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# Effect of Age and Preexisting Antibody on Serum Antibody Response of Infants and Children to the F and G Glycoproteins during Respiratory Syncytial Virus Infection

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**The serum antibody response of 50 infants and children infected with respiratory syncytial virus (RSV) was determined by a glycoprotein-specific enzyme-linked immunosorbent assay, and the effects of age and preexisting antibody titer at the time of RSV infection on response to the G and F glycoproteins of RSV were examined. The immune response to the G and F glycoproteins was assessed with anti-human immunoglobulin A to permit measurement of the response of young infants in the presence of maternally derived immunoglobulin G. The findings suggested that age primarily affects the response to the F glycoprotein and that preexisting antibody titer affects the response to the G glycoprotein.**

It has long been recognized that infants up to 8 months of age have a diminished serum antibody response to infection with respiratory syncytial virus (RSV) when compared with the response of older infants and children (2, 5, 8, 10, 12, 15, 23). Recently, it was shown that this diminished response involves both surface glycoprotein antigens of RSV, that is, the gp90 (G) and gp70 (F or fusion) glycoproteins (10). Two hypotheses have been offered to account for the decreased immune response of the younger infants. First, it has been suggested that immaturity of the immune system is responsible for the poor response (12). Second, the presence of passively acquired maternal antibody in the serum of the young infant might have an immunosuppressive effect on the development of the infant's own immune response (12). In this study we used a glycoprotein-specific enzyme-linked immunosorbent assay (ELISA) to investigate the antibody response of 50 infants and children infected with RSV and examined the effects of age and preexisting antibody titer at the time of RSV infection on the serum antibody response to the G and F glycoproteins. The immune response to the G and F glycoproteins was assessed with anti-human immunoglobulin A (IgA) to quantify the response of the young infant in the presence of maternally derived IgG. Our observations suggested that age primarily affects the response to the F glycoprotein and that preexisting antibody titer affects the response to the G glycoprotein.

Altogether, 50 infants and children aged 2 to 21 months and infected with RSV were studied: 18 were outpatients in the Vanderbilt Vaccine Clinic, whose response to RSV infection has been described previously (10); 7 were controls in an inactivated-RSV vaccine study who were followed closely from 2 months of age for evidence of RSV virus infection (7); 11 who were hospitalized with lower respiratory illness caused by RSV were controls, i.e., received only placebos, in a study to evaluate the therapeutic efficacy of an intravenously administered pooled immunoglobulin preparation; and 14 were hospitalized at Children's Hospital in Washington, D.C., and were part of a long-term project to study the role of RSV in respiratory tract disease (6, 12). Of these infants and children, 35 had bronchiolitis or pneumonia, 12 had upper respiratory tract illness, and 3 were well. Seventeen of the patients were 12 months of age or older. In each of these groups, RSV infection was documented by virus isolation during the acute phase of illness or by the development of an immune response during convalescence from illness. The serum antibody responses to RSV glycoproteins of the hospitalized and nonhospitalized patients were similar enough to combine the results of the two groups for our analysis (data not presented). The majority of the infections were considered to be primary based upon the young age of the patients, intensive prospective laboratory and epidemiologic observations, or the low titer in ELISA of IgA ($\leq$1:40) to the G or F glycoproteins in the preinfection or acute-phase serum specimens. Because some young infants infected with RSV do not develop a detectable immune response (10), it is possible that some of the older children who had lived through two epidemic seasons of RSV could have been reinfected.

IgA and IgG to the RSV G and F glycoproteins in ELISA were measured as described previously, with purified G and F glycoproteins isolated from the Long strain of RSV (10). The titer of neutralizing antibodies was determined by a 60% plaque reduction assay with the A2 and 18537 strains of RSV and HEp-2 cells as previously described (9). For the hospitalized patients, the serum specimens were collected at the time of hospitalization and also from 4 to 6 weeks later. Serum specimens from the outpatients were collected on the average 2.5 months before and 2.83 months after the isolation of RSV at the time of an illness. For the eight outpatients less than 8 months of age, the average interval from the time of collection of preinfection serum to the onset of illness was 0.8 months, with a range of 0.5 to 1.5 months.

