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Type IV Neonatal Early-Onset Group B Streptococcal Disease in a United States Hospital▽

Karen M. Puopolo[1,2,4]* and Lawrence C. Madoff[1,3,4]

Channing Laboratory, Brigham and Women's Hospital, 181 Longwood Avenue, Boston, Massachusetts 02115[1]; Department of Newborn Medicine[2] and Division of Infectious Disease,[3] Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115; and Harvard Medical School, Boston, Massachusetts 02115[4]

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Group B streptococcus (GBS) serotypes causing neonatal disease vary by geographic region. Surveillance at the Brigham and Women's Hospital in Boston, Massachusetts, revealed a case of neonatal early-onset sepsis caused by type IV GBS. Neonatal type IV disease occurs in the Middle East but has not recently been described in U.S. infants.

Maternal intrapartum antibiotic prophylaxis (IAP) against group B streptococcus (GBS) has significantly decreased the incidence of neonatal early-onset sepsis (EOS) caused by GBS (6). Early-onset disease has not been eliminated, however, with persistent disease primarily occurring in premature infants and in infants born to women who have falsely screened GBS negative (22). IAP has had no effect on the incidence of late-onset neonatal GBS sepsis (LOS) (6). In addition to causing neonatal disease, GBS is also a frequent cause of infection in pregnant woman, a significant contributor to preterm birth, and a cause of serious infection in elderly and immunocompromised adults (23). The overall clinical problem of GBS disease in neonates and adult populations will best be addressed by the development of GBS vaccines (5).

Vaccine research to date has focused on the protective efficacy of antibodies to GBS capsular polysaccharide (19). The development of capsular polysaccharide-based vaccines is complicated by the multiple serotypes that cause neonatal disease. Nine antigenically and structurally distinct capsular GBS polysaccharide serotypes (types Ia, Ib, and II to VIII) have been described (8). The genetic basis for this diversity has recently been delineated (7). Geographic differences in the serotype distributions of isolates colonizing the rectovaginal region have been described (16, 17, 21). There has been a shift in the serotype distribution of invasive neonatal and adult disease isolates in the United States over the past 10 years, with the emergence of a significant proportion of type V serotype GBS (11, 14). Two recent studies of invasive disease isolates from neonates and pregnant women both found that serotypes Ia, III, and V were predominant, with the remaining isolates comprising serotypes Ib and II and nontypeable GBS (3, 11).

For the development of an effective multivalent GBS vaccine, ongoing surveillance is needed to detect further shifts in serotype distribution and to detect the potential emergence of historically less frequent serotypes. We conducted surveillance for neonatal GBS disease occurring in infants cared for in the neonatal intensive care unit (NICU) or newborn nurseries at the Brigham and Women's Hospital (BWH) in Boston, Massachusetts, from January 2000 through August 2006. This research was conducted with the approval of the BWH Institutional Review Board. Cases were identified by an electronic search of Microbiology Laboratory records. Total births, birth weight, and clinical and microbiological data were obtained from a review of hospital medical and laboratory records. Identification of streptococcal isolates as GBS was performed in the hospital microbiology laboratory by use of a latex agglutination test (Streptex; Murex Diagnostics). Individual isolates were obtained from the hospital microbiology laboratory on blood agar plates. The capsular polysaccharide serotype was determined by using rabbit serum specific to each GBS capsular polysaccharide (CPS)-tetanus toxoid conjugate vaccine for serotypes Ia, Ib, II, III, IV, V, VI, and VIII, as described previously (20). The reference strains used were as follows: type Ia, strain 090; type Ib, strain H36B; type II, strain 18RS21; type III, strain M781; type IV, strain 3139; type V, strain CJB111; type VI, strain SS1214; and type VIII, strain JM9-130013. The alpha-like surface protein type was determined by PCR with primers specific for the alpha C protein, Alp-1, Alp-2, Alp-3, and Rib (L. C. Madoff, submitted for publication).

