



## Effects of methylprednisolone combined with advanced antibiotics and antiviral drugs on serum immunoglobulin and inflammatory factor levels in patients with viral pneumonia

Lixia Yue<sup>1</sup>, Yihe Yan<sup>2\*</sup>

<sup>1</sup> Department of Rheumatology, Shaoxing People's Hospital, Shaoxing 312000, Zhejiang Province, China

<sup>2</sup> Department of Intensive Care Unit, Shaoxing People's Hospital, Shaoxing 312000, Zhejiang Province, China

### ARTICLE INFO

#### Original paper

#### Article history:

Received: July 25, 2023

Accepted: November 25, 2023

Published: December 31, 2023

#### Keywords:

Methylprednisolone, serum biochemical factors, viral antigen conversion rate, viral pneumonia

### ABSTRACT

Viral pneumonia (VP) is known for its wide transmission and severe pathological damage. ninety cases of VP patients were rolled into an experimental group (group E, methylprednisolone + advanced antibiotics + antiviral drugs) and a control group (group C, methylprednisolone), with 45 cases in each group. General information about the patients, inflammatory factors, serum immunoglobulins, T lymphocyte subsets, and treatment outcomes (efficiency rate, conversion rate to negative) were compared. In group E, interleukin-6 (IL-6) ( $0.18 \pm 0.07$ ) ng/L was inferior to in group C ( $0.33 \pm 0.09$ ) ng/L,  $p < 0.05$ ; tumor necrosis factor-alpha (TNF- $\alpha$ ) ( $17.22 \pm 4.13$ ) ng/L was inferior to group C ( $26.07 \pm 4.08$ ) ng/L,  $p < 0.05$ ; IgA ( $0.81 \pm 0.22$ ) g/L was superior to in group C ( $0.68 \pm 0.17$ ) g/L,  $P < 0.05$ ; IgM ( $1.62 \pm 0.13$ ) g/L was superior to group C ( $1.09 \pm 0.03$ ) g/L,  $p < 0.05$ ; IgE ( $0.19 \pm 0.02$ ) g/L was inferior to group C ( $0.23 \pm 0.03$ ) g/L,  $p < 0.05$ ; CD<sub>4</sub><sup>+</sup>/CD<sub>8</sub><sup>+</sup> ratio ( $1.71 \pm 0.33$ ) was superior to group C ( $1.24 \pm 0.43$ ),  $p < 0.05$ ; the total efficiency rate in group C (77.78%) was inferior to group E (97.78%),  $p < 0.05$ ; the conversion rate to negative of viral antigens in group E (91.11%) was superior to in group C (64.44%),  $p < 0.05$ . methylprednisolone in combination with advanced antibiotics and antiviral drugs is an effective treatment approach for VP.

Doi: <http://dx.doi.org/10.14715/cmb/2023.69.15.27>

Copyright: © 2023 by the C.M.B. Association. All rights reserved.

### Introduction

Viral pneumonia (VP) is a common respiratory infectious disease caused by various viruses, including influenza viruses, and coronaviruses. The clinical manifestations of this disease include fever, cough, and difficulty breathing, with severe cases causing respiratory failure and fatal outcomes (1). Currently, no specific and effective treatment methods or drugs have been found for VP, and treatment options mainly involve antiviral drugs and supportive care. However, people still face challenges of lacking specificity and efficacy in treatment. VP is known for its wide transmission and severe pathological damage (2,3), imposing a significant burden on patients and society. Firstly, VP is highly contagious and can spread rapidly, forming large-scale chains of infection transmission that have a serious impact on public health security. Secondly, patients often experience symptoms such as cough, fever, and difficulty breathing, with serious conditions progressing to pneumonia and respiratory failure, posing a serious threat to patients' lives (4). Additionally, the immune and inflammatory responses triggered by viral infections can lead to acute respiratory distress syndrome (ARDS) and multiple organ failure, further exacerbating the patients' condition (5,6). The outbreaks of VP also cause significant economic impact, with strained healthcare resources and restrictions on social and economic activities. Hence, it is crucial to have a comprehensive understanding of the hazards of VP and to implement appropriate prevention measures and treatment strategies to protect public health and maintain social stability. We need to continuously

strengthen research on VP, seek more effective treatment methods and drugs, enhance public education, and raise awareness of public hygiene to collectively address this global challenge.

Methylprednisolone is a widely utilized glucocorticoid medication in clinical practice, known for its anti-inflammatory and immunomodulatory effects (7). It is commonly utilized to treat rheumatic diseases, autoimmune diseases, asthma, allergic reactions, and other conditions (8). In severe infectious diseases such as VP, methylprednisolone can also be utilized to alleviate inflammatory responses, control excessive immune system activation, reduce tissue damage, and improve patient symptoms (9). Advanced antibiotics and antiviral drugs are also widely utilized to treat infectious diseases. Some studies suggest that the combination of methylprednisolone with advanced antibiotics and antiviral drugs may have potential advantages in the treatment of VP, but their impact on serum biochemical factors and the underlying mechanisms are not yet clear (10,11).

