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Neonatal Herpes Simplex Virus: Epidemiology and Treatment

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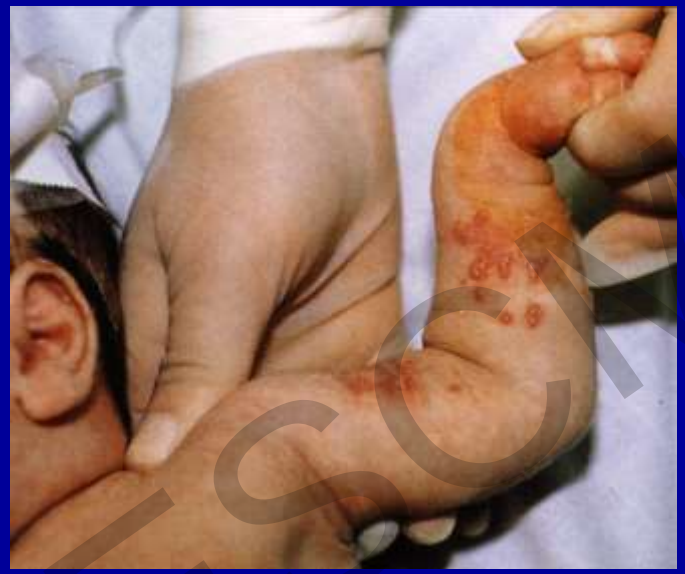
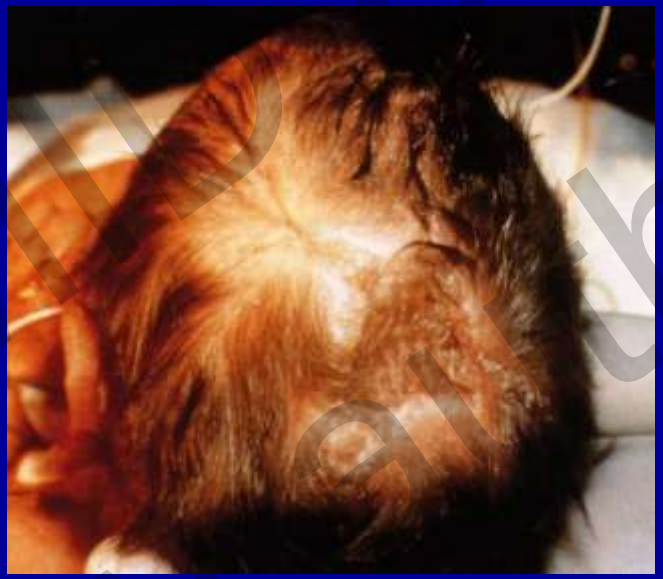
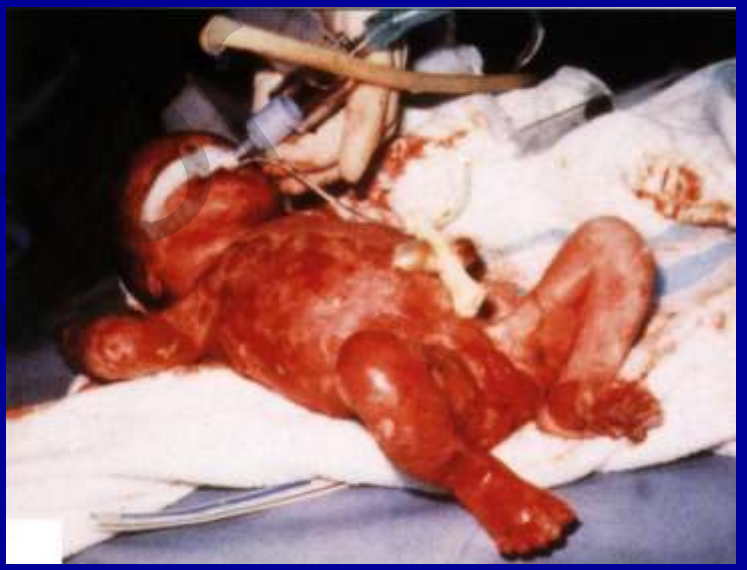
Faculty Disclosure Information

- In the past 12 months, I have had the following financial relationships with the manufacturer of any commercial product(s) and/or provider(s) of commercial service(s) discussed in this CME activity:
  - Alios – Research Grant for RSV study
  - All monies go directly to my university and not to me
- I do intend to discuss an unapproved/investigative use of a commercial product/device in my presentation

Neonatal HSV Disease







Intrapartum and Postpartum HSV Infection

- Disseminated disease ~ 25%
  - DIC
  - Pneumonia
  - Hepatitis
  - CNS involvement (60% to 75%)
- Encephalitis (CNS disease) ~ 30%
  - Seizures
  - Lethargy
  - Irritability
  - Poor feeding
  - Temperature instability
- Skin, eyes, and/or mouth (SEM disease) ~ 45%

Signs and Symptoms Prior to Study Enrollment

	SEM	CNS	Disseminated
Skin Vesicles			
Percentage of Patients	83%	63%	58%
Duration of symptoms*	3.8 ± 0.5	6.1 ± 1.0	3.7 ± 0.6
Lethargy			
Percentage of Patients	19%	49%	47%
Duration of symptoms*	3.3 ± 0.7	4.6 ± 0.7	3.4 ± 0.7
Fever			
Percentage of Patients	17%	44%	56%
Duration of symptoms*	4.6 ± 1.5	3.1 ± 0.4	4.6 ± 0.6
Seizure			
Percentage of Patients	2%	57%	22%
Duration of symptoms*	7.0	2.9 ± 0.5	2.5 ± 0.7

* Days ± SE

Pediatrics 2001;108:223-229

Changes in Characteristics by Extent of Disease

Characteristic	SEM		CNS		Disseminated	
	1981-88	1989-97	1981-88	1989-97	1981-88	1989-97
Premature	41%	20%	27%	36%	28%	41%
Enrollment Age (days ± SE)	11.2 ± 0.9	12.0 ± 2.2	15.2 ± 1.3	19.7 ± 1.6	10.3 ± 1.1	11.4 ± 0.8
Time between earliest HSV and enrollment (days ± SE)	5.9 ± 0.7	5.7 ± 1.3	6.6 ± 0.8	7.4 ± 1.3	5.3 ± 0.7	5.6 ± 0.7

