Peer Review File

Article information: http://dx.doi.org/10.21037/jtd-20-1306

Reviewer comments to author

Reviewer 1

This is essentially a negative report saying that 2 gm of iv vitamin C is ineffective in improving severe viral pneumonia respiratory failure.

1. The number of patients in the vitamin C group is small.

Authors' Response: Thank you for your comments. Although the number of patients with Vitamin C group included in our paper was small (n = 35), the number of patients in vitamin C groups in other papers was 35 to 53 (1-3), similar to this study. In addition, we discussed the statistical significance with the professor of statistics (K.I.S.) and confirmed that the number of patients without problems in showing statistical significance. Besides few papers are vitamin c for severe viral pneumonia with respiratory failure.

2. The dose of vitamin C of 2 gm is probably not sufficient. How the authors determined the dose of vitamin C needs to be mentioned.

Authors' Response : Thank you for pointing out important aspects. We decided to give 6 grams of vitamin C (divided into three equal doses) per day because intravenous vitamin C normalizes leukocyte vitamin C levels in respiratory infections at a dose of 6 g/day (4). So we added this comment on revised manuscript.

Revised manuscript (Material and methods, page 5, paragraph 2)

Viral pneumonia is a lung infection caused by a virus identified by sputum culture and PCR. The study patients were administered with 2 g of intravenous vitamin C every 8 hours for 4 days or until ICU discharge. We decided to give 6 grams of vitamin C (divided into three equal doses) per day because intravenous vitamin C normalizes leukocyte vitamin C levels in respiratory infections at a dose of 6 g/day (4). In addition, vitamin C 6g/day has been used recently with reference to other studies (5)(Supplementary Table 1).

Supplementary Table 1. Variations in vitamin C dose in the control and vitamin C groups.

		Vitamin C Levels (g/Day)	
Trial Year, Title	Participants	Vitamin C Group	Control Group
Mochalkin 1970, Ascorbic acid in the complex therapy of acute pneumonia (6)	70 in control group, 39 in low vitamin C group and 31 in high vitamin C group	High vitamin C : 0.5 to 1.6 G/day Low vitamin C : 0.25 to 0.8 G/day	-
Hunt 1994, The clinical effects of vitamin C supplementation in elderly hospitalised patients with acute respiratory infections (7)	28 vitamin C; 29 placebo, Hospitalised for acute bronchitis (n = 40) or pneumonia (n = 17)	Vitamin C 0.2 G/day	-
Tanaka 2000, Reduction of	37 consecutive	Intravenous vitamin	-

resuscitation fluid volumes in severely burned patients using ascorbic acid administration: a randomized, prospective study (8)	patients with burns over 30% of their total body surface area who were admitted to the ICU within 2 h after the injury	C (66 mg/kg/h)	
Flower 2014, Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis (9)	24 patients with severe sepsis, 8 in placebo group, 8 in low ascorbic acid group, 8 in high ascorbic acid group	High vitamin C: 200 mg/kg/24 h Low vitamin C : 50 mg/kg/24 h	5% dextrose/water
Marik 2017, Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock (2)	47 patients in both treatment and control groups	Vitamin C : 1.5 g every 6 h for 4 days or until ICU discharge	-
Kim 2018, Combined vitamin C, hydrocortisone, and thiamine therapy for patients with severe pneumonia who were admitted to the intensive	99 patients with severe pneumonia, 53 patients in vitamin C group, 46 patients in control group	Vitamin C : 6 g/day	-

care unit: Propensity score-based analysis of a before-after cohort study (1)

3. Plasma vitamin C concentration was not measured (the authors termed this as a limitation of this fact). Why corticosteroids was not used in this study needs to be explained.

Authors' Response : Thank you for your comments. As there were groups using steroids, Table 1 lists whether steroids were used.

Characteristics	Total n = 201	Vitamin C n = 35	Non vitamin C n = 166	p-value
Steroid	132 (65.7)	31 (88.6)	130 (78.3)	0.167

Steroid was given around 90% of patients in vitamin c group. There were no statistical differences between the two groups, so no additional comments were written.