This work aims to conduct a clinical trial on patients with VP to observe the changes in serum biochemical indicators in groups E and C and evaluate treatment efficacy. It hypothesizes that the treatment with methylprednisolone in combination with advanced antibiotics and antiviral drugs can regulate the levels of serum biochemical factors in patients with VP, including inflammatory mediators, cytokines, and immune-related molecules. By studying the changes in serum biochemical indicators, we will attempt to reveal the therapeutic mechanisms of methylprednisolone in combination with advanced antibiotics and anti-

\* Corresponding author. Email: limei2571191598@163.com

viral drugs for VP, particularly their regulatory effects on immune and inflammatory responses. This work aims to provide novel insights and evidence for the treatment of VP and offer a basis for the selection of drugs and optimization of treatment plans in clinical practice.

## Materials and Methods

### Object of study

Ninety patients diagnosed with VP from Shaoxing People's Hospital between 2020 and 2022 were recruited and assigned to the experimental group (group E) and control group (group C), with 45 patients in each group. In group E, there were 25 males and 20 females, with an age range of 11-35 (29.35±3.11) years. In group C, there were 23 males and 22 females, with an age range of 11-36 (29.84±2.79) years. This study has obtained approval from the Shaoxing People's Hospital Medical Ethics Committee. The patients and their families were aware of the research content and methodologies, and they signed the corresponding informed consent forms.

### Inclusion criteria

(I) patients who exhibit clinical manifestations and radiological findings consistent with VP (12); (II) positive results for viral pathogen detection result in the diagnosis of VP; (III) complete clinical data available; (IV) abnormal serum biochemical indicators.

### Exclusion criteria

(I) presence of other respiratory infectious diseases, such as bacterial pneumonia, tuberculosis, etc.; (II) severe organ dysfunction in the heart, liver, kidneys, or other organs; (III) prior treatment with methylprednisolone or related medications; (IV) history of severe allergic reactions.

### Research methodologies

After admission, 90 patients with VP underwent basic examinations. During the examinations, they were communicated with to understand the etiology, progression, medical history, and allergic history. The patients were rolled into two groups. Group C received methylprednisolone treatment twice daily, with a maximum dose of 75 mg per administration. The patients in group E received oseltamivir, along with advanced antibiotics and antiviral drugs. Both groups underwent a one-week treatment period. Throughout the treatment process, the patients' symptoms and physical changes were observed and recorded, and any discomfort or fever-related adverse reactions were inquired about. If there was no significant relief by the eighth day, the observation and recording continued until the symptoms completely disappeared. A comparison was made between groups involving general information, levels of inflammatory factors, serum immunoglobulin levels, T lymphocyte subgroups, and efficacy (response rate and antigen conversion rate), aiming to summarize the effects of methylprednisolone combined with advanced antibiotics and antiviral drugs on the serum biochemical factors in patients with VP.

### Therapeutic method

(I) The method for detecting serum immunoglobulin levels is as follows: before treatment and one week after treatment, 2mL of venous blood was collected. The

samples were centrifuged at 1000rpm for 5 minutes, and the supernatant was collected. Using a reagent kit provided by Shanghai Yanyan Biotechnology Co., Ltd., the levels of serum immunoglobulins (IgA, IgE, IgG, IgM) were observed using the immunoprecipitation turbidimetry method.

(II) The method for detecting T lymphocyte subsets is as follows: CD<sub>3</sub><sup>+</sup>, CD<sub>4</sub><sup>+</sup>, CD<sub>8</sub><sup>+</sup>, and CD<sub>4</sub><sup>+</sup>/CD<sub>8</sub><sup>+</sup> in children were detected using a flow cytometer from Partec, Germany.

(III) The method for detecting inflammatory factors is as follows: the levels of interleukin-6 (IL-6), IL-8, and tumor necrosis factor-alpha (TNF-α) in children were detected using the enzyme-linked immunosorbent assay (ELISA) method. The reagent kit was fabricated by Shanghai Keshun Biotechnology Co., Ltd., and the procedure was strictly followed regarding the instructions.

(IV) The criteria for determining efficacy are as follows: "Significant improvement" refers to the clinical symptoms and vital signs of patients disappearing after treatment. "Effective" indicates that these symptoms and signs have remarkably improved and were relieved after treatment. "Ineffective" refers to the lack of enhancement or worsening of clinical symptoms and vital signs after treatment. The total effective rate is calculated using the equation: ("Significant improvement" + "Effective") / Total number of cases × 100%.

