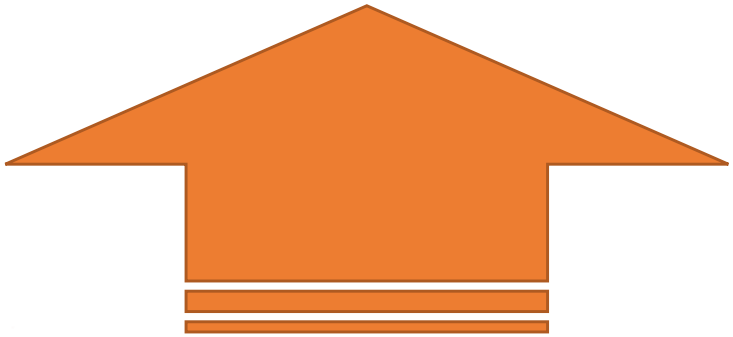
Immunonutrition in Covid-19 Disease

Irmi Syafa'ah
Perhimpunan Dokter Paru Indonesia
Cabang Jawa Timur

Comprehensive Treatment in (Severe) COVID-19



Simptomatic

Pharmacologic

Physic & Psychologic

Supportive

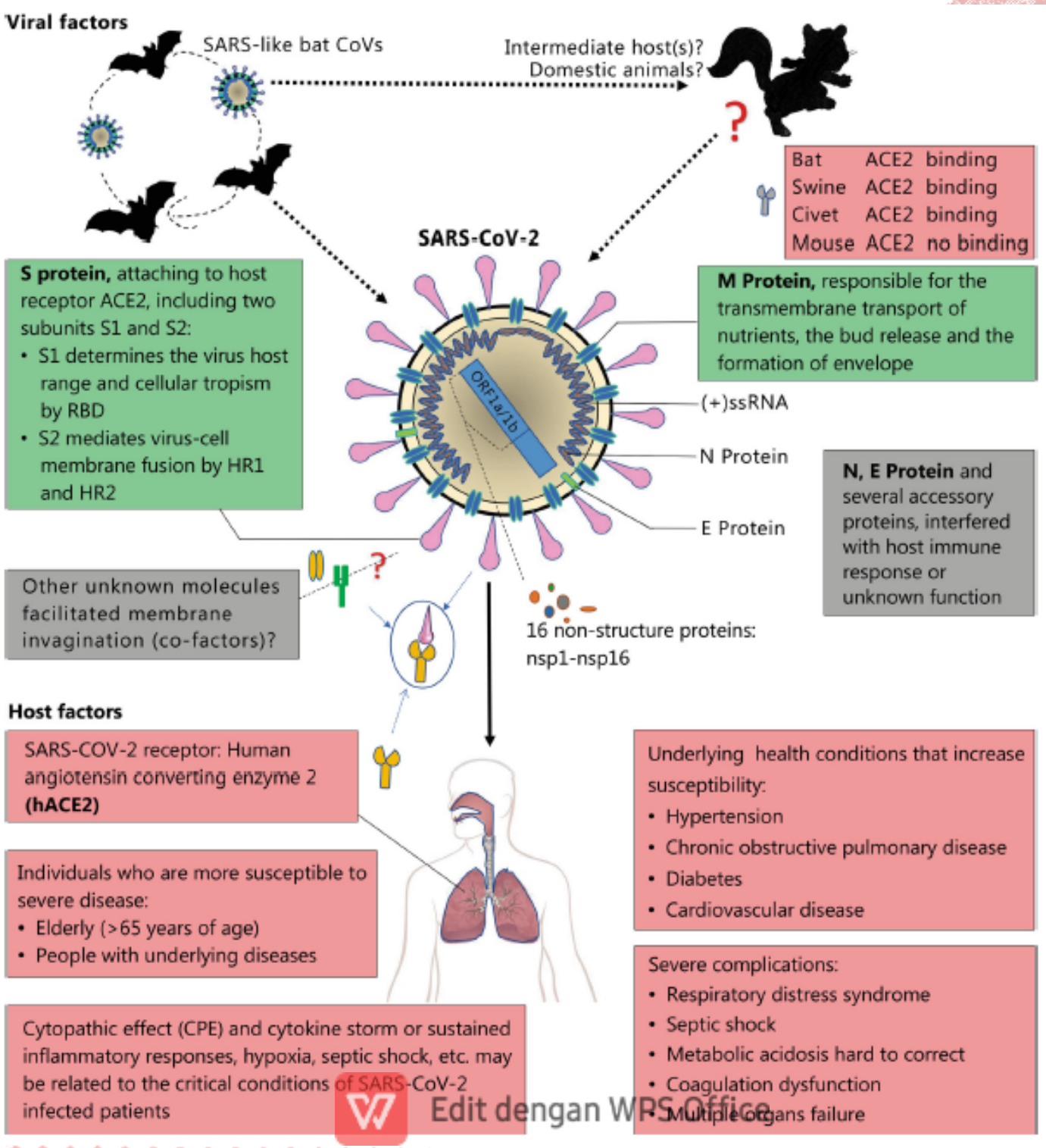
"Expert Consensus on Comprehensive Treatment of Coronavirus in Shanghai 2019"

