

1 Respiratory Syncytial Virus Infection: IgA & LT-E4 Responses
2 and Effects of Host Factors for Infants with Acute Bronchiolitis
3 in Two Iraqi Pediatric Hospitals

Dr. Afrah¹

¹ college of pharmacy -baghdad university

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8 Abstract

Background : Respiratory syncytial virus (RSV) is a leading cause of lower respiratory tract disease in infants and young children. Both the magnitude , intensity of infection and the host response to RSV infection determine the severity and intensity of disease.Objective : Our goal was to evaluate the effect of immune response (RSV IgA) and inflammatory mediators (LT-E4), in addition to the influence of host factors on the severity of the disease.

Index terms— Pediatric; RSV, Respiratory Syncytial Virus IgA (RSV-IgA); Leukotriene E-4(LT-E4), Bronchiolitis.; Cysteinyl Leukotrienes; Secondhand Cigarette Smoke;

17 1 Introduction

18 respiratory syncytial virus (RSV) is the leading cause of serious respiratory tract infections in infants and young
19 children throughout the world (1). RSV replicates for 1-3 days before producing lower respiratory tract symptoms
20 affecting almost 60% of infants and up to 25% of toddlers and preschoolers. Current treatment approaches for
21 severe RSV induced disease are ineffective. Therefore, prevention of disease is a high priority .Immunoglobulin
22 A(IgA) is the most abundant immunoglobulin in mammals. Unlike other antibody isotypes, IgA is targeted
23 to mucosal tissues, and virus-specific IgA in mucosal secretions has been shown to protect from reinfection.
24 IgA, unlike IgG, is able to bind and neutralize viral proteins intracellularly at the site of initial replication in
25 epithelial cells .Therefore; mucosal IgA may be of particular importance in immunity against RSV, which is a
26 mucosally restricted pathogen (2,3). Inflammatory mechanisms in bronchiolitis have been documented recently,
27 including increased airway secretion, mucosal edema, and infiltration of inflammatory cells. Cysteinyl leukotrienes
28 (CysLTs) are released during respiratory syncytial virus (RSV) airway infection in infants, and their levels are
29 significantly elevated. CysLTs are known to cause bronchial obstruction, mucosal edema, and infiltration of
30 eosinophilic granulocytes and to increase bronchial responsiveness (4). CysLTE4 (LTE4), one of the terminal
31 cysLT metabolites, is significantly increased in the infants hospitalized with RSV bronchiolitis (5). The risk of
32 severe RSV disease is increased by factors that compromise the ability to control and withstand a respiratory
33 tract infection. Therefore; environmental factors also play a role, including ones that affect lung R control
34 infants. The severity of RSV bronchiolitis early in life function (e.g., household tobacco use) or that increase
35 exposure to infection (e.g., day care, hospitalization, multiple siblings, crowding) (6,7). The objective of the
36 present randomized, prospective study was to evaluate the effects of immune response, inflammatory mediators,
37 host and environmental factors on the severity of the acute viral bronchiolitis. This prospective study was
38 conducted in two Iraqi pediatric hospitals. Baghdad Health Office/Karkh, Child's Central Teaching Hospital &
39 Karbala Health Office, Karbala Pediatric Teaching Hospital. Inclusion criteria were infants' patients aged >8
40 weeks and <2 years with a respiratory symptom duration of <4 days. Additional inclusion criteria included first
41 episode of wheezing or shortness of breath, randomization within 12 hours of admission and informed consent.
42 Exclusion criteria were any previous hospital admissions with respiratory illnesses, had ever been treated with
43 antiasthma medications before the current illness, corticosteroids treatment in any form during current illness,

5 RESULTS

44 and underlying cardiopulmonary disease. Gender, age, weight, height , body temperature ,family history in
45 (first-degree relatives), of asthma ,atopy, tobacco smoking, usage of kerosene heater ,type of feeding ,duration
46 of exclusive breast feeding, concurrent diseases, and concomitant medications, were recorded for each infants .A
47 total number of 123 patients mean age: 6.99 ± 0.62 with mild to moderate bronchiolitis were divided randomly
48 into eight treatment groups:

49 Group A: Ten infants' patients had received oxygen + intravenous fluid.Group B: Fourteen infants' patients
50 had received study treatment, montelukast pediatric chewable tablet 4mg once daily, if vomiting occurred one
51 additional dose was given (4).Group C: Ten infants patient had received azithromycin suspension (200mg/5ml)
52 ,with a dose of 10 mg /kg once daily. Group D: Ten infants' patients had received hydrocortisone vial (100
53 mg/2ml), with a dose of, 5-10 mg/kg/dose q 6hour IV.Group E: Twenty infants' patients had received salbutamol
54 syrup (2mg/5ml), with a dose of , 0.1-0.3 mg/kg/dose q 8 hour; the method of syrup administration was taught to
55 the caregiver. Any patient who vomited the drug within 15 minutes of ingestion was advised to have a repeat dose
56 (8). Group F: Twenty infants' patients had received salbutamol given in combination as syrup & by nebulization,
57 (oral salbutamol 0.1-0.3mg/kg/dose q8 hour+salbutamol nebulizer 0.01-0.02 mg/kg /dose q6hour). Group G:
58 Twenty infants' patients had received dexamethasone ampule (4mg/1ml), with a dose of, 0.25 -0.5 mg/kg/dose
59 q 12 hours intravenously.Group H: Nineteen infants' patients had received salbutamol solution for nebulizer
60 (5mg/ml), with a dose of, 0.01-0.02 mg/kg /dose q 6 hour.