### Observation indicators

General Information: gender, age, duration of illness, disease severity, clinical symptoms;  
Inflammatory factor levels: IL-6, IL-8, TNF-α;  
Serum immunoglobulin levels: IgA, IgG, IgM, IgE;  
T lymphocyte subsets: CD<sub>3</sub><sup>+</sup>, CD<sub>4</sub><sup>+</sup>, CD<sub>8</sub><sup>+</sup>, CD<sub>4</sub><sup>+</sup>/CD<sub>8</sub><sup>+</sup>;  
Treatment efficacy: cure, significant improvement, effective, ineffective, total effective rate, negative conversion rate of viral antigen.

### Statistical standards

The study utilized SPSS 20.0 statistical software for data analysis. Analyzed using t-tests, continuous variables were presented as mean±standard deviation, and using chi-square tests, categorical variables were presented as percentages (%). Differences were taken as statistically significant if  $P < 0.05$ .

## Results

### General information

Comparison of general information between groups showed neglectable differences in terms of gender, age, duration of illness, disease severity, and clinical symptoms, with  $P > 0.05$ . The specific results are illustrated in Table 1.

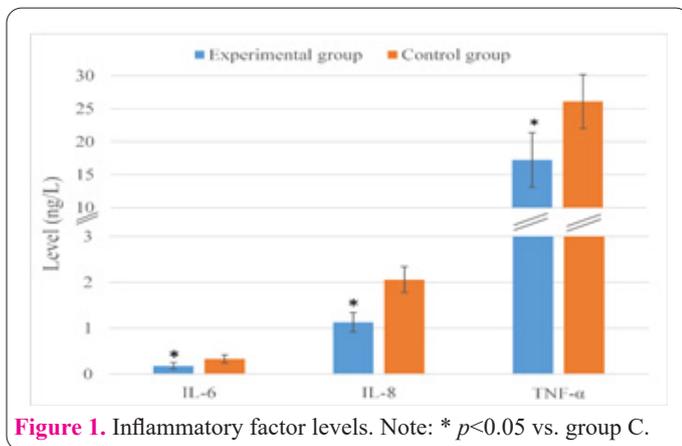
### Comparison of inflammatory factor levels

Post-treatment inflammatory factor levels between groups revealed the following results: the IL-6 level in group E was (0.18±0.07) ng/L, while it was (0.33±0.09) ng/L in group C. The IL-6 level in group E was drastically inferior to group C ( $p < 0.05$ ). The IL-8 level in group E was (1.13±0.21) ng/L, whereas it was (2.06±0.28) ng/L in group C. The IL-8 level in group E was drastically inferior to group C ( $p < 0.05$ ). The TNF-α level in group E was (17.22±4.13) ng/L, while it was (26.07±4.08) ng/L in

**Table 1.** Comparison of general information.

Category	Group E (45 cases)	Group C (45 cases)	t/ $\chi^2$	p
Gender				
Male	25	23	0.651	0.722
Female	20	22		
Age (years)	29.35±3.11	29.84±2.79	2.319	0.076
Duration of illness (h)	98±24	98±25	1.120	0.412
Disease severity				
Mild	23	24	2.108	0.064
Moderate	15	13		
Severe	7	8		
Clinical symptoms				
Cough	20	21		
Dyspnea	9	11	8.634	0.109
Difficulty in breathing	3	4		
Bilateral lung rales and wheezing	13	9		

Note: t represents the t-test, and  $\chi^2$  represents the chi-square test.



**Figure 1.** Inflammatory factor levels. Note: \*  $p < 0.05$  vs. group C.

group C. The TNF- $\alpha$  level in group E was drastically inferior to group C ( $p < 0.05$ ). The specific results are illustrated in Figure 1.

### Serum immunoglobulin levels

Comparison of the post-treatment serum immunoglobulin levels between groups yielded the following results: The IgA level in group E was (0.81±0.22) g/L, while it was (0.68±0.17) g/L in group C. The IgA level in group E was markedly superior to group C ( $p < 0.05$ ). The IgG level in group E was (7.83±2.13) g/L, whereas it was (7.21±2.42) g/L in group C. The IgG level in group E was markedly superior to group C ( $p < 0.05$ ). The IgM level in group E was (1.62±0.13) g/L, while it was (1.09±0.03) g/L in group C. The IgM level in group E was markedly superior to group C ( $p < 0.05$ ). The IgE level in group E was (0.19±0.02) g/L, whereas it was (0.23±0.03) g/L in group C. The IgE level in group E was drastically inferior to group C ( $p < 0.05$ ) (Figure 2).

