THE YALE JOURNAL OF BIOLOGY AND MEDICINE 55 (1982), 291-295

Pathogenesis of Neonatal Group B Streptococcal Infections

ROBERT S. BALTIMORE, M.D.

Departments of Pediatrics and of Epidemiology,
Yale University School of Medicine, New Haven, Connecticut

Received April 29, 1982

Infections of the neonate due to the group B *Streptococcus* have been recognized since the 1930s, but it was during the 1970s that their incidence grew alarmingly throughout the world. A research effort stimulated by this problem has yielded significant new information about many facets of the pathogenesis of these infections. Immunologic investigations have pinpointed a lack of transplacentally acquired antibody as a significant risk factor. In the laboratory, assays of antibody which have a functional endpoint have demonstrated that the type-specific carbohydrate antigens play a major role in stimulating the development of protective antibody. These assays have been shown to correlate with certain tests of primary antigen-antibody interaction which do not have a functional endpoint, but are simpler to use in larger scale epidemiologic studies. These tools may be useful in filling the gaps in our current knowledge of the pathogenesis of this infection.

> . . . The changes in etiology [of neonatal sepsis] are indeed interesting—particularly the rise in Group B strep infections. Why? What is your answer to this shift? How often are group B found in the throat compared to the genital tract? Plenty of questions for you to tackle!
>
> Yours,
> Dorothy*

In the 1970s, a number of "new" diseases were discovered, most of which were known but had been poorly defined in the past. Such "new" diseases included infant botulism; Legionnaire's disease; *Pneumocystis carinii* pneumonia in the immunosuppressed; *Clostridium difficile* toxin-associated, antibiotic-induced pseudomembranous colitis; and rotavirus, yersinia, and campylobacter as agents of acute diarrhea. Group B *streptococcus* (GBS) was recognized as an agent of human disease in the 1930s [1,2], but it has clearly grown in importance during the 1970s. Unlike these other agents, the type of disease and spectrum of common syndromes caused by GBS were apparent to some investigators prior to the 1970s [3], but, as in the case of these "new diseases," research stimulated by an alarming increase in incidence has revolutionized our concept of the pathogenesis of the disease. Despite this new information, we are still unable to account for the rise in incidence which resulted in a worldwide pandemic of neonatal sepsis and meningitis due to this agent.

Clearly the increase in group B streptococcal infections of infants is not a matter of increased recognition but of increased incidence. The causative agent had been isolated and identified using routinely available media and methods long before the 1970s [3] and longitudinal observations at several institutions where neonatal sepsis

*Excerpt from a note to the author from Dr. Horstmann on receiving a reprint of [4].

has been a continuing interest demonstrates this increase. At Yale-New Haven Hospital, records of the bacteriology of neonatal sepsis have been kept since 1928. Prior to 1970 only 14 cases of GBS septicemia were documented. In the years 1970–1978, there were 90 newborns with GBS bacteremia [4] and the vast majority had life-threatening sepsis [5]. At Yale the highest incidence of GBS infection was seen in 1977 (Table 1) and the incidence had only declined slightly by the end of the decade.

MORE QUESTIONS THAN ANSWERS

In 1973 [6] and again in 1976 [7], the clinical experience at Yale with GBS neonatal infections was reviewed in publications. An editorial by Feigin accompanying the second of these reviews listed what he saw as the most vitally needed information about pathogenesis and treatment of neonatal infections due to this species [8]. He referred to the important publications of the early 1970s delineating the major syndromes and posed these, at that time, unanswered questions (which I paraphrase):

1. To what extent does maternal group B streptococcal carriage or infection cause fetal or neonatal morbidity or mortality or both?
2. Should the pediatrician treat all infants born to mothers who at term have vaginal cultures that are positive for group B streptococci?
3. What is the role of maternal antibody in protecting the mother from group B streptococcal carriage or infection?
4. What is the role of transplacentally acquired antibody in protecting the newborn infant from early-onset or late-onset group B streptococcal diseases?
5. Which antibodies are important and what specific concentrations are critical?
6. Does group B streptococcal infection or carriage in the newborn infant stimulate the production of antibody?
7. Is the detection of antibody useful in the diagnosis of infection due to group B streptococci?
8. What is the role of cellular immunity in limiting the extent of or preventing neonatal group B streptococcal septicemia?