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TABLE 1. Serum antibody response of infants and children undergoing primary infection with RSV as determined by ELISA[a]

| Patient age (mo) at time of infection | No. tested | % with antibody response | Response to F glycoprotein[b] | | | | | | | Response to G glycoprotein[b] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | IgG | | | IgA | | | | IgG | | | IgA | | |
| | | | Reciprocal mean $log_2$ titer ± SE | | % with ≥4-fold rise | Reciprocal mean $log_2$ titer ± SE | | % with ≥4-fold rise | Mean $log_2$-fold rise[f] | Reciprocal mean $log_2$ titer ± SE | | % with ≥4-fold rise | Reciprocal mean $log_2$ titer ± SE | | % with ≥4-fold rise | Mean $log_2$-fold rise[d] |
| | | | Preinfection or acute phase[c] | Postinfection[c] | | Preinfection or acute phase[d] | Postinfection[e] | | | Preinfection or acute phase[e] | Postinfection[c] | | Preinfection or acute phase[d] | Postinfection[d] | | |
| 1–8 | 23 | 91 | 9.6 ± 0.5 | 11.3 ± 0.4 | 62 | 4.2 ± 0.2 | 7.1 ± 0.5 | 83 | 3.0 ± 0.4 | 9.5 ± 0.6 | 10.9 ± 0.4 | 48 | 3.7 ± 0.2 | 6.6 ± 0.4 | 61 | 3.0 ± 0.6 |
| 9–21 | 27 | 100 | 6.7 ± 0.5 | 13.8 ± 0.3 | 100 | 4.4 ± 0.3 | 9.3 ± 0.4 | 96 | 4.9 ± 0.4 | 6.7 ± 0.5 | 13.2 ± 0.3 | 96 | 3.9 ± 0.2 | 7.7 ± 0.5 | 78 | 3.8 ± 0.4 |

[a] The lowest dilution tested by ELISA was 1:40. Serum specimens without antibody detectable by ELISA at 1:40 were assigned a titer of 1:10 for the calculation of mean titers. This was because the serial dilutions were fourfold.
[b] Comparison of the means of the postinfection serum antibody titers and $log_2$-fold rises was done by Student's $t$ test.
[c] $P < 0.001$.
[d] Mean differences between age groups not significant.
[e] $P < 0.005$.
[f] $P < 0.025$.

RSV strains have been grouped into two major neutralization groups represented by the prototype Long and 18537 strains (1, 3, 13). The A2 strain is closely related to the Long strain by neutralization assay (13). Because the glycoproteins used in the ELISA were isolated from the Long strain, it was important first to determine whether infection with the 18537 strain of RSV induced antibodies to the G and F glycoproteins of the Long strain in the ELISA. We recently demonstrated that of 19 infants infected with a 18537-like strain of virus, 58% had a rise of antibody titers to each homologous G an F glycoprotein, 47% had a response to the Long F glycoprotein, and 32% had a response to the Long G glycoprotein (M. Hendry and B. R. Murphy, unpublished observations). The pre- and postinfection serum pairs of eight cotton rats infected with strain 18537 of RSV (13) were also tested with the Long strain G and F glycoproteins in an ELISA specific for the detection of cotton rat immunoglobulins (14). Each of the eight animals developed an approximate 50-fold rise in antibody titer to the Long G glycoprotein and a 256-fold rise to the Long F glycoprotein. Thus, the Long strain G and F glycoproteins can detect immune responses of humans and cotton rats infected with the 18537 strain of RSV. Furthermore, 19 isolates from patients in the present study were available for typing to estimate the representation of Long- and 18537-like strains in this group of children; 68% of the isolates were Long-like and 32% were 18537-like strains (M. Hendry and B. R. Murphy, unpublished observations). The distributions of the two RSV strains in the younger versus older patient population was similar; i.e., 4 of 10 isolates in the former group and 2 of 9 in the latter group were 18537-like. Data for which almost all (96%) of the infants and children greater than 8 months of age had a serum antibody rise in reactions to the F and G glycoproteins indicated that the Long strain glycoproteins detected rises in children infected with the 18537-like strain (Table 1). Although the Long strain glycoproteins can detect rises in individuals infected with the 18537 strain, it is important to emphasize that it does so less efficiently and caution must be exercised in the interpretation of the results presented below.