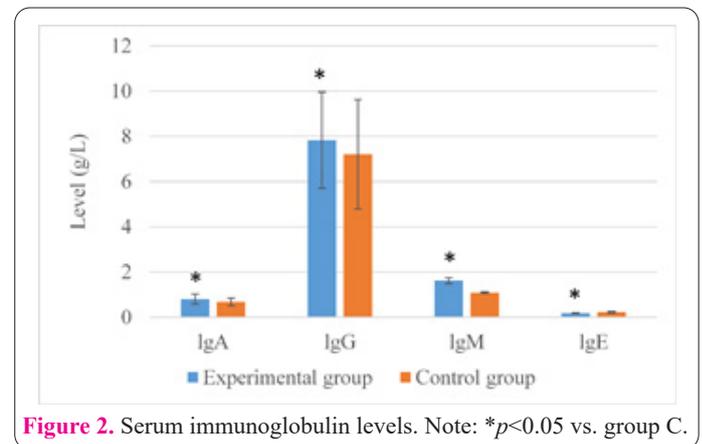
### T lymphocyte subpopulation levels

T lymphocyte subpopulation levels after treatment were compared, and group E had a CD<sub>3</sub><sup>+</sup> content of (69.04±2.48)%, while group C had (63.15±2.32)%. Group E had a higher level compared to group C ( $p < 0.05$ ). The CD<sub>4</sub><sup>+</sup> content in group E was (41.63±2.87)%, while it was (37.22±2.25)% in group C. Group E had a higher level

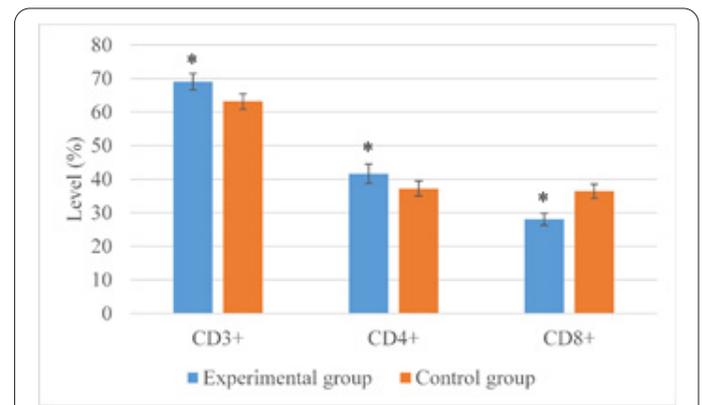
compared to group C ( $p < 0.05$ ). The CD<sub>8</sub><sup>+</sup> content in group E was (28.06±1.79)%, whereas it was (36.43±2.11)% in group C. Group E had a lower level compared to Group C ( $p < 0.05$ ). The CD<sub>4</sub><sup>+</sup>/CD<sub>8</sub><sup>+</sup> ratio in group E was (1.71±0.33), while it was (1.24±0.43) in group C. Group E had a higher ratio compared to group C ( $p < 0.05$ ) (Figures 3,4).

### Treatment efficacy

Comparing the overall efficacy of treatment in the two groups of patients, the results revealed that in group C, 17 cases were cured, 10 cases showed significant improvement, 8 cases demonstrated effectiveness, and 10 cases demonstrated no improvement, the overall effective rate



**Figure 2.** Serum immunoglobulin levels. Note: \*  $p < 0.05$  vs. group C.



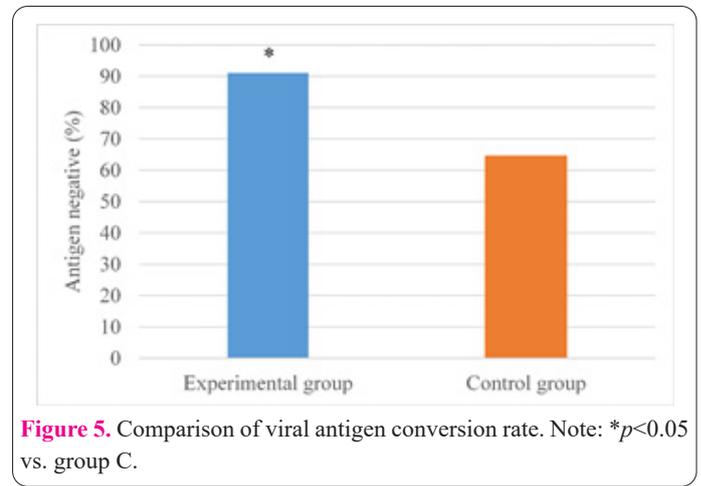
**Figure 3.** CD<sub>3</sub><sup>+</sup>, CD<sub>4</sub><sup>+</sup>, and CD<sub>8</sub><sup>+</sup> levels. Note: \*  $p < 0.05$  vs. group C.

was 35/45 (77.78%). In group E, 23 cases were cured, 11 cases demonstrated significant improvement, 10 cases demonstrated effectiveness, and 1 case demonstrated no improvement, the overall effective rate was 44/45 (97.78%). Group E had a higher overall effective rate compared to group C ( $p<0.05$ ). Specific details are illustrated in Table 2. In group E, viral antigen turned negative in 41 cases, with a conversion rate of 91.11%, while in group C, viral antigen turned negative in 29 cases, with a conversion rate of 64.44%. The conversion rate in group E was superior to group C ( $p<0.05$ ). Specific details are illustrated in Figure 5.

