Bronchiolitis obliterans after severe adenovirus pneumonia: a review of 46 cases

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Research article

Keywords: Bronchiolitis obliterans, Adenovirus, Pneumonia, Children

DOI: https://doi.org/10.21203/rs.3.rs-93838/v1

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Abstract

Background: This study aimed to investigate the risk factors of bronchiolitis obliterans caused by severe adenovirus pneumonia.

Methods: The First Affiliated Hospital of Xiamen University in January, 2019 was collected. The clinical data of 229 children with severe adenovirus pneumonia from January to January 2020 were divided into obliterative bronchiolitis group (BO group) and non obstructive bronchiolitis group (non BO group) according to the follow-up clinical manifestations and imaging data. The clinical data, laboratory examination and imaging data of the children were retrospectively analyzed. Results: Among 229 children with severe adenovirus pneumonia, 46 cases were in BO group. The number of days of hospitalization, oxygen consumption time, LDH, IL-6, AST, D-dimer and hypoxemia in BO group were significantly higher than those in non BO group; The difference was statistically significant (P < 0.05). Univariate logistic regression analysis showed that there were significant differences in the blood routine neutrophil ratio, platelet level, Oxygen supply time, hospitalization days, AST level, whether there was hypoxemia, timing of using hormone, more than two bacterial feelings were found in the two groups, levels of LDH, albumin and Scope of lung imaging (P < 0.05).

Conclusions: The related risk factors of BO caused by severe adenovirus pneumonia were long hospitalization days and oxygen consumption time, elevated platelet levels, AST and LDH levels in laboratory tests, and more than two kinds of bacterial infections, double lung involvement, and hypoxemia. Early use of glucocorticoid had a significant effect on reducing the formation of BO.

Background

Adenovirus infection, an important cause of pulmonary infection in children, accounts for 20.0% – 30% of severe pneumonia. Due to its high mortality, severe sequelae can be left, such as bronchiolitis obliterans (BO), bronchiectasis, interstitial fibrosis, etc. Therefore, in recent years, more and more attention has been paid to severe pneumonia caused by adenovirus infection. Having analyzed the high-risk factors of BO caused by severe adenovirus pneumonia in children, and provided scientific basis for early intervention of severe adenovirus pneumonia, this study has reduce the disability rate of children with adenovirus pneumonia.

Methods

From January 1, 2019 to December 31, 2019, 229 children with adenovirus pneumonia under the age of 14 were treated in the Department of Pediatrics, the First Affiliated Hospital of Xiamen University. All the children were followed up in the outpatient department, and 46 children with BO were clinically diagnosed. The diagnostic criteria of severe adenovirus pneumonia were as follows: adenovirus nucleic acid in respiratory secretions was positive. According to the diagnosis standard of children with community acquired pneumonia(2) According to the diagnostic criteria of severe pneumonia (3)
The patients were divided into BO group and non BO group according to their follow-up. The clinical data, such as fever days, laboratory tests (blood routine, CRP, PCT, LDH, ferritin, IL-6, VitD, etc.), gamma globulin (IVIG) and methylprednisolone (methylprednisolone) usage, and whether there were concurrent infections were analyzed respectively.

Statistics

SPSS 17.0 was used for all statistical analyses. The count data was expressed as percentage (%), with the difference between groups being tested by $x^2$ test, the measurement data with normal distribution being represented by $\bar{x} \pm S$, the data of non normal distribution being represented by median, Independent sample t-tests being selected to compare continuous variables as well. Binary logistic regression was used to analyze the influence factors of BO. Receiver operating characteristic curve (ROC) was used to evaluate the efficacy of each factor in diagnosing BO. P < 0.05 considered that the difference was statistically significant.

