AIMN review
Australasian Institute for Medical Nutrition
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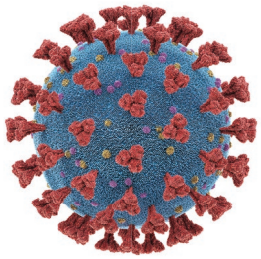
MAR 2020

COVID-19: Novel coronavirus and IVC

Current Guidelines and Clinical Trials



CORONAVIRUS (COVID-19)

PROTECTION FROM AND SUPPORTIVE TREATMENT

The following dissertation on high dose intravenous Vitamin C in the supportive treatment of patients severely affected by the coronavirus (COVID –19) with pneumonia is not meant to infer that it is necessarily the best or only approach to the prevention and treatment of coronavirus (COVID-19) complications. It is causing worldwide concern, threatening to become a pandemic.

Before patients receive intravenous Vitamin C (IVC) they should have normal kidney function and normal G6PD levels. Vitamin C may also produce false positive glucose readings (both reducing agents) on glucometers so insulin dependent patients who have received IVC need to be assessed appropriately.

We are now continually and correctly told about the importance of washing hands regularly and thoroughly with soap and water and to carry an alcoholic sanitizer lotion which can be used several times daily after touching other hands or objects such as hand rails or just routinely a few times a day to reduce hand viral and bacterial load. To avoid people coughing or sneezing on you - turn away, back away to avoid contaminated droplets as much as possible, and avoid coughing or sneezing on other people. Avoid crowded places as much as possible. Limit touching the face on a casual routine basis as much as possible. Avoid shaking hands, hugging and kissing especially to strangers. If necessary, wash hands and/or use sanitizer lotion on hands ASAP. These measures may seem extreme but this coronavirus strain is particularly contagious – so personal responsibility for your own routine hygiene and lifestyle approach requires extra precautions.

Take care with diet and lifestyle to help maintain a healthy immune system. Younger people are much less likely to contract the current epidemic/pandemic corona viral disease but should still practice good hygiene as much as possible.

Once patients have developed a severe form of the coronavirus which has developed into pneumonia requiring hospitalization many treatment protocols may be used including breathing assistance and a number of antiviral medications. A great deal of resources is being used to develop a vaccine to assist in prevention.

Intravenous Vitamin C (IVC) has a long history in assisting in the resolution of many viral diseases including pneumonia and is currently involved in many clinical trials around the world for the supportive treatment of cancer and in combination with intravenous thiamine to reduce symptomology and death rate from sepsis – which may also be involved in serious pneumonia cases. Interestingly there are now three well designed clinical trials underway in China to test the effectiveness of IVC in the treatment of coronavirus (COVID-19) induced pneumonia. One of these Chinese IVC trials is described in the following review. Based on the considerable level of evidence-based medicine and current clinical trials intravenous Vitamin C may be a useful tool to assist in saving lives and/or major organ damage as a result of severe coronavirus (COVID-19) infection.

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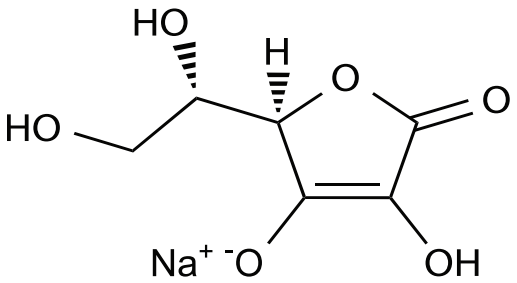

1 General Overview

:: COVID-19 Coronavirus & IVC

Introduction

A current outbreak of the novel coronavirus (COVID-19) has authorities scrambling to try to contain it. In the epicenter of the outbreak (Wuhan China) the number of confirmed infections is approaching 80,000 with the likelihood of a significant increase as time goes on, however due to strict control measures in place the infection rate is declining in Wuhan. Hot spots of community spread are currently being reported in Italy, Iran, Japan and South Korea. However it is highly likely that other centres will soon be added to the list. So far in Australia the infection rate has not climbed significantly, and no community hot spots have been reported. It is unknown which way this infection will go; resolution or pandemic or something in between, however it is anticipated by some that COVID-19 may ultimately become a widespread community based infection. Various countries, including Australia, are preparing or are activating pandemic response plans.