## Discussion

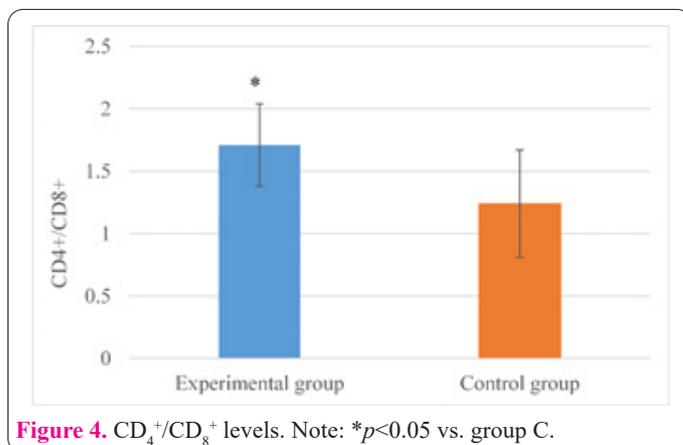
VP is a respiratory infection disease caused by viruses, which is widely prevalent worldwide and poses a significant threat to human health (13,14). Various viruses, such as influenza viruses, coronaviruses, and respiratory syncytial viruses, can cause VP (15). These viruses infect the upper respiratory tract and lung tissues, leading to inflammatory responses and lung tissue damage through droplet transmission or direct contact transmission (16). Over the past few decades, VP has experienced several large-scale outbreaks, posing enormous challenges to global health security and public health systems (17,18). Recently, the COVID-19 pandemic has triggered a crisis on a global scale (19). VP, characterized by its high infectivity, severe pulmonary pathology, and high mortality rate, severely affects human health and daily life (20,21). Currently, the treatment of VP still faces many challenges (22). Due to the diversity and variability of viruses, there are difficulties in the specificity of viral antigens and the development of vaccines (23). In addition, conventional antiviral drugs have varying efficacy against different viruses and may have issues with drug resistance (24-26). Hence, exploring new treatment strategies and drugs for VP is of great value.

Methylprednisolone, as a commonly utilized corticosteroid in clinical practice, has multiple effects such as anti-inflammatory and immune regulation, and is widely utilized in the treatment of respiratory tract infections (27). Broad-spectrum antibiotics and antiviral drugs can provide therapeutic effects against bacterial and viral



**Figure 5.** Comparison of viral antigen conversion rate. Note: \* $p<0.05$  vs. group C.

infections (28,29). Hence, based on this, the efficacy of methylprednisolone in combination with advanced antibiotics and antiviral drugs in VP therapy and its impact on patients' immune function was demonstrated in this study. By comparing the treatment outcomes and relevant indicators between group E and group C, the results show that there were neglectable differences between groups regarding the general characteristics of the patients, including gender, age, course of the disease, disease severity, and clinical symptoms. This indicates that at the beginning of the study, the two groups of patients shared similar baseline situations, and there were no significant deviations, thereby enhancing the reliability of the research results. It has been revealed that inflammatory factor levels (IL-6, IL-8, and TNF-alpha) tend to be elevated in patients with VP, which are considered important indicators reflecting the severity of infection in children (30,31). After treatment, IL-6, IL-8, and TNF-alpha were compared between groups. The results showed that the levels of inflammatory factors in group E were drastically inferior to those in group C. This indicates that methylprednisolone in combination with advanced antibiotics and antiviral drugs can effectively suppress the inflammatory response, reduce the release of inflammatory factors, and have a positive impact on the inflammatory process of VP. In recent years, to improve efficacy, many researchers have suggested including IgA, IgG, and IgM serotypes in the overall treatment regimen, and stabilizing the levels of IgA, IgG, and IgM is an ideal approach to enhance immunity and reduce pathogen toxicity (32,33). By comparing the levels of serum immunoglobulins after treatment between groups of patients, it was revealed that the levels of serum immunoglobulins in group E were markedly superior to those in group C. This indicates that the treatment with methylprednisolone in combination with advanced antibiotics and antiviral drugs can enhance the immune function of patients, increase immunoglobulins, and enhance the body's resistance to viruses. Furthermore, by comparing T lymphocyte subsets ( $CD_3^+$ ,  $CD_4^+$ ,  $CD_8^+$ , and  $CD_4^+/CD_8^+$ ) after treatment between groups of patients, it was suggested that the levels of T lymphocyte subsets in group E were remarkably better than group C. This indicates that