Outline

- Non-Pharmacologic treatment on COVID-19:

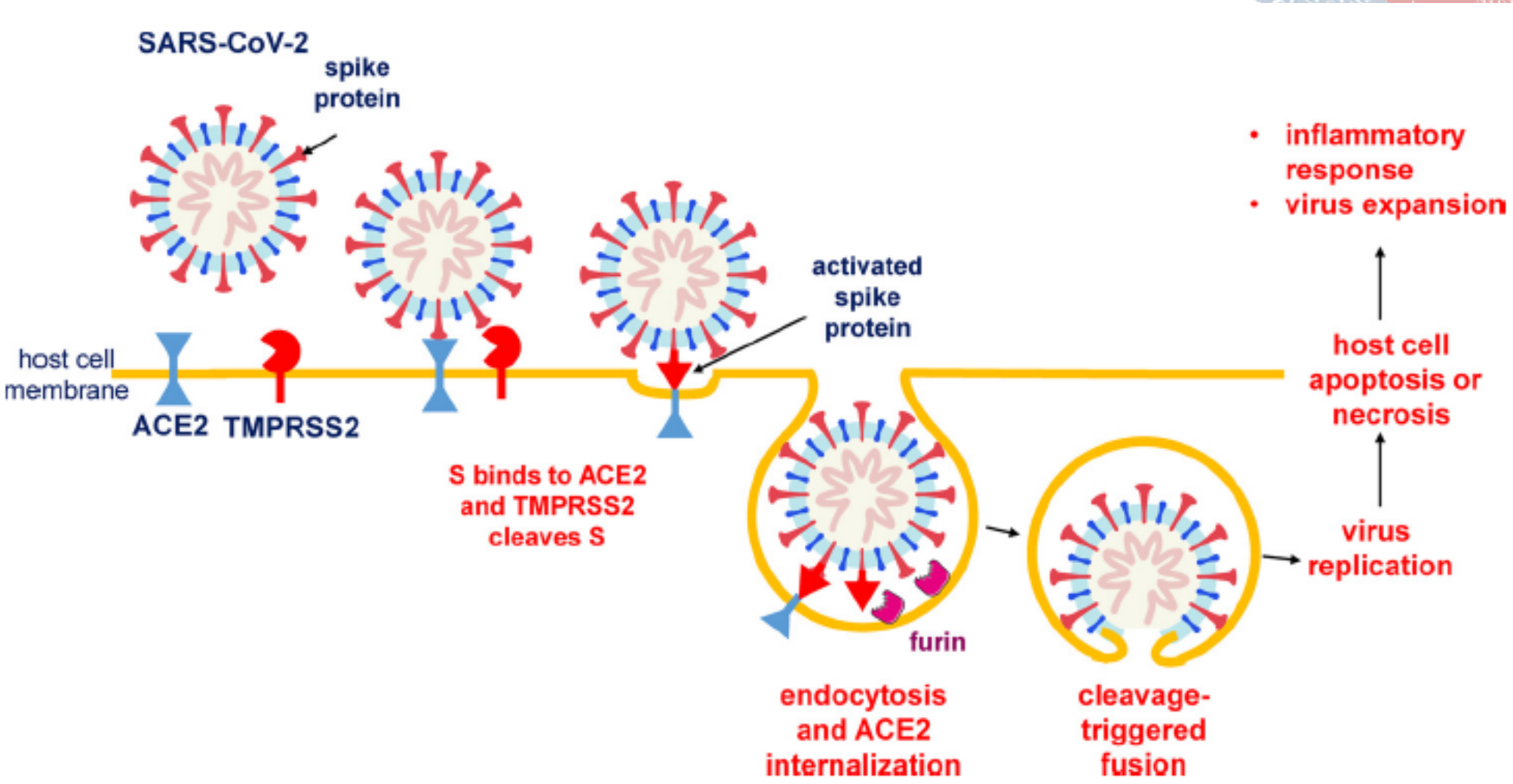
Immuno-pathological changes
Psychology
Nutrition