Results

There were 46 cases in BO group and 183 cases in non BO group. Table 1 shows comparison of demographic characteristics of the two groups, with the ratio of male to female in BO group being 2.14:1, and the age ranging from 2 months to 11 years old.

| Groups   | Total(n) | Male/Female(n) | Age(month) | Personal history of asthma or allergy history(n) | Wheeze(n) | Thermal peak $\geq$ 39°C(n) |
|----------|----------|----------------|------------|-------------------------------------------------|-----------|----------------------------|
| BO group | 46       | 34/12          | 39.0 ± 29.18 | 2(4.4%)                                         | 33        | 45                         |
| non BO group | 183      | 122/61         | 37.2 ± 26.80 | 14(7.7%)                                        | 70        | 169                        |
| t/$x^2$ value | 0.7     | 0.923          | 0.48        | 16.657                                          | 0         | 0.313                      |

The hospitalization days, oxygen use time, mechanical ventilation rate, IL-6, LDH, AST and D-dimer levels in BO group were significantly higher than those in non BO group (P = 0.000). Table 2 shows the clinical findings between two groups. With 66 cases being complicated with bacterial infection, Streptococcus pneumoniae infection was the most common, and the proportion of BO group with more than two kinds of etiology was higher than that of non BO group (P < 0.05); the time of using hormone in BO group was significantly later than that in non BO group. In terms of imaging, patchy shadows were more common in BO groups; chest X-ray or CT findings of 82.6% BO group and 63.9% non BO group were double lung
involvement. The double lung involvement in Bo group was significantly higher than that in control group (P < 0.05).
Table 2
Comparison of clinical data between the two groups (x ± s)

| Group                                      | BO group           | Non BO group       | T value/x2 | P value |
|--------------------------------------------|--------------------|--------------------|------------|---------|
| n                                          | 46                 | 183                |            |         |
| Hospitalization days                       | 17.15 ± 9.83       | 9.86 ± 5.56        | -6.6       | 0.000*  |
| Duration of fever                          | 16.96 ± 8.57       | 15.04 ± 8.90       | -1.3       | 0.191   |
| Oxygen supply time                         | 12.10 ± 9.59       | 4.87 ± 4.95        | -7.135     | 0.000*  |
| Time to start using hormones               | 15.34 ± 6.74       | 12.33 ± 7.21       | -2.354     | 0.02*   |
| Time to start using Gamma globulin         | 14.40 ± 5.96       | 14.44 ± 7.68       | 0.027      | 0.979   |
| Use /without use Gamma globulin (n)        | 40/6               | 131/52             | 4.620      | 0.032   |
| IL-6                                       | 119.98 ± 186.70    | 66.98 ± 85.47      | -2.651     | 0.009*  |
| White blood cell count                     | 8.31 ± 4.14        | 7.96 ± 4.78        | -0.446     | 0.656   |
| Neutrophil ratio                           | 61.65 ± 18.81      | 65.50 ± 17.07      | -1.264     | 0.218   |
| Lymphocyte ratio                           | 32.10 ± 16.98      | 34.20 ± 17.15      | 0.744      | 0.468   |
| Hemoglobin                                 | 109.30 ± 15.57     | 111.88 ± 18.73     | 0.860      | 0.391   |
| Platelet                                   | 304.30 ± 124.38    | 266.79 ± 141.59    | -1.643     | 0.102   |
| LDH                                        | 893.11 ± 538.80    | 591.36 ± 414.59    | -4.104     | 0.000*  |
| CRP                                        | 19.35 ± 20.39      | 23.52 ± 36.04      | 0.755      | 0.451   |
| PCT                                        | 3.70 ± 7.05        | 1.89 ± 5.25        | -1.946     | 0.053   |
| Albumin                                    | 32.52 ± 7.22       | 35.44 ± 4.45       | 3.464      | 0.001*  |
| ALT                                        | 41.93 ± 55.21      | 32.38 ± 61.99      | -0.953     | 0.341   |
| AST                                        | 96.52 ± 63.90      | 63.09 ± 58.57      | -3.397     | 0.001*  |
| FIB                                        | 4.14 ± 5.15        | 3.45 ± 2.21        | -1.382     | 0.168   |
There were 9 statistical differences between the two groups (P < 0.05): platelet level, oxygen supply time, length of stay, AST level, whether there is hypoxemia, the time of hormone use, more than two kinds of bacterial infection, LDH and albumin levels, etc.; while there were no significant differences in gender, age, hemoglobin, C-reactive protein, PCT, ALT levels, mycoplasma. There was no significant difference in other viral infection, IL-6, D-dimer and fib. The patients were divided into three groups: non use of gamma globulin group, gamma globulin group (course of disease < 2 weeks) and gamma globulin group (course of disease ≥ 2 weeks). The influence of different schemes on the occurrence of BO was compared, whose