**Figure 4.** CD<sub>4</sub><sup>+</sup>/CD<sub>8</sub><sup>+</sup> levels. Note: \* $p<0.05$  vs. group C.

**Table 2.** Comparison of treatment efficacy

Group	Cured	Significant improvement	Effective	No Improvement	Overall effective rate
Control Group (45 cases)	17	10	8	10	35(77.78%)
Experimental Group (45 cases)	23	11	10	1	44(97.78%)*

the treatment with methylprednisolone in combination with advanced antibiotics and antiviral drugs can increase CD<sub>3</sub><sup>+</sup> and CD<sub>4</sub><sup>+</sup> cell numbers, and decrease CD<sub>8</sub><sup>+</sup> cell numbers, thereby improving the immune status of patients and promoting immune regulation. Finally, by comparing the overall effective rates of treatment between different groups of patients, it was revealed that the overall effective rate in group E was markedly superior to group C. This indicates that the treatment with methylprednisolone in combination with advanced antibiotics and antiviral drugs has better efficacy in the clinical treatment of VP and can remarkably improve the clinical symptoms and signs of patients.

The combination of methylprednisolone with advanced antibiotics and antiviral drugs is an effective treatment regimen for VP. This approach remarkably improves patients' immune function, suppresses inflammatory reactions, and enhances the overall treatment efficacy. These research findings provide strong evidence for clinical practice and offer new directions and strategies for the treatment of VP. However, further work with larger sample sizes and multicenter designs is still required to validate these results and delve into the treatment mechanisms and potential side effects. This will further enhance the clinical application value of this therapy and provide comprehensive guidance and options for healthcare professionals in the treatment of VP.