Patients with severe viral pneumonia are likely to have a condition requiring steroids. In viral pneumonia, steroid decreases the cytokines, but prolongs the viral replication period. In addition, corticosteroids were not used as routines because there have been reports that mortality increases when corticosteroids are used in viral pneumonia (10-12).

4. Since pneumonia is due to a variety of viruses, is it possible that some specific types of viral pneumonia only will respond to vitamin C?

Authors' Response : Thank you for your comments. A few papers were reported the effect of vitamin c for specific virus. However we could not find any benefits for specific virus, maybe related small numbers of patients.

In manuscript (Discussions, page 9-10, paragraph 3 The use of vitamin C in restraint-stressed mice with H1N1 virus-induced pneumonia resulted in the improvement of survival rates and prolonged survival time (13). This finding suggests that vitamin C may be effective in improving the prognosis of patients with influenza. Fowler Ⅲ AA et al. showed that administration of high-dose intravenous vitamin C into a patient with enterovirus/rhinovirus-induced acute respiratory distress syndrome (ARDS) was associated with rapid resolution of lung injury with no evidence of post-ARDS fibroproliferative sequelae (14). After influenza infection, bacterial pneumonia is likely to follow as a complication (15). It is thought that vitamin C can play a role in both bacterial and viral infections, so it can be effective in improvement of prognosis of viral pneumonia. Kim et al. found that the use of red ginseng and vitamin C in influenza A infection increases immune cell activity and reduces lung inflammation (16).

So, influenza, enterovirus and rhinovirus may respond to vitamin C. However, additional prospective studies are likely to be needed.

5. Use of vitamin B12 would have helped the vitamin C group in recovering earlier?

Authors' Response : Thank you for your comments. In previous studies, the association between vitamin B12 and viral respiratory disease was studied, but not recently (17,18). However, according to the contents of nutrients (19), taking vitamin B12 may help the cell and immune system and help to resist infection. But we did not give vitamin B12 routinely in our practice.

Reviewer 2

1. This study found that 6 g/d vitamin C did not have a significant effect on severe viral pneumonia. The study protocol and results seem to be correct. One question arises: should an affect have been expected? Could the authors briefly discuss in general findings for viral and bacterial infections? It is noted that search with "Vitamin C viral infections" turns up 444 entries at pubmed.gov vs. 157 for bacterial infections.

Authors' Response : Thank you for pointing out important aspects. We expected that vitamin C is effective for viral pneumonia in this study. As we know, most of virus we don't have good drug, but for we have antibiotics for bacteria, so we made hypothesis we could show easily effectiveness of vitamin c in viral pneumonia rather than bacteria. However, the results were different from what we expected. As commented by reviewer, we revised the discussion section as below.

Revised manuscript (Discussions, page9-10, paragraph 3)

Vitamin C has been found to be effective in recovery and prevention from infection in animal experiments, and this effect is thought to be the same for humans (5,20,21). In some studies conducted in humans, vitamin C is also helpful for prevention and treatment of common colds, viral and bacterial infection (1,5,12,20-22). Hunt et al. found an 85 % lower mortality in the vitamin C group compared with the placebo group. However, this comparison was made based on a small number of cases (six cases) (7). Mochalkin et al.'s study reported

that the duration of recovery was reduced from 23.7 days in the control group to 4.6 days (19%) in the low-dose vitamin C group and 8.6 days (36 %) in the high-dose vitamin C group (6). The use of vitamin C in restraint-stressed mice with H1N1 virus-induced pneumonia resulted in the improvement of survival rates and prolonged survival time (13). This finding suggests that vitamin C may be effective in improving the prognosis of patients with influenza.

2. Line 15 biological reactions. A few studies reported that vitamin C can improve the symptoms and prognosis of patients with sepsis and pneumonia. Comment: Yes, but are not most of these infections due to bacteria and not viruses?

Authors' Response: Thank you for pointing out important aspects. Most infections such as sepsis and pneumonia are caused by bacteria. However, respiratory infections are often involved in viral infections (23), and several studies have found that vitamin C is effective for viral infections (4,7,13,14,20,21). As commented by reviewer, we revised the discussion section as below.