Virology
Immunopathogenesis



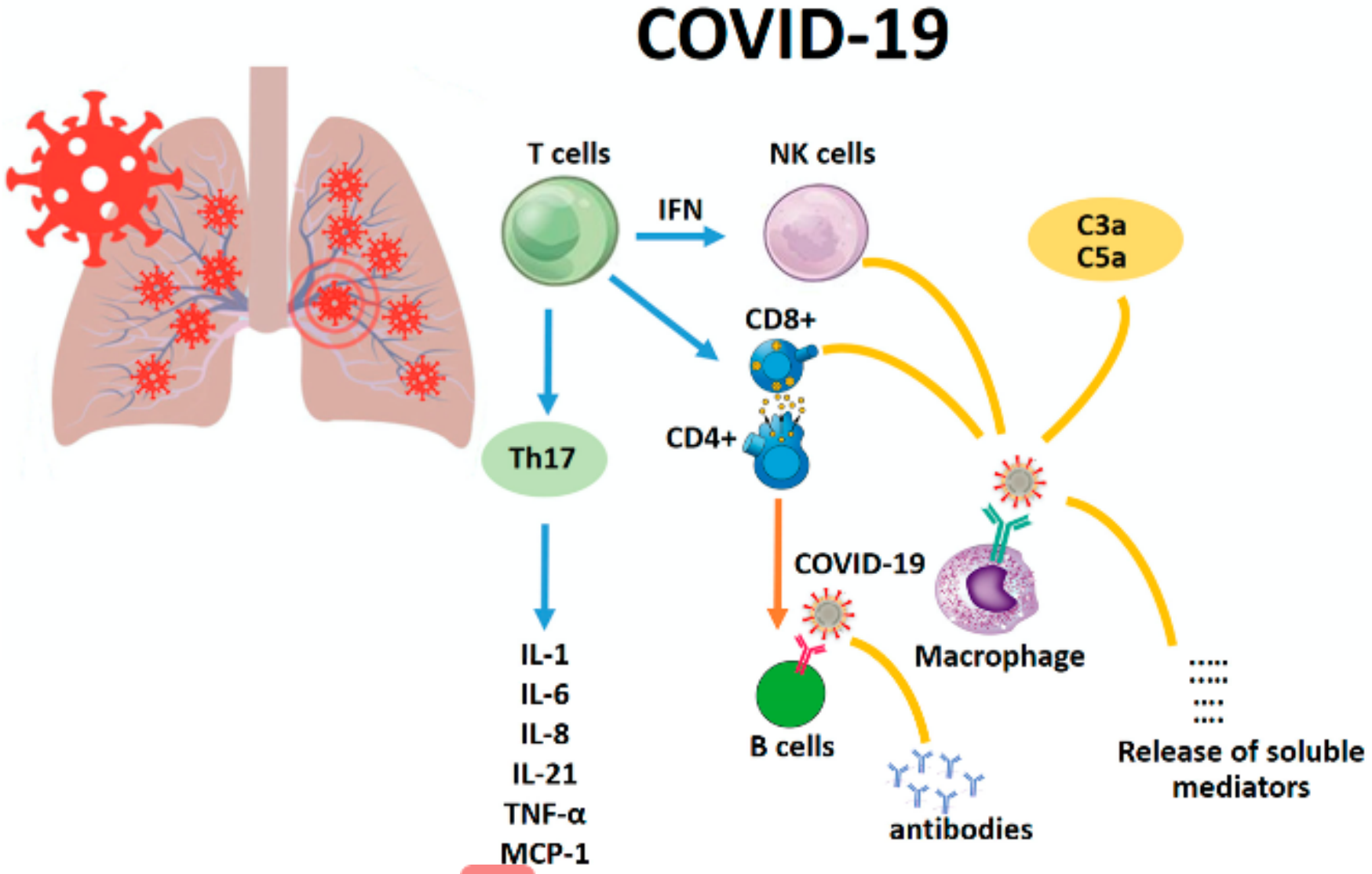
Guo et al. Military Medical Research (2020) 7:

Schematic representation of SARS CoV-2 interaction with a target cell.



