

Hepatitis B and C

What Is New In Perinatal Transmission?

Claudia M Espinosa, MD, MSc
Pediatric Infectious Diseases
University of Louisville
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Disclosure Statement

- I am a principal investigator or sub-investigator of multiple sponsored trials, but I do not receive any direct support from those companies

Off Label Disclosures

- My presentation involves comments or discussion of unapproved or off-label, experimental or investigational use of hepatitis C anti-viral agents

Objectives

- Overview of implementation strategies to decrease hepatitis B perinatal transmission
- Describe the current knowledge of perinatal transmission of hepatitis C
- Discuss the potential rationale for treating pregnant women and their infants after vertical transmission
- Increase awareness about hepatitis C

HEPATITIS B



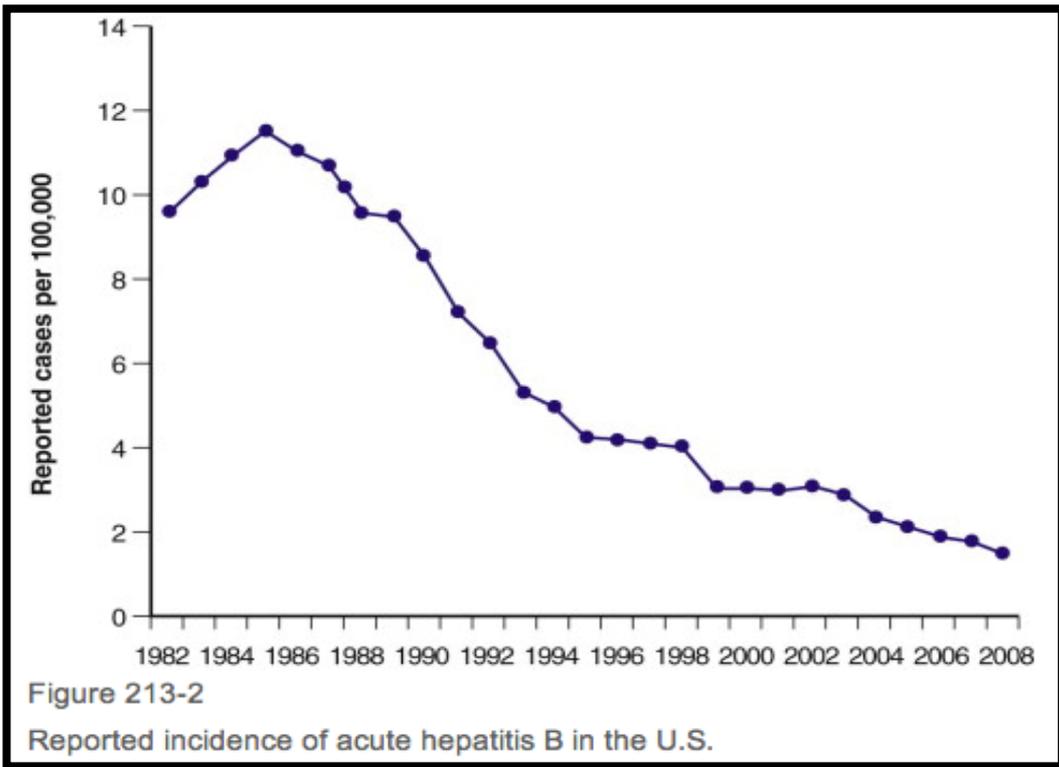
Case

- A baby in a rural KY nursery was born 6 hours earlier by uncomplicated vaginal delivery
- Mother's HBsAg & HBeAg are positive and viral load (VL) is 10^6
- Mother did not receive medications during pregnancy except PNV
- Mother does not want her baby to be immunized because her first child is “autistic due to vaccines”



What would you do?

Epidemiology



- 25000 babies born from HBsAg positive women
- 90% perinatal infections become chronic vs. 5% adult infections
- 1/3 chronic infections are transmitted from mother to child

Mother-to-Child Transmission

Stage	Risk	Comments
Pre-embryonic and assisted reproductive therapy	Unknown	Theoretically possible
Prenatal- In utero	Low (<3% of vertical infections)	HBeAg can cross the placenta
Intra-partum	70-90% if HBsAg & HBeAg positive 5-20% if HBsAg positive & HBeAg negative	Contact with mother's blood or secretions
Breastfeeding	None	BF infants do not have increase rate in transmission

Mother-to-Child Transmission

High risk

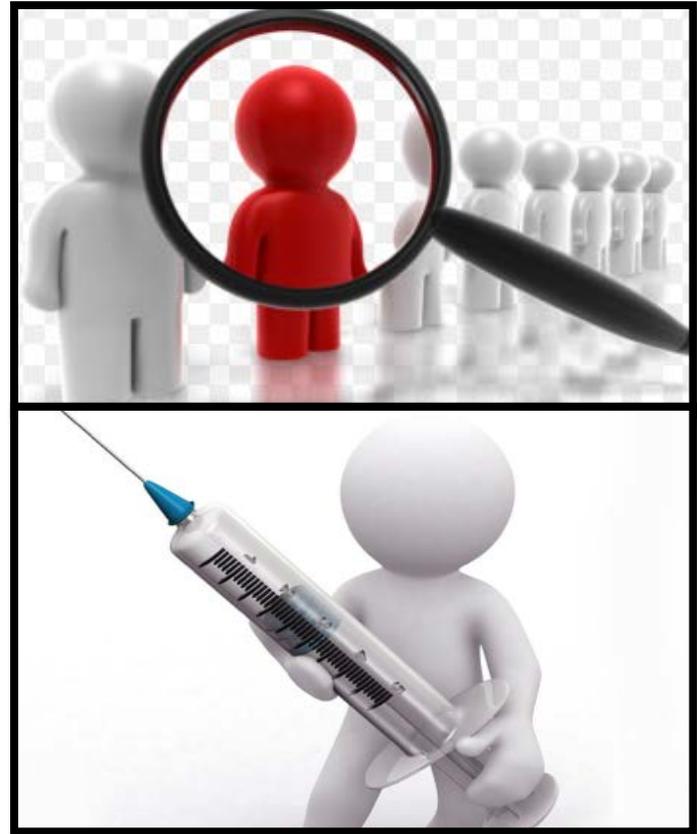
- HBsAg + & HBeAg + (~90%)
- HBV VL $\geq 10^6$ to $\geq 10^8$ copies/mL
- If infection occurs during third trimester

Low risk

- HBsAg + & HBeAg - (~5-20%)
- HBV VL $< 10^6$ copies/mL
- Infection occurs during first or second trimester

Strategies to Reduce Transmission

- Maternal screening
- Universal vaccination
- Post-exposure prophylaxis (PEP)
 - Vaccination at birth
 - Immunoprophylaxis
- Antivirals



Screening

- Obtain HBsAg in all pregnant women at first prenatal visit
- Initiate vaccination if HBsAg negative and or woman is unvaccinated
- Screen or re-screen at delivery if not screened or if the woman has risks factors*
- HBsAg positive test is reported in all states of the US
*Risk factors: household contacts or sex partners of HBsAg positive, injection drug users, ESRD, HIV, chronic liver disease, diabetes

Prevention of Mother-to-Child Transmission

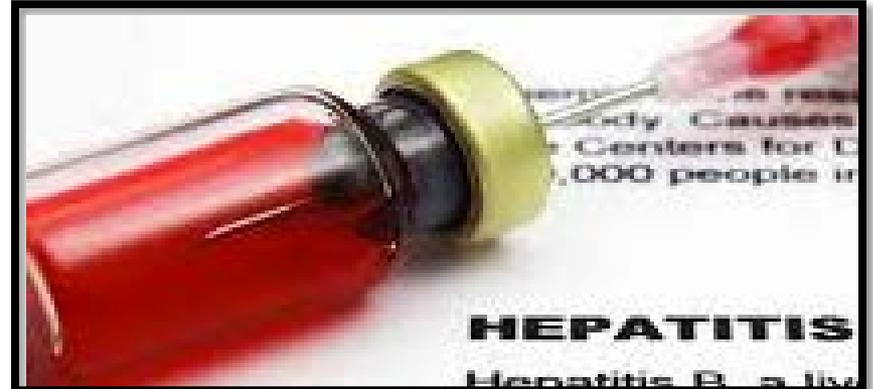
- Universal birth dose
 - Immunogenic
 - Decrease number of doses at 2 months
 - Increase likelihood of completion
 - Prefer within 24 hrs of birth



Prevention of Mother-to-Child Transmission

Post-exposure prophylaxis

- Administer Hep B vaccine and Hep B immunoglobulin (HBIG) within 12 hours of birth
- Complete series within 6 months of birth



Prevention of Mother-to-Child Transmission

Meta-analysis - effect of Hep B vaccine in newborns of positive HBsAg mothers

- Hep B vaccine decreased the risk of Hep B compared with placebo or no intervention (RR 0.28 95%CI 0.2-0.4)
- HBIG decreased the risk of Hep B compared with placebo or no intervention (RR 0.50 95%CI 0.4-0.6)
- Vaccination + HBIG vs. placebo or no intervention reduced Hep B (RR 0.08 95%CI 0.03-0.17)
- Recombinant vs. plasma derived vaccines; high vs. low dose vaccines; different vaccination schedules; and multiple vs. single HBIG did not reduce the risk of Hep B

Outcomes of Infants Born to Women Infected with Hep B

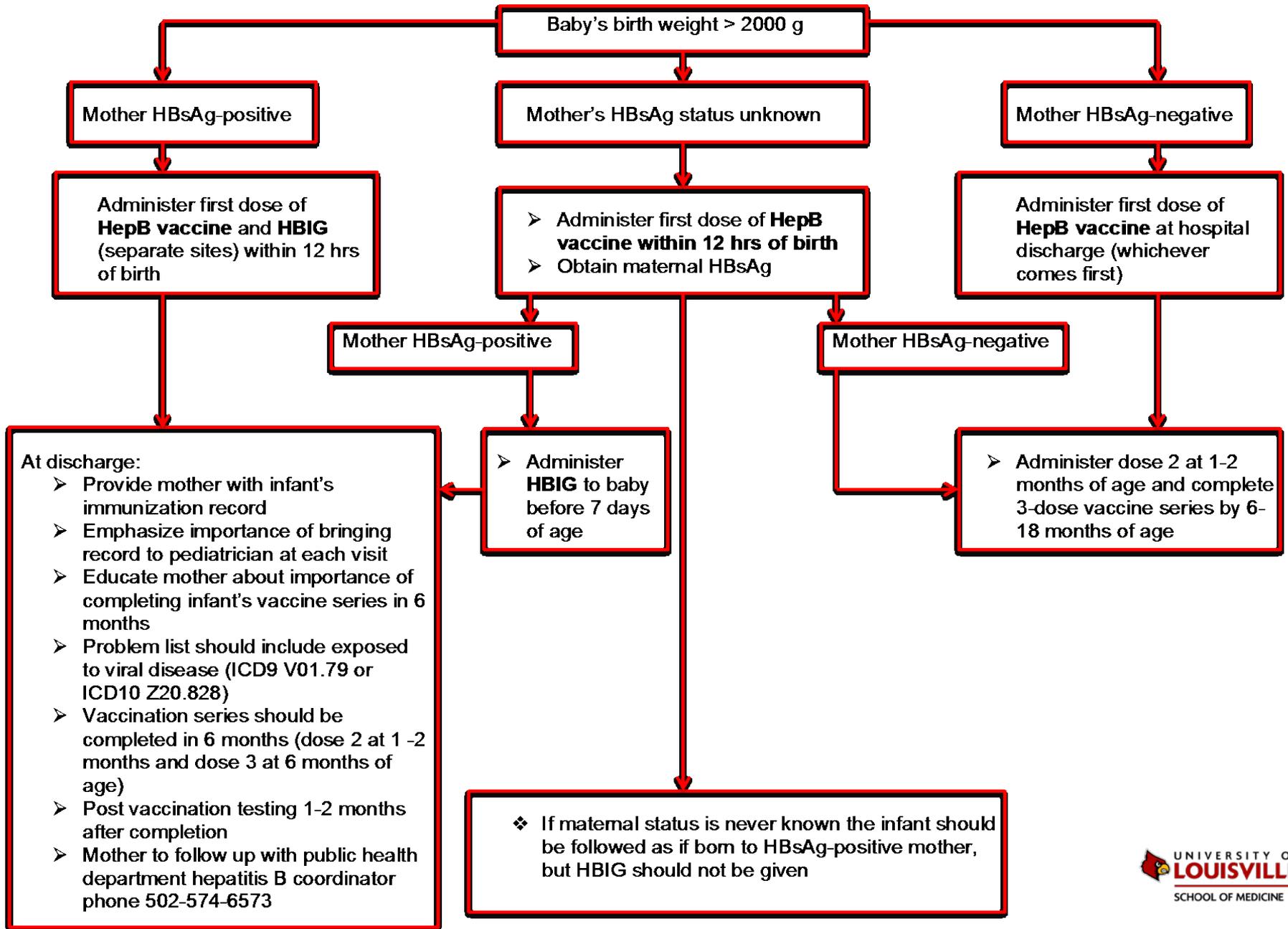
- Prospective study (2007-2013) using data from US funded perinatal prevention Hep B programs
- Analyzed 17951 mother-infants pairs
- HBsAg was available for 9252 (52%) infants
 - 1.1% acquired HBV infection perinatally
- 10760/11335 (95%) received Hep B vaccine and HBIG within 12 hours of birth