## References

- Zhou Y, Fu X, Liu X, Huang C, Tian G, Ding C, Wu J, Lan L, Yang S. Use of corticosteroids in influenza-associated acute respiratory distress syndrome and severe pneumonia: a systemic review and meta-analysis. *Sci Rep* 2020; 10(1): 3044. <https://doi.org/10.1038/s41598-020-59732-7>
- Tan D, Zhu H, Fu Y, Tong F, Yao D, Walline J, Xu J, Yu X. Severe community-acquired pneumonia caused by human adenovirus in immunocompetent adults: a multicenter case series. *PLoS One* 2016; 11(3): e0151199. <https://doi.org/10.1371/journal.pone.0151199>
- Takahashi I, Takahashi T, Tsuchida S, Mikami T, Saito H, Hatazawa C, Takada G. Pulse methylprednisolone therapy in type 3 adenovirus pneumonia with hypercytokinemia. *Tohoku J Exp Med* 2006; 209(1): 69-73. <https://doi.org/10.1620/tjem.209.69>
- Shima T, Yoshimoto G, Nonami A, Yoshida S, Kamezaki K, Iwasaki H, Takenaka K, Miyamoto T, Harada N, Teshima T, Akashi K, Nagafuji K. Successful treatment of parainfluenza virus 3 pneumonia with oral ribavirin and methylprednisolone in a bone marrow transplant recipient. *Int J Hematol* 2008; 88(3): 336-340. <https://doi.org/10.1007/s12185-008-0148-6>
- Sasoni N, Rodriguez Müller M, Posse G, González J, Leonardelli F, Garcia-Effron G. SARS-CoV-2 and Aspergillus section Fumigati coinfection in an immunocompetent patient treated with corticosteroids. *Rev Iberoam Micol* 2021; 38(1): 16-18. <https://doi.org/10.1016/j.riam.2020.11.001>
- Freni F, B Galletti, R Bruno, F Martines, P Abita, F Gazia, F Sireci, F Galletti. Multidisciplinary approach in the removal of post-trauma foreign bodies in the head and neck district: cases report and review of literature. *Acta Med Mediterr* 2019; 35: 405-410. [https://doi.org/10.19193/0393-6384\\_2019\\_1\\_66](https://doi.org/10.19193/0393-6384_2019_1_66)
- Rafiullah M, Siddiqui K. Corticosteroid use in viral pneumonia: experience so far and the dexamethasone breakthrough in coronavirus disease-2019. *J Comp Eff Res* 2020; 9(18): 1247-1254. <https://doi.org/10.2217/cer-2020-0146>
- Póvoa P, Coelho L, Salluh J. When should we use corticosteroids in severe community-acquired pneumonia? *Curr Opin Infect Dis* 2021; 34(2): 169-174. <https://doi.org/10.1097/QCO.0000000000000709>
- Ottolini MG, Curtis SJ, Porter DD, Mathews A, Richardson JY, Hemming VG, Prince GA. Comparison of corticosteroids for treatment of respiratory syncytial virus bronchiolitis and pneumonia in cotton rats. *Antimicrob Agents Chemother* 2002; 46(7): 2299-2302. <https://doi.org/10.1128/AAC.46.7.2299-2302.2002>
- Ni YN, Chen G, Sun J, Liang BM, Liang ZA. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. *Crit Care* 2019; 23(1): 99. <https://doi.org/10.1186/s13054-019-2395-8>
- Wongchai A, D rao Jenjeti, A I Priyadarsini, N Deb, A Bhardwaj, P Tomar. Farm monitoring and disease prediction by classification based on deep learning architectures in sustainable agriculture. *Ecol Modell* 2022; 474: 110167. <https://doi.org/10.1016/j.ecolmodel.2022.110167>
- Matthay MA, Liu KD. Con: corticosteroids are not indicated for treatment of acute lung injury from H1N1 viral pneumonia. *Am J Respir Crit Care Med* 2011; 183(9): 1127-1128. <https://doi.org/10.1164/rccm.201103-0395ED>
- Martín-Loeches I, Bermejo-Martin JF, Vallés J, Granada R, Vidaur L, Vergara-Serrano JC, Martín M, Figueira JC, Sirvent JM, Blanquer J, Suarez D, Artigas A, Torres A, Diaz E, Rodriguez A; SEMICYUC/REIPI/CIBERES H1N1 Working Group. Macrolide-based regimens in absence of bacterial co-infection in critically ill H1N1 patients with primary viral pneumonia. *Intensive Care Med* 2013; 39(4): 693-702. <https://doi.org/10.1007/s00134-013-2829-8>
- Li H, Yang SG, Gu L, Zhang Y, Yan XX, Liang ZA, Zhang W, Jia HY, Chen W, Liu M, Yu KJ, Xue CX, Hu K, Zou Q, Li LJ, Cao B, Wang C; National Influenza A(H1N1)pdm09 Clinical Investigation Group of China. Effect of low-to-moderate-dose corticosteroids on mortality of hospitalized adolescents and adults with influenza A(H1N1)pdm09 viral pneumonia. *Influenza Other Respir Viruses* 2017; 11(4): 345-354. <https://doi.org/10.1111/irv.12456>
- Lee KY, Rhim JW, Kang JH. Early preemptive immunomodulators (corticosteroids) for severe pneumonia patients infected with SARS-CoV-2. *Clin Exp Pediatr* 2020; 63(4): 117-118. <https://doi.org/10.3345/cep.2020.00290>
- Wang L, W Luo. Tripterygium glycosides weakened enteric ischemia/reperfusion detriment via the Nrf2/HO-1 Pathway. *J Biol Regul Homeost Agents* 2022; 36(5): 1467-1477. <https://doi.org/10.23812/j.biol.regul.homeost.agents.20223605.156>
- Moreno G, Rodríguez A, Reyes LF, Gomez J, Sole-Violan J, Díaz E, Bodí M, Trefler S, Guardiola J, Yébenes JC, Soriano A, Garnacho-Montero J, Socias L, Del Valle Ortíz M, Correig E, Marín-Corral J, Vallverdú-Vidal M, Restrepo MI, Torres A, Martín-Loeches I; GETGAG Study Group. Corticosteroid treatment in critically ill patients with severe influenza pneumonia: a propensity score matching study. *Intensive Care Med* 2018; 44(9): 1470-1482. <https://doi.org/10.1007/s00134-018-5332-4>
- Diaz E, Martín-Loeches I, Canadell L, Vidaur L, Suarez D, Socias L, Estella A, Gil Rueda B, Guerrero JE, Valverdú-Vidal M, Vergara JC, López-Pueyo MJ, Magret M, Recio T, López D, Rello J, Rodriguez A; H1N1 SEMICYUC-CIBERES-REIPI Working Group (GETGAG). Corticosteroid therapy in patients with primary viral pneumonia due to pandemic (H1N1) 2009 influenza. *J Infect* 2012; 64(3): 311-318. <https://doi.org/10.1016/j.jinf.2011.12.010>
- Crisan Dabija R, Antohe I, Trofor A, Antoniu SA. Corticosteroids in SARS-COV2 infection: certainties and uncertainties in clinical practice. *Expert Rev Anti Infect Ther* 2021; 19(12): 1553-1562.