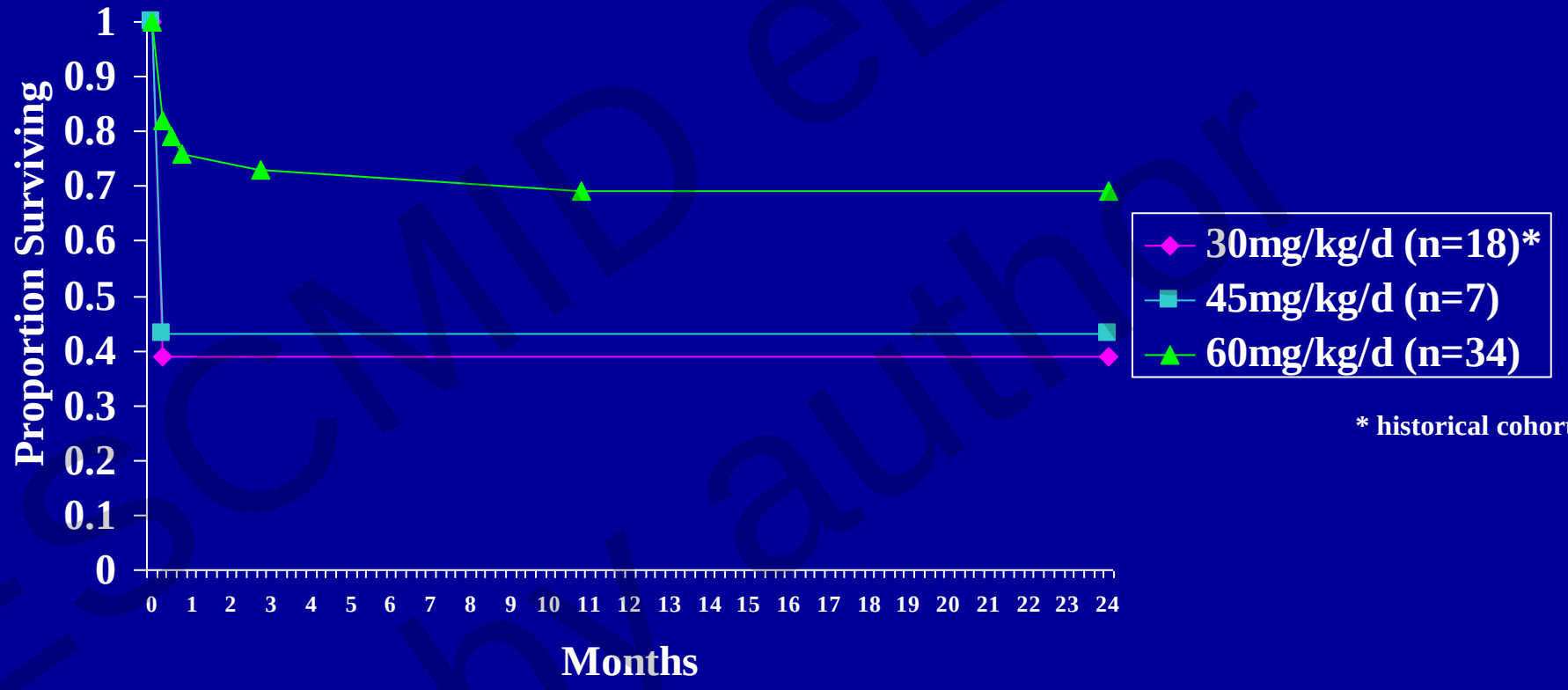
Pediatrics 2001;108:223-229

Diagnosis of Neonatal HSV

- Surface cultures (± PCR)
  - Swabs of mouth, nasopharynx, conjunctivae, anus
- Culture of skin vesicle (± PCR)
- CSF for PCR
- Whole blood for PCR (in addition to standard work-up, above)
  - Should not be used to determine extent of disease (DNAemia and viremia occur in each disease classification)
  - No data exist to support use of serial blood PCR assay to monitor response to therapy
- Blood for alanine aminotransferase (ALT)

Red Book: 2015 Report of the Committee on Infectious Diseases, pp. 432-445

Mortality Among Infants with Disseminated Disease



* historical cohort

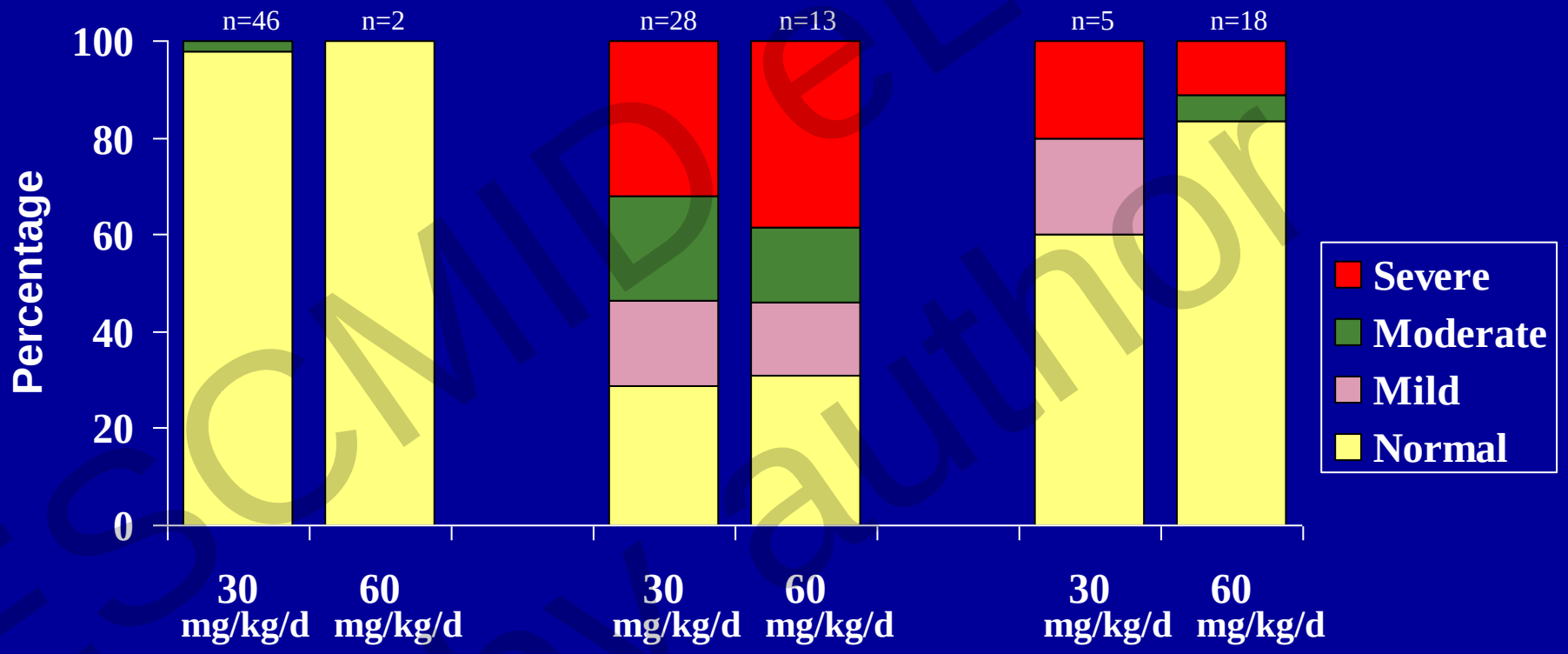
Pediatrics 2001;108:230-238

Mortality Among Infants with CNS Disease

* historical cohort

Pediatrics 2001;108:230-238

Neonatal Morbidity Among Survivors With Known Outcomes After 12 Months



Pediatrics 2001;108:230-238

Suppressive Antiviral Therapy Design of Studies

- Immediate suppression (randomized to active drug)

vs.

- Deferred suppression (randomized to placebo but moved to open-label suppression following the second cutaneous recurrence)

N Engl J Med 2011;365(14):1284-92

Suppressive Antiviral Therapy Bayley Mental Score at 12 Months

	CASG 103 (CNS Involvement Study)		CASG 104 (SEM Study)	
	Acyclovir N=16	Placebo N=12	Acyclovir N=8	Placebo N=7
Median	90.5	66.5	95	84
Adjusted Mean	88.24†	68.12†	91.82‡	84.92‡
P-value by ANCOVA*	0.046		0.263	

