

ANALYSIS OF THE ASSOCIATION BETWEEN SPECIFIC ANTIBODY RESPONSE AGAINST RESPIRATORY SYNCYTIAL VIRUS FUSION PROTEIN CONFORMATIONS AND LIFE-THREATENING INFECTION IN PREVIOUSLY HEALTHY INFANTS



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INTRODUCTION

Respiratory syncytial virus (RSV) is the most important cause for respiratory tract infections in children younger than 1 year of age. The lack of an effective vaccine to prevent severe RSV disease, has prompted several studies to characterize the unknown aspects of the antibody response against the virus, including the immunogenic capacity of the RSV fusion protein F. Specific humoral response against pre-fusion (pre-F) conformation of RSV F protein has been proposed to play a role against severe infection. Post-F displays four antigenic sites (I, II, III, and IV). Pre-F displays two exclusive antigenic sites (Ø and V) on the apex, and retains sites I-IV on the side exhibiting similar structural topology to post-F.

OBJECTIVES

The objective of the present study was to analyze the association of IgG titers against RSV, including the pre-fusion (pre-F) and post-fusion (post-F) conformations of RSV F protein and neutralizing antibody titers in sera from RSV infected pediatric patients with RSV life-threatening disease (LTD).

METHODS

Prospective cohort study including previously healthy infants <12 months, hospitalized with a first RSV infection, in 2017-2019. Patients were defined to have LTD when they required intensive care and ventilatory support. Pre-F exclusive and post-F-specific antibody responses were determined by post-F competition and non-competitive immunoassays, respectively. Total RSV IgG titers were determined by immunoassays and neutralizing activity was measured by plaque reduction neutralization test. Viral load (VL) was assessed by qRT-PCR from nasopharyngeal aspirates collected on admission. Serum samples were collected within 72 h from admission and in convalescence (between 14 to 60 days).

- Seventy-five patients, median age 3 months (IQR 2-5), 30 (40%) females were included. Twenty-one patients developed LTD.
- Post-F IgG titers were significantly higher than pre-F exclusive IgG titers in acute ($p=0.0022$) and convalescent ($p=0.0002$) phases.
- Acute and convalescent post-F, pre-F exclusive and total RSV IgG, as well as neutralizing antibody titers did not associate with LTD (Figure 1) and no difference was found between subtypes.
- Post-F/pre-F exclusive ratios were not different by disease severity or age group.
- Post-F, pre-F exclusive and total RSV IgG, as well as neutralizing antibody titers negatively correlated with age in acute phase ($p<0.0001$, $p<0.0001$, $p=0.0008$ and $p<0.0001$, respectively).
- Patients older than 2 months increased post-F, pre-F exclusive, total RSV and neutralizing antibody titers in convalescence as compared to acute phase, while patients younger than 2 months only increased post-F IgG and neutralizing antibody titers (Figure 2).
- Post-F, pre-F exclusive, total RSV IgG and neutralizing antibody titers were higher in patients younger than 2 months than in patients older than 2 months in acute phase, while post-F and pre-F exclusive titers were higher in patients older than 2 months in convalescence (Figure 2).
- There was a positive correlation between neutralizing antibody titers and post-F, pre-F exclusive and total RSV IgG titers in acute phase and in convalescence (Figure 3).
- Post-F, pre-F exclusive, total RSV IgG and neutralizing antibody titers did not correlate with viral load, and RSV load was not associated with LTD.

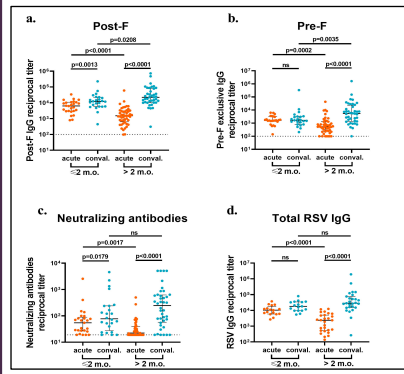


Figure 2. Antibody response against (a) post-F and (b) pre-F conformations of RSV F protein, (c) neutralizing antibodies and (d) total RSV antibodies in acute and convalescent sera of RSV patients according to age group. P values were calculated with Mann-Whitney test or Wilcoxon matched pairs signed rank test. m.o., months old

RESULTS

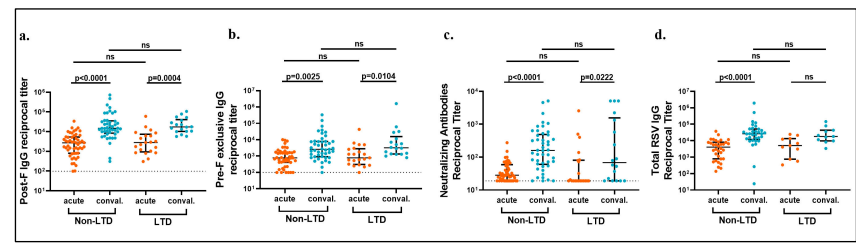


Figure 1. Antibody response against (a) post-F and (b) pre-F conformations of RSV F protein, (c) neutralizing antibodies and (d) total RSV antibodies in acute and convalescent sera of RSV patients with differing disease severity. Median and IQR are shown, lower dotted lines indicate limit of detection. P values were calculated with Mann-Whitney test or Wilcoxon matched pairs signed rank test.

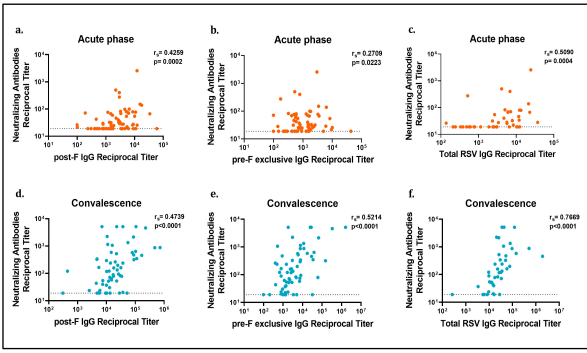


Figure 3. Correlation between neutralizing antibodies and (a,d) post-F and (b,e) pre-F conformations of RSV F protein and (c,f) total RSV antibodies, in (a-c) acute phase and (d-f) convalescence. P values were calculated with Spearman correlation test.

CONCLUSIONS

Infants younger than 2 months did not develop a significant humoral immune response to RSV, probably due to an interference with maternal antibodies and/or immunological immaturity. Pre-F, post-F, total RSV IgG and neutralizing antibodies titers did not associate with LTD, while pre-F, post-F and total RSV IgG titers positively correlated with neutralizing antibody titers. These findings highlight the importance of fully characterizing the humoral and cellular immune responses against RSV and its association with disease severity.