COVID-19 is a coronavirus similar to SARS (Severe Acute Respiratory Syndrome) and MERS (Middle Eastern Respiratory Syndrome). In these previous cases of SARS infection there have been anecdotal reports of doctors using high dose intravenous Vitamin C (HDIVC) in patients with some success. We do not know of any clinical trials or extensive case report summaries in viral pneumonia where patients were infected specifically with SARS, MERS or COVID-19.

This communication serves as a reminder of the previous successes of HDIVC in treating a variety of viral infections, including pneumonia associated with several infections agents. COVID-19 has a similar pathology to SARS and MERS, it is reasonable to expect that HDIVC may have an impact in patients with mild or severe COVID-19 symptoms.

Demographics of COVID-19

Real time statistics are estimates, but as the outbreak spreads and the numbers climb a better overview of the outbreak is emerging. Real time statistics can be found here:

https://arcg.is/0fHmTX
(Dong et al., 2020) (login may be required).

An overview of the outbreak based on various sources of data can be found here:

https://www.worldometers.info/coronavirus/
("Coronavirus Update (Live): COVID-19 Wuhan China Virus Outbreak - Worldometer," 2020).

It is important to note that these statistics are based on case reports – it is likely that the extent of infection is much greater because many people with the infection are asymptomatic or have very mild disease and have not reported or sought treatment at a health facility. Currently the numbers are very fluid, so the following snapshot will be out of date very quickly. Please continue to refer to the real time statistics and interpretations cited above.

Asymptomatic or mild disease: 82%

Serious or Critical disease: 18%

Mortality rate: ..... ~2-3 %?
(Too early to know yet), potentially this is considerably higher.

The current reported mortality rate for patients with an outcome (they either recovered or died) is 7%. As the numbers of infections grow these numbers will change, please continue to monitor the references above for current information.

COVID-19 Fatality Rate by AGE:

AGE	DEATH RATE*
80+ years old	14.8%
70-79 years old	8.0%
60-69 years old	3.6%
50-59 years old	1.3%
40-49 years old	0.4%
30-39 years old	0.2%
20-29 years old	0.2%
10-19 years old	0.2%
0-9 years old	no fatalities

COVID-19 Fatality Rate by AGE:

SEX	DEATH RATE*
Male	2.8%
Female	1.7%

The mortality rate is significantly higher in groups who have pre-existing disease, such as diabetes, immune suppression and pre-existing respiratory diseases.
Currently the outbreak has nowhere near reached the levels of infection this season by influenza viruses. Just in the USA, this season (since September 2019), the Centers for Disease Control (CDC, 2020) estimates that, from October 1, 2019, through February 15, 2020, there have been:

- 29,000,000 – 41,000,000 flu illnesses
- 280,000 – 500,000 flu hospitalizations
- 16,000 – 41,000 flu deaths

At the time of writing, deaths have not yet been reported in the USA due to COVID-19.

What is the potential for HDIVC in this outbreak?

For detailed reviews of the past use and potential use of Vitamin C in a variety of viral diseases we invite you to read these publications:

- AIMNReview - Vitamin C in the treatment of viral diseases (Dettman, 2019)
- AIMNReview: Ebola and Vitamin C (Dettman, 2014)
- AIMNReview: Vitamin C and Zika virus (Dettman, 2016)

The pathological features of COVID-19 resemble those seen in SARS and Middle Eastern respiratory syndrome (MERS) coronavirus infections (Liu et al., 2020; Xu et al., 2020). Because of this, it is reasonable to assume that medical interventions used in similar outbreaks may be of use in COVID-19 cases.

Vitamin C has a long history of use in viral infections, including influenza infections and some discussion about SARS (Dettman, 2019; Hemila, 2003). An excerpt from this review follows:

There is a significant body of work now about Vitamin C and its effects on immunity and some on viruses in respiratory infections. A review of drug therapies in Avian Influenza has highlighted the potential and typical use of Vitamin C in serious Influenza infections (Yuan, 2013). In this review Yuan states that *"effective inhibition of viral replication and apparent symptom alleviation usually requires over 5mM of VC (plasma concentration)"* Yuan comments that oral Vitamin C is inadequate because these levels cannot be obtained.

