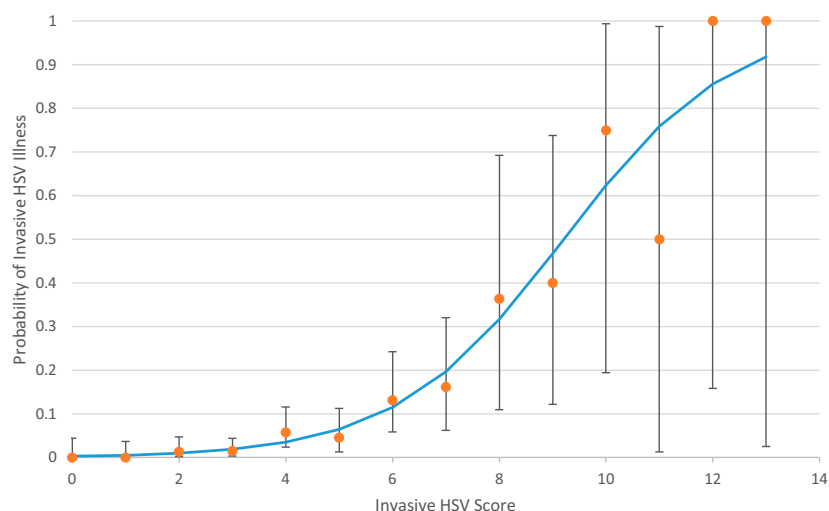


Supplemental Materials



SUPPLEMENTAL FIGURE 3

Observed and predicted invasive HSV infection. The orange markers represent the observed probability of invasive HSV illness in each strata of the invasive HSV; the error bars represent the 95% CI; and the solid blue line represents predicted invasive HSV illness using the invasive HSV score. The number of participants in each strata from score 0 to score 13 was 82, 99, 151, 198, 121, 88, 61, 37, 11, 10, 4, 2, 2, and 1, respectively.

SUPPLEMENTAL TABLE 5 Participating Sites

City	Institution	Included Period	No. in Parent Study	No. HSV Cases (%) ^a
Ann Arbor, MI	CS Mott Children's Hospital	2005–2013	413	3 (0.72)
Atlanta, GA	Children's Healthcare of Atlanta	2011–2013	2071	5 (0.24)
Birmingham, AL	Children's Hospital of Alabama	2005–2009	1195	2 (0.17)
Boston, MA	Boston Children's Hospital	2006–2013	1009	5 (0.50)
Chicago, IL	Lurie Children's Hospital	2012–2013	511	2 (0.39)
Cincinnati, OH	Cincinnati Children's Hospital Medical Center	2009–2013	1856	16 (0.86)
Dallas, TX	Children's Medical Center Dallas	2009–2013	3028	12 (0.40)
Denver, CO	Children's Hospital of Colorado	2005–2013	2037	11 (0.54)
Detroit, Michigan	Children's Hospital of Michigan	2005–2013	1585	16 (1.0)
Edmonton, AB	Stollery Children's Hospital	2005–2012	685	6 (0.88)
Houston, TX	Texas Children's Hospital	2010–2013	1033	7 (0.68)
Minneapolis, MN	Children's Hospitals and Clinics of Minnesota	2007–2013	1619	5 (0.31)
Minneapolis, MN	University of Minnesota Masonic Children's Hospital	2011–2013	36	1 (2.78)
New Haven, CT	Yale New Haven Children's Hospital	2005–2012	1012	4 (0.40)
Philadelphia, PA	Children's Hospital of Philadelphia	2011–2013	1113	5 (0.45)
Providence, RI	Hasbro Children's Hospital	2008–2012	1200	9 (0.75)
Sacramento, CA	University of California, Davis Children's Hospital	2008–2013	219	2 (0.91)
St Louis, MO	St Louis Children's Hospital	2007–2013	1821	5 (0.27)
St Louis, MO	Cardinal Glennon Children's Hospital	2012–2013	192	7 (3.65)
San Diego, CA	Rady Children's Hospital	2009–2011	578	4 (0.69)
Seattle, WA	Seattle Children's Hospital	2009–2013	1046	12 (1.15)
Toronto, ON	The Hospital for Sick Children	2005–2011	1336	6 (0.45)
Wilmington, DE	Alfred I. DuPont Hospital for Children	2009–2013	941	4 (0.43)

^a Within-row percentage.