***Adjusted for covariates at baseline which were unbalanced between treatment groups:**

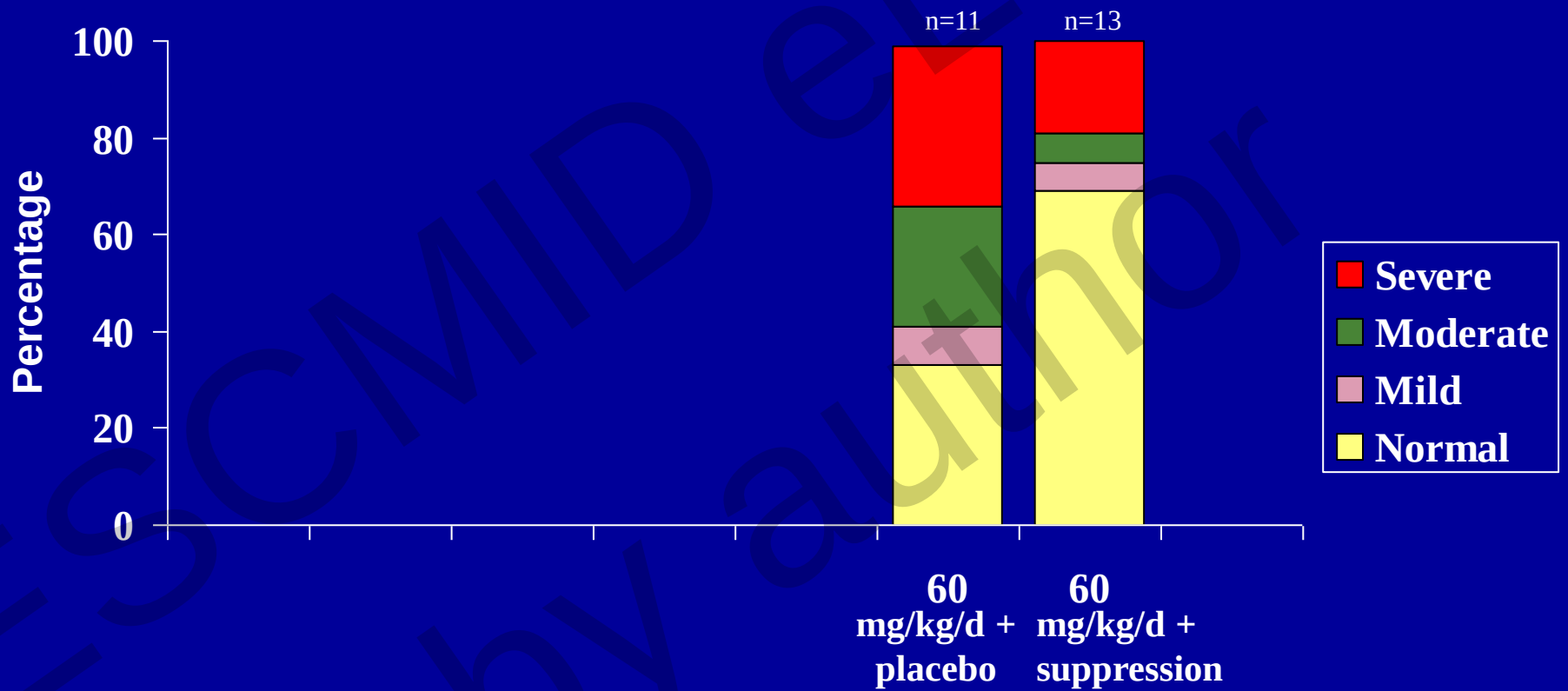
†Head circumference at birth, birth weight, enrollment weight