Revised manuscript (Abstract, page3)

Background: Vitamin C is a well-known antioxidant and essential cofactor for numerous biological reactions. Several studies reported that vitamin C can improve the symptoms and prognosis of patients with sepsis and respiratory infection.

3. Publications to consider citing regarding free radical generation as another mechanism to kill microorganisms.

Yano M, Ikeda M, Abe K, Kawai Y, Kuroki M, Mori K, Dansako H, Ariumi Y, Ohkoshi S, Aoyagi Y, Kato N. Oxidative stress induces anti-hepatitis C virus status via the activation of

extracellular signal-regulated kinase. Hepatology. 2009 Sep;50(3):678-88.

DU WN, Chen ST. Bactericidal Effects of Oxidative Stress Generated by EDTA-Fe and Hydrogen Peroxide. Biocontrol Sci. 2019;24(2):97-101.

Ghosh T, Srivastava SK, Gaurav A, Kumar A, Kumar P, Yadav AS, Pathania R, Navani NK. A Combination of Linalool, Vitamin C, and Copper Synergistically Triggers Reactive Oxygen Species and DNA Damage and Inhibits Salmonella enterica subsp. enterica Serovar Typhi and Vibrio fluvialis. Appl Environ Microbiol. 2019 Feb 6;85(4). pii: e02487-18.

Pei Z, Wu K, Li Z, Li C, Zeng L, Li F, Pei N, Liu H, Zhang SL, Song YZ, Zhang X, Xu J, Fan XY, Wang J. Pharmacologic ascorbate as a pro-drug for hydrogen peroxide release to kill mycobacteria. Biomed Pharmacother. 2019 Jan;109:2119-2127.

Sakagami H, Asano K, Satoh K, Takahashi K, Kobayashi M, Koga N, Takahashi H, Tachikawa R, Tashiro T, Hasegawa A, Kurihara K, Ikarashi T, Kanamoto T, Terakubo S, Nakashima H, Watanabe S, Nakamura W. Anti-stress, anti-HIV and vitamin C-synergized radical scavenging activity of mulberry juice fractions. In Vivo. 2007 May-Jun;21(3):499-505.

Authors' Response : Thank you for pointing out important aspects. As commented by reviewer, we revised the discussion section as below.

Revised manuscript (Discussions, page9, paragraph 2)

Vitamin C is a well-known antioxidant and plays an important role in hormone production and immune response. Vitamin C plays a role in regulating immune cells, which increases the function of phagocytes and promotes the proliferation of T lymphocytes, which are important in bacterial and viral infections (24). Vitamin C has been found to be effective in killing bacteria (25,26), mycobacteria (27), HIV (28), and HCV (29) because it can generate free radicals and H_2O_2. As such, vitamin C plays a number of important roles in reducing oxidative stress caused by infection (5,30,31), balancing the immune system (24), and killing

microorganisms by generating free radicals (25-29). For the reasons described above, we hypothesized that vitamin C would have positive effects in viral pneumonia. In our study, however, vitamin C did not have beneficial effects in patients with severe viral pneumonia with respiratory failure.

4. Line 178 vitamin C in restraint-stressed mice with H1N1 virus-induced pneumonia resulted in the improvement of survival rates and prolonged survival time (15).

Comment: While H1N1 may have initiated pneumonia, did bacteria actually participate in the pneumonia. Martin-Loeches I, van Someren Gréve F, Schultz MJ. Bacterial pneumonia as an influenza complication. Curr Opin Infect Dis. 2017 Apr;30(2):201-207.

Authors' Response: Thank you for your comments. As commented by reviewer, we revised the discussion section as below.