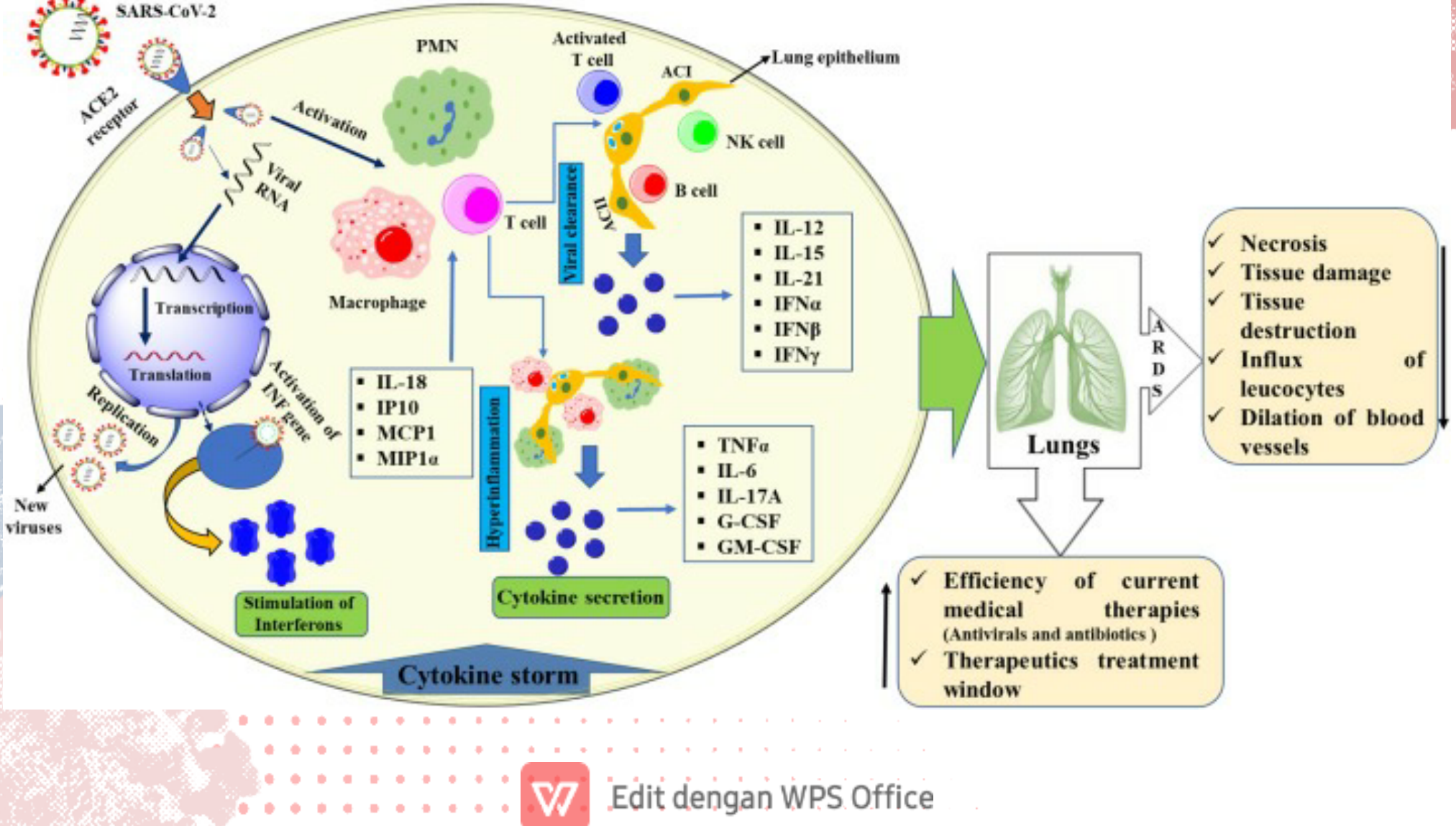
Cytokine and Growth Factor Reviews 53 (2020) 13–24

