

## Analysis of Group B Streptococcal Types Associated with Disease in Human Infants and Adults

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It is important to resolve existing differences of opinion regarding group B streptococcal type distribution in human disease because of the relevance of type prevalence to future programs of prevention. This report compares data obtained from typing 392 group B streptococci isolated from systemic infections in both infants and adults in the United States from 1972 through 1975. The data showed a substantial predominance of type III among strains isolated from cases of infant meningitis and from "late-onset" septicemia but did not confirm a prior report that type Ia causes most cases of "early-onset" infant septicemia. Type II was the predominant serotype among 11 cerebrospinal fluid isolates from adults. The fact that over one-fourth of the isolates were types other than Ia or III means that future epidemiological studies, including definition of immunological factors, must include all five group B types.

Numerous cases of neonatal meningitis and septicemia in the United States each year are caused by group B streptococci. Yow reported that the proportionate number of cases of neonatal meningitis caused by group B *Streptococcus* in the Houston area from 1967 to 1974 increased each year relative to that caused by all other bacteria to such an extent that the former were responsible for 70% of the cases by the end of 1974 (16). An increase in the incidence of group B disease is further suggested indirectly by a recent increase in the number of pages devoted to this subject in the pediatric journals and also by the increasing proportion of group B streptococci relative to other beta-hemolytic streptococci sent to the Center for Disease Control (CDC) for identification from 1970 to 1975 (8 to 52% [unpublished data]). Although the latter situation might reflect a heightened awareness of the human pathogenicity of this organism rather than an absolute increase in incidence, Anthony and Concepcion found that 86% of the beta-hemolytic streptococci isolated in a general hospital and excluded presumptively as group A or D were group B (2).

There are several conflicting opinions regarding group B streptococcal disease and its prevention. One is that there are two forms of neonatal disease: a congenital, fulminant, septicemic form caused exclusively by type Ia, with the onset of symptoms within 48 h after birth ("early-onset" syndrome), and a noncongenital, meningitic form caused primarily by type III, with the onset of symptoms after 10 days of age ("late-onset" syndrome) (9). A corollary to this view is that it

would be beneficial to screen mothers and infants for group B streptococcal carriage and to treat prophylactically those colonized with types Ia or III. The latter opinion is not widely accepted (1, 8), but efficacy studies so far have involved small numbers (10, 13). Another opinion is that all group B streptococcal types cause early-onset septicemia and that type III not only predominates in late-onset meningitis, but also in meningitis of an early onset (5). The sequel to this opinion is that passive immunization of the fetus with vaccines administered to the mother during pregnancy might be a more efficacious way to prevent group B streptococcal disease than would antibiotic prophylaxis (4). This view, however, is also controversial because of limited knowledge regarding which antigens, if any, evoke protective antibodies in humans. More recently, a compilation of published data led Anthony and Okada to the conclusion that there is a continuous rather than bimodal distribution of streptococcal sepsis by age at the onset of symptoms (3). These authors emphasized the likelihood of a variation in type prevalence among different populations. Differences in methodology, populations, and sample sizes among published reports undoubtedly have contributed to the discrepant opinions.

It is important to resolve differences in opinion regarding group B type distribution in human disease because directions taken in future programs of prevention would rely on knowing the type prevalence. In 1973, we published a retrospective study of the type distribution of group B streptococci sent to us from 1967 to 1972 by

public health laboratories and private physicians (14). We concluded that type III predominated in cerebrospinal fluid (CSF) and blood cultures (both of which were primarily from babies) and that this predominance occurred in both early- and late-onset neonatal meningitis. The latter fact supported the conclusions of Baker and Barrett (5) but relied on an analysis of only 16 strains from the CSF of babies <10 days old and 32 strains from those  $\geq 10$  days old. Only three CSF isolates were from adults. The present study extends those observations by presenting type distribution data obtained from typing 343 infant and 49 adult CSF and blood isolates sent to CDC since 1972 and comparing them with the type distribution of 554 group B strains isolated from other sources. It provides additional evidence for the association of type III with neonatal meningitis and of type II with adult meningitis.

#### MATERIALS AND METHODS

The group B streptococcal strains described in this study were those that state health laboratories and a few private investigators sent to CDC for grouping and typing between July 1972 and January 1976. Specimens obtained in special research projects were excluded.

Clinical information was obtained from the report form sent with each culture. "Infant" cultures were defined as those from individuals  $\leq 2$  years old, and "adult" cultures were defined as those from individuals  $\geq 12$  years old. Four blood cultures from patients between 2 and 12 years old were excluded from the study without altering the serotype distribution. Multiple CSF and blood isolates obtained from one patient were listed as one CSF culture. All of the CSF isolates led to a diagnosis of meningitis, and all of the blood isolates included in the study led to a diagnosis of either septicemia or bacteremia. The type distribution of group B isolates from infants with so-called early-onset septicemia was analyzed on the basis of two definitions of early-onset: onset within 2 days (9) and onset within 10 days (6) of age.