Revised manuscript (Discussions, page9-10, paragraph 3)

The use of vitamin C in restraint-stressed mice with H1N1 virus-induced pneumonia resulted in the improvement of survival rates and prolonged survival time (13). This finding suggests that vitamin C may be effective in improving the prognosis of patients with influenza. Fowler Ⅲ AA et al. showed that administration of high-dose intravenous vitamin C into a patient with enterovirus/rhinovirus-induced acute respiratory distress syndrome (ARDS) was associated with rapid resolution of lung injury with no evidence of post-ARDS fibroproliferative sequelae (14). After influenza infection, bacterial pneumonia is likely to follow as a complication (15). Vitamin C can play a role in both bacterial and viral infections, so it is thought that it may be effective in preventing bacterial pneumonia and promoting

prognosis in viral pneumonia.

5. Use of vitamin C for viral infections Kim H, Jang M, Kim Y, Choi J, Jeon J, Kim J, Hwang YI, Kang JS, Lee WJ. Red ginseng and vitamin C increase immune cell activity and decrease lung inflammation induced by influenza A virus/H1N1 infection. J Pharm Pharmacol. 2016 Mar;68(3):406-20.

Authors' Response: Thank you for your comments. As commented by reviewer, we revised the discussion section as below.

Revised manuscript (Discussions, page9-10, paragraph 3)

Vitamin C can play a role in both bacterial and viral infections, so it is thought that it may be effective in preventing bacterial pneumonia and promoting prognosis in viral pneumonia. Kim et al. found that the use of red ginseng and vitamin C in influenza A infection increases immune cell activity and reduces lung inflammation (16). Recently, Kim et al. showed that the use of vitamin C, hydrocortisone, and thiamine resulted in the reduction of mortality (17 % vs. 39 %, p = 0.04) and improvement in the chest radiologic findings (1). However, in our study, use of vitamin C in patients with severe viral pneumonia with respiratory failure did not showed the improvement of prognosis. In the vitamin C group, ECMO was frequently applied, and the group of patients who had ECMO was predicted to have high mortality (32), so we thought that this has influenced the results.

6. Significant digits. The general rule is that no more non-zero digits should be given than are justified by the uncertainty of the value.

See "Too many digits: the presentation of numerical data"

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4483789/

Authors' Response : As commented by the reviewer, we checked the digits written in the paper and made appropriate changes.

7. If the uncertainty is greater than about 7%, only two non-zero digits are justified.

P values should be given to two decimal places unless the first two are 00 or the number lies between 0.045 and 0.050.

Thus,

Line 22 Results: there were differences between the vitamin C group and non-vitamin C group in terms of age (59.6 ± 14.8 vs. 65.9 ± 14.3, p = 0.025), extracorporeal membrane oxygenation (28.6% vs. 5.4%, p < 0.001), and procalcitonin (5.4 ± 10.2 vs. 12.6 ± 27.4, p = 0.039)

Should be

Results: there were differences between the vitamin C group and non-vitamin C group in terms of age (60 ± 15 vs. 66 ± 14, p = 0.03), extracorporeal membrane oxygenation (28.6% vs. 5.4%, p < 0.001), and procalcitonin (5 ± 10 vs. 13 ± 27, p = 0.04)

Authors' Response : We are sorry to make confusion. We checked the number written in the paper and made appropriate changes.

8. Regarding percentages, with 201 patients, use of one decimal place is marginally OK.

Please review all numbers in abstract, text, tables, and figures and adjust accordingly.

Authors' Response : We are sorry to make confusion. As commented by reviewer, we checked the numbers in all papers and adjusted them accordingly.

9. Line 26: the propensity-matched group, the 28-day mortality was not different between the two groups (20.0 % vs. 37.1 %, p = 0.073).

should state

the propensity-matched group, the 28-day mortality was not significantly different between the two groups (20.0 % vs. 37.1 %, p = 0.073).

Authors' Response : Thank you for your comments. As commented by reviewer, we revised the discussion section as below.

Revised manuscript (Abstract, page3)

In the propensity-matched group, the 28-day mortality was not significantly different between the two groups (20.0 % vs. 37.1 %, p = 0.07).

10. Question: why was 6 g vitamin C used? Did any other trials use higher doses, especially those that were successful, if any. It would be useful to present the results of other studies in a table and include the vitamin C dose used.