‡Enrollment weight

N Engl J Med 2011;365(14):1284-92

N Engl J Med 2011;365(14):1284-92

Suppressive Antiviral Therapy Bayley Mental Score at 12 Months

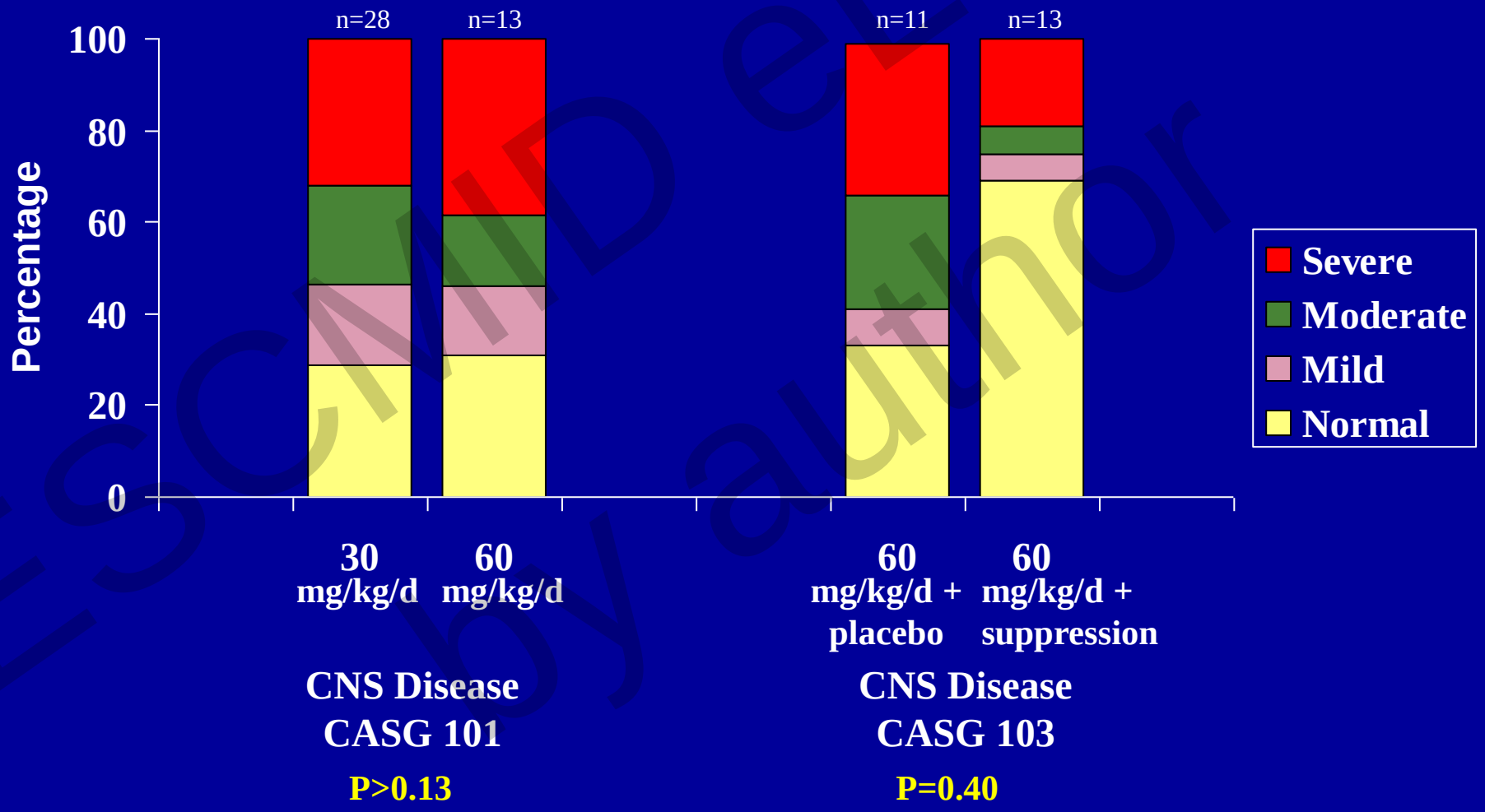


CNS Disease
CASG 103

P=0.40

N Engl J Med 2011;365(14):1284-92

Suppressive Antiviral Therapy Bayley Mental Score at 12 Months



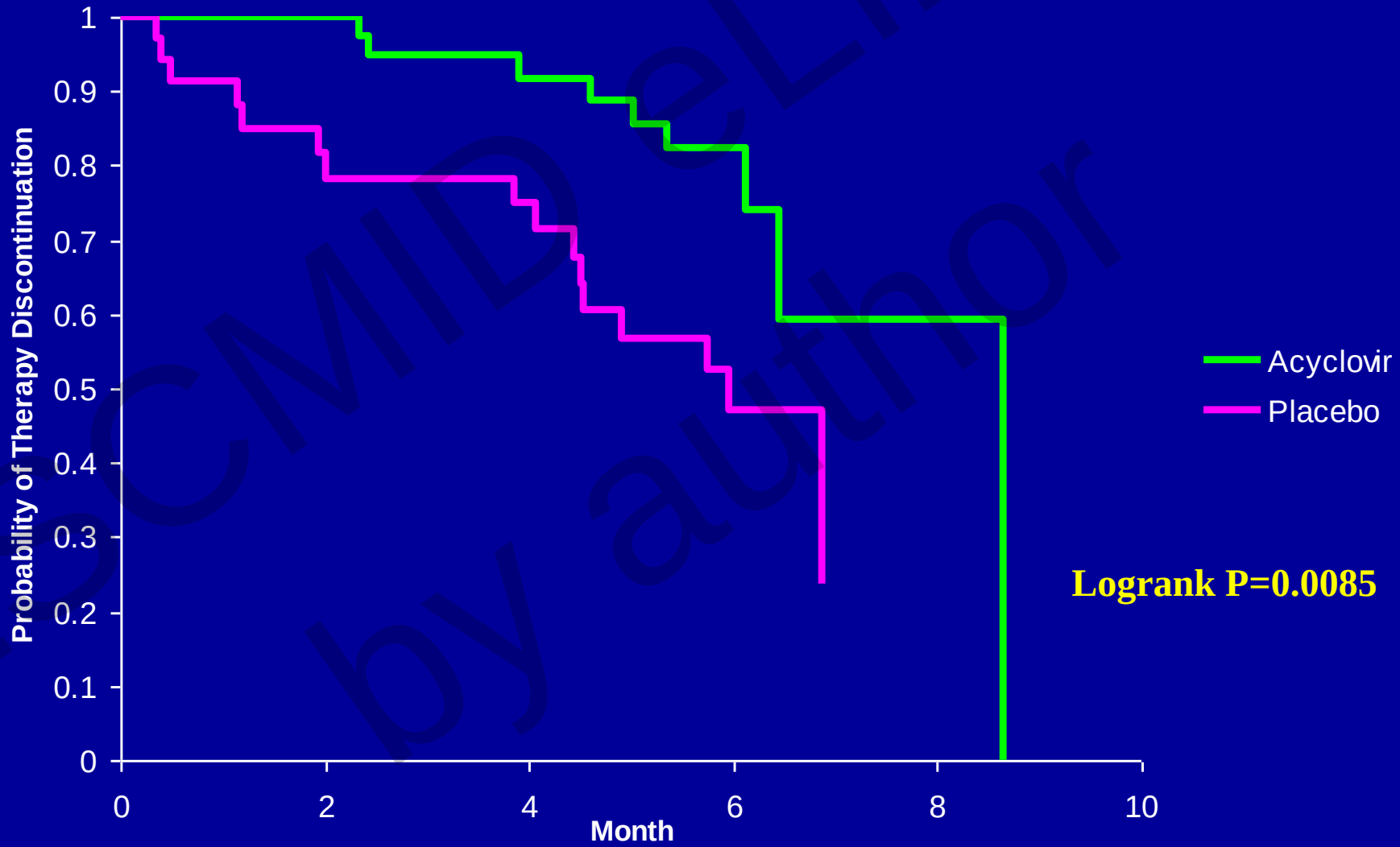
Incrementally Higher Bayley Scores with Longer Antiviral Suppression

	Mean (± SE) Bayley Mental Score	Median Bayley Mental Score
Active suppression for 6 months (n=15)	85 (± 5)	91
Active suppression for < 6 months (n=6)	80 (± 8)	70
No active suppression (n=7)	73 (± 10)	58

N Engl J Med 2011;365(14):1284-92

N Engl J Med 2011;365(14):1284-92

Prevention of Cutaneous Recurrences Time to Blinded Drug Discontinuation



PCR Results
Post-therapy CSF Specimens

Outcome	PCR Negative (n = 11)	PCR Positive (n = 19)	
Normal	6 (54)	1 (5)	$P < 0.001$
Mild	0 (0)	0 (0)	
Moderate	1 (9)	3 (16)	
Severe	2 (18)	10 (53)	
Dead	0 (0)	5 (26)	
Unknown	2 (18)	0 (0)	

J Infect Dis 1996;174:1162-7

Incidence of Neonatal HSV Infection

Country	Population	Rate of neonatal HSV
USA	7 Census Regions (ICD9)	1 in 1,300
USA	Seattle, WA	1 in 3,200
USA	Birmingham, AL	1 in 2,700
UK	National voluntary reporting	1 in 60-70,000
Switzerland	National	1 in 62,500
Netherlands	National	1 in 35,000
Australia	National	1 in 30,000
Norway	National (CNS only)	1 in 25,000
Sweden	Stockholm	1 in 15,000
Japan	National	1 in 14-20,000

Special Challenges of Neonatal HSV Disease Prevention

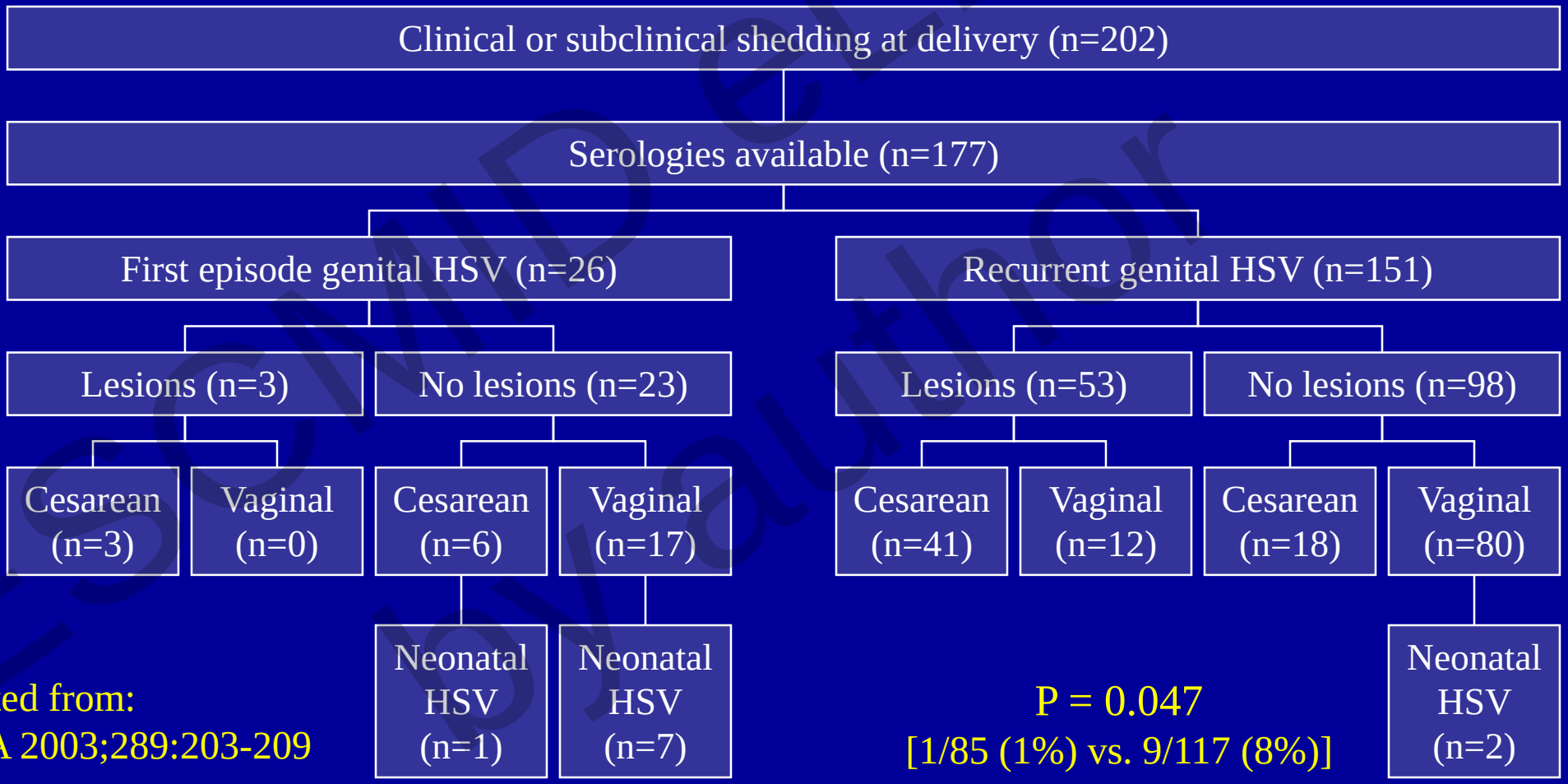
- History not generally available
  - 60-80% of infected infants are born to mothers with no maternal history of genital HSV
- History not particularly helpful
  - Women with known history of genital HSV are at lesser risk compared with women acquiring HSV during pregnancy

