HEPATITIS C IN CHILDREN

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On Behalf of the Gastroenterology Section of
the Portuguese Society of Pediatrics

Lisbon, 18th-19th November 2010
Hepatitis C in children - Epidemiology

• Chronic Hepatitis C in children: “A rare disease?”

  True prevalence unknown

• Seroprevalence* (global/ pediatric): USA: 1.8%
  0.2% < 12 ys
  0.4% 12-19 ys

Portugal: 1.5%*
  children ?? (0.1%....)

- natural history unknown
- pathogenesis insufficiently understood
- infraclinic expression....

** www.apef.com, Marinho R et al, J Gastroenterol Hepatol 2001
Hepatitis C in children - natural history

Multicenter study (retrospective/prospective data)*
1990-2005 (15 ys)

Italy National Observatory: Childhood Hepatitis C Infection

N= 504 assymptomatic children
no associated disease

Perinatal transmission: 56.2%
Parenteral transmission: 31.3%
Undetermined transmission: 12.5 %

1992 (blood screening)
> 90% cases: Vertical transmission, no-comorbidities

*Bortolotti F. Gastroenterology 2008, Vergani M, Arch Dis Child 2005
Hepatitis C Virus genotypic profile in children

Multicenter retrospective study, Italy (1990-2002) n= 373 children ARN VHC +
No HIV or VHB co-infection, no co-morbidities

<table>
<thead>
<tr>
<th>Genotype</th>
<th>1a</th>
<th>1b</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>others</th>
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Genotypes 1b, 3 e 4: transfusions / IV maternal drug abuse
Genotypo 2: percutaneous exposure

quasispecies diversity - age increase

Bortolotti F, Gut 2005
Gerotto M, Infection, 2006
Hepatitis C in children - Epidemiology

• Pregnancy seroprevalence (USA, Europe)*: 1-2%
  UK: 0.1-0.8%
  Portugal: ???

• Rate of Perinatal Transmission**: 4-10%
  0 - 1% if no maternal viremia
  5 % if intrapartum (+) RNA
    - high viral load, chronic liver disease
  7.5% - 40% if HIV co-infection (<< risk if HAART)

Hepatitis C at pediatric age
Epidemiology in Portugal

PERINATAL TRANSMISSION OF HEPATITIS C VIRUS
Santo André Hospital, Leiria 2002-2006 (follow-up protocol > 2002)

• **Aims:** To characterize the population of children born to HCV(+) mothers,
  - identify risk factors for perinatal HCV transmission
  - to improve the approach to HCV screening

• **Methods:**
  - retrospective study enrolling children born to HCV(+) mothers
    > Jan 2002 - Dec 2006
  - transversal analysis to repeat anti-HCV in cases that didn’t meet current recommendations for HCV screening and in those without any HCV screening.
Results:
total 12985 births / 5 years
59 children born to HCV(+) mothers ≈ medium prevalence rate: 0.45%.

Perinatal HCV transmission rate was 2.9%.

high rate of inadequate pregnancy surveillance, prematurity and low birth weight, mainly in children born to addicted mothers (54% drug abuse; 20% co-infection) (VS control)

1 child with HCV infection without any risk factor for perinatal transmission

50% children anti-HCV(+) at age 9 months, became (-) at 18 months
Hepatitis C in children - Epidemiology

• When does mother to child transmission of hepatitis C virus occur?

• Mok J et al, European Paediatric Hepatitis C Virus Network, Arch Dis Fetal NEonatal Ed 2005 Rate of Perinatal Transmission**: 4-7%
• Prospective cohort study

• 54 mother/children pairs tested < 3rd day life

• Intrauterine (child ARN + < 3 th day) 30%

• Peripartum (lateintrauterine/ intrapartum): 50%
  child ARN + > 3th day and at 4 wks

• Postnatally?... Low… (breastfeeding??)

  Influence of genotype??.....
Hepatitis C in children - Epidemiology

- No preventive strategy for mother-child transmission

  Transmission risk is proportional to viral maternal load (last trimester)

  No association: type of delivery, IV drug abuse (HIV -)

  Breast feeding transmission assumed as rare (HIV -)


Hepatitis C in children - natural history

Children from anti-HCV (+) mothers

Hepatitis C in children - natural history

Children from anti-VHC (+) mothers

Hepatitis C in children - Epidemiology

Vertical Transmission - Diagnosis

- **Age 2 months**: RNA (+) on 2 occasions > 3 months apart

  and/or

- **Anti-HCV antibodies (+)** > age 18 months
Hepatitis C in children - Epidemiology