SUPPLEMENTAL TABLE 6 Candidate Predictors of HSV Infection Selected A Priori On the Basis of Literature Review

Clinical Predictor, Chart Abstraction Definition	Invasive HSV, <i>n</i> = 90, <i>n</i> (%)	SEM HSV, <i>n</i> = 59, <i>n</i> (%)	Controls, <i>n</i> = 1340, <i>n</i> (%)
History			
Age, median (IQR), d	13.0 (8.0–19.2)	14.0 (9.0–31.0)	23.0 (11.0–38.2)
< 14 d	49 (54.4)	27 (45.8)	420 (31.3)
14 to 28 d	31 (34.4)	15 (25.4)	388 (29.0)
>28 d	10 (11.1)	17 (28.8)	523 (39.7)
Maternal HSV history: maternal history of HSV infection	7/54 (13.0)	6/47 (12.8)	28/514 (5.4)
Prematurity: birth before 37 wk gestation	14/85 (16.5)	3/57 (5.3)	125/1139 (9.9)
Vaginal delivery	64/85 (75.3)	46/58 (79.3)	763/1092 (69.9)
Poor feeding: decreased or poor intake, inability to feed, feeding less than usual, feeding poorly or not well	40/84 (47.6)	7/55 (12.7)	576/1237 (46.6)
Irritability: irritable, fussy, inconsolable	20/77 (26.0)	6/52 (11.5)	497/1162 (42.8)
Lethargy: inactive, lethargic, not vigorous, stuporous	31/82 (37.8)	5/50 (10.0)	269/1116 (24.1)
Seizures at home: report of any seizure at or before presentation by caregiver or provider	17/77 (22.1)	3/55 (5.5)	63/1084 (5.8)
Physical examination			
Ill appearance: “sick, toxic, shocky,” altered or decreased mental status, fussy, inconsolable, meningismus (ie, positive Kernig or Brudzinski sign or stiff neck), petechial rash, decreased perfusion, decreased pulses ¹¹	27/77 (35.1)	5/56 (8.9)	199/1213 (16.4)
Abnormal temperature: triage temperature $\geq 38.0^{\circ}\text{C}$ (100.4°F) or $< 36.4^{\circ}\text{C}$ (97.5°F)	46/82 (56.1)	9/51 (17.6)	488/1151 (42.4)
Any rash: vesicular, maculopapular, petechial or urticarial rash	28/82 (34.2)	40/57 (70.2)	154/1237 (12.5)
Vesicular rash: any vesicular rash	20/82 (24.2)	33/57 (57.9)	12/1237 (1.0)
Laboratory results			
Elevated transaminases			
ALT ≥ 50 U/L ¹⁵	30/65 (46.2)	1/39 ^a	25/276 (9.1)
AST ≥ 140 U/L ¹⁵	25/63 (39.7)	0/38	10/269 (3.7)
Hypoglycemia: serum glucose < 40 mg/dL	3/68 (4.4)	0/33 (0)	1/713 (0.1)
Neutropenia: ANC < 1000 cells per mm^3	10/79 (12.7)	4/49 (8.2)	56/1140 (4.9)
Thrombocytopenia: Platelets $< 150\,000$ per mm^3 ¹⁷	16/77 (20.8)	0/48	33/1140 (2.9)
CSF pleocytosis: CSF WBC > 15 cells per mm^3 if ≤ 28 d; ≥ 10 cells per mm^3 if > 28 d	36/62 (58.1)	15/46 ^b (26.1)	194/1033 (18.8)
Traumatic CSF: CSF RBC > 500 per mm^3 ¹⁷	24/65 (36.9)	20/45 (44.4)	300/1020 (29.4)
Hypoglycorrachia: CSF glucose < 40 mg/dL ¹⁷	25/67 (37.3)	10/48 (20.8)	152/1103 (13.8)

All data are *n* (%) unless otherwise indicated. ANC, absolute neutrophil count; RBC, red blood cell count.

^a One 12-d-old infant had an ALT of 65 U/L, had HSV detected from skin vesicles and from the mouth, had negative PCR results from blood and CSF, and was treated as SEM disease for 14 d.