Prevention of Neonatal HSV by Cesarean Section Delivery

Type of Delivery	# infected/# cases
Vaginal	9/18 (50%)
Cesarean Section	
ROM ≥ 6 hrs	4/ 4 (100%)
Intact membranes or ROM ≤ 4 hrs	0/ 4 (0%)

Am J Obstet Gynecol 1971;110:825-34

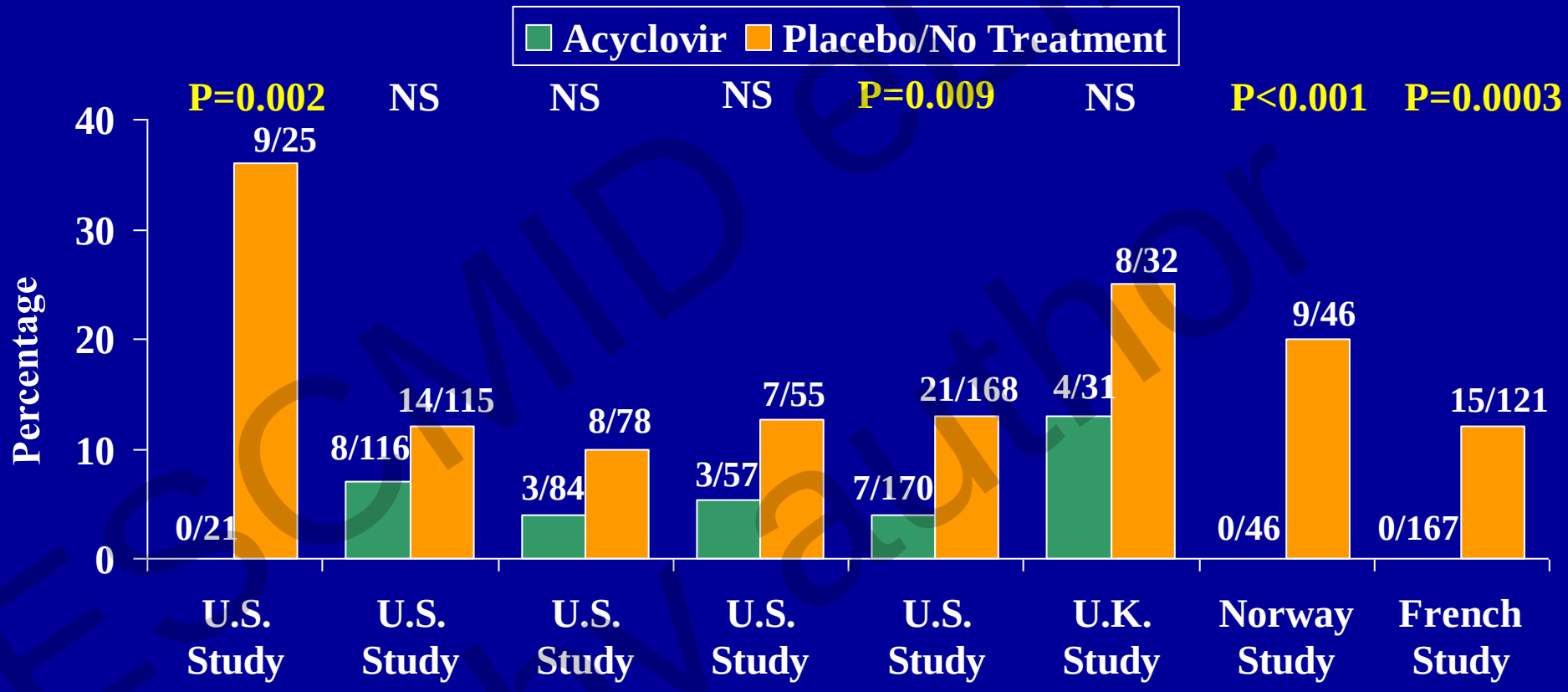
Prevention of Neonatal HSV by Cesarean Section Delivery



Adapted from:
JAMA 2003;289:203-209

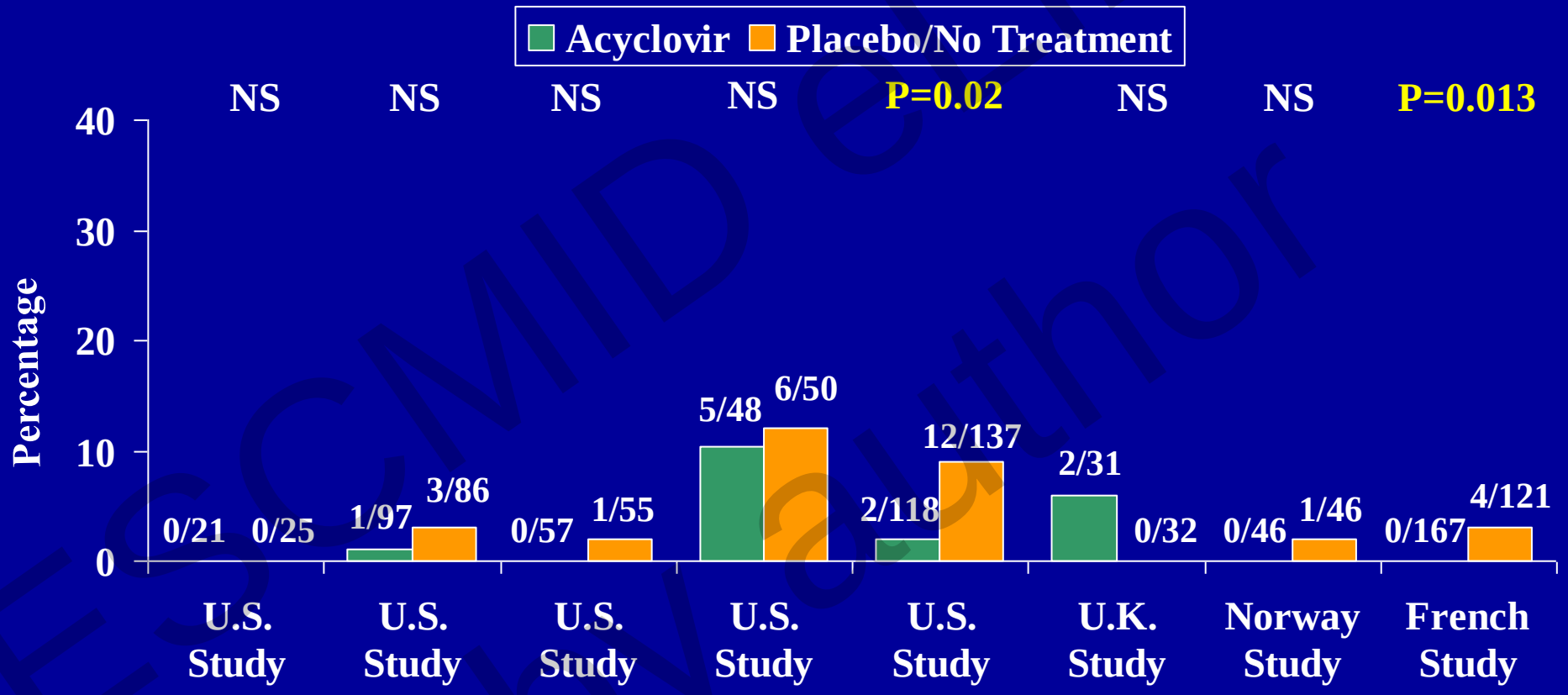
P = 0.047
[1/85 (1%) vs. 9/117 (8%)]