The main immunological response to COVID-19



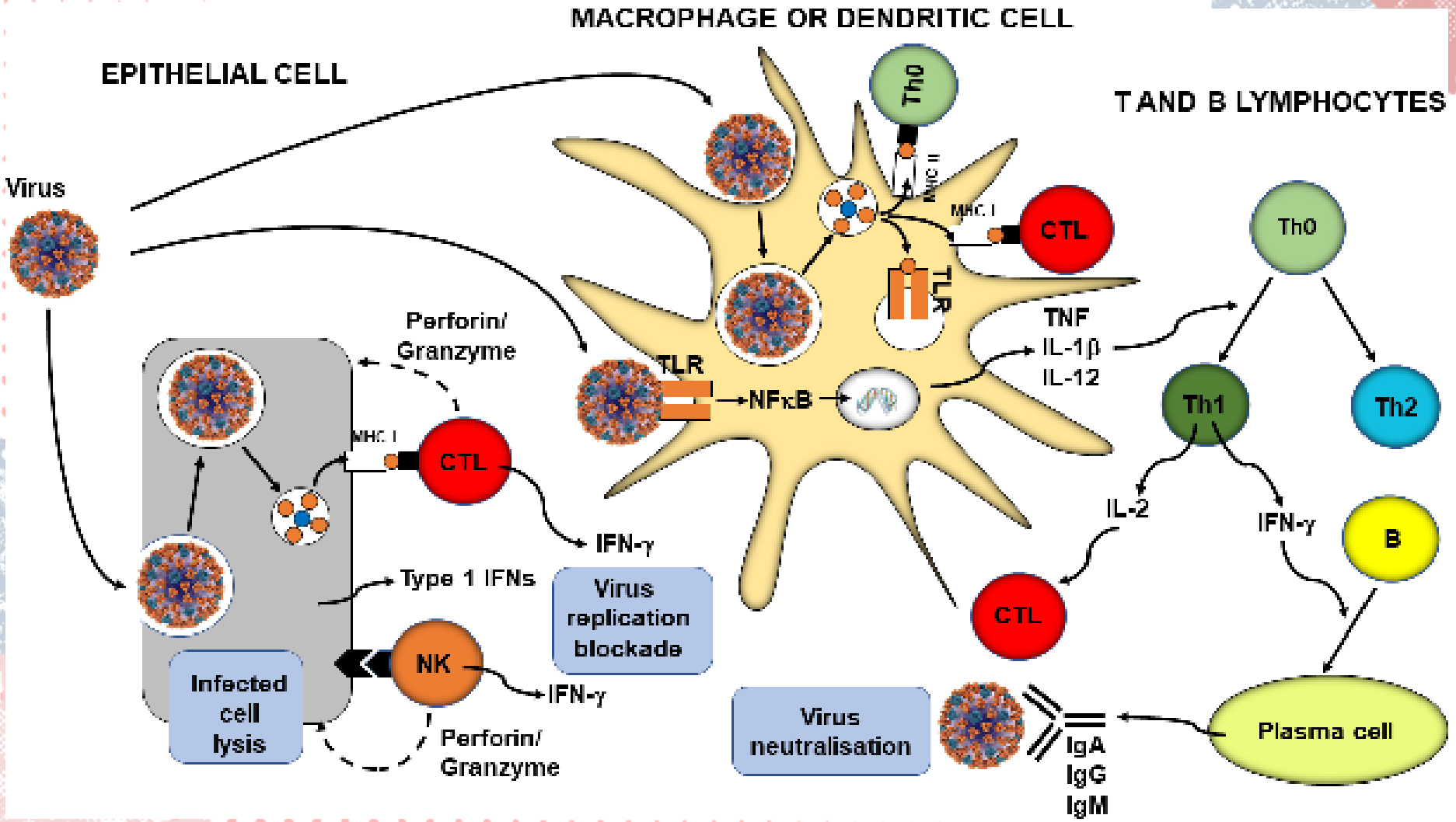
Int. J. Mol. Sci. **2020**, *21*, 3104

The main immunological response to COVID-19



Cytokine and Growth Factor Reviews 53 (2020) 66–7

ANTIVIRAL IMMUNITY



Calder PC. Nutrition, immunity and COVID-19. BMJ Nutrition, Prevention & Health 2020;**0**