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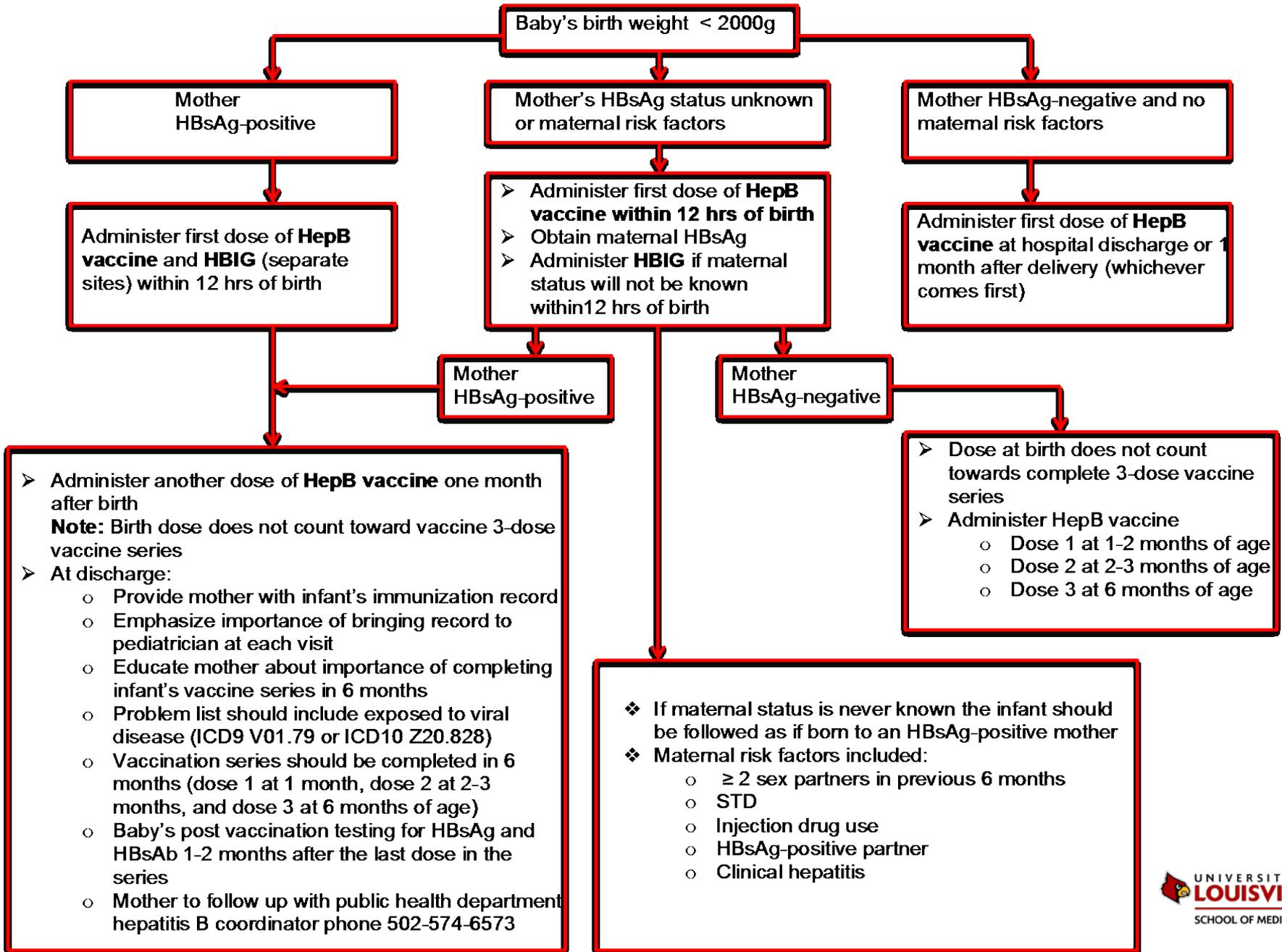
- Factors associated with perinatal infection
 - Young maternal age (p 0.01)
 - Race - Asian Pacific Islander (p<0.01)
 - Maternal HBeAg positive (p<0.01)
 - Maternal HBeAg antibody negative (p<0.01)
 - Maternal VL \geq 2000 IU/mL (p 0.04)
 - Non completion of vaccination series (p 0.01)

**The recommendations seem straightforward
but there is still a lot of work to do**

Prevention of Hepatitis B Transmission in Nursery and NICU



Prevention of Hepatitis B Transmission in Nursery and NICU



Post-Vaccination Testing

- Recommended for all infants born to HBsAg +
- Obtain HBsAg and anti-HBs
- 1-2 months after last vaccine dose ≥ 9 months
- 90% of infants that received PEP had protective levels
- If not protective levels a second Hep B series is given
- Long term protection is maintained in responding children

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In 2008 post-vaccination testing was known for <60% of infants exposed

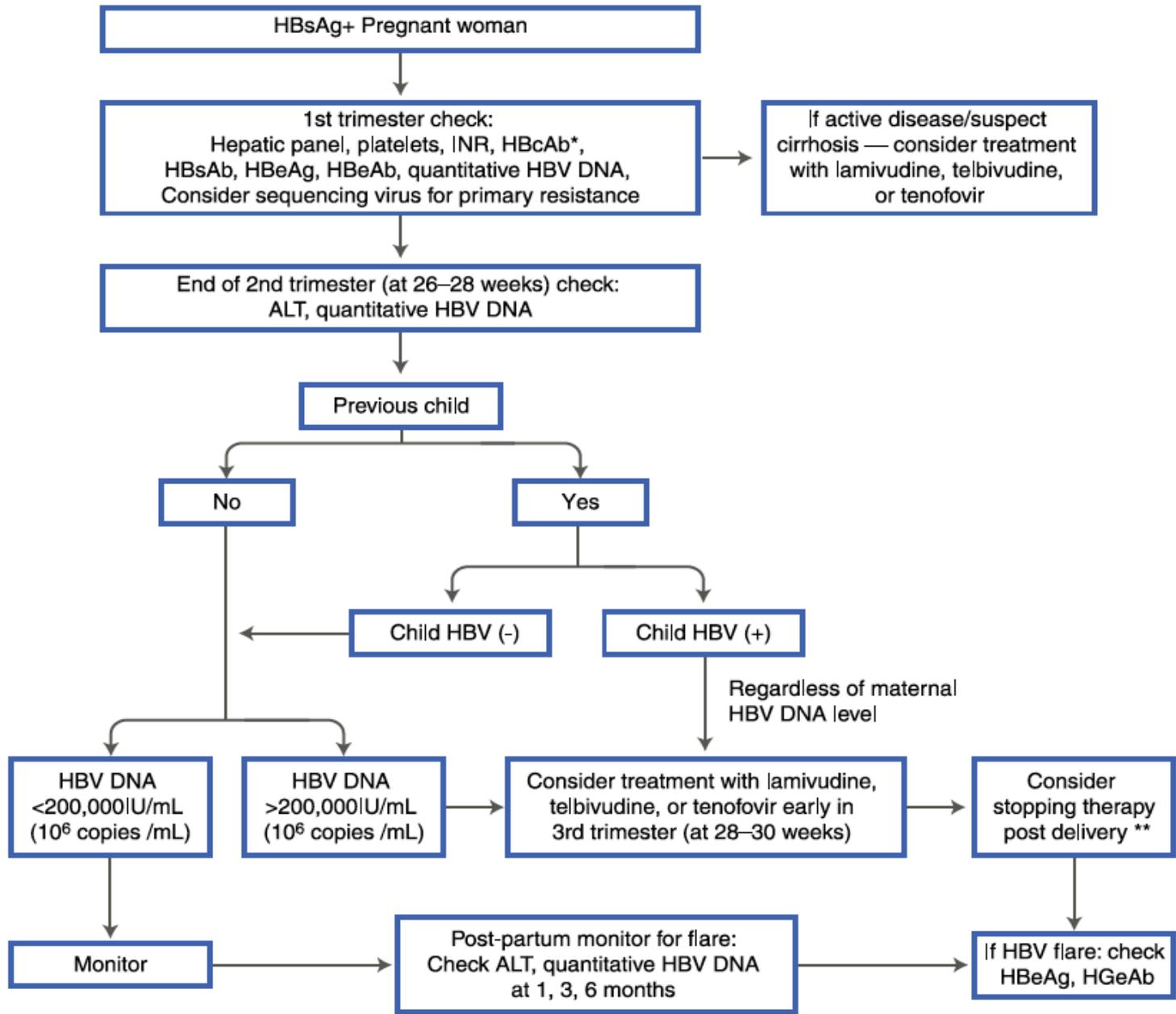


HBV and Pregnancy

- Symptoms are indistinguishable from other types of hepatitis (most are asymptomatic)
- Gestational diabetes, antepartum hemorrhage and preterm labor (acute infection) are associated with HBV
- Rupture/bleeding of esophageal varices if cirrhosis
- High adrenal steroids & estrogen can increase VL
- Hepatic flare may occur at the end of pregnancy or postpartum

Management of HBsAg-Positive Pregnant Women

- No universal policy exists, but ACIP recommends
 - All HBsAg+ women should receive evaluation and treatment for chronic HBV infection
- Algorithms for liver disease assessment are similar for pregnant and non-pregnant women
 - Test for HBeAg, quantitative HBV DNA, and LFT's
 - Results guide therapy and timing of intervention
 - Consensus recommendations



** discontinue therapy between 0 and 6 months-ideal time to discontinue remains unclear

Chronic Hepatitis B Treatment

- FDA approved 7 drugs
 - Category B: telbivudine, tenofovir
 - Category C: lamivudine, adefovir, entecavir
 - Category X: interferon (standard, pegylated)

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Table 1 Antiretroviral pregnancy registry data

Proportion of defects reported with an exposure to:	Earliest trimester of exposure	
	1st trimester birth defects/live births	2nd/3rd trimester birth defects/live births
Lamivudine	122/3966 (3.1 %)	178/6427 (2.8 %)
Tenofovir	27/1219 (2.2 %)	15/714 (2.1 %)
Telbivudine	0/8	0/9
Adefovir dipivoxil	0/43	0/0
Entecavir	1/30	0/2
Any NRTI	165/5582 (3.0 %)	216/7772 (2.5 %)
Any NtRTI	27/1262 (2.1 %)	15/712 (2.1 %)



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Treatment during Pregnancy and Delivery

- Antiviral prophylaxis in late pregnancy if high VL is effective reducing transmission
- Recommended if
 - VL $>10^5$ copies/mL (>20000 IU/mL)
 - Evidence of liver disease
- Not recommended for immune tolerant or low VL
- Gaps on treatment: start, stop, flares, safety of BF while taking antivirals

Efficacy and Safety of Telbivudine

- Prospective study from Feb 2008-Dec 2010
 - HBeAg positive (2nd or 3rd trimester)
 - 362 received telbivudine vs. 92 untreated
 - HBV DNA prior to delivery
 - 2.73 treatment group vs. 7.94 log₁₀ copies/mL (p<0.001)
 - HBsAg positive at birth
 - 11.8% treatment group vs. 20.7%
 - HBV DNA at 7 months detected
 - 0% treatment group vs. 9.3% control (p<0.001)
- Treatment was safe

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What would you do?