Cesarean Section Due to HSV at Delivery



Obstet Gynecol 1996;87:69-73
Infect Dis Obstet Gynecol 2002;10:71-77
Am J Obstet Gynecol 2003;188:836-843
Am J Obstet Gynecol 2006;194:774-781
Obstet Gynecol 2006;108:141-147
Br J Obstet Gynaecol 1998;105:275-280
Lancet 1990;336:756
Eur J Obstet Gynecol Reprod Biol 2001;96:55-58

Asymptomatic Viral Shedding During Therapy or At Delivery



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Neonatal HSV Disease Despite Maternal Antenatal Antiviral Suppressive Therapy

- Multicenter case series
- 7 infants whose mothers received antiviral suppressive therapy near the end of pregnancy
  - Days of life 1, 1, 4, 5, 8, 9, 27
  - 5/7 SEM
  - 2/7 CNS
  - 6/7 delivered vaginally
- None of the 7 mothers had active herpetic lesions at delivery
- 6/6 mothers with genital HSV tested positive for group B Streptococcus and were treated appropriately

J Pediatr 2012;161:134-138

AAP COID/COFN
Pediatrics
2013;131(2):e635-e646

Classification of Maternal HSV Genital Infection

	PCR/Culture from Genital Lesion	Maternal HSV-1 and HSV-2 IgG Antibody Status
Documented First-Episode Primary Infection	Positive, either virus	Both negative
Documented First-Episode Nonprimary Infection	Positive for HSV-1	Positive for HSV-2 AND negative for HSV-1
	Positive for HSV-2	Positive for HSV-1 AND negative for HSV-2
Assume First-Episode (Primary or Non-Primary) Infection	Positive for HSV-1 OR HSV-2	Not available
	Negative OR not available†	Negative for HSV-1 and/or HSV-2, OR not available
Recurrent Infection	Positive for HSV-1	Positive for HSV-1
	Positive for HSV-2	Positive for HSV-2

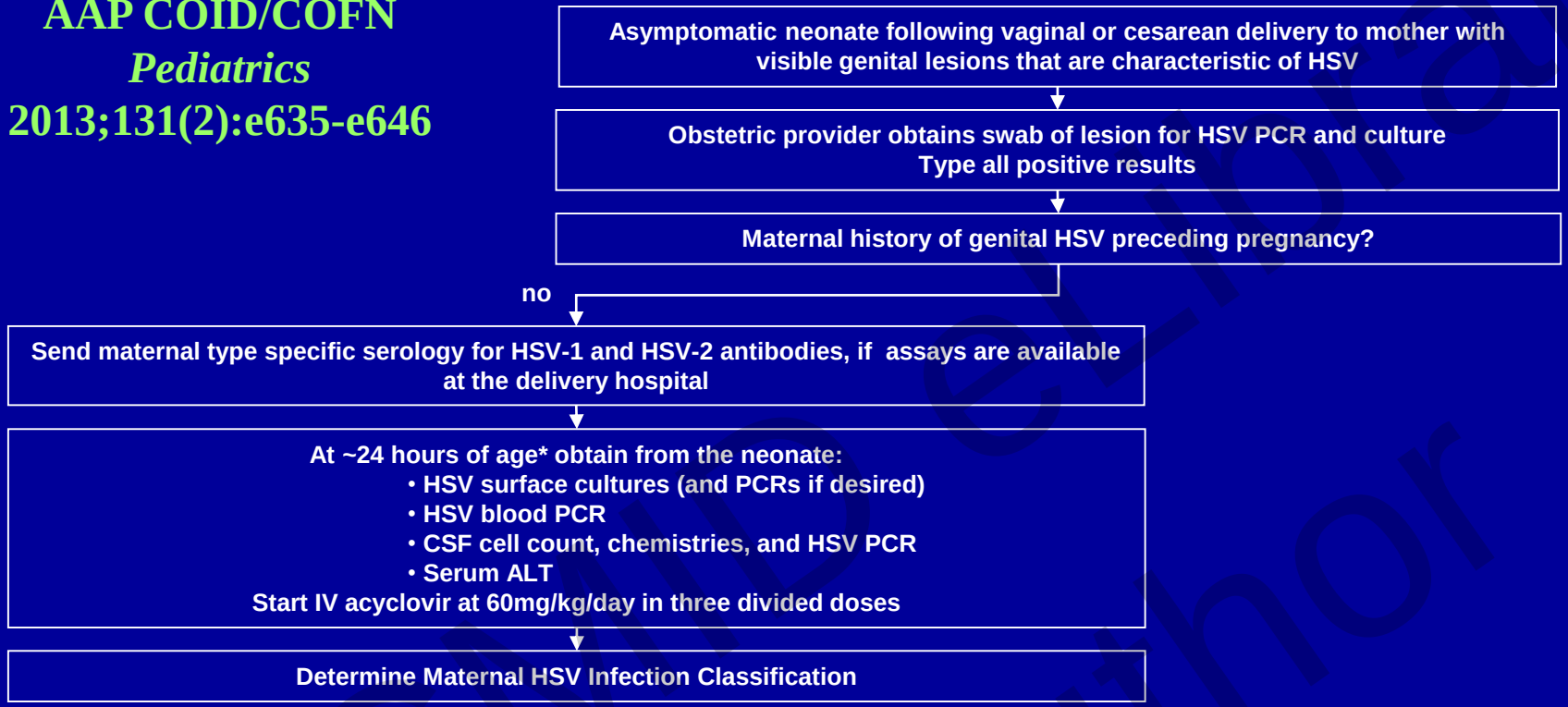
† When genital lesion is strongly suspicious for HSV, clinical judgment should supersede the virologic test results. If in retrospect the genital lesion was not likely to be caused by HSV and the PCR/culture is negative, departure from the algorithm may be warranted.