A mouse study by Li et al. looked at Vitamin C levels and pathology in influenza infected mice. The gulo-/- mice used cannot make Vitamin C. The mice were split into two groups; prior to infection one group got Vitamin C and one group did not (Li et al., 2006). They found that the lung is more susceptible to Vitamin C deficiency than the liver. *"At d 7 after infection, vitamin C–deficient mice had significantly greater lung pathology compared with vitamin C–adequate mice."*

Several authors have called for the use of high dose Vitamin C in influenza, in particular in relation to highly pathogenic strains such as avian flu. Ely (Ely, 2007) reviewed the potential use of Vitamin C in Avian flu: *"Now, we consider a person who is malnourished but not in extremely poor health, although his resistance to many diseases is rather marginal. Such a person can still survive a mild infection of flu if the amount of flu virus is not exceeding his ability to: (i) provide sufficient white blood cells for defense; and (ii) stimulate interferon production to go into adjacent cells, preventing the virus from reproducing in them."* Ely follows on the heels of a long history of use of Vitamin C in infections, including influenza and other viral infections, and cites previous reviews on the material by Linus Pauling.

> *"At day 28, mortality was 46.3% (38/82) in the placebo group vs 29.8% (25/84) in the vitamin C group."*

> *"This communication serves as a reminder of the previous successes of HDIVC in treating a variety of viral infections, including pneumonia associated with several infections agents."*

Carr et al. have recently undertaken an extensive review of the role of Vitamin C in immune response (Carr and Maggini, 2017). They document numerous functions of Vitamin C and conclude that: *"Vitamin C deficiency results in impaired immunity and higher susceptibility to infections. In turn, infections significantly impact on vitamin C levels due to enhanced inflammation and metabolic requirements. Furthermore, supplementation with vitamin C appears to be able to both prevent and treat respiratory and systemic infections."*

Some other specific studies and reviews related to respiratory infections include:

- **Critical care management of adults with community-acquired severe respiratory viral infection** (Arabi et al., 2020) *"The recent CITRIS-ALI trial demonstrated that 96-h infusion of vitamin C (50mg/kg in dextrose 5% in water) compared with placebo in a relatively small number (n = 167) of patients with sepsis and ARDS did not improve the primary outcome of organ dysfunction scores or alter markers of inflammation and vascular injury. However, mortality, which was one of the forty-six pre-specified secondary endpoints, was significantly lower with vitamin C."* At day 28, mortality was 46.3% (38/82) in the placebo group vs 29.8% (25/84) in the vitamin C group. IVC at 50mg/kg (3 grams for a 60 kg person) is considerably lower than the typical dose being used by general practitioners treating patients with severe viral infections. Doses with a single infusion of ascorbic acid ranging from 25-50 grams (Marcial-Vega et al., 2015) and 100g/day (Gonzalez et al., 2015) are reported.

- **Effects of a nutrient mixture on infectious properties of the highly pathogenic strain of avian influenza virus A/H5N1** (Deryabin et al., 2008, p. 1). The nutrient mixture

contained lysine, proline, ascorbic acid, green tea extract, N-acetyl cysteine, selenium and other micro nutrients, and the mixture was applied to virus infected cultured cells. *"(the nutrient mixture) demonstrated high antiviral activity evident even at prolonged periods after infection. NM antiviral properties were comparable to those of conventional drugs (amantadine and oseltamivir); however, NM had the advantage of affecting viral replication at the late stages of the infection process."*

- **Combined inhalational and oral supplementation of ascorbic acid may prevent influenza pandemic emergency: A hypothesis** (Banerjee and Kaul, 2010)