In a relatively short time studies designed to answer each of these questions have appeared. While it is probably true that the final word on none of them is available, we have come a long way. The state of the art was recently reviewed by Baker [9], but already the questions relating to antibiotic prophylaxis and the role of the vaginal carrier have been addressed in important newer studies. The questions numbered 4 and 5 above concern protection by transplacentally acquired antibody, the specificity of antibody, and the potency of antibody. I shall review the newer information and methodology used to answer these critical questions.

FUNCTIONAL ANTIBODY TO GROUP B *STREPTOCOCCUS: IN VITRO* AND ANIMAL STUDIES

The presence of antibody to group B *Streptococcus* can be measured in the laboratory using serologic tests of primary antigen-antibody interaction such as im-

TABLE 1
Incidence of Group B Streptococcal Infections in Infants at Yale-New Haven Hospital 1970–1979

Year	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979
Incidence[a]	0.41	0.44	1.69	1.01	1.91	1.94	2.08	2.45	1.50	1.56

[a]Cases of group B streptococcal bacteremia and/or meningitis per 1,000 live births. (Data from [5].)

munoprecipitation or a radioactive antigen binding assay (RABA) [10] or indirectly as in indirect immunofluorescence [11]. While these tests have demonstrated antibody in animals and humans, functional tests of antibody have been used to investigate the antigenic specificity of antibody and the antigens involved in the *protective* antibody response. Animal protection studies to investigate GBS antibody response were pioneered by Lancefield using rabbit antisera to protect adult mice from lethal infection. Lancefield and associates were able to show that antibody to the type-specific carbohydrates of types Ia, Ib, and Ic is protective, and antibody to other antigenic determinants were responsible for weaker cross-protection between serotypes. Other animal models of protection include the infant rat [12], infant mice [13], and chicken embryos [14].

An *in vitro* model of protection, the opsonophagocytic assay, was utilized by Baltimore et al. to demonstrate type-specific antibody in rabbit antisera to all five serotypes of GBS: Ia, Ib, Ic, II, and III. They demonstrated the functional cross-reaction due to the shared Ibc protein and the Iac carbohydrate [15]. Since Lancefield had never reported on a mouse protection test for GBS serotype III, the serotype of major importance in human neonatal infections, this was the first demonstration that antibodies to type III are functional and serotype-specific. In this study it was also demonstrated that antibody to type Ia also opsonized type III strains, a finding not previously reported but confirmed subsequently in the chicken embryo protection test [14] and in the mouse protection test when Baltimore et al. developed the methods to enhance the virulence of GBS type III in mice [16].

FUNCTIONAL ANTIBODY TO GROUP B *STREPTOCOCCUS*: HUMAN SERA

At the time Baltimore et al. reported on the opsonophagocytic assay for demonstration of the antigens to which rabbit antibodies were directed [15], Hemming and associates reported that opsonic antibody could be measured in human sera as well, using the technique of neutrophil chemiluminescence [17]. They showed that most newborns born to women colonized vaginally with GBS had serum opsonins but infants who developed sepsis or meningitis lacked opsonins in the serum. This finding has been confirmed by others, using a number of non-functional assays and with larger numbers of human subjects. One of these studies, by Baker and Kasper, measured antibody binding to the serotype III-specific carbohydrate in a RABA. The blood of mothers whose babies developed GBS infections was significantly deficient in antibody compared with the maternal blood of babies whose mothers were colonized with GBS but who escaped invasive infection [18]. They felt that protective antibody was directed specifically to this type-specific carbohydrate. Functional assays have lent support to this thesis. Baltimore et al. demonstrated that the antigen used in this RABA absorbed out all activity of the rabbit antiserum to GBS serotype III from rabbits immunized with the whole organism [15], and all mouse-protective activity from this serum as well [16]. These serum absorptions were serotype-specific. The RABA was "validated" as predictive of functional immunity in human sera in a demonstration of excellent correlation of antibody concentration measured by RABA and titer of opsonins [19] and mouse protection titer [20]. This correlation was established with sera from volunteers immunized with a preparation of the GBS serotype III-specific carbohydrate. While these functional assays are neither simple to perform nor are they the most sensitive, it is possible to determine the biologic importance of the various antigen-antibody interactions in pathogenesis rather than chemical affinity alone. Such tests can also

validate non-functional assays by statistical correlation. These non-functional assays may be more suitable for use when large numbers of sera are to be studied and when maximal reproducibility and sensitivity are required.