HEPATITIS C



Hepatitis C

- 3.2 million in US have chronic HCV infection
- 17000 new infections are diagnosed annually
- 0.6-2.4% of pregnant women are affected
- Perinatal transmission rate is 5-15%
- In USA 70% of all HCV isolates are genotypes 1a & 1b
- Before 1992 the most common cause of HCV transmission in children was

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- Perinatal transmission rate is 5-15%
- In USA 70% of all HCV isolates are genotypes 1a & 1b
- Before 1992 the most common cause of HCV transmission in children was **blood transfusion**
- After implementation of universal testing of blood products, the most common source of transmission in children is **vertical**

Case

- 32-year-old G4P3 pregnant woman comes in labor
- Her HIV status is known to be positive from previous pregnancies
- She discloses regular IV drug use
- She lives in Austin, Indiana



What Is Particular About This Town?

Rural Indiana Struggles to Contend With H.I.V. Outbreak

HIV Outbreak: Why Austin? Why Indiana?

NEWS RELEASE , from Indiana State Health Commissioner Jerome M. Adams, MD, MPH 10:34 a.m. EDT May 19, 2015

How an HIV outbreak hit rural Indiana – and why we should be paying attention

With 150 cases is Indiana HIV outbreak reaching its peak?

So, what was the perfect storm here? Is Austin so different from other cities? Will it be the only small city to have to battle an HIV epidemic that's primarily due to intravenous drug use? Or is it the first?



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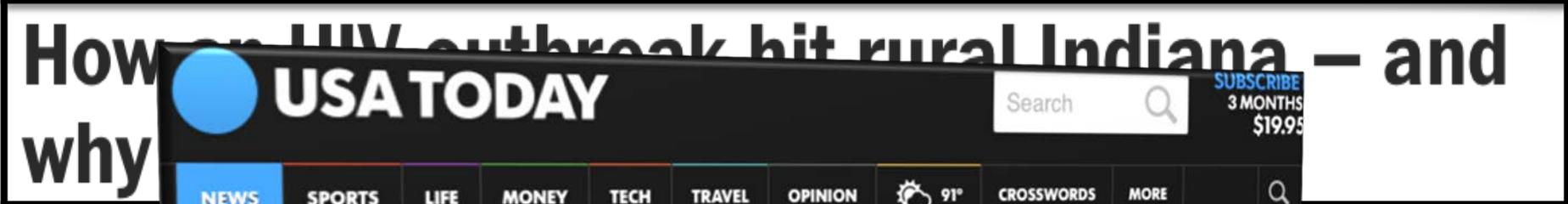


KOSAIR
CHILDREN'S
HOSPITAL

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Indiana community's HIV outbreak a warning to rural America

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Aftermath

> 160 HIV infected and ~ 85% are co-infected with HCV

Perinatal Transmission

- Transmission rate is low → 5-15%
 - 50% of infants resolve infection → 3-5%
- HIV co-infection was a risk factor
 - 20-25% pre-HAART but rate is same now
- Mode of delivery does not affect transmission
 - Transmission at delivery or early in utero ?
- Amniotic fluid is negative for HCV
- Discordant transmission in twins
- Peripheral blood mononuclear cell (PBMC) infection
- Past or ongoing maternal IV drug use

Transmission of Hepatitis C from Mother to Child

- 7698 women tested for Hep C antibodies
- 53 women HCV +
- 7 infants infected

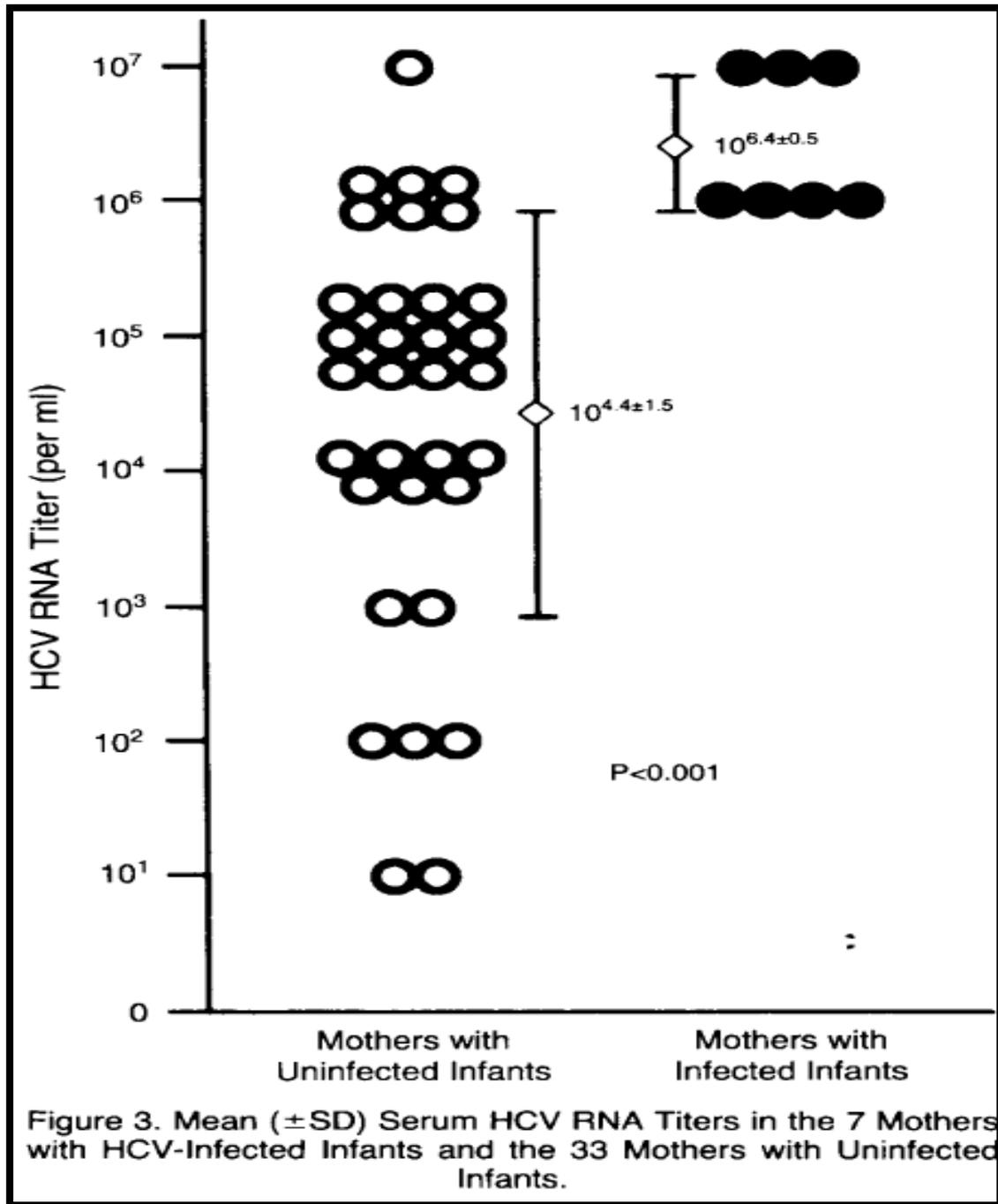


Table 2. Risk of hepatitis C virus (HCV) infection among infants born to HCV RNA-positive, HIV-negative mothers, by maternal characteristics (univariate analysis).

Maternal characteristic	Infants, no. (%)		RR (95% CI)	P
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>10 ⁶ , <10 ⁷	87 (47.8)	2 (2.3)	...	
≥10 ⁷	34 (18.7)	4 (11.8)	...	
Age at delivery, years				
≥30	100 (55.3)	5 (5.0)	2.0 (0.4–10.2)	.46
<30	81 (44.8)	2 (2.5)	...	
Prior pregnancies, no.				
>4	73 (40.1)	2 (2.7)	0.6 (0.1–3.0)	.70
≤4	109 (59.9)	5 (4.6)	...	
ALT level at delivery, U/L				
>35	45 (24.7)	3 (6.7)	2.3 (0.5–9.8)	.37
≤35	137 (75.3)	4 (2.9)	...	
Mode of delivery				
Vaginal	151 (83.4)	6 (4.0)	1.0 (reference)	1.0
Elective cesarean	12 (6.6)	0 (0.0)	Undefined	
Emergency cesarean	18 (9.9)	1 (5.5)	1.4 (0.2–11.1)	
Fetal monitoring				
Internal	16 (8.8)	3 (18.8)	7.7 (1.9–31.6)	.02
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- Cohort 244 infants born to HCV + mothers
- 9/190 (5%) of those born to RNA + mothers were infected
- 0/54 of those born to RNA – were infected
- 3 infected infants resolved their infection



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Breast Milk and Perinatal Transmission

- HCV is detected in BM at levels 100-1000 times lower than in plasma
- Studies attributing transmission through BM did not exclude in utero or peripartum
- Clinical guidelines do not prohibit breastfeeding in women HCV infected
- Human milk lipases with antiviral activity against enveloped viruses