### Table: Influencing factors of BO after adenovirus pneumonia

| Group                                      | BO group (n%) | Non BO group (n%) | T value/x² | P value |
|--------------------------------------------|---------------|-------------------|------------|---------|
| D-dimer                                    | 3.70 ± 6.21   | 2.14 ± 2.26       | -2.759     | 0.006*  |
| Combined with bacteria / virus / mycoplasma | 18/13/23      | 48/48/117         | 9.158      | 0.057   |
| More than two pathogens were combined (n%) | 12(26.1)      | 18(9.83)          | 8.528      | 0.003*  |
| More than two kinds of bacteria were combined (n) | 8            | 2                 | 13.535     | 0.000*  |
| Hypoxemia (n)                              | 10(21.7)      | 15(8.19)          | 6.932      | 0.008*  |
| administering oxygen inhalation through nasal catheter (n) | 17(37.0)      | 83(45.4)          | 1.054      | 0.305   |
| High flow oxygen inhalation or Non-invasive Ventilato (n) | 6(13.0)       | 18(9.83)          | 0.819      | 0.845   |
| Mechanical ventilation (n)                 | 18(39.1)      | 13(7.1)           | 28.519     | 0.000*  |
| consolidation images                       | 10(21.7)      | 37(20.2)          | 0.052      | 0.819   |
| patchy shadows                             | 42(91.3)      | 158(86.3)         | 0.981      | 0.322   |
| Unilateral lung involvement                | 4(8.7)        | 46(25.1)          | 5.166      | 0.023*  |
| One half to two-thirds of the lungs be involved | 4(8.7)       | 16(8.7)           | 0.003      | 0.96    |
| Two thirds to the whole lung be involved   | 0(0.0)        | 2(1.1)            | 0.507      | 0.476   |
| Bilateral lung involvement                 | 38(82.6)      | 117(63.9)         | 5.861      | 0.015*  |
| Atelectasis                                | 0(0.0)        | 2(1.1)            | 0.507      | 0.476   |
| Pleural effusion                           | 6(13.0)       | 22(12.0)          | 0.036      | 0.85    |
results showed that there were no significant differences among the three groups. Table 3 shows the Binary logistic comparison of clinical data between the two groups.

### Table 3

The Binary logistic comparison of clinical data between the two groups

| Group                                      | B    | OR   | 95%CI          | P      |
|--------------------------------------------|------|------|----------------|--------|
| Platelet                                   | 0.003| 1.003| 1.001–1.006    | 0.042* |
| Oxygen supply time                         | 0.149| 1.16 | 1.090–1.235    | 0.000* |
| Hospitalization days                       | 0.124| 1.132| 1.072–1.196    | 0.000* |
| ALT                                        | 0.005| 0.995| 0.988–1.001    | 0.122  |
| AST                                        | 0.006| 1.006| 1.000–1.011    | 0.043* |
| LDH                                        | 0.001| 1.001| 1.000–1.002    | 0.031* |
| Hypoxemia                                  | -1.093| 0.335| 0.140–0.801    | 0.014* |
| Combined with more than two kinds of bacterial infection | -2.676| 0.069| 0.010–0.478    | 0.007* |
| Albumin                                    | -0.076| 0.927| 0.860–0.998    | 0.045* |
| IL-6                                       | 0.001| 1.001| 0.998–1.004    | 0.45   |
| Timing of using hormone                    | 0.109| 1.115| 1.020–1.218    | 0.016* |
| Gamma globulin used or not                 | -0.767| 0.464| 0.180–1.196    | 0.112  |
| Gamma globulin was used in the course of less than 2 weeks | 0.351| 0.755| 0.379–1.504    | 0.424  |
| Gamma globulin was used after 2 weeks      | -0.317| 0.728| 0.367–1.443    | 0.363  |

ROC curve The results showed that there were significant differences in hospitalization days, oxygen consumption time, LDH, platelet, D-dimer and AST between the two groups (P < 0.05), as shown in Table 4.
Table 4
ROC curve of two groups of children

| Group                                | AUC  | Sensitivity (%) | Specificity (%) |
|--------------------------------------|------|-----------------|-----------------|
| Hospitalization days > 8 days        | 76.4 | 91.1            | 84.4            |
| Oxygen supply time > 3.5 days        | 74   | 50.8            | 50.8            |
| LDH > 914 IU/L                       | 65.7 | 46.5            | 84.9            |
| AST > 77.5                           | 71.9 | 63              | 79.2            |
| Timing of using hormone > 7.5 days   | 63.3 | 90              | 35.5            |
| PLT > 283.5*10^9                     | 61.4 | 62.2            | 62.1            |