Management of asymptomatic neonates born to women with active genital herpes lesions

AAP COID/COFN

Pediatrics

2013;131(2):e635-e646



** Immediate evaluation and treatment may be considered if:*

- *prolonged rupture of membranes (> 4-6 hours)*
- *prematurity (≤ 37 weeks gestation)*

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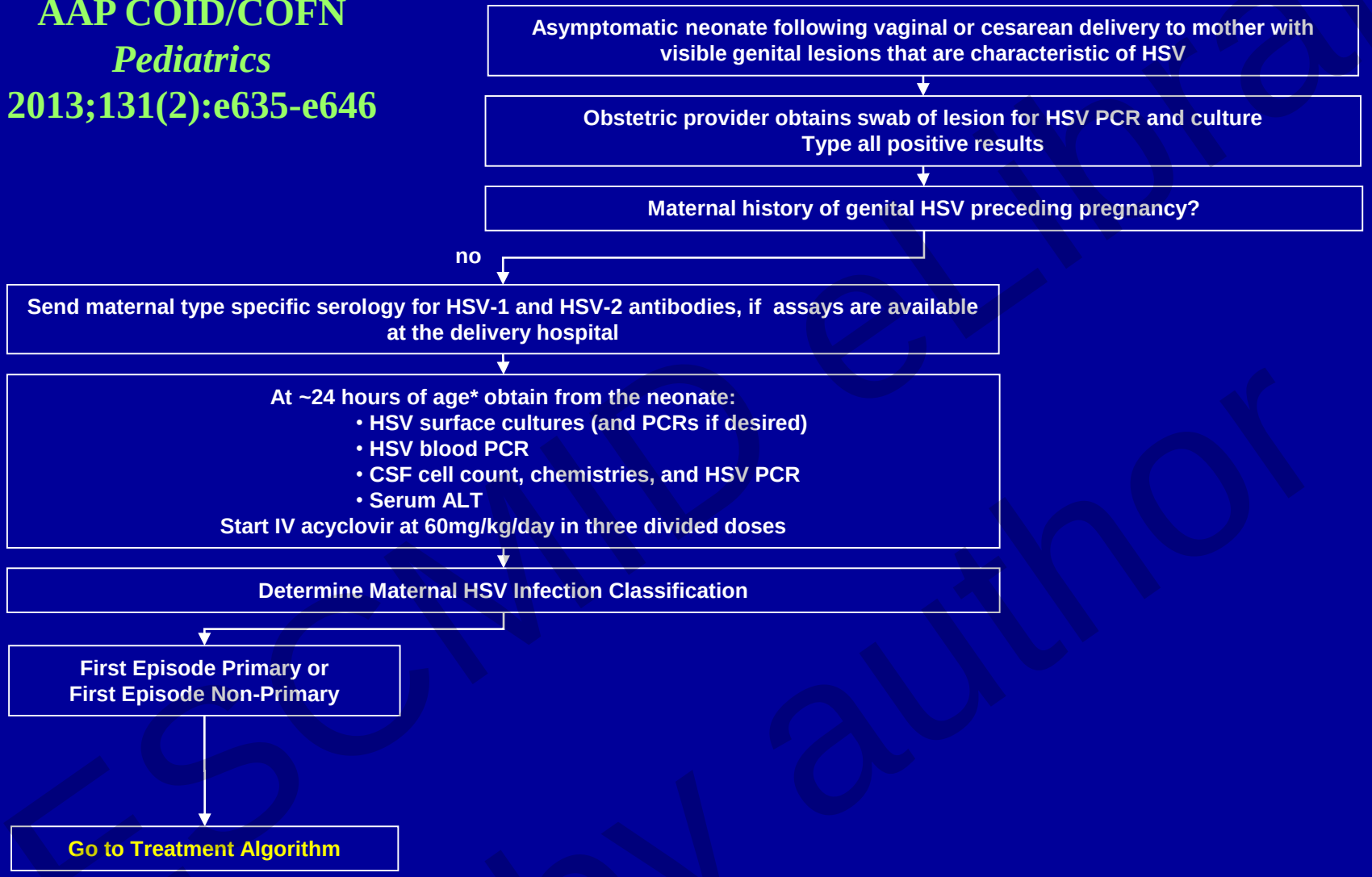

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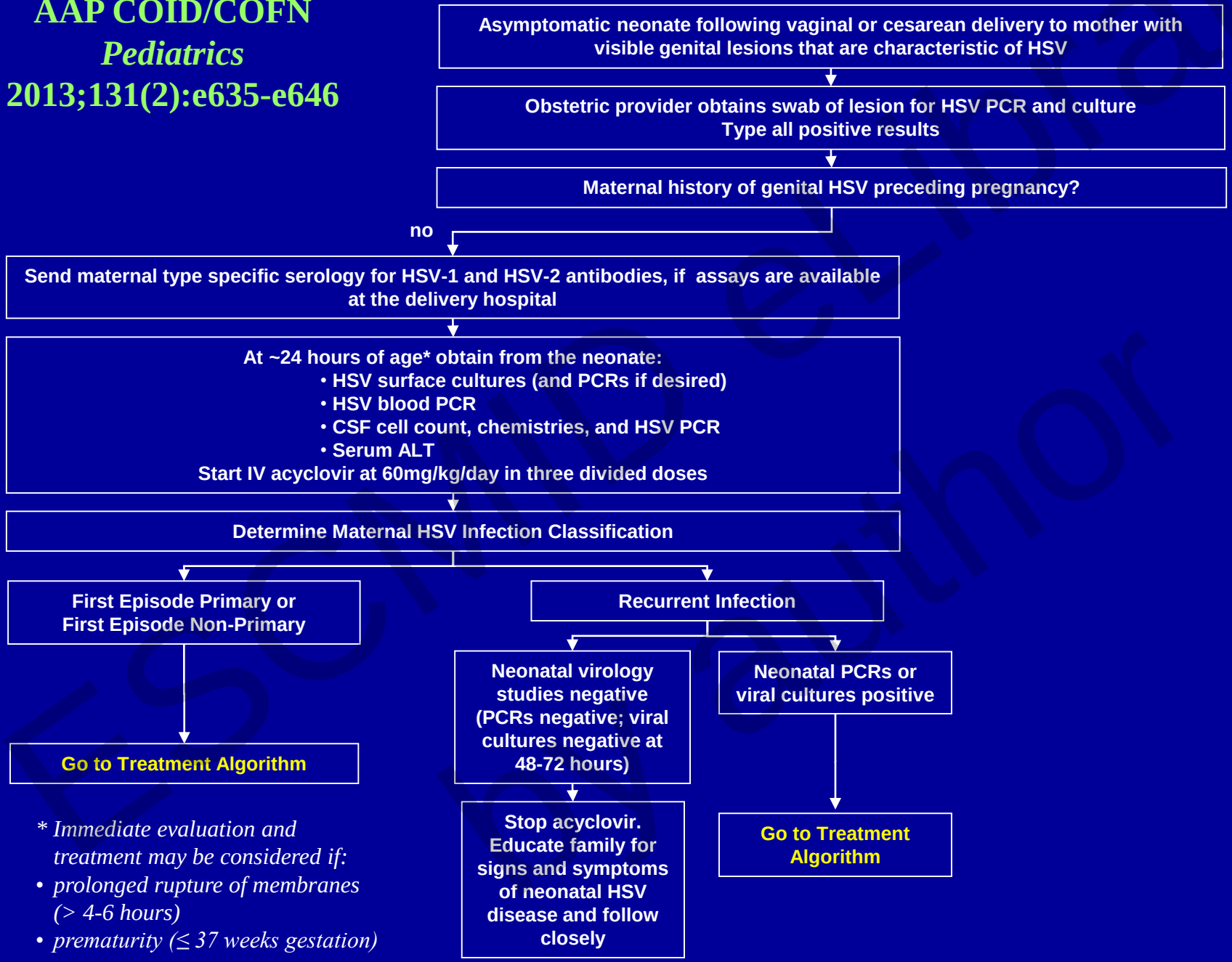

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2013;131(2):e635-e646

Asymptomatic neonate following vaginal or cesarean delivery to mother with visible genital lesions that are characteristic of HSV

Obstetric provider obtains swab of lesion for HSV PCR and culture
Type all positive results

Maternal history of genital HSV preceding pregnancy?