61 From all enrolled infants, blood samples were taken and try to measure both (RSV IgA) & LT-E4, antibody
62 to RSV & inflammatory mediators that release during RSV acute bronchiolitis, respectively. These parameters
63 were measured by the enzyme linked immunoassays (ELISA), to investigate the etiology of acute respiratory
64 infections in hospitalized infants .The test was explained to the parents and they signed the informed consent
65 form. The obtained optical density (OD) of the standards (y-axis, linear) are plotted against their concentration
66 (x-axis, logarithmic) either on semilogarithmic graph paper or using an automated method (9,10) .

67 Other type of samples that taken from the patients that put on the study treatment, montelukast pediatric
68 chewable 4mg tablets, was the nasal swab. In the present study, we prospectively tried to examine the association
69 between the presence of nasal eosinophils and severity of acute bronchiolitis and the effect of montelukast on
70 nasal eosiphil. In this study we tried to quantify the number of neutrophils and eosinophils in nasal secretions
71 by utilizing the semiquantitative nasal cytology grading score by Meltzer (11,12).

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75 4 Materials & Methods

76 Table ?? : Demographic data and baseline characters of patients and control infants. The data were expressed
77 as number (n), and percentage (%).

78 Table (1), demonstrated that, there were no significant differences between the groups in terms of demographic
79 variables. The values of weight,& duration of exclusive were expressed as mean \pm standard error of mean (SEM).
80 III.

81 5 Results

82 Table ?? : Relationships between host factors and RSV IgA titer for infants' patients with acute viral bronchiolitis
83 and for the control infants. Data were expressed as mean \pm standard error of mean (SEM), number (n) and
84 percent (%).

85 The table (2) showed the RSV IgA values for infants' patients with acute viral bronchiolitis, together with
86 RSV IgA values for the control infants. There was a significant increase in RSV IgA values in patients compared
87 to the control infants.

88 There was a significant relationships between titer of the antibody against RSV(RSV IgA) and family history
89 of atopy,tobacco smoking ,and the ages of infants patients. ??able 3 : Relationships between host factors and
90 leukotriene -E4 for infants' patients with acute viral bronchiolitis and for the control infants. Data were expressed
91 as mean \pm standard error of mean (SEM), number (n) and percent (%).

92 Table (3) showed the leukotriene E4 values in infants patients with acute bronchilitis, together with leukotriene
93 values of the control infants. There was a significant increase in the leukotriene E4 values in patients compared
94 to the control infants As the table shown, only the gender and family history of tobacco smoke showed significant
95 differences. ?? : Effects of host factors on length of stay (LOS) and oxygen saturation (S P O₂) for the infants
96 patients with acute viral bronchiolitis .Data were expressed as mean \pm standard error of mean (SEM) ,number
97 (n) and percent (%).

98 Table (4) showed the effects of host factors on the length of hospital stay (LOS) and oxygen saturation (S P
99 O₂) in infants patients with acute viral bronchiolitis. As the table shown, only the host factors of family history
100 of atopy and breast feeding of infants showed significant effects on duration of hospital stay and oxygen saturation
101 of blood.

102 Concerning nasal swab from infants' patients with acute viral bronchiolitis before and after treatment with
103 montelukast chewable 4 mg tablets once daily; according to Meltzer grading there was a significant differences in
104 the count of eosinophils -neutrophils before and after treatment with montelukst ; 1.6 ± 0.32 versus 0.33 ± 0.16
105 respectively. This could indicated eosinophil-recruiting chemokines were strongly produced and released from
106 bronchial epithelial cells after in vivo stimulation with RSV.

107 RSV is a highly infectious and prevalent virus. More than other respiratory viruses, RSV infection can
108 occur very early in life despite maternal antibodies, and reinfection can readily occur throughout life without
109 significant antigenic change .The relative contribution of viral versus various host factors to RSV pathogenesis
110 remains controversial (6). The immune response to primary RSV infection is generally inefficient and consequently
111 subsequent reinfections are common throughout life.In RSV infection, innate and adaptive immunity are out of
112 balance (13).