Systemic Disorders

Fever, Cough, Fatigue, Sputum Production, Headache

Haemoptysis,

Acute Cardiac Injury

Hypoxemia

Dyspnoea, Lymphopenia

Diarrhoea

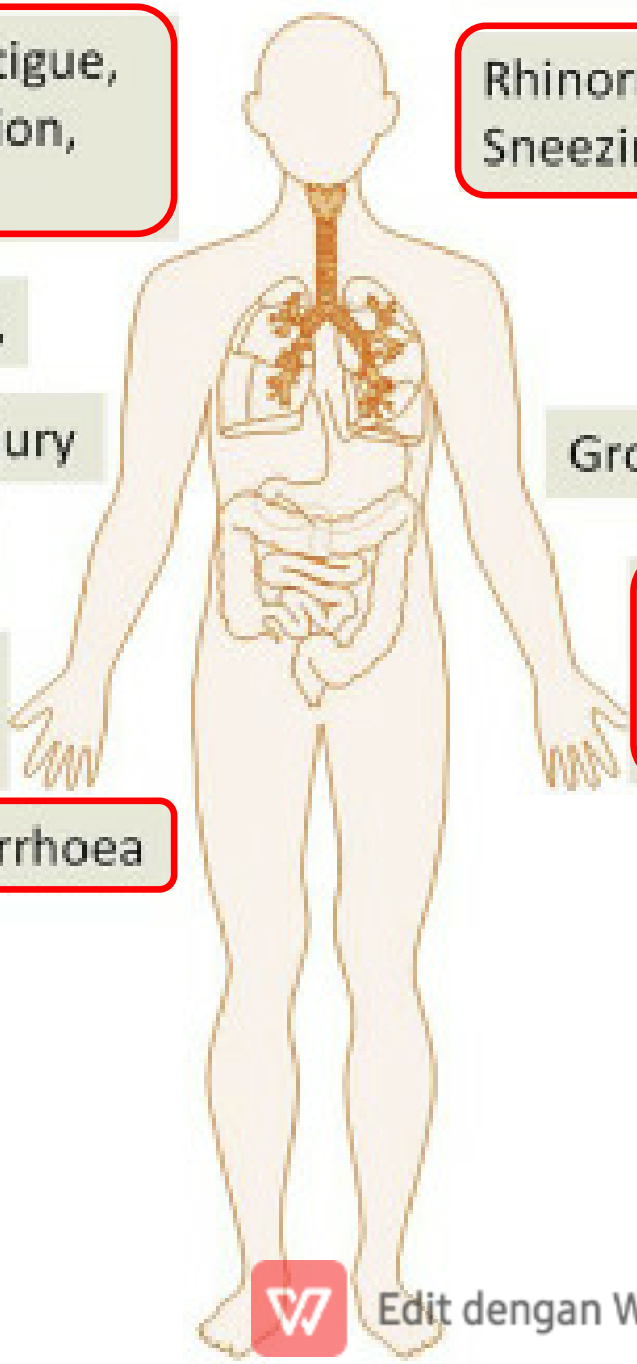
Respiratory Disorders

Rhinorrhoea, Sneezing, Sore Throat

Pneumonia

Ground-glass Opacities

RNAaemia, Acute Respiratory Distress Syndrome



J Autoimmun. 2020 May;109:102433

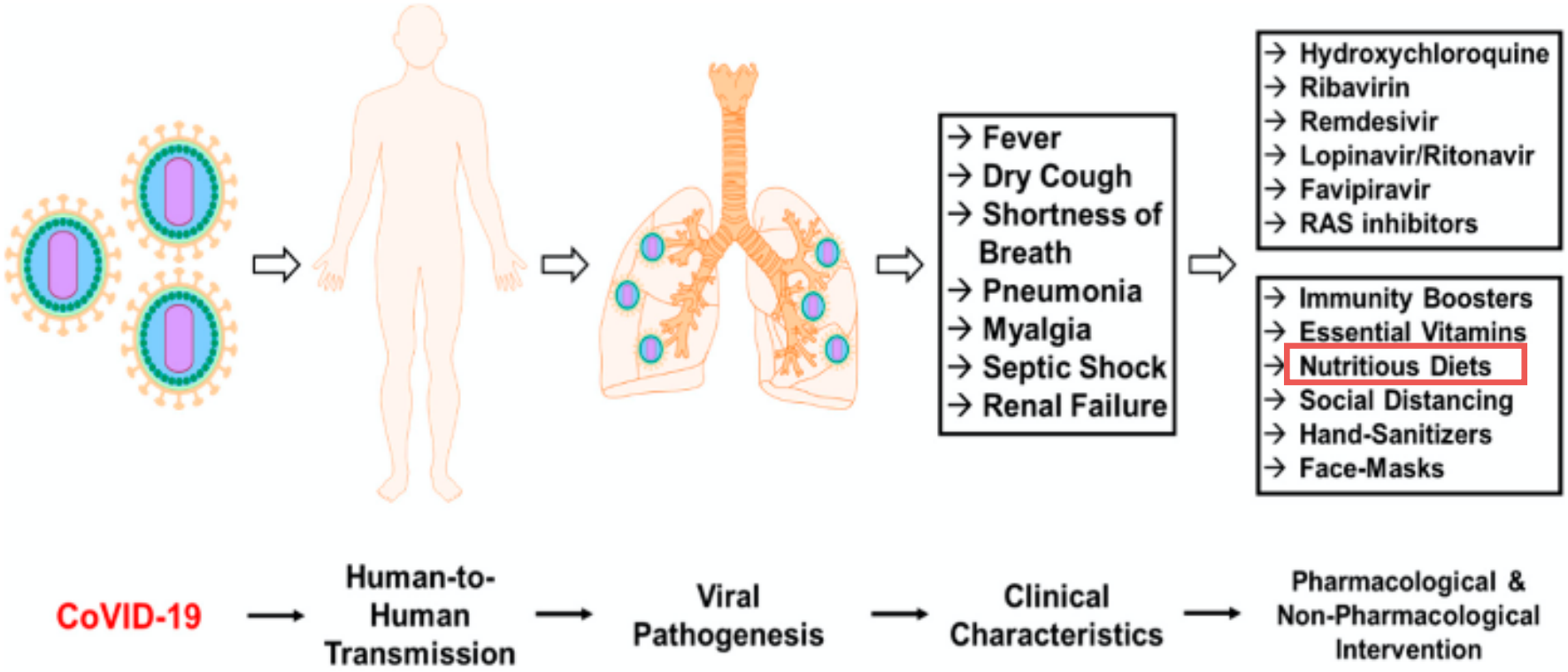
Gambaran klinis

- **Periode Inkubasi**
  - Periode inkubasi COVID-19 diperkirakan sekitar 4 sampai 14 hari setelah pajanan
  - Rata-rata onset dari gejala awal hingga rawat inap adalah 7 hari
- **Spektrum Keparahan**
  - Ringan (tanpa atau dengan pneumonia ringan) 81%.
  - Berat 14%.
  - Kritis 5 %.