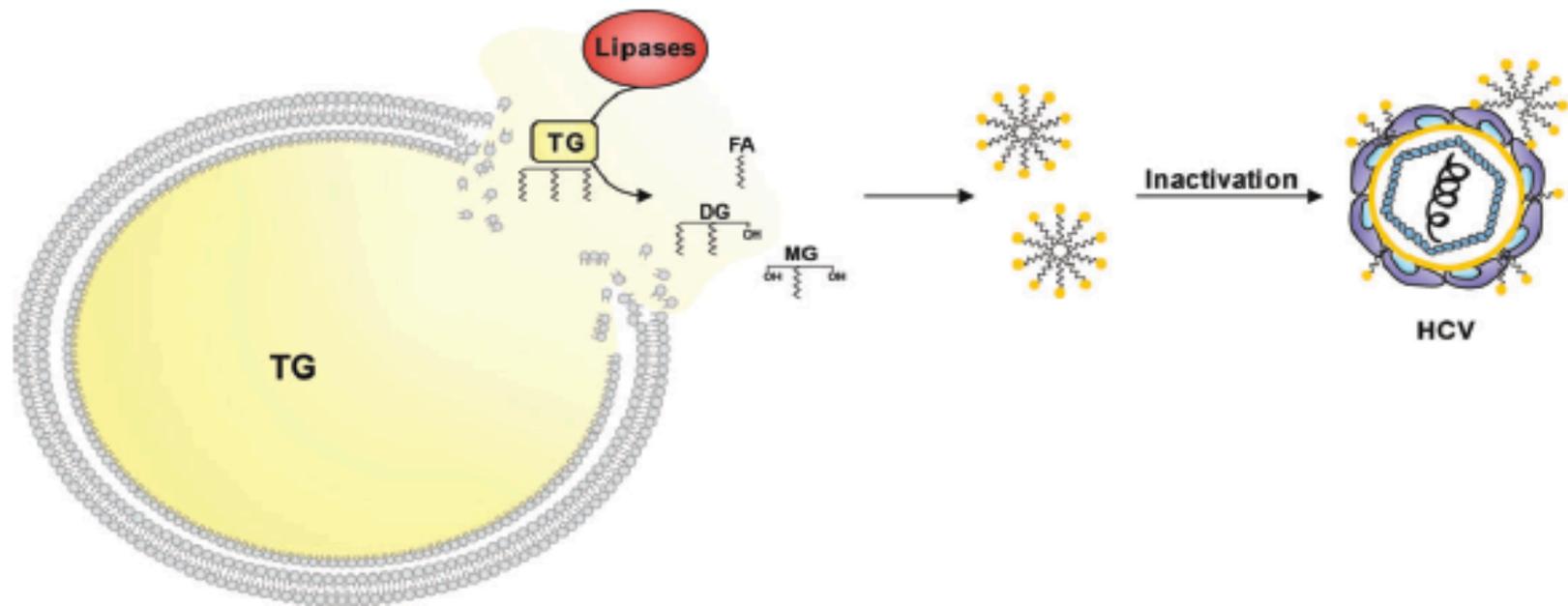
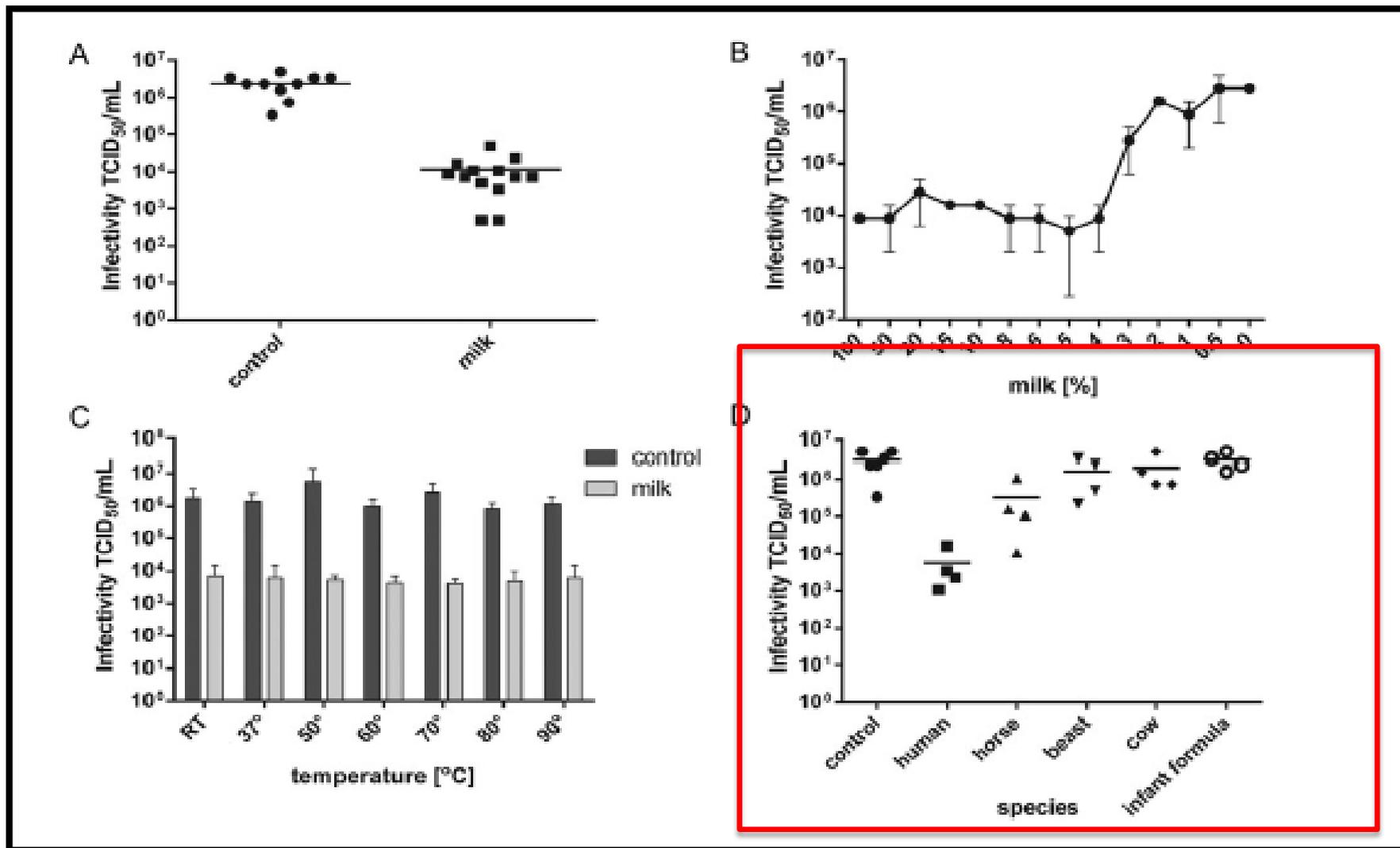


Figure 6. Hypothetical model for inactivation of HCV by human breast milk. Due to a disruption of the milk fat globular membrane (gray), milk lipases (red) get access to the triglyceride (TG) core (yellow). Following milk digestion free fatty acids (FA), monoglycerides (MG), and diacylglycerides (DG) are released. These are able to disrupt the viral envelope of HCV (schematic depiction, showing the glycoproteins E1 and E2 (blue), the viral envelope (yellow) and the capsid formed by the core protein (light blue), which protects the viral RNA). Abbreviation: HCV, hepatitis C virus.

Figure 1. Human breast milk reduces HCV infectivity



Pregnancy and HCV

- 12 HCV pregnant women compared with matched 12 HCV non pregnant
- 2 point biopsies done
- Pregnant had fibrosis score deterioration (42% vs. 8%)
- Pregnant had necroinflammatory deterioration (83% vs. 25%)

Fontaine H et al. Lancet, 2000

Pregnancy and HCV

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- 2 point biopsies done
- Pregnant had fibrosis score deterioration (42% vs. 8%)
- Pregnant had necroinflammatory deterioration (83% vs. 25%)
- 201 women received a survey regarding prior pregnancies, menopause and the use of contraceptives
- Rate of fibrosis was higher in post-menopausal and nuliparous
- Pregnancy may have a beneficial effect

Fontaine H et al. Lancet, 2000

Di Martino V et al. Hepatology, 2004

Pregnancy and HCV

- Women with chronic infection usually have uneventful pregnancy
 - 370 pregnant women with HCV infection
 - ALT was elevated in 56% during first trimester but only 7% during third trimester
 - ALT returned to elevated level 6 months after delivery in 54%

HCV Resolution and Pregnancy

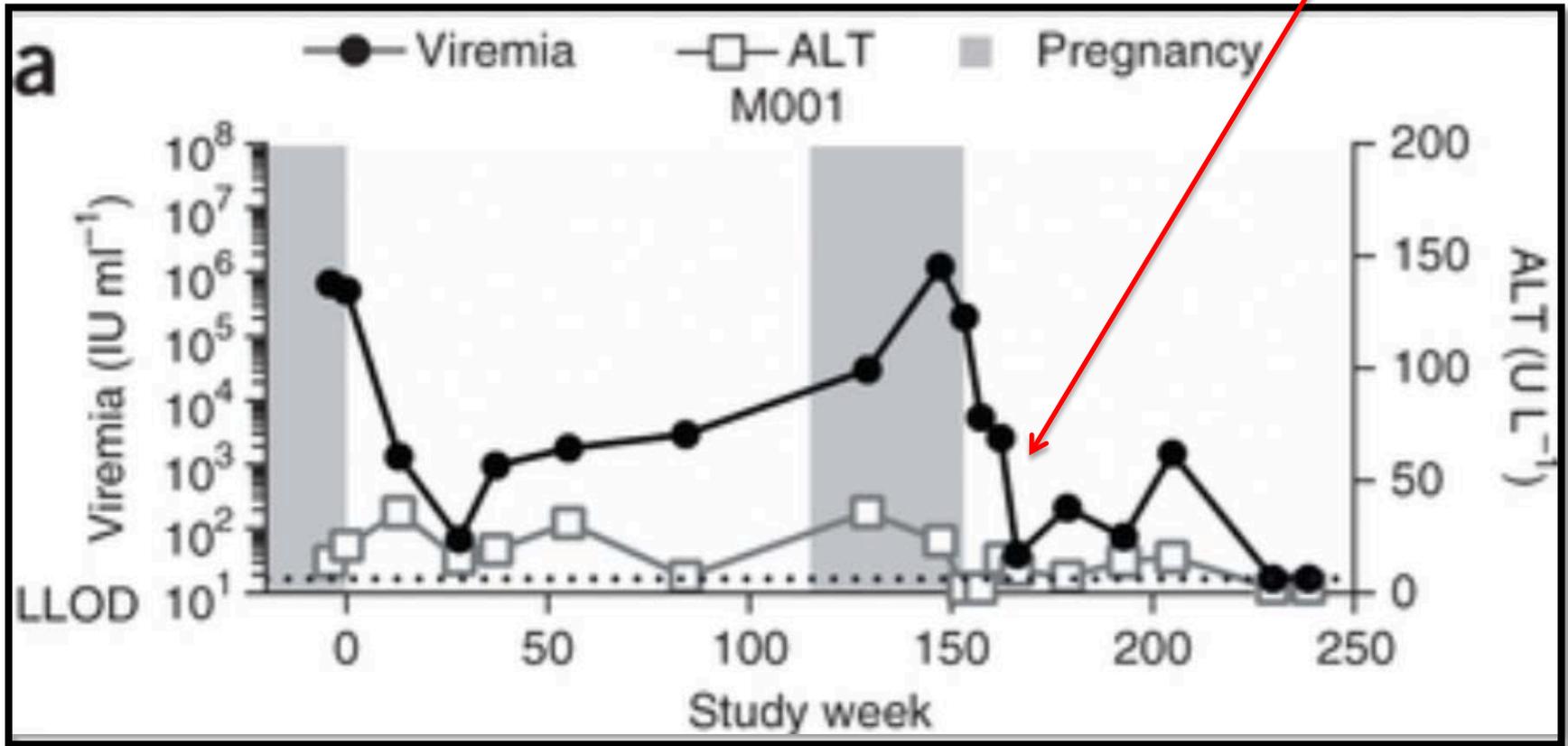
- Compared 10 HCV RNA + pregnant vs. 8 HCV RNA + non-pregnant
- All pregnant women had drop in HCV levels after delivery
- 2/10 pregnant became undetectable after delivery
- Compared 22 pregnant vs. 120 non-pregnant
- 2 pregnant patients loss their HCV RNA vs. 1 non-pregnant
14% vs. 2% $p=0.03$

Lin HH et al. BJOG, 2000

Hattori Y et al. J Med Virol, 2003

HCV RNA & T Cell Surge

Drop is due to surge in HCV specific T-cells after delivery



Honegger R et al. Nat Med, 2013

Pregnancy and HCV

- Pregnancy complications (controlling for IV drug)
 - Infants are more likely to be low birth weight and SGA
 - Infants require more NICU care and mechanical ventilation
 - Women have increased risk for gestational diabetes
 - Increase preterm birth

Pregnancy Symptoms

- Viremia 2-26 wks – resolved by cellular immune response mediate by HCV-specific CD4 and CD8
- Chronic infection – exhausted phenotype
- Humoral response is generated but does not neutralize the virus



Management of HCV Infected Women and Their Children

European Pediatric HCV Network

Table 1
Does HCV infection satisfy the criteria for introduction of routine antenatal screening?