- **[Pharmacologic ascorbate treatment of influenza in vivo]** (Cheng et al., 2014). The study investigated the effects of C against Influenza A/CA/7/09 (H1N12009) in mice. *"Mice infected with influenza virus and treated with pharmacologic ascorbate had higher survival and less weight loss, and had lung viral titers reduced by as much as 10 to 100-fold compared to the controls. Pathologic study of the lungs showed that the treated animals had little inflammation (bronchiolitis, perivasculitis, alveolitis, and vasculitis) compared to the controls.IL-1, IL-6, and IFN-alpha lung levels were lower in the treated animals compared to the controls."*

- **A new mechanism of vitamin C effects on A/FM/1/47(H1N1) virus-induced pneumonia in restraint-stressed mice** (Cai et al., 2015). *"Results showed that restraint stress significantly increased the mortality and the severity of pneumonia in mice caused by A/FM/1/47(H1N1) virus infection, which was attenuated by oral administration of vitamin C (125 and 250 mg/kg). Moreover, vitamin C administration significantly decreased expression of susceptibility genes, including mitochondrial antiviral signaling (MAVS) and interferon regulatory factor 3 (IRF3), and increased expression of NF-κB. These work in conjunction to induce type I interferons (IFNs) and elicit innate antiviral response"*. The authors found that the above was also related to inhibition of excess CORT (corticosterone) synthesis by regulating steroid hydroxylating enzymes in adrenal gland, which reduces susceptibility to the infection.

- **Vitamin C and Infections** (Hemilä, 2017). *"Three controlled trials found that vitamin C prevented pneumonia. Two controlled trials found a treatment benefit of vitamin C for pneumonia patients."*

- **Vitamin C and SARS coronavirus** (Hemila, 2003) *"There is also evidence indicating that vitamin C may affect pneumonia. In particular, three controlled trials with human subjects reported a significantly lower incidence of pneumonia in vitamin C-supplemented groups, suggesting that vitamin C may affect susceptibility to lower respiratory tract infections under certain conditions."*

Summary

COVID-19 pathology is essentially similar to other serious coronavirus infections such as SARS and MERS. Previously high dose intravenous vitamin C (HDIVC) has been used by several doctors working with SARS patients (unpublished). Clinical data and case reports looking at the effects of various doses and dose forms of Vitamin C in COVID-19 patients have not been published, though we are aware already that some doctors in China have started using HDIVC in COVID-19 cases. We do not know at this stage if this data will be published. Vitamin C in high dose, in many cases intravenously, has a long history of uses in viral infections, including severe influenza/pneumonia. Because of this it is prudent to consider the use of HDIVC in COVID-19 cases. Potentially HDIVC may buy sufficient time for an infected patient to mount an effective immune response before the pathology overcomes them.

What is missing?

Clinical trials need to be done. Success has been reported with high dose Vitamin C usage in glandular fever, various mosquito borne infections like Dengue fever, Chikungunya, Ross River fever etc., shingles, various other herpes infections and respiratory infections. Clinical trials using Vitamin C in the management of sepsis have been successful; many other similar trials are recruiting or running. Dose ranging needs to be done in this area to best understand the effects and limitations of high dose Vitamin C and its place in the management of sepsis. Severe sepsis and severe acute viral infections share some similar immune response features, there is no reason to doubt that there should be some impact of Vitamin C in severe viral infections. Large studies looking at dose ranging, length of treatment and short term and long-term outcomes for the use of Vitamin C in a variety of serious viral infections have not been done. The use of high dose Vitamin C in serious infections such a bird flu and Ebola have not been investigated. Given the pedigree of Vitamin C in viral infections, it would seem it is time to investigate the effect of high dose Vitamin C in the field. Vitamin C is largely non-toxic, major precautions include assessing renal function and glucose 6 phosphate dehydrogenase (G6PD) deficiency prior to treatment. For the vast majority of patients these issues do not exist, are not clinically relevant, or can be managed.

> *"Vitamin C has a long history of use in viral infections, including influenza infections and some discussion about SARS."*
>
> *Dettman, 2019; Hemila, 2003*

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2 Current Chinese Clinical Trial & Guidelines in the Application of IVC and COVID-19:

:: Vitamin C Infusion for the Treatment of Severe 2019-nCoV Infected Pneumonia

SOURCE: *NIH US National Library of Medicine :: ClinicalTrials.gov*

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT04264533
Recruitment Status : Not yet recruiting
First Posted : February 11, 2020
Last Update Posted : February 11, 2020

Sponsor:
ZhiYong Peng
Information provided by (Responsible Party):
ZhiYong Peng, Zhongnan Hospital.