See:

Hemilä H. Vitamin C and Infections. Nutrients. 2017 Mar 29;9(4). pii: E339.

Authors' Response : Thank you for your comments. As you know adequate doses of vitamin C were not determined. Among studies, doses of vitamin c were different. As commented by reviewer, we revised the discussion section as below.

Revised manuscript (Material and methods, page5, paragraph 2)

Viral pneumonia is a lung infection caused by a virus identified by sputum culture and PCR. The study patients were administered with 2 g of intravenous vitamin C every 8 hours for 4 days or until ICU discharge[11,14]. We decided to give 6 grams of vitamin C (divided into three

equal doses) per day because intravenous vitamin C normalizes leukocyte vitamin C levels in respiratory infections at a dose of 6 g/day (4). In addition, vitamin C 6g/day has been used recently with reference to other studies (5)(Supplementary Table 1).

Supplementary Table 1. Variations in vitamin C dose in the control and vitamin C groups.

		Vitamin C Levels (g/Day)	
Trial Year, Title	Participants	Vitamin C Group	Control Group
Mochalkin 1970, Ascorbic acid in the complex therapy of acute pneumonia (6)	70 in control group, 39 in low vitamin C group and 31 in high vitamin C group	High vitamin C : 0.5 to 1.6 G/day Low vitamin C : 0.25 to 0.8 G/day	-
Hunt 1994, The clinical effects of vitamin C supplementation in elderly hospitalised patients with acute respiratory infections (7)	28 vitamin C; 29 placebo, Hospitalised for acute bronchitis (n = 40) or pneumonia (n = 17)	Vitamin C 0.2 G/day	-
Tanaka 2000, Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid	37 consecutive patients with burns over 30% of their total body surface	Intravenous vitamin C (66 mg/kg/h)	-

administration: a randomized, prospective study (8)	area who were admitted to the ICU within 2 h after the injury		
Flower 2014, Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis (9)	24 patients with severe sepsis, 8 in placebo group, 8 in low ascorbic acid group, 8 in high ascorbic acid group	High vitamin C: 200 mg/kg/24 h Low vitamin C : 50 mg/kg/24 h	5% dextrose/water
Marik 2017, Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock (2)	47 patients in both treatment and control groups	Vitamin C : 1.5 g every 6 h for 4 days or until ICU discharge	-
Kim 2018, Combined vitamin C, hydrocortisone, and thiamine therapy for patients with severe pneumonia who were admitted to the intensive care unit: Propensity score-based analysis of a before-after cohort study (1)	99 patients with severe pneumonia, 53 patients in vitamin C group, 46 patients in control group	Vitamin C : 6 g/day	-

11. These publications might be cited

Can early and high intravenous dose of vitamin C prevent and treat coronavirus disease 2019 (COVID-19)?

Cheng RZ.

Med Drug Discov. 2020 Mar;5:100028. doi: 10.1016/j.medidd.2020.

Carr AC. A new clinical trial to test high-dose vitamin C in patients with COVID-19. Crit Care. 2020 Apr 7;24(1):133. doi: 10.1186/s13054-020-02851-4.

Authors' Response : Thank you for your comments. As commented by reviewer, we revised the discussion section as below.

Revised manuscript (Discussions, page11, paragraph 5)

2019 Novel Coronavirus (2019-nCoV) is the first virus found in Wuhan, China. And now it is spreading rapidly all over the world and was declared as a global concern (pandemic) by the World Health Organization (WHO). Since then, clinical trials have been conducted for various antiviral agent and vaccines, but there are no definite drugs that shown to be effective (33-35). Coronavirus infections can cause cytokine storms, which can increase oxidative stress and damage capillary endothelial cells (36,37). Vitamin C is a well-known antioxidant and reduces oxidative stress and improves in endothelial and epithelial barrier functions (38,39). The use of vitamin C for COVID-19 is being attempted (39,40) because it takes time to find effective vaccines and antiviral agents. The use of vitamin C 24g/day for 7days in severe COVID-19 pneumonia patients is going on trial (40).