Criteria	Evidence regarding HCV	Satisfied in the context of antenatal HCV screening?
The condition is an important public health problem	Global prevalence 3%; estimated antenatal prevalence in Europe 1–2.5% [4]	Yes
The natural history is well understood	Natural history in children is poorly clarified [56]	No
A safe, valid and reliable screening test is available which is acceptable to those being tested	Third generation ELISA assays have high sensitivity (98–100%) and satisfactory specificity (66–99%) [84–86] although low positive predictive value	Yes
Treatment or an intervention of proven effectiveness is available	Available treatment is contra-indicated during pregnancy [87,88], no interventions available	No
The risk of harm, both physical and psychological, is less than the chance of benefit	Positive result in pregnancy associated with considerable anxiety, no benefit of diagnosis during pregnancy as no interventions	No

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Universal screening of pregnant women is not recommended

Guidelines for Screening

Screening is recommended in pregnancy if

- Exposure to blood and derivatives before 1990 (in developed countries)
- Past or current IV drug abuse
- Partner with history of drug abuse
- Multiple sexual partners
- Infection with Hep B virus or HIV
- Absence of prenatal care

Guidelines for Screening

- If positive screen antibody perform PCR quantitative by 3rd trimester
- Avoid invasive procedures for antenatal diagnosis
- Vaginal delivery should not be discouraged
- Mothers should be encouraged to breast feed
- A mother who infected her first child is not at greatest risk of infecting the second

Guidelines for Screening

Screening is recommended in general if

- Risk behaviors: injection-drug use
- Risk exposures: hemodialysis, tattoos, healthcare workers, mother HCV-infected, prior recipients of transfusions or organ transplant, inmates
- Other: HIV infection, unexplained chronic liver disease, solid organ donors
- Periodic testing if ongoing risks

Treatment Pregnant Women

Rationale

- Clear mother's chronic HCV
- Prevent vertical transmission

Efficiency

- Women who will not likely resolve their viremia after delivery
- Women who have high risk of transmission

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Can we predict who will transmit HCV?

If we were to treat pregnant women, when?
Who? And with what?

Treat Every Woman

Pros

- HIV approach without 25% transmission rate
- Most women will benefit of a sustained virologic response
- Will prevent transmission that leads to chronic infection

Cons

- Very expensive at current prices
- Would mandate active screening by OB
- Expose 95% infants to treatment
 - NNT is high

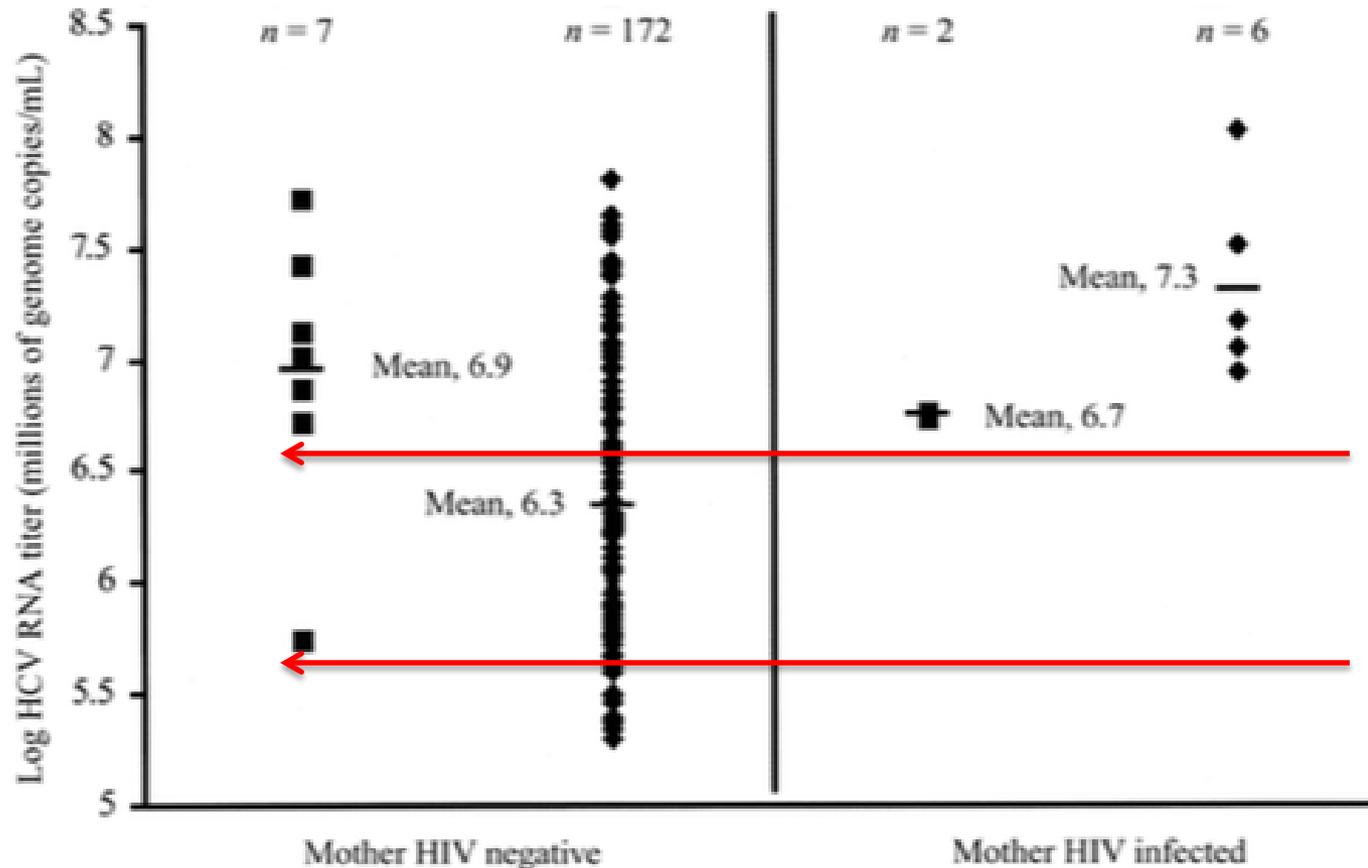
Treat According to HCV RNA

Pros

- Evolving HBV approach (tenofovir in high risk if HBV $>10^6$)
- Less costly
- More efficient benefit to risk ratio

Cons

- Requires coordination of care
- Would miss some as threshold is not well defined
- Right time is questionable



Where do you draw the line?

Figure 1. Hepatitis C virus (HCV) RNA levels among mothers who transmitted HCV to their infants (■) and mothers who did not transmit (◆), by maternal HIV infection status.

Treat According to Other Risk Factors

Pros

- Would allow for more precise patient identification
- Even more efficient benefit to risk ratio
- Potentially less costly if patients easily identified

Cons

- Requires studies that prove a marker is reliable
 - Fibrosis is not easily determined during pregnancy
- May miss some
- Would require integration of screening and intervention with PNC

But what would that risk factor be?

IL28B as Risk Factor

- Since 2009, SNPs in IL28B gene are associated with SVR
- Predicted spontaneous clearance in adults
- Could it predict which mothers would transmit?

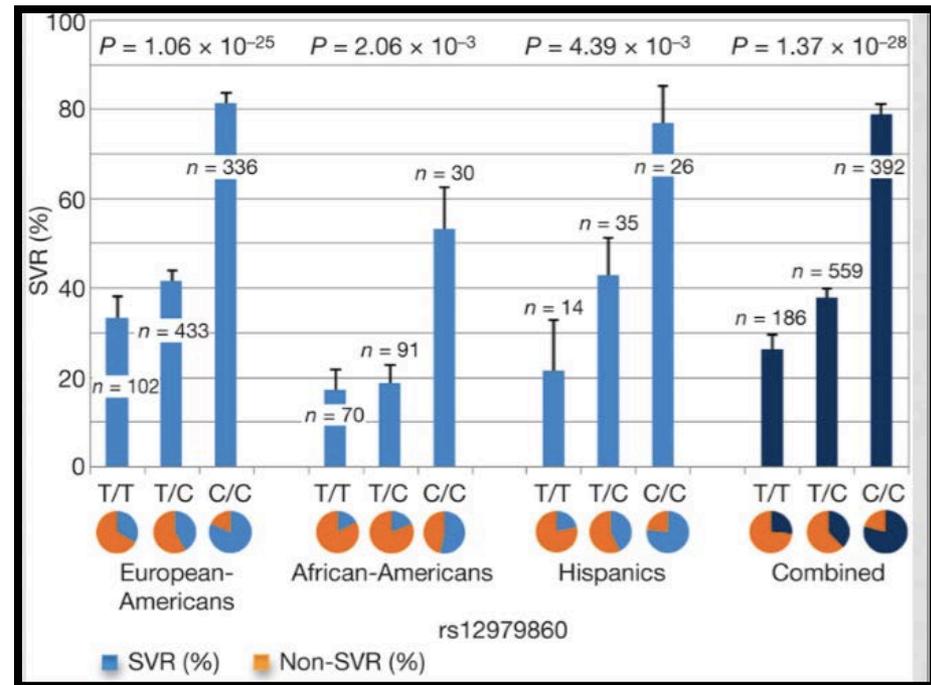
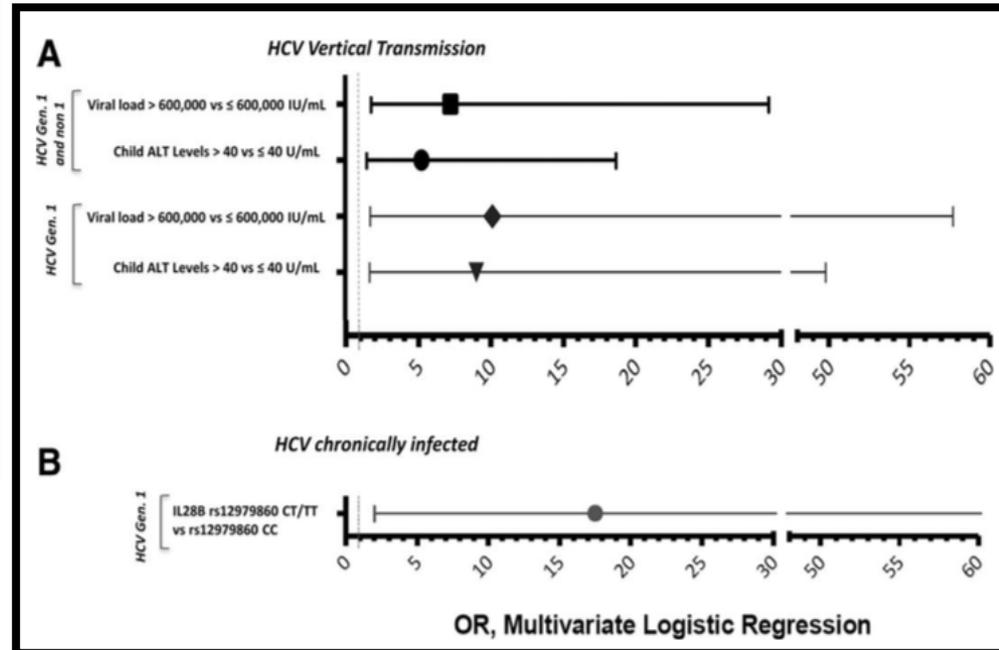


Table 4. Role of IL28B in HCV Vertical Transmission and Chronic HCV Infection in Viral Genotype 1 Infants

HCV Vertical Transmission			
Risk Factors/Infection Status n=74	Infected n=15 (20%)	Noninfected n=59 (80%)	P-Value
Mother's IL-28B status			
CC (19)	7 (37)	12 (63)	ns
Non-CC (55)	8 (15)	47 (85)	
Child's IL-28B status			
CC (25)	6 (24)	19 (76)	ns
Non-CC (46)	9 (20)	37 (80)	
HCV Chronification			
Risk Factors/Infection Status n=15	Chronic n=8 (53%)	Transient Viremia n=7 (47%)	P-Value
Mother's IL-28B status			
CC (7)	3 (43)	4 (57)	ns
Non-CC (n=8)	5 (63)	3 (37)	
Child's IL-28B status			
CC (n=6)	1 (17)	5 (83)	0.04
Non-CC (n=9)	7 (78)	2 (22)	

IL28B does not predict HCV vertical transmission

Fig 2. Multivariate log regression
A. Vertical transmission.
B. Infants chronically infected



Forget Pregnancy

Pros

- Avoids risks
- Simple
- Allows the women that would clear a chance to do it on their own
- Cheaper

Cons

- Misses opportunity
- Risk of dropping out of care after pregnancy
- Reinforces the notion that we are afraid to treat pregnant women

The Future

- Continue working toward option for treatment with collateral benefits
- We need to find better ways to predict transmission
- Enroll in trials in late pregnancy and support a pregnancy registry
- As the cost decreases, it is possible that in the future we will treat all HCV RNA+ (pregnant or not)

What should we do in the meantime?

