Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Review

Interleukin 8 Association with respiratory syncytial virus bronchiolitis: a systematic review and meta-analysis

Li Peng, Fanzheng Meng*, Yuhuan Liu[1], Li Zhang

Department of Pediatric Respiration, The First Hospital of Jilin University, Changchun, 130021, China

*Correspondence to: prof.lililuolililuo253@gmail.com

Received November 16, 2019; **Accepted** May 3, 2020; **Published** May 15, 2020

Doi: http://dx.doi.org/10.14715/cmb/2020.66.2.12

Abstract: Infants with the respiratory syncytial virus (RSV) and human rhinovirus respiratory infection (HRV) produce inflammatory interleukins (ILs) in the respiratory epithelium. The aim of this study was to evaluate the levels of interleukin-8 in RSV negative and RSV positive patients. This study search was conducted without a time limit until 2020 through the databases of PubMed, Wiley, Springer, ScienceDirect and Google Scholar search engines, by two researchers independently. The random-effects model was used to compare of interleukin-8 in RSV negative vs. RSV positive patients, using Revman software version 5 meta-analysis software. Totally, 921 patients were evaluated (207 RSV-negative and 714 RSV-positive). The mean concentration of IL8 in RSV positive patients was 15.02 pg/ml (95% CI: 13.68- 16.35%). According to the meta-analysis results, the standardized mean difference (SMD) of IL8 concentration between RSV-positive and negative patients was 6.31 pg/ml) (95% confidence interval: 2.50- 10.13%). subtotal analysis of the IL8 laboratory assessment method revealed that there was no significant SMD deference in the studies that have used chemiluminescence (P=0.21). while IL8 concentrations were significantly higher in RSV positives in ELISA and Magnetic bead-based assays (P<0.05). It appears that RSV positive patients may have greater levels of IL8 than RSV negative ones; whereas the synthesis of IL8 tends to be more secreted into the nasopharyngeal space; whereas the evaluation approach can also affect the results.

Key words: Respiratory syncytial virus; Interleukin-8; Respiratory infection.

Introduction

Acute bronchiolitis is one of the most common causes of hospitalization (1). It is a viral respiratory infection that occurs in winter epidemics and causes respiratory distress and sometimes leads to fatal respiratory failure (2). In at least 70% of cases, it is caused by RSV (2). Bronchiolitis is a type of inflammation in the lungs that is most commonly seen in children under 2 years old with symptoms such as cough and shortness of breath (3). Bronchiolitis is characterized by the necrosis of the bronchial epithelium, increased mucus secretion, and cell infiltration and edema surrounding the mucosa caused by the virus (1). These changes lead to the formation of mucosal blocking bronchioles and the subsequent distal or collapsing lung tissue (4). Although not a fatal disease, patients with bronchiolitis need to be hospitalized (5). Epidemiological studies have suggested a number of risk factors, such as being premature, having lung or heart disease (10). Bronchiolitis occurs following recurrent weaning periods and it seems that certain markers found during the acute period, particularly the presence of eosinophils and eosinophilic cationic proteins in the blood, are associated with these recurrences (5). Excessive acute allergic reactions caused by these cells is a major factor in upper respiratory disorders (6). It rarely results in permanent damage to the lungs, such as chronic bronchitis. Other complications of bronchiolitis include bronchiectasis, recurrent pneumonia, and rarely chronic obstructive pulmonary disease (4,7). Various studies have shown that neutrophils are the most evoked cells in the bronchoalveolar lavage fluid from neonates with bronchiolitis (8,9). Clinical studies have shown high levels of interleukin-8 in plasma and nasal secretions of neonates with bronchiolitis (10). Interleukin 8 was identified in 1987 as a new type of neutrophil activator cytokine (11). Interleukin 8, which is classified as a CXC chemokine, specifically plays major a role in white blood cell chemotaxis, especially neutrophils and lymphocytes, which stimulate and enhance angiogenesis (8–10). Research has shown that interleukin-8 has many pro-inflammatory effects and is secreted by natural cells such as fibroblasts and monocytes. This cytokine is secreted by a variety of tumor cells such as the prostate, lung, breast, stomach, and uterus (12). Interleukin-8 has been implicated as an important mediator in the host response to inflammatory damage, as well as neutrophils, neutrophil chemotactic and basophils (12). Several additional cytokines related to interleukin-8, but induced by different genes have also been identified (11,12). Neomacrolides such as azithromycin reduce the production of interleukin-8 and decrease the uptake of neutrophils into the airways (13). As many studies have evaluated the IL8 level in RSV, we conducted this meta-analysis based on different methodological differences in these studies.