Discussion

Adenovirus infection accounted for 4% – 10% (3) of the pathogens causing pneumonia in children. About 20% – 50% of the patients still had respiratory complications after adenovirus pneumonia treatment(1), such as bronchiolitis obliterans(4), bronchiectasis, hyperlucenct lung, pleurisy, atelectasis, chronic pneumonia, unilateral(4) clear lung syndrome, etc. The most common werebronchiolitis obliterans (BO) and recurrent asthma Interest. According to the data of 92 cases of adenovirus pneumonia, Li l et al. found that 52.6% of severe children had BO(5), a kind of chronic irreversible obstructive pulmonary disease caused by chronic inflammation and injury of the airway and the repair of airway fibrosis, thus leading to small airway obstruction and / or occlusion. The histological classification of BO can be divided into proliferation type and constriction type(6). Mauad T and other studies have found that 97% of bronchiolitis obliterans in children are constrictive type(7). There are three forms of BO: post infection BO, lung transplantation BO, and bone marrow transplantation (BMT) or hematopoietic stem cell transplantation (HSCT), among which post infectious BO (PiBO) was the most common one so far, as well as being common in children with adenovirus infection.

After adenovirus infection, epithelial cells were damaged and necrotic, replaced by T cells and neutrophils, followed by matrix degradation, collagen deposition and fibroblast stimulation, resulting in fibrosis of airway BO (8).Studies have shown that glucocorticoids can inhibit inflammatory response and slow down the process of fibrosis(9)· being part and parcel in the treatment of BO. There is no clear conclusion about the duration of inflammation in patients with BO. Studies have shown that long-term oral glucocorticoid treatment can improve the hypoxemia of patients with bronchiolitis obliterans, significantly reducing the number of wheezing and hospitalization (8). Pulmonary fibrosis (10)of BO may be caused by granulation tissue with loose connective tissue or scar formed by dense connective tissue. Glucocorticoid can reduce the former reversibly. When granulation tissue extends to the alveoli, the lesion is called tissue pneumonia (BOOP), whose study has shown that glucocorticoids can completely eliminate alveolar granulation(11). Our study found that glucocorticoids were used earlier in the non BO
group than in the BO group. The timing of glucocorticoid use was based on the duration of the disease to the use of corticosteroids. It is speculated that the use of glucocorticoids in the early stage of adenovirus pneumonia may reduce the incidence of BO by reducing granulation tissue formation. This conclusion is consistent with the literature that glucocorticoid should be used during the development of the disease and agreed as soon as possible before the formation of airway fibrosis Give agreement as soon as possible\(^6\). On the other hand, our research on the use of gamma globulin in BO shows that gamma globulin has no obvious effect on reducing the formation of BO caused by adenovirus infection. Relevant studies have found that gamma globulin can effectively shorten the treatment time of severe adenovirus pneumonia, and will not increase the incidence of adverse reactions. However, there is no clear effect on reducing the formation of BO.

Bronchiolitis obliteration is the result of the centripetal narrowing of the wall fibrosis and the collapse of the small airway after inflammation. Cytokines are major factors in the establishment and maintenance of fibrosis, and IL-6, as one of the cytokines, is associated with the severity of adenovirus infection\(^12\). Another study showed that fibrosis depends on IL-6\(^13\), which increases rapidly under stress, and IL-6 is almost always increased in chronic inflammation\(^14\). In this study, IL-6 in BO group was significantly higher than that in non BO group. It was speculated that inflammatory response in BO group was stronger than that in non BO group. However, whether the determination of IL-6 value can help us identify BO earlier remains to be discussed.