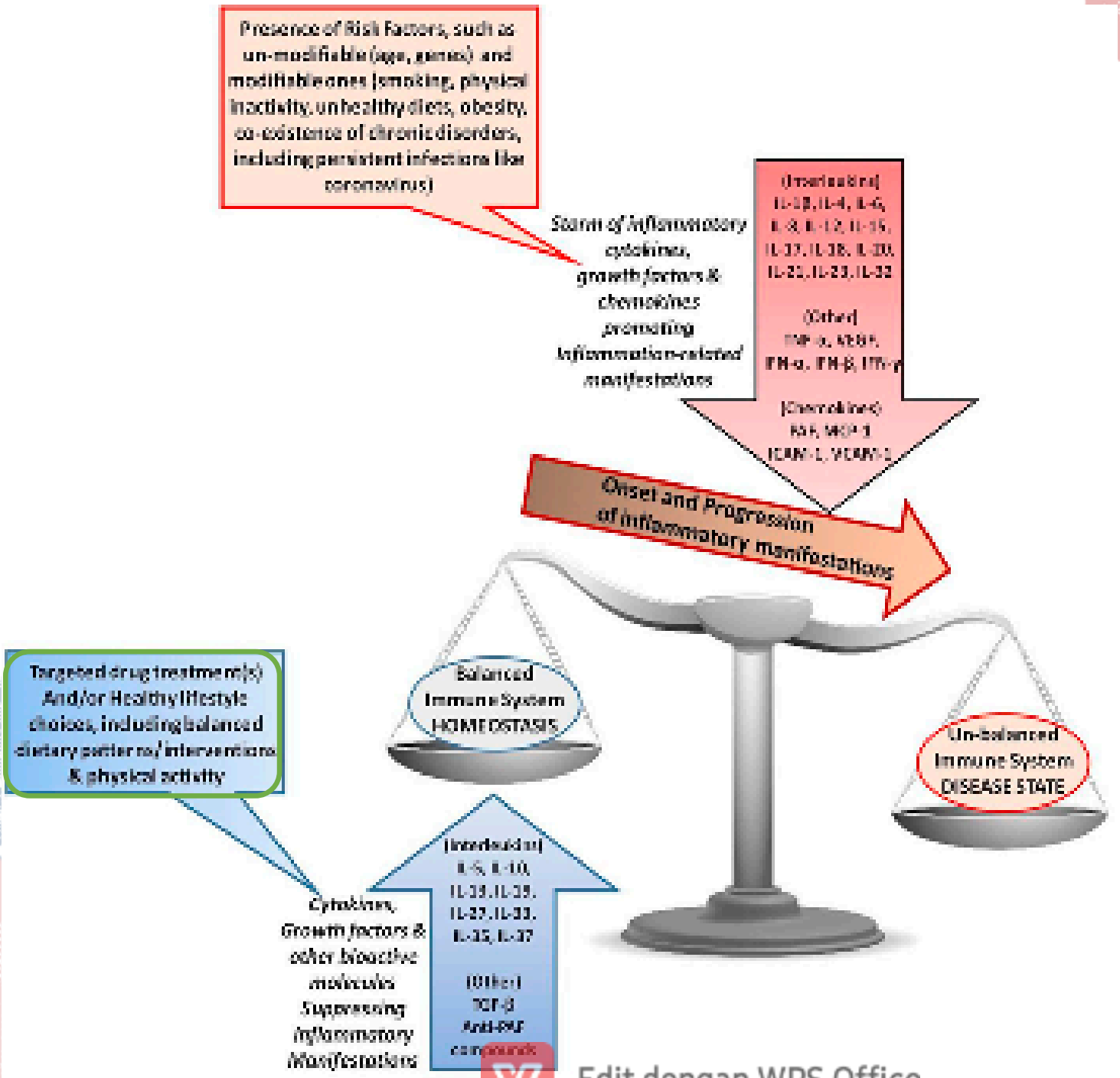
  Komorbid seperti penyakit **kardiovaskular, diabetes mellitus, penyakit paru-paru kronis, hipertensi dan malignansi** dapat meningkatkan risiko kematian.
- **Manifestasi Klinis:** pada awal penyakit antara lain:
  - Demam 88-99 %
  - Kelelahan/ fatigue 38-70 %
  - Batuk kering 59-68%
  - Anoreksia 40 %
  - Myalgia 15-35 %
  - Sesak nafas 19-31 %
  - Berdahak/ *sputum production* 27-34 %

International Pulmonologist's Consensus on COVID-19: 2nd Edition. Published on 22nd April 2020