Materials and Methods

This study was a systematic review and meta-ana-

lysis conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. PubMed, Wiley, Springer, ScienceDirect and Google Scholar search engines were used for searching related studies. Articles were searched using keywords associated with all possible word combinations as Interleukin 8, Bronchiolitis, respiratory syncytial virus.

Criteria for selection and evaluation of articles quality

Initially, a list of titles and abstracts of all articles in the databases were provided by the researcher and were independently reviewed to identify and select relevant titles. The main inclusion criterion to select the articles in this study was to estimate the level of IL8 in RSV-positive or negative patients. Exclusion criteria were: Review studies, books, not giving a proper report of IL8 level in each group, or to making the comparison. The search was performed independently by two researchers and the results of duplicated searches were excluded. In the second step, after identifying the relevant studies in terms of titles, the abstracts of the selected papers were evaluated by the researcher using a STROBE checklist, which is a standard checklist. The checklist consists of 43 different sections and evaluates various aspects of the methodology including sampling methods, variables measurement, and statistical analysis, study bias and study objectives. In this checklist, a minimum score of 40 was considered to be required for the inclusion of the study in review. Finally, the top articles that received the least scores on the checklist questions were entered into the study and their associated data were extracted to perform the meta-analysis process. In fact, the following eligibility checks went through the checklist filter with a score above 40 and went into the meta-analysis process; so as we have checked studies based on the bias in STORBE checklist, there was no need for further evaluation of study bias in the form of funnel plot using Beggar's and Egger's tests. Finally, 8 articles were selected for meta-analysis.

To extract the data, a data extraction checklist was designed based on the purpose of the study. This checklist included sections including authors' names, year of publication, place of study, average IL8 level in each group, sample taking origin, and method of assessing IL8 level.

Statistical analysis

In this section, all mean levels of IL8 of RSV-positive and negative patients were collected and then the variance in the study was determined. Based on these variances, the weight of each study was initially inverted according to the Fixed Effect Model. Then, by weighing each study, mean differences of IL-8 values were combined using techniques adapted for intra- and inter-group heterogeneity to calculate the overall mean difference of Interleukin in Bronchiolitis patients. Cochran test and I2 index were used to evaluate the heterogeneity of the studies. The rate of heterogeneity in these studies was 100%, which is a high heterogeneity. After estimating the heterogeneity of studies based on the model (Random Effect), the best estimate of the SMD was calculated. All analysis was performed by Revman software version 5.

Results

As shown in Table 1, eight studies were included in the meta-analysis (14–21) of comparing RSV positive patients with RSV-negative patients, based on IL8 concentrations. Totally, 921 patients were evaluated (207 RSV-negative and 714 RSV-positive).

The mean concentration of IL8 in RSV positive patients was 15.02 pg/ml (95% CI: 13.68- 16.35%). According to the meta-analysis results, the standardized mean difference (SMD) of IL8 concentration between RSV-positive and negative patients was 6.31 pg/ml) (95% confidence interval: 2.50- 10.13%) and it revealed a statistically significant difference (P<0.005). there was high heterogeneity between studies (I2=100%). Subtotal analysis of the IL8 laboratory assessment method revealed that there was no significant mean difference in the chemiluminescence group (P=0.21). While IL8 concentrations were significantly higher in RSV positives in ELISA and Magnetic bead-based assays (P<0.05) (Figure 1).

While, Subtotal analysis was performed based on the sample in which IL8 was measured (Plasma vs. Nasopharyngeal sample), which didn't reveal any

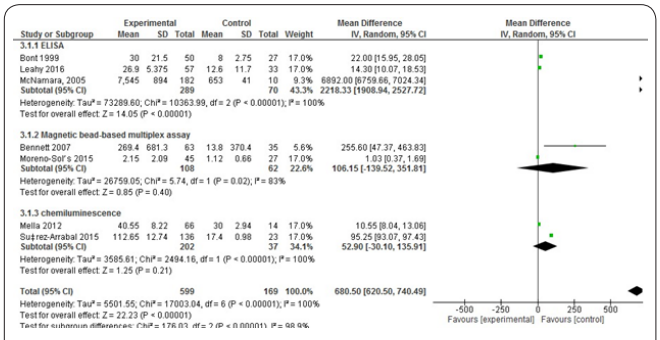

Figure 1. Forest plot of the standardized mean difference based on the method of assessment.