^b Of the 15 infants with SEM and an apparent CSF pleocytosis (all of whom had negative CSF HSV PCRs), 10 had grossly traumatic lumbar punctures, and the remaining 5 had CSF WBC ranging from 17 to 76 with no seizures; 1 had a normal EEG, and 3 of 5 had normal CNS imaging. All 5 received 14-d courses of therapy and were deemed to have non-CNS disease by the treating clinicians.

SUPPLEMENTAL TABLE 7 Multivariable Analyses Excluding Controls With Invasive Bacterial Illness With the Presence of Invasive HSV Infection Being the Dependent Variable ($n = 90$ Cases and 778 Controls)

Candidate Predictor	aOR (95% CI)
Age	
<14 d	8.2 (3.0 to 22.4)
14–28 d	6.3 (2.2 to 17.8)
>28 d	Ref
Prematurity	2.3 (1.1 to 5.2)
Had seizure at home	5.8 (2.1 to 15.9)
Ill appearance ^a	4.7 (2.3 to 9.4)
Abnormal triage temperature ^b	3.0 (1.6 to 5.6)
Vesicular rash	51.4 (15.2 to 173.9)
Thrombocytopenia ^c	4.1 (1.4 to 11.9)
CSF pleocytosis ^d	3.7 (1.2 to 11.2)

Ref, reference group.

^a “Sick, toxic, shocky,” altered or decreased mental status, fussy, inconsolable, meningismus (ie, positive Kernig or Brudzinski sign or stiff neck), petechial rash, decreased perfusion, decreased pulses).

^b Triage temperature $\geq 38.0^{\circ}\text{C}$ or $< 36.4^{\circ}\text{C}$.

^c Platelet count $< 150\,000$ per mm^3 .

^d CSF WBC > 15 per mm^3 (≤ 28 d) or ≥ 10 per mm^3 (> 28 d).

SUPPLEMENTAL TABLE 8 Multivariable Analyses Only Including Controls With HSV Testing, With the Presence of Invasive HSV Infection Being the Dependent Variable ($n = 87$ Cases and 347 Controls)

Candidate Predictor	aOR (95% CI)
Age	
<14 d	6.3 (1.8 to 22.3)
14–28 d	6.1 (1.7 to 21.4)
>28 d	Ref
Ill appearance ^a	4.1 (1.8 to 9.2)
Abnormal triage temperature ^b	2.1 (1.1 to 4.0)
Vesicular rash	20.8 (6.3 to 68.4)
Thrombocytopenia ^c	3.6 (1.2 to 10.6)
CSF pleocytosis ^d	3.7 (1.5 to 9.2)

Ref: reference group.

^a “Sick, toxic, shocky,” altered or decreased mental status, fussy, inconsolable, meningismus (ie, positive Kernig or Brudzinski sign or stiff neck), petechial rash, decreased perfusion, decreased pulses).

^b Triage temperature $\geq 38.0^{\circ}\text{C}$ or $< 36.4^{\circ}\text{C}$.

^c Platelet count $< 150\,000$ per mm^3 .

^d CSF WBC > 15 per mm^3 (≤ 28 d) or ≥ 10 per mm^3 (> 28 d).

SUPPLEMENTAL TABLE 9 Performance of the Invasive HSV Risk Score at Different Cut-points

Cut Point	Sensitivity, %	Specificity, %	Correctly Classified, %	LR+	LR-
≥0	100	0	5.19	1	—
≥1	100	9.98	14.65	1.1108	0
≥2	100.00	22.02	26.07	1.2824	0
≥3	95.56	40.15	43.02	1.5965	0.1107
≥4	88.89	63.87	65.17	2.4602	0.174
≥5	73.33	77.74	77.51	3.294	0.343
≥6	64.44	87.96	86.74	5.3508	0.4042
≥7	46.67	94.40	91.93	8.3391	0.5649
≥8	33.33	98.18	94.81	18.2666	0.6791
≥9	24.44	99.03	95.16	25.1167	0.763
≥10	15.56	99.76	95.39	63.9333	0.8465
≥11	8.89	99.88	95.16	73.069	0.9122
≥12	6.67	100	95.16	—	0.9333
≥13	2.22	100	94.93	—	0.9778
>13	0	100	94.81	—	1

LR, likelihood ratio; —, not applicable.