Infant HCV

- Identification is challenging
- Maternal antibodies last for 12-18 months
- Detection of HCV RNA by NAAT might be done at 1st well child visit (1-2 months of age)
 - During the first year children can have intermittent episodes of viremia

Infant HCV

- Most labs have converted to real-time PCR-based assay
 - Improve sensitivity
 - No studies in HCV exposed infants
 - Re-test ~ 4-6 months
 - If both tests negative infant unlikely to be infected

What Is New?

- Current NICHD MFMU network study
 - Observational study of HCV in pregnancy
 - 14 sites to recruit 1800 women
 - 1200 HCV RNA positive
 - Controls are healthy, otherwise uninfected
 - Analysis of maternal risk factors
 - Infants follow up at 2-6 months and 18-24 months using HCV RNA and antibody

Perinatal HCV Exposure Protocol

- Screen pregnant women with risk factors
- Obtain HCV RNA PCR at the end of pregnancy
- Add problem to problem list in discharge paper work
- Referral to ID clinic is encouraged
- HCV PCR to be done at 1-2 months of age
- Repeat PCR at 4 months of age (chronological age)
- PMD may consider HepC antibody at 18 months of age – optional
- If HepC positive at any time refer to ID clinic

Case

- 32-year-old G4P3 pregnant woman comes in labor
- Her HIV status is known to be positive from previous pregnancies
- She discloses regular IV drug use
- She lives in Austin, Indiana



Screen mother for HCV, if positive report mother and neonate to HD and ensure proper follow up including PCR in the baby at ~ 2 months of age



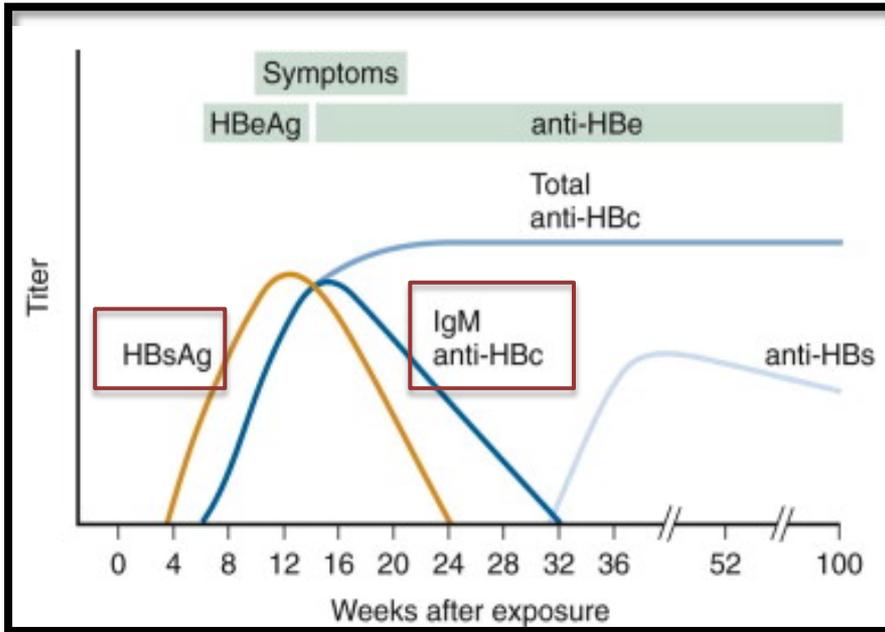
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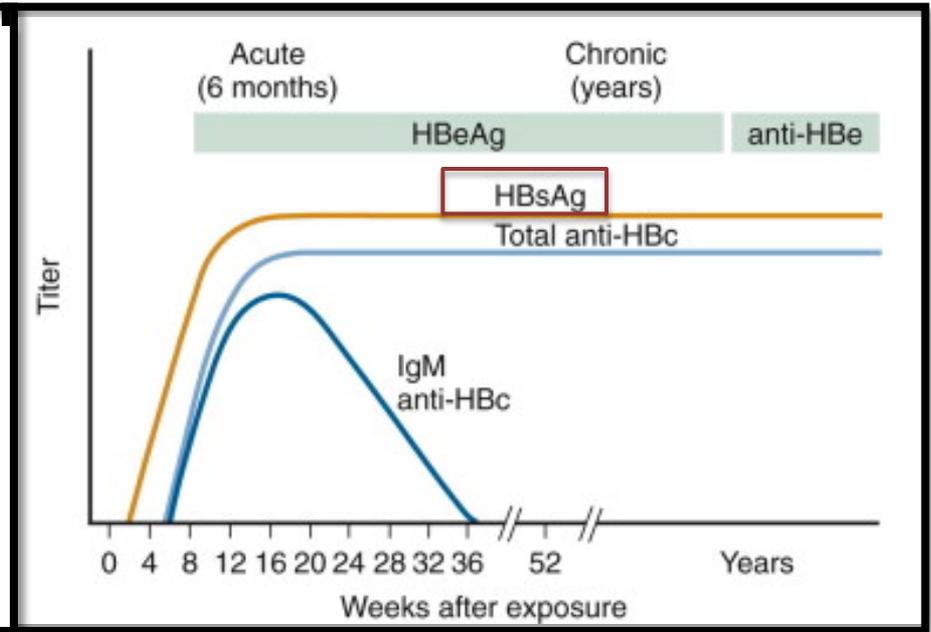
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CHILDREN'S
HOSPITAL

Questions

Hepatitis B Serology



Acute infection with recovery



Chronic infection

Prevention of Mother-to-Child Transmission

Bathing

- Skin contamination might increase the risk of transmission
- Skin contamination can present a risk for occupational exposure

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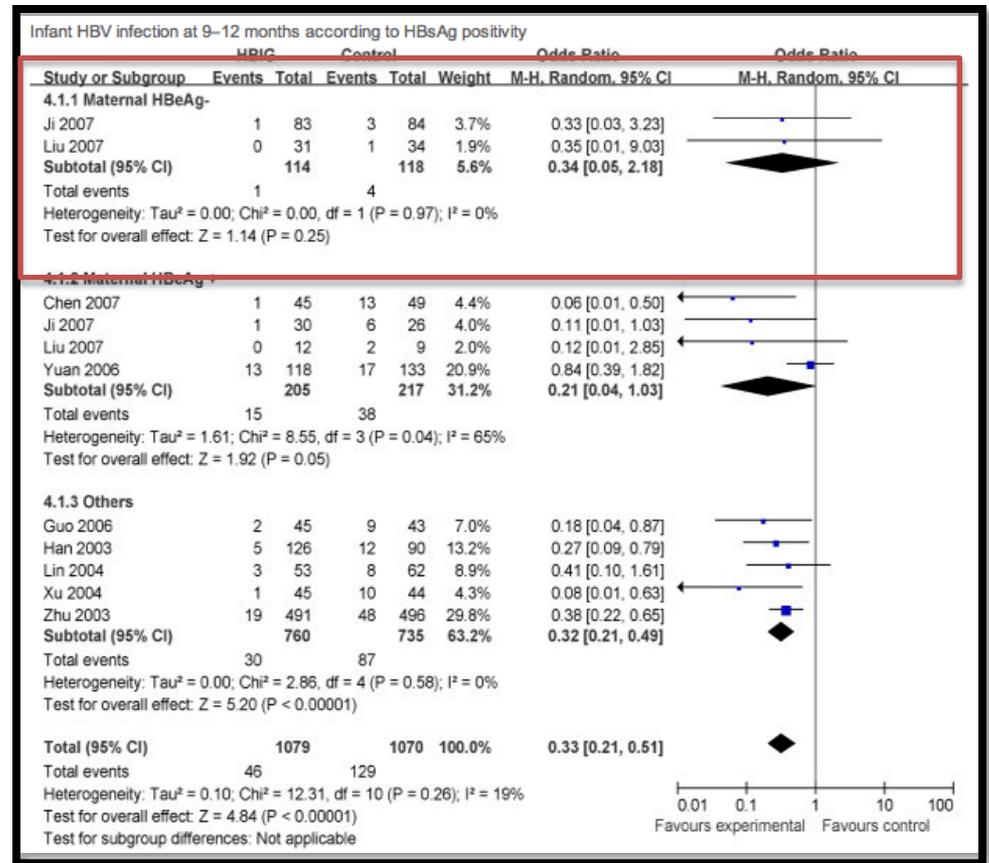
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Neonatal Vaccination

Status	Doses	Follow up
Mother HBsAg pos	1, 2, 6 months	HBsAg at 9-18 months If neg and HBsAb <10mIU/mL repeat 3 dose series
Mother HBsAg unknown	1, 2, 6 months	HBsAg at 9-18 months If neg and HBsAb <10mIU/mL repeat 3 dose series
Mother HBsAg neg	1, 2, and 6-18 months	

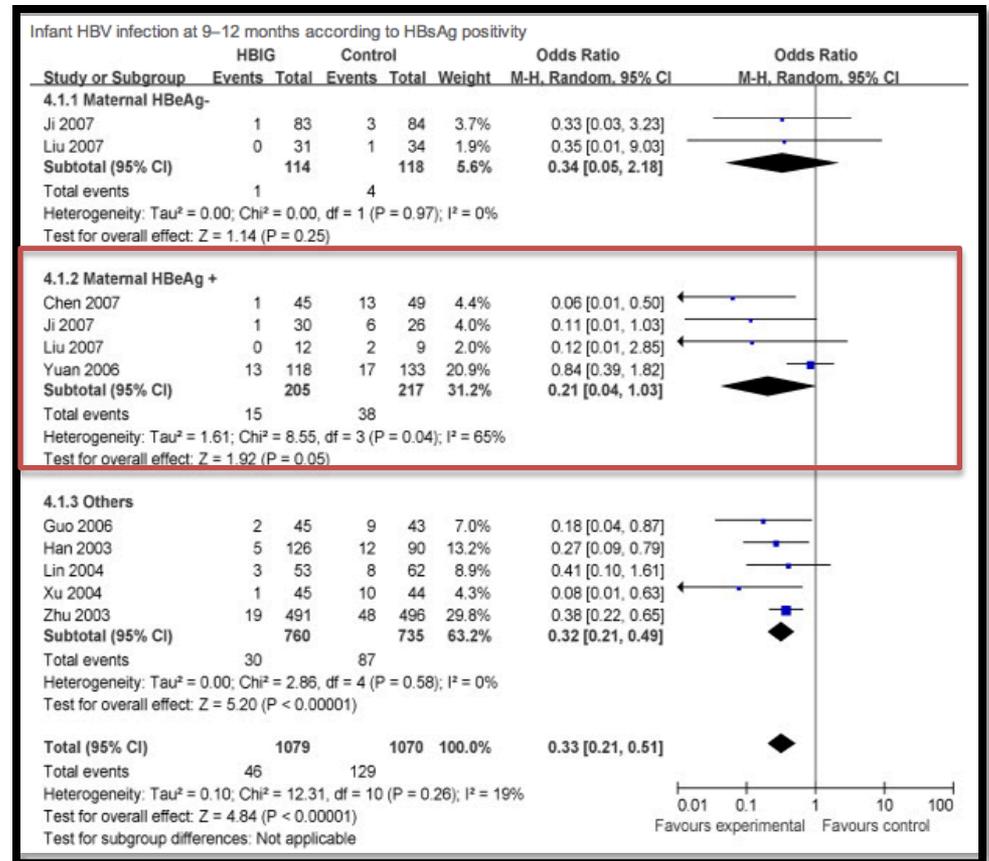
HBIG During Pregnancy

- Meta-analysis evaluated 37 RCT
- Multiple small doses of HBIG in late pregnancy
- All received PEP
- Results suggest decreasing transmission (but less efficient if VL $\geq 10^8$ copies/mL)
- Mechanism of protection and optimal dose are unknown