UNANSWERED QUESTIONS WHICH REMAIN

Human experimentation with group B streptococcal infections is not practical. Other than immunization of volunteers with safe, non-living antigenic preparations, no human experiments have been performed or are likely to be performed. Functional assays and animal models have relevance to protection in humans and their use has led to important discoveries about the pathogenesis of GBS disease. Such studies have provided the rationale of vaccinating antibody-deficient women with a carbohydrate antigen of GBS to protect by transplacental antibody. Such a vaccine might be administered before or during pregnancy.

A number of unanswered questions still exist. Antibody studies should be helpful in answering some of these questions. Answers to the following questions should improve our understanding of the pathogenesis of group B streptococcal infections.

1. What was responsible for the rise in incidence of group B streptococcal infection in the 1970s? Was it a change in the bacterium, the host, or the environment?
2. What is responsible for the peculiar age-specific incidence of infections due to GBS? Why is the first month of life, especially the first 48 hours, the period of such high susceptibility?
3. What is responsible for the "late-onset" infections which occur after the first week of life until several months of age? What protective mechanisms develop in the infant so that after six months of age the disease is practically never seen in childhood?

REFERENCES

1. Lancefield RC: Serological differentiation of human and other groups of hemolytic streptococci. J Exp Med 57:571-595, 1933
2. Fry RM: Fatal infections by haemolytic streptococcus group B. Lancet i:199-201, 1938
3. Eickhoff TC, Klein JO, Daly AK, et al: Neonatal sepsis and other infections due to group B beta-hemolytic streptococci. New Engl J Med 271:1221-1228, 1964
4. Freedman RM, Ingram DL, Gross I, et al: A half century of neonatal sepsis at Yale: 1928-1978. Am J Dis Child 135:140-144, 1981
5. Roberts CW: Risk factors for death in group B streptococcal sepsis and meningitis. Unpublished M.D. Thesis, Yale University School of Medicine, 1982
6. Echeverria P: Observations concerning infections with beta hemolytic streptococci, not Group A or D, in neonates. J Pediatr 83:499-500, 1973
7. Ablow RC, Driscoll SG, Effmann E, et al: A comparison of early-onset group B streptococcal neonatal infection and respiratory distress syndrome of the newborn. New Engl J Med 294:65-70, 1976
8. Feigin RD: The perinatal group B streptococcal problem: More questions than answers. New Engl J Med 294:106-107, 1976
9. Baker CJ: Group B streptococcal infections. Adv Intern Med 25:475-501, 1980
10. Baker CJ, Kasper DL, Davis CE: Immunochemical characterization of the "native" type III polysaccharide of group B *Streptococcus*. J Exp Med 143:258-270, 1976
11. Vogel LC, Kretschmer RR, Boyer KM, et al: Human immunity to group B streptococci measured by indirect immunofluorescence: correlation with protection in chick embryos. J Infect Dis 140: 682-689, 1979
12. Fisher GW, Lowell GH, Crumrine MH, et al: Demonstration of opsonic activity and *in vitro* protection against group B streptococci type III by *Streptococcus pneumoniae* type 14 antisera. J Exp Med 148:776-786, 1978
13. Furtado D: Experimental group B streptococcal infections in mice; hematogenous virulence and mucosal colonization. Infect Immun 13:1315-1320, 1976

14. Tieffenberg J, Vogel L, Kretschmer RR, et al: Chicken embryo model for type III group B beta-hemolytic streptococcal septicemia. Infect Immun 19:481–485, 1978
15. Baltimore RS, Kasper DL, Baker CJ, et al: Antigenic specificity of opsonophagocytic antibodies in rabbit anti-sera to group B streptococci. J Immunol 118:673–678, 1977
16. Baltimore RS, Kasper DL, Vecchitto JS: Mouse protection test for type III strains of group B *Streptococcus*. J Infect Dis 140:81–88, 1979
17. Hemming VG, Hall RT, Rhodes PG, et al: Assessment of group B streptococcal opsonins in human and rabbit serum by neutrophil chemiluminescence. J Clin Invest 58:1379–1387, 1976
18. Baker CJ, Kasper DL: Correlation of maternal antibody deficiency with susceptibility to neonatal group B streptococcal infections. New Engl J Med 294:753–756, 1976
19. Kasper DL, Baker CJ, Baltimore RS, et al: Immunodeterminant specificity of human immunity to type III group B *Streptococcus*. J Exp Med 79:327–339, 1979
20. Baltimore RS, Baker CJ, Kasper DL: Antibody to Group B *Streptococcus* type III in human sera measured by a mouse protection test. Infect Immun 32:56–61, 1981