Table 1. Studies characteristics in the different countries.

Year	RSV +	RSV-	Male RSV+	Male RSV-	Age	Country
Moreno-Solís G, 2015	45	27	24	15	1-11 month	Spain
Suárez-Arrabal MC, 2015	136	23	84	15	<24months	USA
Díaz PV, 2015	115	38	67	20	<24months	Chile
Bennett BL, 2007	63	35	40	22	<24months	USA
Bont L, 1999	50	27	29	17	<13months	Netherlands
Leahy TR, 2016	57	33	31	14	<18months	Ireland
Mella C, 2012	66	14	40	9	<24months	USA
McNamara, 2005	182	10	NA	NA	<24months	UK

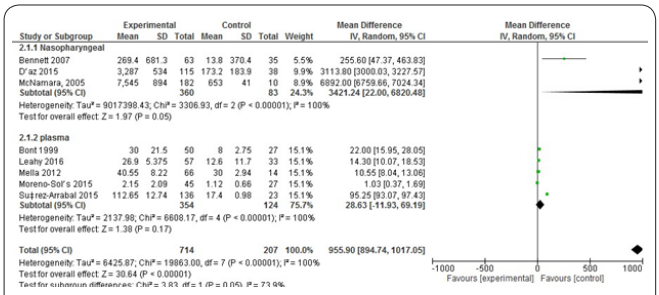

Figure 2. Forest plot of the standardized mean difference based on sample origin.

significant SMD in plasma (p=0.17), while the IL8 SMD in Nasopharyngeal samples was significant and mean IL8 level was higher in RSV-positive ones (P=0.05) (Figure 2).

Discussion

Interleukin 8, which is classified as a CXC chemokine, specifically plays a role in white blood cell chemotaxis, especially neutrophils and lymphocytes, which stimulate and enhance angiogenesis (22). Acute respiratory syncytial viral bronchiolitis (RSV-AB) is one of the major causes of neonatal hospitalisation. The immune and inflammatory mechanism involved in RSV-AB and the factors affecting its severity have not been clearly elucidated although the imbalances of Th1 and Th2 tend to be crucial. RSV is an inflammation of the respiratory tract, one of the hallmarks of which is an increase in inflammatory cytokinins (23). RSV and recently described by human rhinovirus (HRV) are the main causes of acute respiratory tract infection (ARI) in children under 2 years of age. It can occur in infants with preterm birth, ranging from mild upper respiratory infection to severe disease with bronchiolitis and pneumonia. The severity of the disease varies and can vary from hours of mild illness to severe illness (24). Straliotto et al. indicated that cough, cyanosis and atelectasis have been noted to be seen more commonly in children with RSV positive bronchiolitis (25).

Many research attempted to correlate the severity of the RSV disease with unstimulated concentrations of serum cytokines, with contradictory results most likely related to variations in the nature of the test. Such studies showed a phenotype characterized by increased T-helper 1 and 2 plasma concentrations, chemokines and soluble markers of activation (26–28). While the present meta-analysis showed that evaluation of plasma levels of IL8 was not helpful as it may tend to raise in nasopharyngeal samples. Also, there was no significant mean difference between RSV-positive and negative patients in the studies using chemiluminescence versus studies using other methods of assessing IL8 concentrations.

Tabarani et al. found that in more than 478 children <12 months old, the concentration of anti-inflammatory cytokines obtained from nasopharyngeal lavage was positively related to the severity of the disease and was selected as RSV lower respiratory tract infection (LRTI) (29), and in another study of 18 infants, this association was found to be negatively correlated (30). But, the present study didn't find enough data to analyze the IL8 association with disease severity.

Conclusion

It seems that RSV positive patients may have higher IL8 levels than RSV negative ones; while the production of IL8 seems to be more secreted into nasopharyngeal space; while the method of assessment can also be responsible in conflicts between studies as studies using chemiluminescence did not indicate a significant difference in IL8 levels.