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HIV-negative women

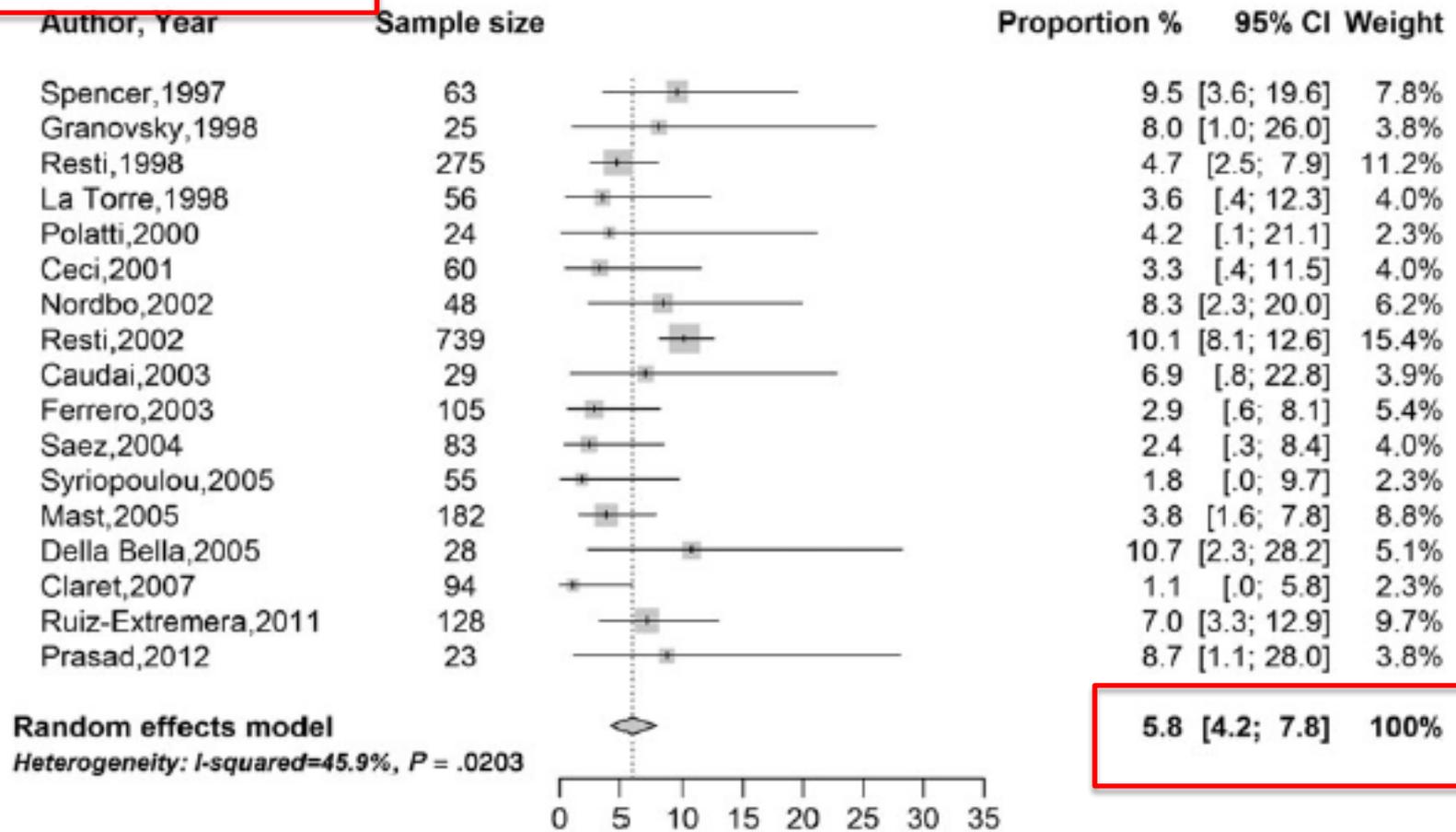


Figure 3. Pooled estimates of risk of hepatitis C virus (HCV) vertical transmission among children ≥ 18 months born to HCV antibody–positive and **RNA-positive mothers**, by maternal HIV serostatus

HIV-positive womer

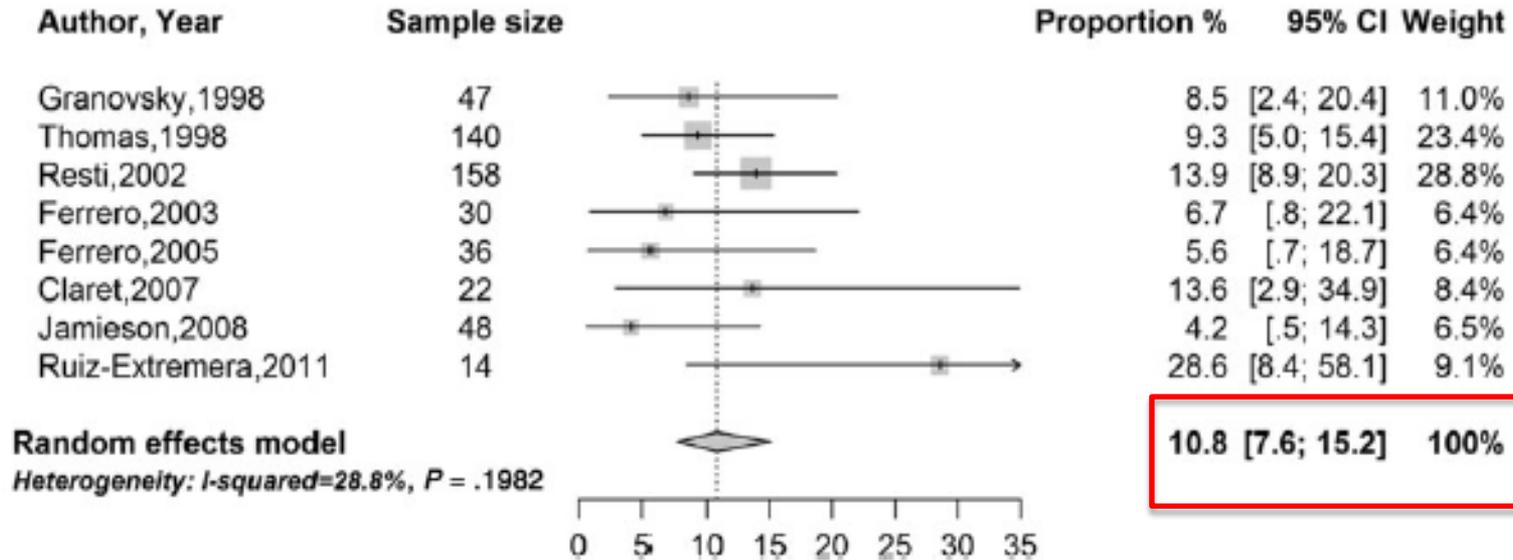


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Treatment of Pregnant Women

- Would avoid treating early in pregnancy to prevent teratogenicity
- May be able to compress into late 2nd or early 3rd trimester because most regimens are usually 12 weeks
- Some patients could get only 8 weeks

Guidelines for Follow Up

Recommended management of infants born of anti-HCV positive mothers

- Definition of perinatal HCV infection
 - Born to anti-HCV positive mother and any of the following
 - HCV RNA detected by PCR in at least 2 different samples during the first year of life
 - Anti-HCV positive after 18-24 months of life

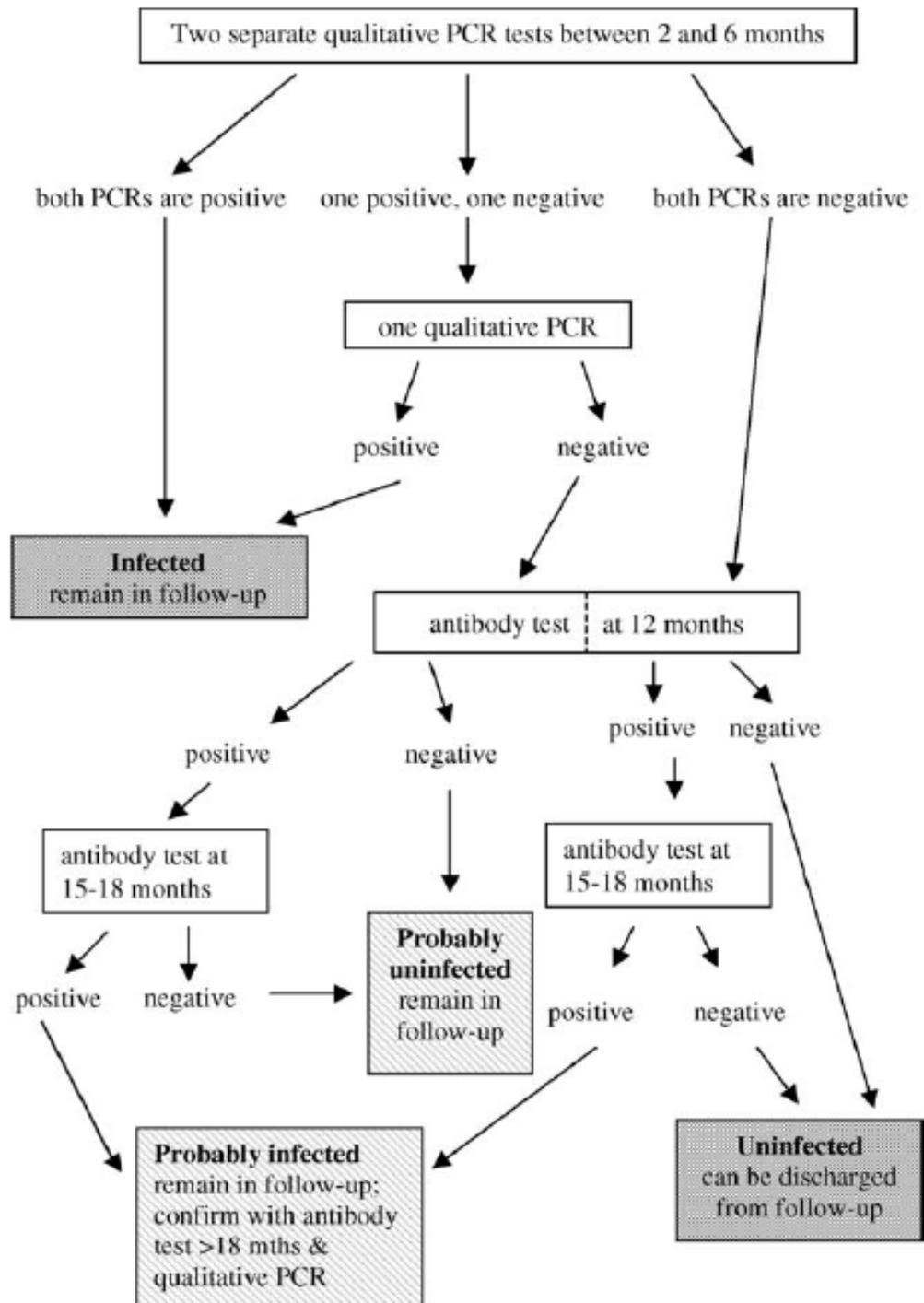


Fig. 2. Recommended follow-up schedule for early diagnosis of infection in infants born to HCV infected women.