Reviewer 3

1. Line 71: Please indicate the name of your hospital

Authors' Response : Thank you for your comments. As commented by reviewer, we revised the discussion section as below.

Revised manuscript (Patients and study design, page 5, paragraph 1)

We reviewed the medical records of patients with viral pneumonia admitted to asan medical center (seoul, republic of korea)'s medical intensive care unit (MICU) from January 2015 to April 2017. Of 1,971 patients admitted to the MICU, 201 were included. Patients who were younger than 18 years, those with bacterial pathogens (n = 1751), and those who did not use a ventilator (n = 19) were excluded (Figure 1).

References

1. Kim WY, Jo EJ, Eom JS, et al. Combined vitamin C, hydrocortisone, and thiamine therapy for patients with severe pneumonia who were admitted to the intensive care unit: Propensity score-based analysis of a before-after cohort study. J Crit Care. 2018;47:211-8.
2. Marik PE, Khangoora V, Rivera R, et al. Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study. Chest. 2017;151:1229-38.
3. Ahn JH, Oh DK, Huh JW, et al. Vitamin C alone does not improve treatment outcomes in mechanically ventilated patients with severe sepsis or septic shock: a retrospective cohort study. Journal of Thoracic Disease. 2019;11:1562-70.
4. Hume R, Weyers E. Changes in leucocyte ascorbic acid during the common cold.

Scott Med J. 1973;18:3-7.

5. Hemila H. Vitamin C and Infections. Nutrients. 2017;9.

6. Mochalkin NI. [Ascorbic acid in the complex therapy of acute pneumonia]. Voen Med Zh. 1970;9:17-21.

7. Hunt C, Chakravorty NK, Annan G, et al. The clinical effects of vitamin C supplementation in elderly hospitalised patients with acute respiratory infections. Int J Vitam Nutr Res. 1994;64:212-9.

8. Tanaka H, Matsuda T, Miyagantani Y, et al. Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration: a randomized, prospective study. Arch Surg. 2000;135:326-31.

9. Fowler AA, 3rd, Syed AA, Knowlson S, et al. Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis. J Transl Med. 2014;12:32.

10. Yang Z, Liu J, Zhou Y, et al. The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. J Infect. 2020; doi:10.1016/j.jinf.2020.03.062.

11. Ni YN, Chen G, Sun J, et al. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. Crit Care. 2019;23:99.

12. Zhou Y, Fu X, Liu X, et al. Use of corticosteroids in influenza-associated acute respiratory distress syndrome and severe pneumonia: a systemic review and meta-analysis. Sci Rep. 2020;10:3044.

13. Cai Y, Li YF, Tang LP, et al. A new mechanism of vitamin C effects on A/FM/1/47(H1N1) virus-induced pneumonia in restraint-stressed mice. Biomed Res Int. 2015;2015:675149.

14. Fowler Iii AA, Kim C, Lepler L, et al. Intravenous vitamin C as adjunctive therapy for enterovirus/rhinovirus induced acute respiratory distress syndrome. World J Crit Care

Med. 2017;6:85-90.

15. Martin-Loeches I, van Someren Gréve F, Schultz MJ. Bacterial pneumonia as an influenza complication. Curr Opin Infect Dis. 2017;30:201-7.

16. Kim H, Jang M, Kim Y, et al. Red ginseng and vitamin C increase immune cell activity and decrease lung inflammation induced by influenza A virus/H1N1 infection. J Pharm Pharmacol. 2016;68:406-20.

17. Dorogi B. The influence of vitamin B12 on viral respiratory diseases. Indian J Med Sci. 1962;16:42-6.

18. Thaller G. [Vitamin B12 in the prevention of influenza]. Munch Med Wochenschr. 1957;99:1977-8.

19. Calder PC, Carr AC, Gombart AF, et al. Optimal Nutritional Status for a Well-Functioning Immune System Is an Important Factor to Protect against Viral Infections. Nutrients. 2020;12.