References

1. Øymar K, Skjerven HO, Mikalsen IB. Acute bronchiolitis in infants, a review. Scandinavian journal of trauma, Resusc Emerg Med. 2014; 22(1):23.
2. Hervás D, Reina J, Yañez A, Del Valle JM, Figuerola J, Hervás JA. Epidemiology of hospitalization for acute bronchiolitis in children: differences between RSV and non-RSV bronchiolitis. Europ J Clinic Microb Inf Dis 2012; 1;31(8):1975-81.
3. Marguet C, Lubrano M, Gueudin M, Le Roux P, Deschildre A, Forget C, Couderc L, Siret D, Donnou MD, Bubenheim M, Vabret A. In very young infants severity of acute bronchiolitis depends on carried viruses. Plos One. 2009; 4(2). e4596
4. Caballero MT, Polack FP, Stein RT. Viral bronchiolitis in young infants: new perspectives for management and treatment. J de Pediatria. 2017 Nov 1;93:75-83.
5. Cavallaro EC, Bouchier T, Liang KK, Forsyth K, Dixon DL. The Interplay Between Neutrophils and Alveolar Epithelial Cells in IL-26 Production: A Role in Bronchiolitis Pathogenesis. InC31. Mechan Insght into Lung Inf. 2018; 4:714-717).
6. Hashemi S A, Abediankenari S, Madani S A. Evaluation of systemic allergy in infectious and inflammatory disorders of upper respiratory tract. Int J Med Invest 2013; 2 (1).
7. Hosakote YM, Rayavara K. Respiratory Syncytial Virus-Induced Oxidative Stress in Lung Pathogenesis. InOxid Stres in Lung Dise 2020 (pp. 297-330). Springer, Singapore.
8. Hasegawa K, Pérez-Losada M, Hoptay CE, Epstein S, Mansbach JM, Teach SJ, Piedra PA, Camargo CA, Freishtat RJ. RSV vs. rhinovirus bronchiolitis: difference in nasal airway microRNA profiles and NFκB signaling. Pedi Res 2018;83(3):606-14.
9. Kerrin A, Fitch P, Errington C, Kerr D, Waxman L, Riding K, McCormack J, Mehendele F, McSorley H, MacKenzie K, Wronski S. Differential lower airway dendritic cell patterns may reveal distinct endotypes of RSV bronchiolitis. Thorax. 2017; 72(7):620-7.
10. Pinto LA, Leitão LD, Mocellin M, Acosta P, Caballero MT, Libster R, Vargas JE, Polack F, Comaru T, Stein RT, De Souza AP. IL-8/IL-17 gene variations and the susceptibility to severe viral bronchiolitis. Epid Infect. 2017;145(4):642-6.
11. Baggiolini M, Clark-Lewis I. Interleukin-8, a chemotactic and inflammatory cytokine. FEBS letters 1992; 307(1):97-101.
12. Harada A, Sekido N, Akahoshi T, Wada T, Mukaida N, Matsushima K. Essential involvement of interleukin-8 (IL-8) in acute inflammation. J Leuko Biol 1994;56(5):559-64.
13. Verleden GM, Vanaudenaerde BM, Dupont LJ, Van Raemdonck DE. Azithromycin reduces airway neutrophilia and interleukin-8 in patients with bronchiolitis obliterans syndrome. Am J Respir Crit Care Med. 2006;174(5):566-70.
14. McNamara PS, Flanagan BF, Hart CA, Smyth RL. Production of chemokines in the lungs of infants with severe respiratory syncytial virus bronchiolitis. J Infect Dis 2005;191(8):1225-32.
15. Mella C, Suarez-Arrabal MC, Lopez S, Stephens J, Fernandez S, Hall MW, Ramilo O, Mejias A. Innate immune dysfunction is associated with enhanced disease severity in infants with severe respiratory syncytial virus bronchiolitis. The J Infect Dis 2013;

