportional frequencies of NKT and γδ–T cells higher in placenta than cord blood
• Cytotoxicity of NK and NKT cells was enhanced in placenta
• Placenta is an active innate immunological organ that provides antiviral protection against HCV transmission
• The increase in preterm labor in HCV-seropositive mothers may be due to enhanced cytotoxicity of NKT cells


Adverse Outcome in HCV Positive Mothers

• Independent associations of maternal HCV infection with:
  • Gestational diabetes
  • Chronic HCV increases the risk of insulin resistance
  • Preterm delivery
  • Possible alterations including increased cytotoxicity of placental NK T cells
  • Low birth weight
  • Small for gestational age
  • Cholestasis of pregnancy


New Mexico Findings

• 351 pregnancies were followed from January 2000-2006 from a drug dependence and treatment program
  • 159 (53%) were HCV antibody reactive
  • 141 (47%) were nonreactive
  • 51 (15%) not tested


Infant Testing Recommendations

• Antibody screening after 18 months of age
  • 3 immunoassays:
    • EIA (enzyme immunoassay)
    • Microparticle EIA
    • Chemiluminescence immunoassay
  • EIA and microparticle EIA are recommended for screening
  • HCV RNA
    • Quantitative tests are recommended for diagnosis in patients with positive anti-HCV antibody tests

Additional Testing Options

• Genetic test determining the single nucleotide polymorphisms (SNPs) in the IL-28B gene
  • Specific polymorphisms are associated with spontaneous clearance of HCV genotype 1 in infant infected by perinatal transmission
  • Favorable genotype of CC IL-28B increases the chances of spontaneous elimination of HCV more than twice compared to CT and TT genotypes combined
    • (OR = 2.7; 90% CI 1.3-5.8)
  • Genotypes CC rs12979860 and TT rs8099917 in IL-28B gene were associated with higher sustained virologic response (SVR) rates in PegIFN-based treatment

Test Results Interpretation

• Antibody test positive, HCV RNA positive:
  • Acute or chronic HCV
• Antibody test positive, HCV RNA negative:
  • Resolution of HCV infection or acute infection with low-level viremia
• Antibody test negative, HCV RNA positive:
  • Early acute disease, chronic HCV in immunocompromised person, or false-positive HCV RNA test
• HCV RNA can be detected in serum or plasma as early as 1-2 weeks after exposure to the virus

Additional Genetic Testing

• RNA titers checked at week 12; if a 2 log decrease in viral load achieved then considered early virologic response and continued with treatment
• RNA was repeated after 24 weeks of therapy; if positive considered a non-responder and therapy discontinued
• Therapy continued for 48 weeks and RNA titer obtained to determine end of treatment response.
• 24 Weeks after completion of therapy RNA titer obtained and those negative were sustained virologic response
Treatment

- Current recommendation: FDA-approved PEG-IFN-α with ribavirin for adults and children age 3 years and older
- Achieves sustained virological response (SVR) in ~50% of genotype 1 and ~80% of genotype 2 and 3
- Interferon-alpha increases the immune response against virus
- Protease inhibitors approved for use in adults
- If vertical transmission could be interrupted, it would eliminate the majority of the pediatric cases

Non “Medical” Treatments?

- Laccase is extracted from oyster mushroom
- Proficient in inhibiting the HCV replication rate
- Mechanism of action is not known
- Proanthocyanidin is extracted from blueberry leaves
- Reported to stop HCV replication
- Rhizomes of the Chinese herb Rhodiola kirilowii
- May act as a possible inhibitor of HCV

Treatment

- IFN-α was the first agent approved
- Originally approved for 24 week course
- Suppressed HCV RNA to undetectable levels during therapy
- The frequency of sustained viral response doubled when duration was extended to 48 weeks
- Sustained viral response (SVR) improved when longer-acting pegylated IFNs were used
- SVR improved to ~40% when ribavirin was added
- Ribavirin added additional side effects.....

What About Vitamin D?

- Vitamin D levels have been identified as potential predictors of response to HCV therapy in children
- Study in Egypt showed children treated with vitamin D (previously deficient with decreases in bone density) showed higher early and sustained virological responses

Issues with Treatment

- PEG-IFN and ribavirin treatment have severe side effects
  - Anemia
  - Cytopenias – Neutropenia and Thrombocytopenia
  - Headache
  - Myalgias or arthralgias
  - Fever
  - Anorexia
  - Nausea or vomiting
  - Fatigue
  - Abdominal pain
  - Insomnia
  - Pruritis
  - Irritability
  - Anxiety / psychosis

Treatment Response

- Response is better in patient <40 years old
- Young females respond well
- HIV or HBV co-infection and excessive use of alcohol decrease response to treatment
- Children <3 years of age are currently not approved for treatment
- Fetal abnormality and fatality are important side effects of ribavirin
  - A well-known teratogen
  - Treatment not recommended during pregnancy
Treatment Response

- Virus has a high mutation rate
  - High replication rate
  - Error prone polymerase causes mutations continuously
  - Viral production estimated at one trillion virions per day
- The envelop protein E2 has highly mutated sites
  - Known as hypervariable region HVR1
  - Causes immune escape mutants of the virus


Treatment Response

- SVR rates are generally lower in persons with insulin resistance
- If SVR is achieved and patient does not have cirrhosis, retesting should be done at 48 weeks post-treatment
  - If HCV RNA is negative, and ALT is normal, patient can be “discharged”


Newer Treatments

- October 2014:
  - Ledipasvir/sofosbuvir - Harvoni
  - Sofosbuvir is a nucleotide inhibitor
  - Ledipasvir is an inhibitor of NS5A
  - This combination resulted in 100% SVR at least 4 weeks after treatment (n=25) in genotype 1-infected persons
- December 2014:
  - Ombitasvir/paritaprevir/ritonavir plus dasabuvir – “IFN-sparing” regimen - Viekira
  - Paritaprevir/ritonavir is an inhibitor of the HCV NS3 serine protease
  - Dasabuvir in a non-nucleoside inhibitor of the HSSb HCV polymerase
  - Ombitasvir is an NS5A-targeted drug
  - When this combination was given to prior null responders, SVR rates of 89-95% were achieved

Newer Treatments

- Ombitasvir/Paritaprevir/Ritonavir
- +/- Dasabuvir
- +/- Ribavirin
- Clinical trials have shown promising results, specifically in genotypes 1 and 4
- Study completed to confirm “real-world” results
- 209 patients with chronic hepatitis C enrolled
  - Only 2 patients were non-responders to therapy


Treatment for Children

- Acute hepatitis C: no treatment; monitor to see if infection clear
- Chronic hepatitis C: PEG IFN and ribavirin for children >3 years of age
- No medication currently approved for children <3 years of age
- Newer medications are approved for adults; not yet approved in children

Questions?