There are many hypothesised risk factors for the formation of thin post infection, including but not limited to viral load, environmental and genetic factors, length of hospital stay, etc. Many studies have shown that mechanical ventilation is a risk factor for the formation of BO\(^15,16\), 67.7% (155 / 229) of children with severe adenovirus pneumonia received different levels of oxygen support. The rate of mechanical ventilation and hypoxemia were significantly higher in the wave group than in the non-wave group (39.1% and 7.1%, respectively,\(P = 0.000\)), suggesting that the risk factors for mechanical ventilation and hypoxemia were adenovirus infection due to bronchiolitis obturator, which is consistent with Wu Peiqiong et al\(^17\). On the one hand, hypoxemia significantly affects the expression of cytokines, chemokines and chemokine receptors, which significantly increases the incidence and severity of BOS. Colom AJ et al. Regarded the presence of hypoxemia in patients with post infectious BO as an important indicator of BO score, so as to highly accurately predict the diagnosis of postinfectious BO\(^15\). Based on the above study, we believe that hypoxemia as a BO score index is reasonable and worthy of promotion.

It was found that LDH in BO group was significantly higher than that of non-BO group. The best cut-off value for diagnosing BO was 914iu / L, with a sensitivity of 46.5% and a specificity of 84.9%. Literature shows that LDH exists in all important organs as a cytoplasmic enzyme, LDH is associated with many lung diseases, such as obstructive disease, microbial lung disease and interstitial lung disease. Chen x\(^18\) showed that LDH was as high as 1458.5 (634.8-3244.8) in 8 children with severe adenovirus pneumonia who needed modified outer membrane oxygenation support, which was significantly higher than that in children with ordinary adenovirus pneumonia (408.0 (282.0-639.0). Therefore, it can be
inferred that patients with significantly elevated LDH (especially those ≥ 914 IU/L) should be on alert for bronchiolitis obliterans. There was no significant difference in fever peak, gender, age, hemoglobin, C-reactive protein, PCT, ALT levels, D-dimer and FIB between the two groups, Hadith little effect on distinguishing whether bronchiolitis obliterans occurred after severe adenovirus infection.

This study showed that more than half of the children in the two groups were complicated with Mycoplasma pneumoniae infection. Patients with more than two pathogens and two kinds of bacterial infection in BO group were more than those in non BO group (P < 0.05). It is consistent with the literature that bacterial and viral infections increase the risk of BO\(^6\). The prevalence of adenovirus co infection may be related to the increased susceptibility to bacterial infection after viral infection. Research\(^\text{19}\) has showed that viral infection can increase bacterial binding and decrease barrier function in innate and adaptive immune level, and cause secondary bacterial infection. The interaction between bacteria and virus can affect the severity of disease.

The imaging diagnosis of bronchiolitis obliterans includes direct signs such as wall thickening and occlusion of bronchioles, and indirect signs such as bronchiectasis, mosaic perfusion, and lung volume reduction\(^20\). In this study, we found that both groups had patchy or consolidation imaging, most of which were patchy shadows. Typical mosaic perfusion signs were seen, with unilateral or bilateral lung involvement being seen as well. The proportion of double lung involvement in BO group was 82.6%, and 63.9% in non BO group (P < 0.05).

the follow-up time limited the assessment of long term prognosis.

**Conclusions**

The related risk factors of BO caused by severe adenovirus pneumonia were long hospitalization days and oxygen consumption time, platelet levels, AST and LDH levels in laboratory tests, and more than two kinds of bacterial infections, double lung involvement, and hypoxemia. Early use of glucocorticoid has a significant effect on reducing the formation of BO. In our study, the effect of adenovirus, a common pathogen in post infectious bronchiolitis obliterans, on BO was carried out separately, with the ROC curve being used to obtain the best cut-off value, so as to evaluate the influencing factors of bronchiolitis obliterans in patients with adenovirus pneumonia, contributing to the related factors of intervention in the process of clinical treatment, early recognition of adverse outcomes, thus reducing the adverse prognostic effect on the quality of life. Early identification of the occurrence of poor prognosis, so as to reduce the impact of poor prognosis on the quality of life.

**Abbreviations**

BO
Bronchiolitis obliterans
BOOP
Bronchiolitis obliterans organizing pneumonia

Declarations

Ethics approval and consent to participate

Our article was published with the consent of the child's parents and approved by the Xiamen First Hospital ethics committee. All recruits signed an informed consent form. The reference number is 2020 (024).

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Funding

This work was sponsored by Xiamen science and technology plan project (3502z20184018). The funders had no role in the study design, data collection or analysis, decision to publish, or preparation of the manuscript.

Consent for publication

Not applicable.

Authors’ contributions

LYM and YYG designed the study and draft the manuscript, LYM, YYG, LXL, CQH performed the experiments and statistical analysis. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

Not Applicable.

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