Cultures were grouped and typed as described previously (14).

#### RESULTS

Blood and CSF isolates comprised 41% of the group B streptococci received in the Streptococcus Laboratory, CDC, from July 1972 through December 1975. Their type distribution is shown in Table 1 and is compared with that of 554 isolates from other sources. The latter were distributed almost equally among types I, II, and III, with 33% being types Ia, Ib, and Ic, 31% being types II and II/Ic, and 34% being type III. In contrast, among the isolates received from July 1972 through December 1975, there were substantially more type III isolates from the CSF (87%) and blood (49%) of infants and more type II isolates (64%, including II/Ic) from the CSF of adults. Of the 946 strains tested, 1.7% were nontypable and 1.0% were nonhemolytic.

The sex of the patient was specified for 122 infant CSF isolates, with the group composed of 43% males and 57% females. With the age of the infant at the onset of meningitis being given for 133 CSF isolates, the ratio of late-onset ( $\geq 10$ -day-old) to early-onset (<10-day-old) infants was approximately 2:1. The type distribution of these strains is shown in Table 2. Type III predominated in both early-onset (85%) and late-onset (91%) meningitis. One strain from a case of early-onset meningitis was nonhemolytic.

In contrast to the data obtained from the CSF isolates, approximately twice as many isolates from the blood of infants were from early-onset cases as from late-onset cases (Table 3). A total of 44% of the early-onset isolates were type I (47% after strains from infants 2 to 10 days old were eliminated from the analysis). Therefore, less than half of the early-onset isolates were type I, whether the definition of "no more than 10 days old" (6) or "no more than 2 days old" (9) is used. Type III comprised 32% (<10 days

TABLE 1. Type distribution of group B streptococcal strains isolated from the CSF and blood of infant and adult patients<sup>a</sup>

Culture source	No. of strains	% of strains of serological type:						
		Ia	Ib	Ic	II	II/Ic	III	NT <sup>b</sup>
Infant CSF	142	1	5	6 <sup>c</sup>	<1	<1	87	0
Adult CSF	11	0	9	18 <sup>c</sup>	46	18	9	0
Infant blood	201	10	8 <sup>c</sup>	14	10	8	49 <sup>c</sup>	1
Adult blood	38	11	24 <sup>c</sup>	5	13	18	24 <sup>c</sup>	5
Other <sup>d</sup>	554	9	13 <sup>c</sup>	11	19	12	34 <sup>c</sup>	2

<sup>a</sup> Infant,  $\leq 2$  years old; adult,  $\geq 12$  years old.

<sup>b</sup> NT, Nontypable.

<sup>c</sup> One strain was nonhemolytic.

<sup>d</sup> Genitourinary, gastrointestinal, respiratory, epithelial, and wound cultures from patients of all ages.

<sup>e</sup> Two strains were nonhemolytic.

TABLE 2. Type distribution of group B streptococcal strains isolated from the CSF of infants <10 days old and those  $\geq 10$  days old

Age of patients (days)	No. of CSF isolates	% of strains of serological type:						
		Ia	Ib	Ic	II	II/Ic	III	NT <sup>a</sup>
$\geq 10$	87	2	5	1	0	1	91	0
<10	46	9	2	4 <sup>b</sup>	0	0	85	0

<sup>a</sup> NT, Nontypable.<sup>b</sup> One strain was nonhemolytic.TABLE 3. Type distribution of group B streptococcal strains isolated from the blood of infants <10 days old and those  $\geq 10$  days old

Age of patients (days)	No. of blood isolates	% of strains of serological type:						
		Ia	Ib	Ic	II	II/Ic	III	NT <sup>a</sup>
$\geq 10$	34	3	9	0	3	0	85	0
<10	72 <sup>b</sup>	12	8 <sup>c</sup>	24	21	3	32 <sup>c</sup>	0
$\leq 2$	48	10	10 <sup>c</sup>	27	21	6	25 <sup>c</sup>	0

<sup>a</sup> NT, Nontypable.<sup>b</sup> Includes the 48 isolates from infants  $\leq 2$  days old.<sup>c</sup> One strain was nonhemolytic.

old) or 25% ( $\leq 2$  days old) of the early-onset isolates. When the blood isolates from infants  $\geq 10$  days old were analyzed, however, type III comprised 85% of the total. This predominance is responsible for the high overall Table 1 value for type III infant blood isolates (49%). Of the infant blood cultures received, 176 were designated by the sex of the patients; 48% were male and 52% were female. Two strains were nonhemolytic.