During the study period, 62,033 births occurred at BWH and 1,364 very-low-birth-weight (VLBW; birth weight, <1,500 g) infants were cared for in the BWH NICU. Twenty-eight cases of neonatal invasive GBS disease were identified: 20 cases of EOS and 8 cases of LOS (Tables 1 and 2). We have previously reported the clinical characteristics, but not the serotype, of the early-onset cases that occurred from 2000 to 2003 (22). Most of the EOS cases occurred in term infants, with an average gestational age of 36.9 weeks (range, 25 to 42 weeks) and an average birth weight of 2,969 g (range, 850 to 4,370 g). The overall incidence of EOS from 2000 to 2006 was 0.32 cases/1,000 live births; the incidence for 2004 to 2006 was 0.18 cases/1,000 live births. The EOS cases that occurred from 2004 to 2006 continued trends that we observed previously: EOS occurred in two infants born to mothers with negative prenatal GBS screening cultures, i.e., in one premature infant whose

* Corresponding author. Mailing address: Channing Laboratory, Brigham and Women's Hospital, 181 Longwood Avenue, Boston, MA 02115. Phone: (617) 525-7737. Fax: (617) 731-1541. E-mail: kpuopolo@partners.org.

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TABLE 1. Clinical and microbiological characteristics of early-onset neonatal disease isolates

Case no.	Yr	Birth wt (g)	Gestational age (wk)	Maternal GBS status	Strain	CPS serotype	Surface protein
1	2000	1,240	28	Positive	KMP101	Ia	Alp-1
2	2000	3,090	37	Negative	KMP105	III	Rib
3	2000	3,929	40	Negative	–[b]		
4	2000	890	25	Unknown	–		
5	2000	2,290	33	Unknown	KMP104	V	Alp-3
6	2000	4,030	41	Negative	KMP102	Ia	Alp-1
7	2000	3,657	40	Negative	KMP100	V	Alp-3
8	2000	3,374	39	Positive	KMP108	V	Alp-3
9	2001	1,380	30	Positive	–		
10	2001	3,459	42	Positive	KMP107	Ia	Alp-1
11	2002	3,070	37	Negative	KMP110	Ia	Alp-1
12	2002	2,722	35	Negative	KMP109	IV	Alp-1
13	2003	4,370	42	Unknown	KMP113	II	ACP[a]
14	2003	4,281	41	Negative	KMP114	III	Alp-3
15	2003	4,300	41	Negative	–		
16	2003	3,119	40	Negative	–		
17	2004	3,402	39	Negative	KMP116	V	Rib
18	2004	2,495	36	Positive	KMP117	Ia	ACP
19	2006	1,470	33	Unknown			
20	2006	2,825	38	Negative	KMP121	III	Rib

[a] ACP, alpha C protein.
[b] –, strain not available for analysis.

TABLE 2. Clinical and microbiological characteristics of late-onset neonatal disease isolates

Case no.	Yr	Birth wt (g)	Gestational age (wk)	Age (days)	Strain	CPS serotype	Surface protein
1	2000	680	25	85	–[a]		
2	2000	730	26	21	KMP103	III	Rib
3	2003	1,360	28	21	KMP111	Ia	Alp-1
4	2003	1,360	28	40	KMP112	Ia	Alp-1
5	2004	1,340	28	38	KMP115	III	Rib
6	2004	650	24	18	KMP118	V	Alp-3
7	2005	870	27	21	KMP119	Ia	Alp-1
8	2005	750	25	51	KMP120	III	Rib

[a] –, strain not available for analysis.

birth circumstance did not allow the administration of IAP and in one term infant whose GBS-positive mother did not receive IAP due to obstetrical error. The clinical isolates were available for serotyping in 14/20 (75%) of EOS cases. The predominant serotypes were type Ia (36%), type V (29%), and type III (21%), consistent with those reported in the two most recent multicenter reports (3, 11).

The overall incidence of LOS was 5.9 cases/1,000 VLBW admissions. All eight cases occurred in VLBW infants with an average birth weight of 968 g (range, 650 to 1,360 g) and an average gestational age of 26.4 weeks (range, 24 to 28 weeks). The average age of onset of illness was 37 days (range, 18 to 85 days). All infants became significantly ill beyond their baseline clinical status, but there were no cases of meningitis or death directly attributable to the GBS infection. Two cases occurred in the same infant (LOS cases 3 and 4). This infant received standard antibiotic therapy for the first episode of GBS sepsis. The isolates from both episodes were of identical serotype and surface protein type, suggesting that illness was due to recurrent disease. Recurrent GBS disease is known to occur in up to 3% of infected infants, and prematurity is a significant risk factor for recurrent disease (8, 12).