113 Comparing the risk factors with RSV IgA values of infants' patients , only the age, history of atopy and passive
114 tobacco smoking showed significant differences (14). In the age category older infants' patients (over 1 year) had
115 significantly higher RSV IgA value compared to younger patients (below 1 year) . Patients with negative family
116 history of atopy had significantly higher RSV IgA value compared to patients with positive history of atopy.
117 On the other hand patients with positive history of passive tobacco smoking had significantly higher RSV IgA
118 value compared with those of negative history of passive tobacco smoking. This could indicate that, parental
119 smoking did not inhibit the production of antimicrobial IgA, suggesting that other factors are responsible for
120 the increased susceptibility to infection in these infants. Infants who lived in tobacco smoking environments had
121 increased severity of disease, as results of Th2 predominance, with decreased expression of Th1 cytokines (15) ,
122 and IgA titer was less effective for protecting against RSV infection (2) . Lanari et al. (2002) (14) , demonstrated
123 that exposure to cigarette smoke, in general, seems to worsen the severity of the viral bronchiolitis.

124 Comparing the risk factors with LTE4 values, only the gender and family history of tobacco smoke showed
125 significant difference. Concerning the gender, the value in female babies was significantly higher than male babies.
126 This could indicate that the females infants had more sever RSV infections compared to male infants; this has
127 been attributed to the tendency of parents to bring sick male babies to the hospital earlier than female babies
128 (3) .CysLT increased in infants who exposed to the tobacco smoke. This could indicated that, the exposure to
129 the tobacco smoke increases the severity of RSV bronchiolitis, which was described here by the increased level of
130 LTE4 in the infants who lived in tobacco smoking environments (16,17,18) .

131 Comparing the effects of host factors (age, sex, family history of asthma, atopy, tobacco smoking, kerosene
132 heating, presence of pets at home, breast or bottle feeding and number of family members) on the length of
133 hospital stay and oxygen saturation in infants with acute viral bronchiolitis; only the host factors of family
134 history of atopy and breast feeding of infants showed a significant effects on duration of hospital stay and oxygen
135 saturation of blood (19) . Infants with a positive family of atopy showed a shorter duration of hospital stay and
136 a higher value of blood oxygen saturation compared to infants with acute viral bronchiolitis and have no family
137 history of atopy. Breast feeding of infants with acute viral bronchiolitis showed a significant effects on the blood
138 oxygen saturation and length of hospital stay. Breast feeding is protective, through either transfer of maternal
139 antibody or enhancement of virus-specific lymphocyte transformation activity. Infants with breast feeding have
140 a shorter length of stay and higher value of blood oxygen saturation relative to infants without having breast
141 feeding and have bottle fed. This finding is substantiated further by the fact that infants with a higher O₂
142 saturation spent less time in the hospital than infants with a lower O₂ saturation (14) .

143 Regarding to the effects of RSV IgA level on the length of hospital stay and patients oxygen saturation, there
144 were a significant effects on both length of hospital stay and patient oxygen saturation.

145 infants with low titer of RSV IgA showed longer period of hospital stay & lower values of oxygen saturation
146 compared to the patients with a high titer of RSV IgA , which could indicated effects of immune response of
147 the patients on the resolution of symptoms and the time at which patients were fit to the discharge (7,20) .
148 Regarding to the effects of inflammatory mediators cysteinyl leukotriene and its metabolite LTE4 on the period
149 of hospital stay and oxygen saturation of infants patients with acute viral bronchiolitis, there were a significant
150 effects. High titers of LTE4 associated with prolong hospital stay and lower value of blood oxygen saturation
151 .Female,younger infants ,negative family history of atopy, and absence of breast feeding ,showed longer period of
152 hospital admission & lower value of blood oxygen saturation.

153 According to Meltzer grading there were a significant differences in the counts of eosinophilsneutrophils before
154 and after treatment with montelukst tablet for the infants patients with acute viral bronchiolitis. This could
155 indicated that eosinophilrecruiting chemokines are strongly produced and released from bronchial epithelial cells
156 after stimulation with RSV (12) ;and montelukast treatment has been shown to reduce eosinophils in nasal
157 mucosa of infants The relationships between risk factors and RSV IgA titer in infants with viral bronchiolitis,
158 only age, family history of atopy and tobacco smoking showed significant effects.Patients with low titer of RSV
159 IgA showed longer period of hospital stay & lower values of oxygen saturation comparing to the patients with a
160 high IV.

161 6 Discussion

162 V.

163 7 Conclusion

164 titer of RSV IgA. Concerning the relationships between risk factors of infants with bronchilitis and leukotriene E4
165 level, only the gender and family history of tobacco smoke showed significant difference. There were a significant
166 effects of high level of LTE4 on the period of hospital stay compared to the low level of LTE4.

167 Host factors of family history of atopy and breast feeding of infants showed significant effects on duration of
168 hospital stay and oxygen saturation of blood. Infants exposed to postnatal cigarette smoke from the mother had
169 a lower O₂ saturation than those not exposed. Infants with a family history of atopy especially a maternal
170 history of asthma had a higher O₂ saturation. Infants with highest blood oxygen saturation, have shorter length
171 of hospital stay.

172 There were significant differences in the count of eosinophils -neutrophils before and after treatment with
173 montelukast, which could indicated that, there was a correlation between nasal eosinophil and severity of viral
174 bronchiolitis. ^{1 2}

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