Mother-child transmission

Current Recommendations for screening (anti-HCV)*

• Pregnancy

1. No formal recommendation for systematic screening
   (not available effective intervention; ribavirine TT contra-indication)

2. Recommended (high risk settings):
   - present/ past history of drug abuse
   - transfusions/ transplant/ hemodialysis
   - sexual risk behavior
   - HIV infection
   - persistently high AST /ALT

Mother-child transmission
Current Recommendations for screening (anti-HCV)*

- **Infant Screening**
  if mother anti-HCV (+):
  
  - 1st screening: > 18 months; ELISA > Western BLOT
  - late seroconversions 18-24 months;
  - high false positivity rate before 18 months, no false negative rate

  anti-HCV (+) ➞ confirmation by RNA (PCR) 2x
  (6 months apart, fluctuation of viremia)

  anti-HCV (-): not infected

  - breast feeding recommended, except if HIV- co-infection
    (contraindication)

Hepatitis C in children – natural course

RNA HCV (+): 94.6% (477/504)

24.7% (118/477): INF-α standard: 27.9% SVR

75.3% (359/477) no TT

Indetectable viremia: 7.5% (27)

Persistent Viremia: 92.0% (332)

Decompensated cirrhosis: 1.8% (6)

# Spontaneous eradication: rare

# Terminal Liver disease: in a small subset perinatal exposure (age related-risk), maternal drug abuse genotype 1a

Bortolotti F. Gastroenterology 2008
Influence of genotype

Possible eradication within the first 3-5 years / rare < 3 years

Bortolotti F et al
Gastroenterology 2008
Hepatitis C - Treatment at pediatric age

**IN FAVOUR**

- Slight disease / initial stage
- Comorbidity rare

**AGAINST**

- Asymptomatic disease
- Slow rate of progression
- Few cases with advanced disease
- Suboptimal treatment
- Treatment cost
- Adverse effects
- New drugs on pipeline ....

Familial compliance
- No social stigmata
- Neurocognitive sequelae
- Direct / indirect costs
Hepatite C crónica na criança - histologia hepática

**Bortolotti F et al**
*Gastroenterology 2008*

1990-2005
12 centros Italia
Sem outra patologia

CIRROSE VHC Descompensada
6 / 332 = 1.8%
idade: 2 a 15 anos
TH: n=2

**McDiarmid SA et al**
*SPLIT registry*  
*Pediatr Transplant 2004*

Cirrose VHC: 0.8 %
8/ 1092 TH en EEUU 1995-2002

**Jara P**  
*HI La Paz*  
*Madrid*

Cirrose VHC: 0.2 %
1/ 491 TH 1986-2008
Hepatitis C in children - Treatment
IFN alpha 2b + ribavirine

1998-2001
29 centers Europe, Israel, Canada

Farmacocinetics: RBV + IFN alpha

IFN α-2b: 3 MU/m² (3x/week) > Exposure child vs adult

RBV: optimal dosage -15 mg/kg (vs 8 -12 mg/kg)

Gonzalez-Peralta et al
International Pediatric Hepatitis C Group
Hepatology 2005
# Hepatitis C treatment in children

**Alpha Interferon:** SVR 36% (50% G2/3 vs 10% G1) (4 studies)

**Peg-interferon alpha 2a:** SVR 38% (G1) (1 study)

**Interferon alpha + ribavirine:** SVR 46% (1 multicenter study)  
*Pharmacokinetics; FDA approval (2003)*

**Peginterferon a2b + ribavirine:** SVR 55% (2 pilot studies)  
International study; *FDA approval (2008)*

**PEDS-C: PEGIFN a2b vs PEGIFN + Ribavirine** (1 study)  
International randomized, placebo controlled study (ongoing)

**Antiviral (telaprevir/boceprevir)+Peg+Ribavirine** (not evaluated)
PegIFN + RBV at pediatric age
2 pilot studies

Jara P et al
Pediatr Infect Dis J 2008

Wirth S et al
Hepatology 2005

30 children
pegIFN alpha2b 1 µg/kg/week + RBV 15 mg/kg/d

61 children
pegIFN alpha2b 1.5 µg/kg/week + RBV 15 mg/kg/d

Results

<table>
<thead>
<tr>
<th></th>
<th>Genotype 1</th>
<th>Genotype 2/3</th>
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<tbody>
<tr>
<td>Spain</td>
<td>46.6%</td>
<td>100%</td>
</tr>
<tr>
<td>Germany</td>
<td>47.8%</td>
<td>100%</td>
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Chronic hepatitis C at pediatric age
Current treatment consensus