- <https://doi.org/10.1080/14787210.2021.1933437>
20. Favé G, Coste TC, Armand M. Physicochemical properties of lipids: new strategies to manage fatty acid bioavailability. *Cell Mol Biol (Noisy-le-grand)* 2004; 50(7): 815-831.
  21. Cheng VC, Tang BS, Wu AK, Chu CM, Yuen KY. Medical treatment of viral pneumonia including SARS in immunocompetent adult. *J Infect* 2004; 49(4): 262-273. <https://doi.org/10.1016/j.jinf.2004.07.010>
  22. Dinarello CA. Role of pro- and anti-inflammatory cytokines during inflammation: experimental and clinical findings. *J Biol Regul Homeost Agents* 1997; 11(3): 91-103.
  23. Cao B, Gao H, Zhou B, Deng X, Hu C, Deng C, Lu H, Li Y, Gan J, Liu J, Li H, Zhang Y, Yang Y, Fang Q, Shen Y, Gu Q, Zhou X, Zhao W, Pu Z, Chen L, Sun B, Liu X, Hamilton CD, Li L. Adjuvant corticosteroid treatment in adults with influenza A (H7N9) viral pneumonia. *Crit Care Med* 2016; 44(6): e318-328. <https://doi.org/10.1097/CCM.0000000000001616>
  24. Brun-Buisson C, Richard JC, Mercat A, Thiébaud AC, Brochard L; REVA-SRLF A/H1N1v 2009 Registry Group. Early corticosteroids in severe influenza A/H1N1 pneumonia and acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2011; 183(9): 1200-1206. <https://doi.org/10.1164/rccm.201101-0135OC>
  25. Amaral JD, Xavier JM, Steer CJ, Rodrigues CM. The role of p53 in apoptosis. *Discov Med* 2010; 9(45): 145-152.
  26. Ahmadikia K, Hashemi SJ, Khodavaisy S, Getso MI, Alijani N, Badali H, Mirhendi H, Salehi M, Tabari A, Mohammadi Ardehali M, Kord M, Roilides E, Rezaie S. The double-edged sword of systemic corticosteroid therapy in viral pneumonia: A case report and comparative review of influenza-associated mucormycosis versus COVID-19 associated mucormycosis. *Mycoses* 2021; 64(8): 798-808. <https://doi.org/10.1111/myc.13256>
  27. Kumar A, Sinha N, Bhardwaj A, Goel S. Clinical risk assessment of chronic kidney disease patients using genetic programming. *Comput Methods Biomech Biomed Engin* 2022; 25(8): 887-895. <https://doi.org/10.1080/10255842.2021.1985476>
  28. Rodriguez-Garcia JL, Sanchez-Nievas G, Arevalo-Serrano J, Garcia-Gomez C, Jimenez-Vizueté JM, Martinez-Alfaro E. Baricitinib improves respiratory function in patients treated with corticosteroids for SARS-CoV-2 pneumonia: an observational cohort study. *Rheumatology (Oxford)* 2021; 60(1): 399-407. <https://doi.org/10.1093/rheumatology/keaa587>
  29. Mori T, Morii M, Terada K, Wada Y, Kuroiwa Y, Hotsubo T, Fuse S, Nishioka S, Nishioka T, Tsutsumi H. Clinical characteristics and computed tomography findings in children with 2009 pandemic influenza A (H1N1) viral pneumonia. *Scand J Infect Dis* 2011; 43(1): 47-54. <https://doi.org/10.3109/00365548.2010.515607>
  30. Kudo K, Takasaki J, Manabe T, Uryu H, Yamada R, Kuroda E, Kobayashi N, Matsushita T. Systemic corticosteroids and early administration of antiviral agents for pneumonia with acute wheezing due to influenza A(H1N1)pdm09 in Japan. *PLoS One* 2012; 7(2): e32280. <https://doi.org/10.1371/journal.pone.0032280>
  31. Choi YJ, Jeon JH, Oh JW. Critical combination of initial markers for predicting refractory *Mycoplasma pneumoniae* pneumonia in children: a case control study. *Respir Res* 2019; 20(1): 193. <https://doi.org/10.1186/s12931-019-1152-5>
  32. Ceccato A, Russo A, Barbetta E, Oscanoa P, Tiseo G, Gabarrus A, Di Giannatale P, Nogas S, Cilloniz C, Menichetti F, Ferrer M, Niederman M, Falcone M, Torres A. Real-world corticosteroid use in severe pneumonia: a propensity-score-matched study. *Crit Care* 2021; 25(1): 432. <https://doi.org/10.1186/s13054-021-03840-x>
  33. Anstey MH, Luu J, Myers E, Palmer RN, Wibrow B, Ho KM. Vitamin C and corticosteroids in viral pneumonia. *Acute Crit Care* 2021; 36(2): 169-171. <https://doi.org/10.4266/acc.2020.01081>