20. Hemila H, Douglas RM. Vitamin C and acute respiratory infections. Int J Tuberc Lung Dis. 1999;3:756-61.

21. Hemila H, Louhiala P. Vitamin C for preventing and treating pneumonia. Cochrane Database Syst Rev. 2013; doi:10.1002/14651858.CD005532.pub3:Cd005532.

22. Marik PE. Vitamin C for the treatment of sepsis: The scientific rationale. Pharmacol Ther. 2018; doi:10.1016/j.pharmthera.2018.04.007.

23. Zhang N, Wang L, Deng X, et al. Recent advances in the detection of respiratory virus infection in humans. J Med Virol. 2020;92:408-17.

24. Li Y, Li G. Is Vitamin C Beneficial to Patients with CAP? Curr Infect Dis Rep. 2016;18:24.

25. Ghosh T, Srivastava SK, Gaurav A, et al. A Combination of Linalool, Vitamin C, and Copper Synergistically Triggers Reactive Oxygen Species and DNA Damage and

Inhibits Salmonella enterica subsp. enterica Serovar Typhi and Vibrio fluvialis. Appl Environ Microbiol. 2019;85.

26. Du WN, Chen ST. Bactericidal Effects of Oxidative Stress Generated by EDTA-Fe and Hydrogen Peroxide. Biocontrol Sci. 2019;24:97-101.

27. Pei Z, Wu K, Li Z, et al. Pharmacologic ascorbate as a pro-drug for hydrogen peroxide release to kill mycobacteria. Biomed Pharmacother. 2019;109:2119-27.

28. Sakagami H, Asano K, Satoh K, et al. Anti-stress, anti-HIV and vitamin C-synergized radical scavenging activity of mulberry juice fractions. In Vivo. 2007;21:499-505.

29. Yano M, Ikeda M, Abe K, et al. Oxidative stress induces anti-hepatitis C virus status via the activation of extracellular signal-regulated kinase. Hepatology. 2009;50:678-88.

30. Fukui H, Iwahashi H, Endoh S, et al. Ascorbic acid attenuates acute pulmonary oxidative stress and inflammation caused by zinc oxide nanoparticles. J Occup Health. 2015;57:118-25.

31. Chen Y, Luo G, Yuan J, et al. Vitamin C mitigates oxidative stress and tumor necrosis factor-alpha in severe community-acquired pneumonia and LPS-induced macrophages. Mediators Inflamm. 2014;2014:426740.

32. Sukhal S, Sethi J, Ganesh M, et al. Extracorporeal membrane oxygenation in severe influenza infection with respiratory failure: A systematic review and meta-analysis. Ann Card Anaesth. 2017;20:14-21.

33. Esposito S, Noviello S, Pagliano P. Update on treatment of COVID-19: ongoing studies between promising and disappointing results. Infez Med. 2020;28:198-211.

34. Murthy S, Gomersall CD, Fowler RA. Care for Critically Ill Patients With COVID-19. Jama. 2020; doi:10.1001/jama.2020.3633.

35. Pang J, Wang MX, Ang IYH, et al. Potential Rapid Diagnostics, Vaccine and

Therapeutics for 2019 Novel Coronavirus (2019-nCoV): A Systematic Review. J Clin Med. 2020;9.

36. Meng L, Zhao X, Zhang H. HIPK1 Interference Attenuates Inflammation and Oxidative Stress of Acute Lung Injury via Autophagy. Med Sci Monit. 2019;25:827-35.

37. Fujishima S. Pathophysiology and biomarkers of acute respiratory distress syndrome. J Intensive Care. 2014;2:32.

38. Secor D, Li F, Ellis CG, et al. Impaired microvascular perfusion in sepsis requires activated coagulation and P-selectin-mediated platelet adhesion in capillaries. Intensive Care Med. 2010;36:1928-34.

39. Cheng RZ. Can early and high intravenous dose of vitamin C prevent and treat coronavirus disease 2019 (COVID-19)? Med Drug Discov. 2020;5:100028.

40. Carr AC. A new clinical trial to test high-dose vitamin C in patients with COVID-19. Crit Care. 2020;24:133.