The fact that 88% of the blood and CSF isolates were from infants emphasizes the importance of group B streptococci in neonatal disease. However, 38 blood and 11 CSF isolates submitted to CDC during the study period were from adults, whereas during the preceding 5 years, 26 blood and only 3 CSF isolates were from adult patients (14). A total of 64% of the adult CSF isolates in the present study were type II (including II/Ic), and 91% contained either the II polysaccharide antigen, Ibc protein antigens, or both. Only one strain was type III. These data are especially interesting when compared with the 87% type III predominance and the 1.4% distribution of type II among infant CSF isolates. Only 12% of the latter contained II or Ibc antigens. One of the adult CSF isolates was nonhemolytic, and the others were beta-hemolytic. The five male and six female patients from whom these cultures were isolated ranged from 12 to 75 years old (Table 4). Other complications were noted in 73% of the patients, and 27% of the cases were terminal.

In contrast to the CSF isolates, no striking predominance of any one type was observed in the blood cultures from adult patients (Table 1). Two strains were nonhemolytic.

TABLE 4. Adult patients with group B streptococcal meningitis

Patient no.	Age & sex	Associated illness	Terminal	Group B type isolated from CSF
1	58F	Multiple sclerosis	No	II
2	68M		No	II
3	62M	Osteomyelitis, diabetes mellitus	No	Ib
4	26F	Probable vasculitis	Yes	II
5	63F		No	Ic
6	50F	Brain herniation into left orbit	No	II/Ic
7	12F	Otalgia	No	II/Ic
8	44M	Multiple sclerosis	Yes	Ic <sup>a</sup>
9	60M	Endocarditis	No	II
10	75F		Yes	II
11	59M	Endocarditis	No	III

<sup>a</sup> Nonhemolytic.

## DISCUSSION

An analysis of the data obtained from serotyping 343 group B streptococci from infant blood and CSF isolates supports the conclusions of Baker and Barrett (5). Type III was the predominant organism isolated from the CSF of infants, regardless of their age at the onset of symptoms. This type also predominated among the blood isolates of infants  $\geq 10$  days old. Blood isolates from infants <10 days old, however, had a type distribution of 44% type I (including Ia, Ib, and Ic), 24% type II (including II/Ic), and 32% type III. These data differ from those in the study of Franciosi et al. (9), in which Ia was the only type isolated from nine cases of early-onset infant septicemia. In the latter study, however, early onset was defined as within 2 days after birth.

Accordingly, blood isolates from infants  $\leq 2$  days old were analyzed. The type distribution did not change markedly: 42% type I, 27% type II, and 25% type III.

The type distribution pattern observed with group B isolates from the blood of adults was similar to that observed in infants  $< 10$  days old: 40% type I, 31% type II, and 24% type III. Type II strains predominated, however, among the isolates from the CSF of adults, of whom 73% had associated illnesses and 27% died. Bayer and associates (7) emphasized the fact that many of their adult patients with group B streptococcal disease had underlying illnesses. Lerner noted the association of type II with two cases of adult group B meningitis (11). It is still not known why type II predominates in adult CSF, with type III being rarely found, whereas the reverse is true of infant CSF cultures.

Several further observations were made about the overall study group of 946 group B streptococcal isolates. Only 1.7% were nontypable, and 0.95% were nonhemolytic. Of the 3,000 group B strains tested by CDC since 1972, approximately 2% were nonhemolytic (unpublished data). Whether the incidence of these organisms is increasing as suggested by the results of a recent study (12) is unproven. Data on CDC isolates may not reflect the true incidence because of the common laboratory practice of selecting only beta-hemolytic strains from some sources for further study. It is apparent, however, that the incidence of type II strains containing the Ibc protein antigen is increasing, with 39% of the type II strains containing Ibc antigens in this study as opposed to only 12% in the preceding 5-year period (14). This antigen and the polysaccharide type antigens are found in types Ib and Ic and in some type II strains designated II/Ic for convenience (15). Accordingly, 92% of the CSF isolates from adults contained the II antigen, the Ibc antigen, or both, whereas this was true for only 12% of the infant CSF isolates and 51% of the isolates from sources other than CSF or blood.

The results of this study allow the following conclusions regarding the distribution of group B types in human infections. Type III is predominantly associated with neonatal meningitis, although the other four types are isolated occasionally. There may be a similar association of type II with adult meningitis, but other types (especially those with Ibc antigens) are also found. Type III is isolated almost exclusively from the blood of infants  $\geq 10$  days old, whereas there is no predominance of any one type in blood isolates from infants  $< 10$  days (or  $< 2$  days) old. The slightly greater proportion of types Ia,

Ib, and Ic in the latter early-onset group might reflect a respiratory route of infection since we and others have observed proportionately more type I isolates from respiratory cultures and more type II and III isolates from genital and intestinal cultures (and hence, colonized infants) (14). Over one-fourth of the 343 strains from infected infants were types other than Ia or III. For this reason, programs aimed at the prevention of group B streptococcal disease should include epidemiological and immunological studies of all five types.

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