no

Send maternal type specific serology for HSV-1 and HSV-2 antibodies, if assays are available at the delivery hospital

At ~24 hours of age* obtain from the neonate:
- HSV surface cultures (and PCRs if desired)
- HSV blood PCR
- CSF cell count, chemistries, and HSV PCR
- Serum ALT

Start IV acyclovir at 60mg/kg/day in three divided doses

Determine Maternal HSV Infection Classification

First Episode Primary or First Episode Non-Primary

Go to Treatment Algorithm

Recurrent Infection

Neonatal virology studies negative (PCRs negative; viral cultures negative at 48-72 hours)

Stop acyclovir. Educate family for signs and symptoms of neonatal HSV disease and follow closely

Neonatal PCRs or viral cultures positive

Go to Treatment Algorithm

yes

At ~ 24 hours of age* obtain from the neonate:
- HSV surface cultures (and PCRs if desired)
- HSV blood PCR

If infant remains asymptomatic, do not start acyclovir

Neonatal surface cultures negative, AND blood and surface PCRs negative

Educate family on signs and symptoms of neonatal HSV disease and follow closely

Neonatal surface cultures positive, OR blood or surface PCRs positive

Obtain CSF for cell count, chemistries, and HSV PCR. Send serum ALT. Start IV acyclovir at 60mg/kg/day in three divided doses

Go to Treatment Algorithm

** Immediate evaluation and treatment may be considered if:*
- *prolonged rupture of membranes (> 4-6 hours)*
- *prematurity (≤ 37 weeks gestation)*

Treatment Algorithm

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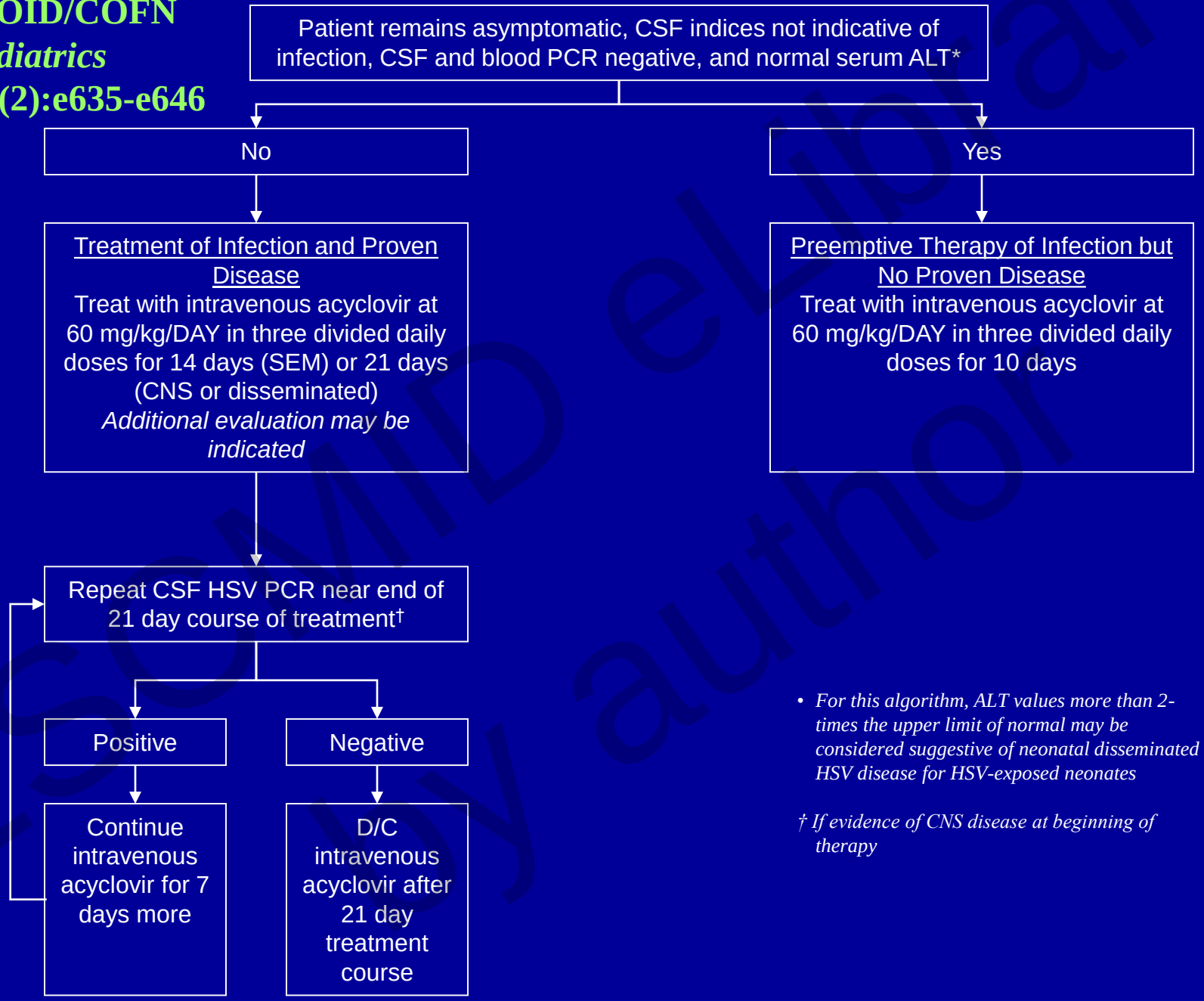

- *For this algorithm, ALT values more than 2-times the upper limit of normal may be considered suggestive of neonatal disseminated HSV disease for HSV-exposed neonates*

† If evidence of CNS disease at beginning of therapy

When Should You Start Acyclovir in a Neonate?

- Caviness et al.
  - 10 cases from ~ 10,000 admissions over 5 years
  - Rash, lethargy, respiratory distress, or ↑ transaminases present in all 10
  - Abnormal CSF indices with PMN predominance can make bacterial meningitis more likely
  - Abnormal CSF indices with mono predominance does not make neonatal HSV more likely
  - Enteroviral meningitis 20-times more likely than HSV CNS disease in febrile neonate with CSF pleocytosis during enteroviral season
  - SBI 23-times more likely than neonatal HSV

J Pediatr 2008;153:164-169

When Should You Start Acyclovir in a Neonate?

- Kimberlin editorial
  - Do not routinely use amp, gent, and acyclovir for r/o sepsis
  - Work-up for neonatal HSV and begin IV acyclovir for:
    - Skin vesicles
    - Seizures
    - Marked ↑ in transaminases
    - Sepsis-like picture (including hypothermia)
    - Infant more ill appearing than would be expected in clinician's judgement
    - ± CSF pleocytosis with mononuclear cell predominance outside of enteroviral season

J Pediatr 2008;153:155-156

Changes In Practice in Management of Neonatal HSV

- Management algorithm for approach to neonate exposed to HSV at delivery available
  - Stratifies use of preemptive therapy by risk of transmission
- Diagnosis of HSV-infected infant requires full evaluation (INCLUDING SURFACE CULTURES AND CSF PCR) prior to starting therapy
- Treatment of neonatal HSV disease
  - Acyclovir 60 mg/kg/DAY administered intravenously in three divided doses (20 mg/kg/DOSE)
  - 21 days for CNS disease or disseminated disease
  - 14 days for SEM disease

Changes In Practice in Management of Neonatal HSV

- If patient has CNS involvement, repeat lumbar puncture for HSV PCR prior to stopping parenteral antiviral therapy
- Following completion of neonatal HSV parenteral therapy, initiate oral acyclovir suppressive therapy at 300 mg/m^2/DOSE orally three times daily for 6 months
  - Monitor ANCs at 2 and 4 weeks, then monthly