- **Start treatment**: > 3 ys / before adolescence
- Exclusion of co-morbidities / other etiologies
- Liver biopsy not required (…)

- **PEG-IFN(1-1.5 ug/Kg/ week) + Ribavirine (1.5 mg/Kg/d)**
- **Aim**: SVR (viremia negativation at 24th week post-TT)
- **Duration**:
  - genotype 2/3: 6 months
  - genotype 1 / others: 12 months
- **Stop**: no ARN VHC decrease at 12th week post-TT

- Monitoring (growth.), biochemical, viral load
- **Pre TT pregnancy test**
- hepatitis B and hepatitis A immunization
Hepatitis C at pediatric age
Epidemiology in Portugal

CHRONIC HCV INFECTION AT TERTIARY CENTERS

Pediatric Gastroenterology Units / Pediatric Departments (NHS)

Retrospectively collected data (> 1993 – 2008): 16 years period

Exclusion criteria:
- period before universal donor screening (<1992)
- current age: < 2 ys, ≥ 16 ys

Number of patients (no gender predominance):

HS. João, Porto : 9 cases
H. Maria Pia, Porto : 8 cases
H. S. Marcos, Braga : 2 cases
H. Pediátrico Coimbra : 2 cases
H. Garcia Orta, Almada : 4 cases
HD. Estefânia, Lisboa : 6 cases
H. Santa Maria, Lisboa : 17 cases

TOTAL : 48 cases
Hepatitis C at pediatric age
Epidemiology in Portugal

CHRONIC HCV INFECTION AT TERTIARY CENTERS

Pediatric Gastroenterology Units / Pediatric Departments (NHS)

Retrospectively collected data (> 1993 – 2008): 16 years

TOTAL: 48 cases

“Cumulative prevalence”: 2.7 cases/ year

Underestimation......
Hepatitis C at pediatric age
Epidemiology in Portugal

CHRONIC HCV INFECTION AT TERTIARY CENTERS

Pediatric Gastrenerology Units / Pediatric Departments (NHS)

Number “newborns” 2008: 10.4/ 1000 inhabitants
104.000 / 10 million inhabitants

If estimated pregnancy seroprevalence 0.2%: 200 anti VHC (+) / 100.000 pregnancies

If estimated vertical transmission 2% : 4 anti-VHC(+) children/ 200 infected mothers

“ Expected number children anti-VHC (+) / 2008: 4 cases” (underestimation?...)
Hepatitis C at pediatric age
Epidemiology in Portugal

CHRONIC HCV INFECTION AT TERTIARY CENTERS

route of infection:
- vertical: 47/48 cases
- sexual: 1 case
- 2 siblings

Ethnic background: Caucasian
- 39/40: Portugal
- 1/40: Ucrania

Mean age: 9.2 ys (range 2-17 ys)

no gender predominance

HIV-HCV co-infection: 2 cases  Mother HIV-VHC: 6 cases

Parental IV drug abuse: 16/40 (not reported: 32 cases)

Other comorbidities: none
Hepatitis C at pediatric age
Epidemiology in Portugal

CHRONIC HCV INFECTION AT TERTIARY CENTERS

Genotypes:
ND: 25
  1: 70% reported cases
  1a: 10
  1b: 6
  3a: 3
  4: 4 (4 cd: 3, 4 ab: 1)

Spontaneous negativation: 4/48 cases (10%)
(at ages 5, 6, 7,7 ys)

Treatment
12 / 48 cases (6 under TT)

Outcome

Viremia Negativation > 24th TTw (SVR): 4/12 (30%)
Decrease viral load: 8/12
Hepatitis C at pediatric age
Conclusions

• Predominance of vertical transmission

• Spontaneous eradication is rare but possible

• Treatment efficacy (IFN + Ribavirine) ~ adult

• Influence of genotype in natural course and treatment response

• No vaccination! Disease control depends on:
  - control of transmission routes
  - treatment of infected patients
Chronic hepatitis C at pediatric age: persisting questions....

• Ideal treatment timing? Individual basis....

• Indications for pre tt liver biopsy?

• Optimal treatment schema? Is ribavirine necessary?

• Predictive factors of response to treatment?

• Duration of ARN VHC indetectable after treatment negativation? (longterm outcome impact of treatment)

• Special cases (co-infection HCV/HIV, HCV/HBV, liver transplant)....

• New drugs/ new treatment regimens .....early treatment in pregnancy??
Chronic hepatitis C at pediatric age: a change in natural course?..... or a disease in extinction?.......
Special Thanks to

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