We identified one case of EOS caused by type IV GBS. The serotype was confirmed both by exclusive reactivity with type IV-specific antisera and by genetic means by a PCR with primers designed to be specific for a unique portion of the CpsH gene that is specific to the type IV capsule cluster (7, 15). Neither disease, colonization in pregnant women, nor neonatal EOS caused by type IV GBS was reported in studies from the United States from 1992 to 2002 (3, 4, 11, 13, 14, 17, 25). A recent PCR-based genetic study of a series of American GBS isolates that were nontypeable with the use of CPS reference sera found evidence of multiple CPS gene types, but no type IV genes were identified (24). A single case of invasive nonpregnant adult disease type IV GBS was reported in a surveillance study in Maryland in 1992 (13). Type IV has been reported to be the dominant colonizing serotype in a recent study of pregnant women in the United Arab Emirates (2) and the second most common colonizing serotype in a study of pregnant women in Turkey (9). Other reports from Kuwait (1), Israel (18), and Turkey (10) have not found a significant proportion of type IV GBS isolates in studies of maternal GBS colonization, suggesting that type IV GBS transmission is found in highly localized populations even in similar geographic regions. The mother of the case infant in our study was Caucasian, was born in the United States, and had no known recent travel history. This case illustrates the importance of ongoing surveillance for the emergence of historically less frequent serotypes as efforts to develop and market a multivalent GBS vaccine proceed.

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REFERENCES

1. **Al-Sweih, N., M. Hammoud, M. Al-Shimmiri, M. Jamal, L. Neil, and V. Rotimi.** 2005. Serotype distribution and mother-to-baby transmission rate of Streptococcus agalactiae among expectant mothers in Kuwait. Arch. Gynecol. Obstet. **272:**131–135.
2. **Amin, A., Y. M. Abdulrazzaq, and S. Uduman.** 2002. Group B streptococcal serotype distribution of isolates from colonized pregnant women at the time of delivery in United Arab Emirates. J. Infect. **45:**42–46.
3. **Andrews, J. I., D. J. Diekema, S. K. Hunter, P. R. Rhomberg, M. A. Pfaller, R. N. Jones, and G. V. Doern.** 2000. Group B streptococci causing neonatal bloodstream infection: antimicrobial susceptibility and serotyping results from SENTRY centers in the Western Hemisphere. Am. J. Obstet. Gynecol. **183:**859–862.
4. **Blumberg, H. M., D. S. Stephens, M. Modansky, M. Erwin, J. Elliot, R. R. Facklam, A. Schuchat, W. Baughman, and M. M. Farley.** 1996. Invasive group B streptococcal disease: the emergence of serotype V. J. Infect. Dis. **173:**365–373.
5. **Centers for Disease Control and Prevention.** 2002. Prevention of perinatal group B streptococcal disease: revised guidelines from CDC. Morb. Mortal. Wkly. Rep. **51**(RR-11)**:**15–16.
6. **Centers for Disease Control and Prevention.** 2005. Early-onset and late-onset neonatal group B streptococcal disease—United States, 1996–2004. Morb. Mortal. Wkly. Rep. **54:**1205–1208.
7. **Cieslewicz, M. J., D. Chaffin, G. Glusman, D. Kasper, A. Madan, S. Rodrigues, J. Fahey, M. R. Wessels, and C. E. Rubens.** 2005. Structural and genetic diversity of group B streptococcus capsular polysaccharides. Infect. Immun. **73:**3096–3103.
8. **Edwards, M. S., V. Nizet, and C. J. Baker.** 2006. Group B streptococcal

infections, p. 403–405, p. 414–415, and p. 434–435. *In* J. S. Remington, J. O. Klein, C. B. Wilson, and C. J. Baker (ed.), Infectious diseases of the fetus and newborn infant, 6th ed. Elsevier Saunders, Philadelphia, PA.