Study Description

Summary:

2019 new coronavirus (2019-nCoV) infected pneumonia, namely severe acute respiratory infection (SARI) has caused global concern and emergency. There is a lack of effective targeted antiviral drugs, and symptomatic supportive treatment is still the current main treatment for SARI.

Vitamin C is significant to human body and plays a role in reducing inflammatory response and preventing common cold. In addtion, a few studies have shown that vitamin C deficiency is related to the increased risk and severity of influenza infections. We hypothize that Vitamin C infusion can help improve the prognosis of patients with SARI. Therefore, it is necessary to study the clinical efficacy and safety of vitamin C for the clinical management of SARI through randomized controlled trials during the current epidemic of SARI.

Condition or disease	Intervention/ treatment	Phase
Vitamin CPneumonia, ViralPneumonia, Ventilator-Associated	Drug: Vit CDrug: Water for infusion	Phase 2

Detailed Description:

At the end of 2019, patients with unexplained pneumonia appeared in Wuhan, China. At 21:00 on January 7, 2020, a new coronavirus was detected in the laboratory, and the detection of pathogenic nucleic acids was completed at 20:00 on January 10. Subsequently, the World Health Organization officially named the new coronavirus that caused the pneumonia epidemic in Wuhan as 2019 new coronavirus (2019-nCoV), and the pneumonia was named severe acute respiratory infection (SARI). Up to February 4, 2020, over 20000 cases have been diagnosed in China, 406 of which have died, and 154 cases have been discovered in other countries around the world. Most of the deaths were elderly patients or patients with severe underlying diseases. SARI has caused global concern and emergency.

Statistics of the 41 patients with SARI published in JAMA initially showed that 13 patients were transferred into the ICU, of which 11 (85%) had ARDS and 3 (23%) had shock. Of these, 10 (77%) required mechanical ventilation support, and 2 (15%) required ECMO support. Of the above 13 patients, 5 (38%) eventually died and 7 (38%) were transferred out of the ICU. Viral pneumonia is a dangerous condition with a poor clinical prognosis. For most viral infections, there is a lack of effective targeted antiviral drugs, and symptomatic supportive treatment is still the current main treatment.

Vitamin C, also known as ascorbic acid, has antioxidant properties. When sepsis happens, the cytokine surge caused by sepsis is activated, and neutrophils in the lungs accumulate in the lungs, destroying alveolar capillaries. Early clinical studies have shown that vitamin C can effectively prevent this process. In addition, vitamin C can help to eliminate alveolar fluid by preventing the activation and accumulation of neutrophils, and reducing alveolar epithelial water channel damage. At the same time, vitamin C can prevent the formation of neutrophil extracellular traps, which is a biological event of vascular injury caused by neutrophil activation. Vitamins can effectively shorten the duration of the common cold. In extreme conditions (athletes, skiers, art workers, military exercises), it can effectively prevent the common cold. And whether vitamin C also has a certain protective effect on influenza patients, only few studies have shown that vitamin C deficiency is related to the increased risk and severity of influenza infections. In a controlled but non-randomized trial, 85% of the 252 students treated experienced a reduction in symptoms in the high-dose vitamin C group (1g / h at the beginning of symptoms for 6h, followed by 3 * 1g / day).

Among patients with sepsis and ARDS, patients in the high-dose vitamin group did not show a better prognosis and other clinical outcomes. There are still some confounding factors in the existing research, and the conclusions are different.

Therefore, during the current epidemic of SARI, it is necessary to study the clinical efficacy and safety of vitamin C for viral pneumonia through randomized controlled trials.