207(4):564-73.
16. Leahy TR, McManus R, Doherty DG, Grealy R, Carr MJ, Slattery D, Ryan T. Viral bronchiolitis is associated with altered cytokine gene expression and lymphocyte activation status. The Pedi Infect Dis J 2016; 35(11): e326-38.
17. Bont L, Heijnen CJ, Kavelaars A, van Aalderen WC, Brus F, Draaisma JT, Geelen SM, Van Vught HJ, Kimpen JL. Peripheral blood cytokine responses and disease severity in respiratory syncytial virus bronchiolitis. Europ Resp J 1999;14(1.
18. Bennett BL, Garofalo RP, Cron SG, Hosakote YM, Atmar RL, Macias CG, Piedra PA. Immunopathogenesis of respiratory syncytial virus bronchiolitis. The J Infect Dis 2007; 195(10):1532-40.
19. Díaz PV, Valdivia G, Gaggero AA, Bono MR, Zepeda G, Rivas M, Uasapud P, Pinto RA, Boza ML, Guerrero J. Pro-inflammatory cytokines in nasopharyngeal aspirate from hospitalized children with respiratory syncytial virus infection with or without rhinovirus b. Med 2015; 94(39): e1512.
20. Suárez-Arrabal MC, Mella C, Lopez SM, Brown NV, Hall MW, Hammond S, Shiels W, Groner J, Marcon M, Ramilo O, Mejias A. Nasopharyngeal bacterial burden and antibiotics: Influence on inflammatory markers and disease severity in infants with respiratory syncytial virus bronchiolitis. J Infect 2015; 71(4):458-69.
21. Moreno-Solís G, Torres-Borrego J, de la Torre-Aguilar MJ, Fernandez-Gutierrez F, Llorente-Cantarero FJ, Perez-Navero JL. Analysis of the local and systemic inflammatory response in hospitalized infants with respiratory syncytial virus bronchiolitis. Allerg et Immun; 43(3): 264-71.
22. Alfaro C, Teijeira A, Oñate C, Pérez G, Sanmamed MF, Andueza MP, Alignani D, Labiano S, Azpilikueta A, Rodriguez-Paulete A, Garasa S. Tumor-produced interleukin-8 attracts human myeloid-derived suppressor cells and elicits extrusion of neutrophil extracellular traps (NETs). Clinic Canc Res 2016; 22(15):3924-36.
23. Pickles RJ, DeVincenzo JP. Respiratory syncytial virus (RSV) and its propensity for causing bronchiolitis. J Pathol. 2015; 235(2):266-76.
24. Chen WJ, Arnold JC, Fairchok MP, Danaher PJ, McDonough EA, Blair PJ, Garcia J, Halsey ES, Schofield C, Ottolini M, Mor D. Epidemiologic, clinical, and virologic characteristics of human rhinovirus infection among otherwise healthy children and adults: rhinovirus among adults and children. J Clinic Viro 2015; 64:74-82.
25. Straliotto SM, Roitman B, Lima JB, Fischer GB, Siqueira MM. Respiratory syncytial virus (RSV) bronchiolitis: comparative study of RSV groups A and B infected children. Revista da Sociedade Brasileira de Med Trop. 1994; 27(1): 1-4.
26. Pinto RA, Arredondo SM, Bono MR, Gaggero AA, Diaz PV. T helper 1/T helper 2 cytokine imbalance in respiratory syncytial virus infection is associated with increased endogenous plasma cortisol. Peditrc 2006;117: e878–86.
27. Alonso Fernandez J, Roine I, Vasquez A, Caneo M. Soluble interleukin-2 receptor (sCD25) and interleukin-10 plasma concentrations are associated with severity of primary respiratory syncytial virus (RSV) infection. Eur Cytokin Netw 2005; 16:81–90.
28. Tripp RA, Moore D, Barsky A, et al. Peripheral blood mononuclear cells from infants hospitalized because of respiratory syncytial virus infection express T helper-1 and T helper-2 cytokines and CC chemokine messenger RNA. J Infect Dis 2002;185:1388–94.
29. Tabarani CM, Bonville CA, Suryadevara M, et al. Novel inflammatory markers, clinical risk factors and virus type associated with severe respiratory syncytial virus infection. Pediatr Infect Dis J. 2013; 32: e437–e442.
30. Garcia C, Soriano-Fallas A, Lozano J, et al. Decreased innate immune cytokine responses correlate with disease severity in children with human respiratory syncytial virus and human rhinovirus bronchiolitis. Ped Infect Dis J 2012; 31:86–89.