9. **Ekin, I. H., and K. Gurturk.** 2006. Characterization of bovine and human group B streptococci isolated in Turkey. J. Med. Microbiol. **55:**517–521.
10. **Eren, A., M. Kucukercan, N. Oguzoglu, N. Unal, and A. Karateke.** 2005. The carriage of group B streptococci in Turkish pregnant women and its transmission rate in newborns and serotype distribution. Turk. J. Pediatr. **47:** 28–33.
11. **Ferrieri, P., C. J. Baker, S. L. Hillier, and A. E. Flores.** 2004. Diversity of surface protein expression in group B streptococcal colonizing & invasive isolates. Indian J. Med. Res. **119**(Suppl.)**:**191–196.
12. **Green, P. A., K. V. Singh, B. E. Murray, and C. J. Baker.** 1994. Recurrent group B streptococcal infections in infants: clinical and microbiologic aspects. J. Pediatr. **125:**931–938.
13. **Harrison, L. H., J. A. Elliott, D. M. Dwyer, J. P. Libonati, P. Ferrieri, L. Billmann, A. Schuchat, et al.** 1998. Serotype distribution of invasive group B streptococcal isolates in Maryland: implications for vaccine formulation. J. Infect. Dis. **177:**998–1002.
14. **Hickman, M. E., M. A. Rench, P. Ferrieri, and C. J. Baker.** 1999. Changing epidemiology of group B streptococcal colonization. Pediatrics **104:**203–209.
15. **Kong, F., S. Gowan, D. Martin, G. James, and G. L. Gilbert.** 2002. Serotype identification of group B streptococci by PCR and sequencing. J. Clin. Microbiol. **40:**216–226.
16. **Lachenauer, C. S., D. L. Kasper, J. Shimada, Y. Ichiman, H. Ohtsuka, M. Kaku, L. C. Paoletti, P. Ferrieri, and L. C. Madoff.** 1999. Serotypes VI and VIII predominate among group B streptococci isolated from pregnant Japanese women. J. Infect. Dis. **179:**1030–1033.
17. **Lin, F. Y., J. D. Clemens, P. H. Azimi, J. A. Regan, L. E. Weisman, J. B. Philips III, G. G. Rhoads, P. Clark, R. A. Brenner, and P. Ferrieri.** 1998. Capsular polysaccharide types of group B streptococcal isolates from neonates with early-onset systemic infection. J. Infect. Dis. **77:**790–792.
18. **Marchaim, D., M. Hallak, L. Gortzak-Uzan, N. Peled, K. Riesenberg, and F. Schlaeffer.** 2003. Cell wall proteins of group B streptococcus and low incidence of neonatal disease in southern Israel. J. Reprod. Med. **48:**697–702.
19. **Paoletti, L. C., and D. L. Kasper.** 2003. Glycoconjugate vaccines to prevent group B streptococcal infections. Expert Opin. Biol. Ther. **3:**975–984.
20. **Paoletti, L. J., J. Bradford, and L. C. Paoletti.** 1999. A serotype VIII strain among colonizing group B streptococcal isolates in Boston, Massachusetts. J. Clin. Microbiol. **37:**3759–3760.
21. **Persson, E., S. Berg, B. Trollfors, P. Larsson, E. Ek, E. Backhaus, B. E. B. Claesson, L. Jonsson, G. Radberg, T. Ripa, and S. Johansson.** 2004. Serotypes and clinical manifestations of invasive group B streptococcal infections in western Sweden 1998–2001. Clin. Microbiol. Infect. **10:**791–796.
22. **Puopolo, K. M., L. C. Madoff, and E. C. Eichenwald.** 2005. Early-onset group B streptococcal disease in the era of maternal screening. Pediatrics **115:** 1240–1246.
23. **Puopolo, K. M., L. C. Madoff, and C. J. Baker** 2006. Group B streptococcal infection in pregnant women. *In* B. D. Rose (ed.). UpToDate, Waltham, MA.
24. **Ramaswamy, S. V., P. Ferrieri, A. E. Flores, and L. C. Paoletti.** 2006. Molecular characterization of nontypeable group B streptococcus. J. Clin. Microbiol. **44:**2398–2403.
25. **Zaleznik, D. F., M. A. Rench, S. Hillier, M. A. Krohn, R. Platt, M. L. Lee, A. E. Flores, P. Ferrieri, and C. J. Baker.** 2000. Invasive disease due to group B streptococcus in pregnant women and neonates from diverse population groups. Clin. Infect. Dis. **30:**276–281.