The G and F antibody responses in the ELISA to RSV infection of 1- to 8-month-old infants and 9- to 21-month-old infants and children are presented in Table 1. As expected, the 1- to 8-month-old infants had higher titers of preinfection or acute-phase IgG titers to the F and G glycoproteins, but their preinfection or acute-phase IgA titers were similar. The magnitude of the postinfection IgG titers to the proteins was significantly lower in the younger individuals, which confirms our previous observations (10). This was also true for the postinfection IgA titer to glycoprotein F. An immune response in the younger age group was detected most efficiently by a rise in IgA to the G and F glycoproteins. This observation confirmed our prediction that a rise in RSV IgA titer would serve as the most sensitive indicator of an immune response in the presence of maternally derived IgG.

We next sought an additional method to confirm the suppression of an immune response to the RSV G and F glycoproteins in the younger infants. Because the G and F glycoproteins induce neutralizing antibodies (16, 18–21), it was reasonable to suppose that the younger infants would have lower neutralizing antibody responses. Furthermore, a neutralizing antibody response could be quantified with the 18537 and A2 strains of RSV, and thus a rise from either or both prototype strains could be determined. The titer (including the maximum) and frequency of response to each strain is presented and compared between the two age groups (Table 2). The mean maximum titer and the frequency of a neutralizing antibody response to either strain were significantly lower in the younger individuals (Table 2). The fourfold difference in mean maximum neutralizing antibody titers (Table 2) is similar to the corresponding differences in the postinfection IgG titers to glycoproteins G and F in the ELISA (Table 1). Considered together, the data can reasonably be interpreted to indicate that the younger infants had a decreased response to both surface glycoproteins of RSV.

We next sought to examine whether age or preexisting immune status was the factor primarily responsible for the diminished response of the younger individuals (Table 3) to the G and F glycoproteins. To analyze this question, we quantitated the magnitude of the immune response with the difference between acute-phase or pre- and postinfection IgA titers to the F or G glycoprotein in the ELISA. The IgA ELISA was chosen to measure the immune response because both age groups had similar titers of this antibody to the F and G glycoprotein in their acute-phase or preinfection sera and because the immune responses of the infant or child were not obscured by the presence of maternal IgG (Table 1). The age of the individual was correlated with the magnitude of the $log_2$-fold rise in IgA titer to the F or G glycopro-

TABLE 2. Serum neutralizing antibody response of infants and children undergoing primary infection with RSV

| Patient age (mo) at time of infection | No. tested | Neutralizing antibody response[a] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | A2 | | | 18537 | | | | |
| | | Reciprocal mean $\log_2$ titer ± SE | | % with ≧4-fold rise | Reciprocal mean $\log_2$ titer ± SE | | % with ≧4-fold rise | Mean maximum titer[b] | % with ≧4-fold rise to either strain[c] |
| | | Preinfection or acute phase | Postinfection | | Preinfection or acute phase | Postinfection | | | |
| 1 to 8 | 23 | 5.5 ± 0.3 | 6.5 ± 0.4 | 39 | 5.7 ± 0.4 | 7.4 ± 0.5 | 52 | 7.8 ± 0.5 | 52 |
| 9 to 21 | 27 | 3.8 ± 0.1 | 9.0 ± 0.4 | 85[d] | 4.2 ± 0.3 | 8.0 ± 0.4 | 81 | 9.8 ± 0.3 | 93 |

[a] Titers are reciprocal mean $\log_2$ titers. The lowest dilution of serum tested in the neutralization assay was 1:20. The titers of specimens with undetectable antibody activity were assigned a value of 1:11 in the 60% plaque inhibition assay.
[b] Achieved in postinfection serum against strains A2 or 18537. $P < 0.001$ for mean differences between age groups as determined by Student's $t$ test.
[c] $P < 0.001$ as determined by Fisher's exact test.
[d] Only 26 of 27 tested.