Pembrey et al. J Hepatology, 2005

Treatment

- Pegylated-interferon + ribavirin x 24-48wks – 40-90% achieve sustained virologic response (genotype dep)
 - SQ administration (weekly), AE, growth arrest, lack of FDA approval (pregnancy/children)
- Boceprevir and Telaprevir (protease inhibitors approved in 2011) improved response rates to 60-80% for genotype 1
- Simeprevir – increase potency and fewer AE
- Sofosbuvir – HCV polymerase inh approved in 2013
 - Oral (w ribavirin), 12 wks, response rate 90%

Pediatric HCV

- Age and developmental stage of immune system or liver are important factors in resolution
 - About 50% of infected infants will resolve viremia and hepatitis
 - Same results in a cohort of children infected by blood products
- ~ 20% of children with vertically acquired HIV and HCV developed cirrhosis by the end of adolescence

Direct-Acting Antiviral Drugs

- Near universal response
- Costs will limit access
- Pregnant women and children will wait the longest
- Better understanding of risk factors for transmission and resolution of viremia will help guide therapy
- Testing methods require validation in infancy

Treat Infants

- We would like
 - Specific formulation for infants
 - Rapid decline in viral RNA
 - Abbreviated regimen if possible
 - 4 weeks vs. now 8-12 weeks

Infants Symptoms

- Infection is acute and almost always asymptomatic
- Episodic and later onset viremia
- Robust cellular response
- No evidence of negative effect on growth or development
- Elevation of LFT's and high VL (1st year)
- Risk of cirrhosis in childhood 1-2%

Vertical Transmission

		HCV-RNA					
		Birth	4 months	8 months	12 months	18 months	24 months
Group A*							
n = 30	30	-	-	-	-	-	-
Group B†							
n = 22	3	+	-	-	-	-	-
	7	-	+	-	-	-	-
	12	-	-	+	-	-	-
Group C‡							
n = 8	6	-	-	+	+	-	-
	2	-	-	+	+	+	+

* Infants who remained HCV-RNA-negative during follow-up.
 † Infants who were HCV-RNA-positive on one occasion.
 ‡ Infants who were HCV-RNA-positive on at least two consecutive testing.
 HCV, hepatitis C virus.

TABLE 2. HCV-RNA and RIBA data of babies born to HCV-RNA-positive mothers

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		Birth	4 months	8 months	12 months	18 months	24 months
Group A*	30	-	-	-	-	-	-
Group B†	3	+	-	-	-	-	-
n = 22	7	-	+	-	-	-	-
	12	-	-	+	-	-	-
Group C‡	6	-	-	+	+	-	-
n = 8	2	-	-	+	+	+	+

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Pediatric HCV

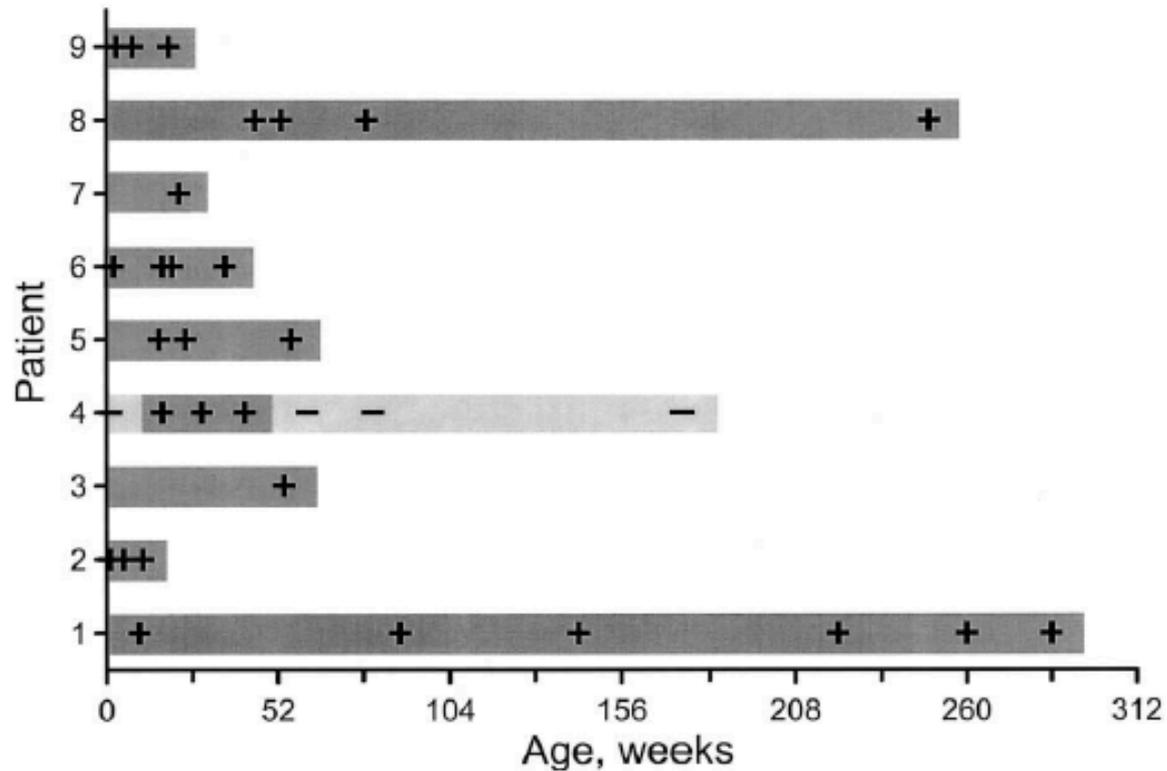


Figure 1. Follow-up investigation of hepatitis C virus (HCV)-infected children by HCV polymerase chain reaction. +, Positive result; -, negative result.

The Future

- There is no appropriate formulation for infants ...yet
 - Approve therapy for children > 3 years of age
 - Pediatric studies are underway for > 3 years old for new agents
 - We will need specific studies in infants and decide who to target

Treatment of Infected Children

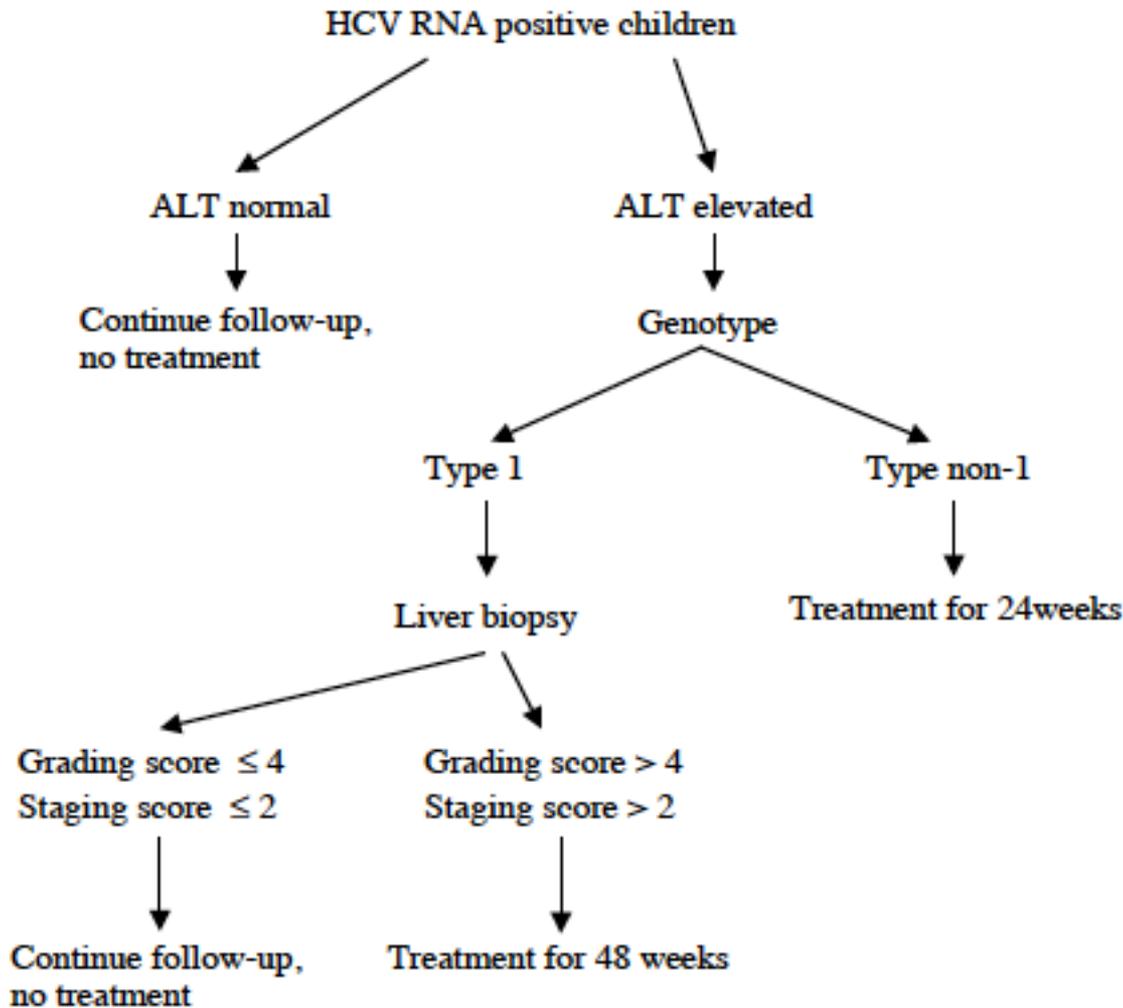


Fig. 3. Recommended criteria for initiation and duration of combination treatment in children with chronic infection.

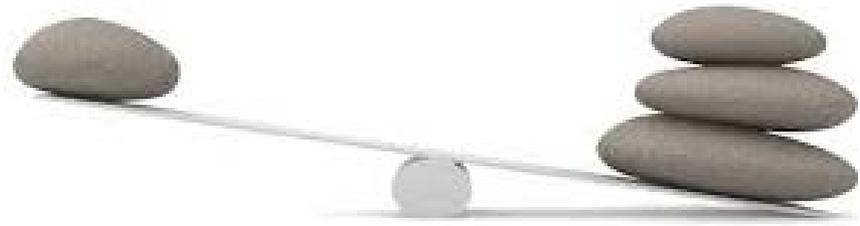
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Hepatology, 2005*

Pediatric HCV Treatment

- No indication for treatment in younger children
 - Lack of symptoms
 - Slow fibrosis
 - Side effects
 - Poor efficacy
- Expected expansion of treatment indications with direct-acting antiviral drugs

Eradication of HCV for some

Peg-IFN-Rib



Liver biopsy used to decide

- Poor SVR
- High AEs
- Complicated administration

Pediatric HCV Treatment

- No indication for treatment in younger children
 - Lack of symptoms
 - Slow fibrosis
 - Side effects
 - Poor efficacy
- Expected expansion of treatment indications with direct-acting antiviral drugs

- High SVR
- Low AEs
- All oral dosing

Scale is shifted in favor of near universal treatment



DAA's

Progress to long-term complications

Co-infection

- ~ 20% of children with vertically acquired HIV and HCV developed cirrhosis by the end of adolescence
- Rates of sustained viral response were very low
- Cohort= 50 patients mean age 20 (SD \pm 4.5)
- CD4 788 (516-980)
- HIV-RNA levels <50 copies/ml in 88%
- Genotypes 1 (66%), 4 (21%), 3 (11%) and 2 (2%)
- 40/50 had liver fibrosis (progression occurs slowly)
- 15/50 received therapy but only 5/15 (33%) showed sustained virological response