Study Design

Layout table for study information	
Study Type:	Interventional (Clinical Trial)
Estimated Enrollment:	140 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Triple (Participant, Care Provider, Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	Vitamin C Infusion for the Treatment of Severe 2019-nCoV Infected Pneumonia: a Prospective Randomized Clinical Trial
Estimated Study Start Date:	February 10, 2020
Estimated Primary Completion Date:	September 30, 2020
Estimated Study Completion Date:	September 30, 2020

Arms and Interventions

Arm	Intervention/treatment
Experimental: Vitamin C	Drug: Vitamin C
24g Vitamin C + water for injection, total volume 50ml. 7ml/h; infusion pump.	24g Vitamin C will be infused in the experimental group per day for 7 days by the infusion pump with a speed of 7ml/h. Other Name: Vitamin C
Placebo Comparator: Water for injection	Drug: Water for infusion
50ml water for injection. 7ml/h; infusion pump.	50ml water for infusion will be infused in the placebo comparator group per day for 7 days by the infusion pump with a speed of 7ml/h.

Outcome Measures

Primary Outcome Measures :

1. Ventilation-free days [Time Frame: on the day 28 after enrollment] days without ventilation support during 28 days after patients' enrollment

Secondary Outcome Measures :

1. 28-days mortality [Time Frame: on the day 28 after enrollment] whether the patient survives
2. ICU length of stay [Time Frame: on the day 28 after enrollment] days of the patients staying in the ICU
3. Demand for first aid measurements [Time Frame: on the day 28 after enrollment] t t the rate of CPR
4. Vasopressor days [Time Frame: on the day 28 after enrollment] days of using vasopressors
5. Respiratory indexes [Time Frame: on the day 10 and 28 after enrollment] P O2/Fi O2 which reflects patients' respiratory function
6. Ventilator parameters [Time Frame: on the day 10 and 28 after enrollment] Ecmo or ventilator
7. APACHE II scores [Time Frame: on the day 10 after enrollment] Acute Physiology and Chronic Health Evaluation
8. SOFA scores [Time Frame: on the day 10 after enrollment] Sepsis-related Organ Failure Assessment Eligibility Criteria

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Eligibility Criteria

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Layout table for eligibility information	
Ages Eligible for Study:	18 Years and older (Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

1. ≥ 18 years old;
2. Diagnosed as serious or critical SARI (according to the 4th version of Diagnosis and Clinical management of 2019-nCoV infected pneumonia);
3. Being treated in the ICU.

Exclusion Criteria:

1. Allergic to vitamin C;
2. Dyspnea due to cardiogenic pulmonary edema;
3. Pregnant or breastfeeding;
4. Expected life is less than 24 hours;
5. There is a state of tracheotomy or home oxygen therapy in the past;
6. Previously complicated with end-stage lung disease, end-stage malignancy, glucose-6-phosphate dehydrogenase deficiency, diabetic ketoacidosis, and active kidney stone disease;
7. The patient participates in another clinical trial at the same time.

Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier (NCT number): NCT04264533

Contacts

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Locations

Layout table for location information
China, Hubei Zhongnan Hospital of Wuhan University Wuhan, Hubei, China, 430000
Sponsors and Collaborators ZhiYong Peng

Investigators

Principal Investigator:
Zhiyong Peng, professor Wuhan University

Responsible Party:	ZhiYong Peng, Professor; Chief physician, Zhongnan Hospital
ClinicalTrials.gov Identifier:	NCT04264533 History of Changes
Other Study ID Numbers:	2020001
First Posted:	February 11, 2020 Key Record Dates
Last Update Posted:	February 11, 2020
Last Verified:	February 2020
Individual Participant Data (IPD) Sharing Statement:	
Plan to Share IPD:	No

Layout table for additional information	
Studies a U.S. FDA-regulated Drug Product:	No
Studies a U.S. FDA-regulated Device Product:	No

Additional relevant MeSH terms:

table for MeSH terms	
Pneumonia, Ventilator-Associated	Vitamins
Pneumonia, Viral	Ascorbic Acid
Pneumonia	Micronutrients
Lung Diseases	Nutrients
Respiratory Tract Diseases	Growth Substances
Respiratory Tract Infections	Physiological Effects of Drugs
Cross Infection	Antioxidants
Infection	Molecular Mechanisms of Pharmacological Action
Virus Diseases	Protective Agents

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