tein (Table 3). It can be seen (Table 3) that there is a significant positive correlation between age at the time of infection and the F antibody response. This is also evident in Table 1 when the magnitudes of postinfection IgG titers to the F glycoprotein of two age groups are compared. However, for the G glycoprotein there is not a significant correlation between the magnitude of response and age. Because the younger individuals have higher acute-phase or preinfection titers of F and G antibodies in their serum (Table 1), the effect of age on the response of individuals who have the same titers of preexisting RSV glycoprotein antibody must be examined. Accordingly, infants and children were matched by acute-phase or preinfection antibody titer; i.e., they were divided into five groups with similar antibody titers. For preexisting IgG to the G glycoprotein, the titers of each group were 11.3 to 15.3, 9.3, 7.3, 5.3, and 3.3. The effect of age on antibody response within each group was then determined. The respective correlation coefficients were then averaged to obtain the overall correlation between a primary variable (e.g., age) and response (e.g., rise in IgA titer to G glycoprotein) when one of the remaining primary variables (e.g., preinfection IgG G titer) is held constant. It is evident that if subjects are matched by preexisting titers to the G glycoprotein, there is a highly significant correlation between age and IgA antibody response to F but virtually no correlation between age and IgA response to the G glycoprotein. The same is true of the corresponding results obtained with matching by preexisting titer to the F glycoprotein. These data suggest that age is a determinant in the response to the F glycoprotein but not to the G glycoprotein. A similar analysis suggests that preexisting IgG titer (to either the G or F glycoprotein) rather than age is the primary determinant of the IgA response to the G glycoprotein. The latter analysis was carried out by the matching of infants and children according to age and by the determination with each age group of the effect of preexisting (i.e., maternal) antibody titer on the IgA response to the F or G glycoprotein. As indicated above, the respective correlation coefficients were

TABLE 3. Effect of age or preexisting antibody titer on serum antibody response of infants and young children to RSV infection

| Primary variable | Match to indicated IgG G antibody titer ($-\log_2$) or to patient age (mo) | No. of patients in group | Avg rise in IgA F titer ($-\log_2$) | Correlation coefficient of rise in IgA F antibody titer to primary variable[a] | Avg rise in IgA G titer ($-\log_2$) | Correlation coefficient of rise in IgA G antibody titer to primary variable[b] |
|---|---|---|---|---|---|---|
| Age[c] | unmatched | 50 | 3.8 | 0.45[d] | 3.3 | −0.15 |
| | 11.3–15.3[e] | 13 | 3.2 | 0.46 | 1.4 | 0.21 |
| | 9.3 | 10 | 3.4 | 0.46 | 3.6 | −0.27 |
| | 7.3 | 10 | 3.6 | 0.62 | 4.4 | −0.30 |
| | 5.3 | 11 | 5.1 | 0.23 | 4.2 | −0.07 |
| | 3.3 | 6 | 5.7 | 0.10 | 4.3 | 0.14 |
| Preexisting IgG G antibody titer[g] | unmatched | 50 | 3.8 | −0.39[d] | 3.3 | −0.39[d] |
| | 1 to 2[f] | 6 | 3.0 | −0.96 | 3.3 | −0.76 |
| | 3 to 5 | 10 | 2.9 | 0.25 | 2.8 | −0.67 |
| | 6 to 8 | 7 | 4.2 | −0.38 | 2.9 | −0.08 |
| | 9 to 11 | 10 | 4.2 | −0.04 | 4.0 | 0.09 |
| | 12 to 15 | 9 | 5.8 | 0.29 | 3.1 | −0.62 |
| | 16 to 21 | 8 | 5.8 | −0.38 | 4.5 | −0.03 |

[a] Average correlation coefficient with age variable was 0.40 ($P < 0.005$) and with IgG G antibody titer was −0.13 ($P > 0.10$).
[b] Average correlation coefficient with age variable was −0.06 ($P > 0.10$) and with IgG G antibody titer was −0.33 ($P < 0.02$).
[c] When matched to pre-IgG F antibody titer, the correlation coefficient between age and rise in IgA F antibody titer was 0.39 (<.005) and that for age and IgA G antibody titer was 0.06 ($P > 0.10$).
[d] $P < 0.02$.
[e] Preexisting IgG G glycoprotein antibody titer.
[f] Age in months.
[g] When unmatched, the correlation coefficient between preexisting IgG titer to glycoprotein F and rise in IgA titer to the same protein was −0.39 ($P < 0.005$) and for IgA G titer was −0.32 ($P < 0.02$). When matched by age, the average correlation coefficient between IgG F titer and rise in IgA F titer was −0.15 ($P > 0.10$) and that for rise in IgA G antibody titer was −0.32 ($P < 0.02$).

averaged for subjects matched by age (in months): 1 to 2, 3 to 5, 6 to 8, 9 to 11, 12 to 15, and 16 to 21. It is important to emphasize that it cannot be determined whether preexisting G or F antibody or both cause the decrease in response to the G glycoprotein, because both are present in the maternally derived antibody and the levels of G and F antibodies are highly correlated ($r = 0.83$, $p < 0.001$). Considered together, these results suggest that the F antibody response of the young infant is primarily affected by age and that the G antibody response is primarily affected by preexisting antibody titer. The numbers tested were not large enough to identify an additional suppressive effect of preexisting antibody titer or age on the F and G antibody responses, respectively.

We next sought to examine the age at which the infant escapes suppression of the F antibody response. This was done by comparing the titers of IgG F antibody achieved in the postinfection sera of infants and children of various ages. Children 1 to 4 months old had a mean IgG F titer (reciprocal $\log_2$) of 10.9 in their postinfection sera, those of 5 to 8 months had a titer of 12.1, and those of greater than 8 months had a titer of 13.8. Thus, by 5 to 8 months of age, the response to the F glycoprotein has begun to increase. Similarly, the titer of maternal IgG that affects the G glycoprotein antibody response was studied. Infants 1 to 4 months old who had a pre-IgG titer to glycoprotein G of 10.4 developed a postinfection titer of 11.0. Children 5 to 8 months of age who had a preinfection titer of 7.8 developed a postinfection titer of 10.6, i.e., equivalent to that of the younger individuals. Children 9 to 21 months of age who had a preinfection titer of 6.7 developed a mean titer of 13.3. Thus, the level of maternal G antibody that is associated with decreased responsiveness is approximately 7.8 or greater. Importantly, this immunosuppressive effect of maternal antibody to G glycoprotein appears to extend slightly longer (i.e., up to 8 months of age) than the effect of age on response to the F glycoprotein.

Considered together, these data suggest that both immaturity of the immune system and antibody-mediated immune suppression affect the immune response of the infant to RSV, the former primarily affecting the response to the F protein and the latter influencing the response to the G protein. The poor neutralizing antibody response in the young infants is thus primarily a consequence of a decreased immune response to F or G glycoproteins, both of which induce neutralizing antibodies (16, 18–21). The ratios of neutralizing antibody titer to F or G glycoprotein antibody titer are similar in each age group, indicating that the antibody generated is qualitatively similar but lower in magnitude in the younger infants. The interpretation of the finding of a different effect of age and preexisting immunity on the serum antibody response to the RSV G and F glycoprotein is offered with three caveats: (i) the infecting strain of RSV was unknown in the majority of the individuals, (ii) the timing of serum pair collection varied in 18 of the individuals, and (iii) some of the older children might have had secondary infections. Each of these three factors could have affected the magnitude of the rise in IgA titers to glycoproteins G and F or the correlation coefficients presented in Table 3. However, the findings are of sufficient interest to warrant consideration and form the basis for further investigation. Other data have been recently obtained that demonstrate a different response of the young infant to the F and G glycoproteins (11). Young infants vaccinated with Formalin-inactivated RSV had a poor response to the G glycoprotein but not to the F glycoprotein component of the vaccine. In contrast, older children and cotton rats had a vigorous response to both glycoproteins (11, 14). In the context of the present observations, it is reasonable to suggest that the maternally derived antibody in the young vaccinees suppressed the G but not the F antibody response.

It has previously been suggested that the high carbohydrate content of the G protein (estimated to be about 65% carbohydrate and 35% protein) might be responsible for the poor immune response of the infant to this glycoprotein, because age is known to be a factor in antibody response to polysaccharide antigens (4, 22). The present results suggest that age does not primarily affect the response to the G glycoprotein but does influence the response to the less heavily glycosylated F protein. Additional evidence has recently been obtained that the G glycoprotein is recognized by the immune system of infants and young children as a typical protein antigen with a predominant IgG response in the IgG1 and IgG3 subclasses (17). The mechanisms underlying the different effects that age and prior antibody titer can have on the antibody response to the G and F glycoproteins are not presently understood but warrant further investigation.

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