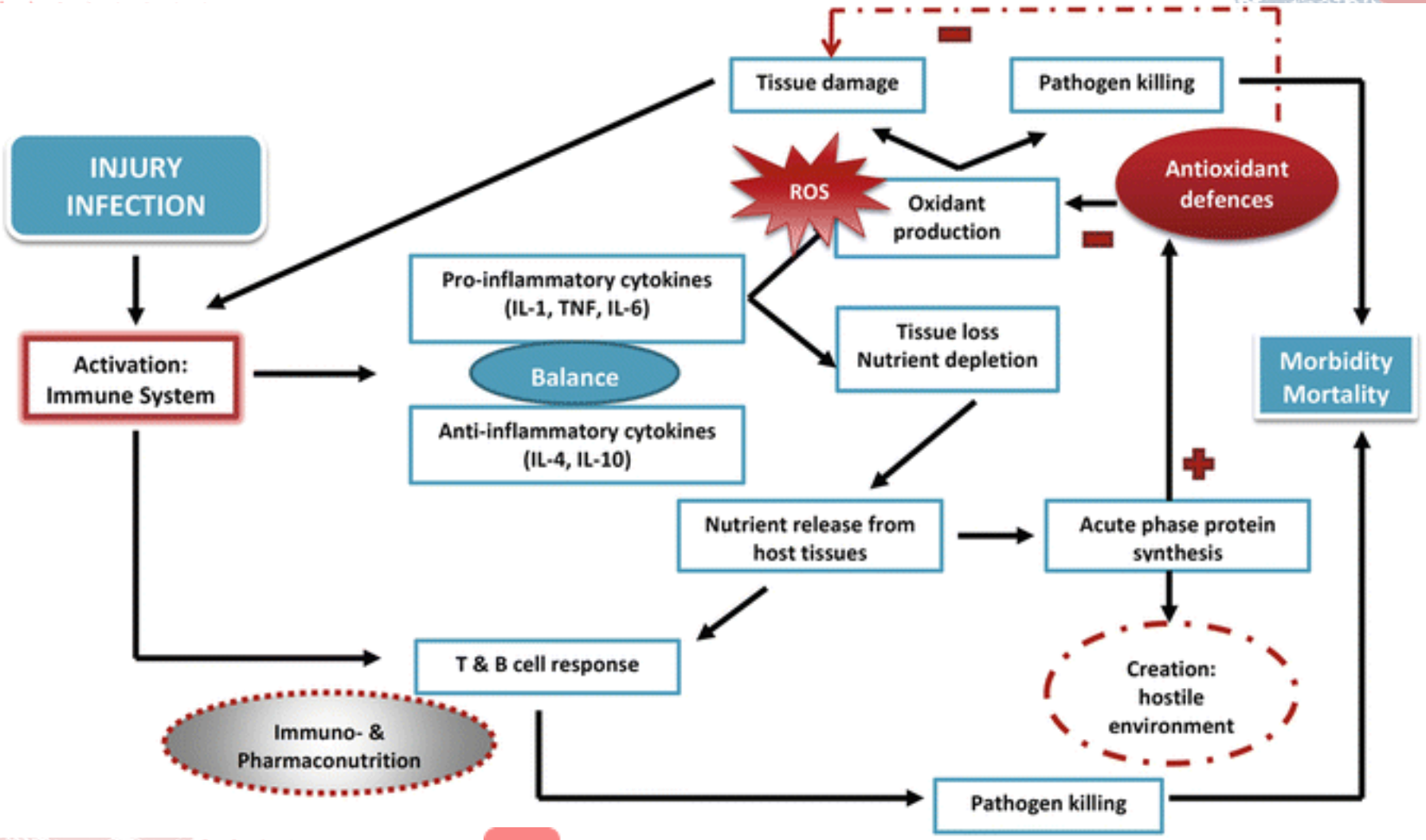
THERAPEUTIC STRATEGIES



Int. J. Environ. Res. Public Health **2020**, *17*(12), 4279



KEY FEATURES OF INFLAMMATORY RESPONSES



Diet and Nutrition in Critical Care, 2014. pp 1-15

IMMUNONUTRITION in COVID-19

- Dipengaruhi status nutrisi pasien sebelum terinfeksi
- Kondisi Malnutrisi → usia tua ››, keluhan GIT

TENTUKAN !!

- Acute Condition
- Critical Illness (SIRS, Sepsis, ARDS, etc)
  → Adequate proteins (1.5–2.0 g/kg/hari mungkin dibutuhkan),
  → Energy (105–160 kj/kg/hari atau 25–40 kcal/kg/hari),
  → Vitamins dan
  → Trace elements

Front Med (Lausanne). 2020; 7: 146

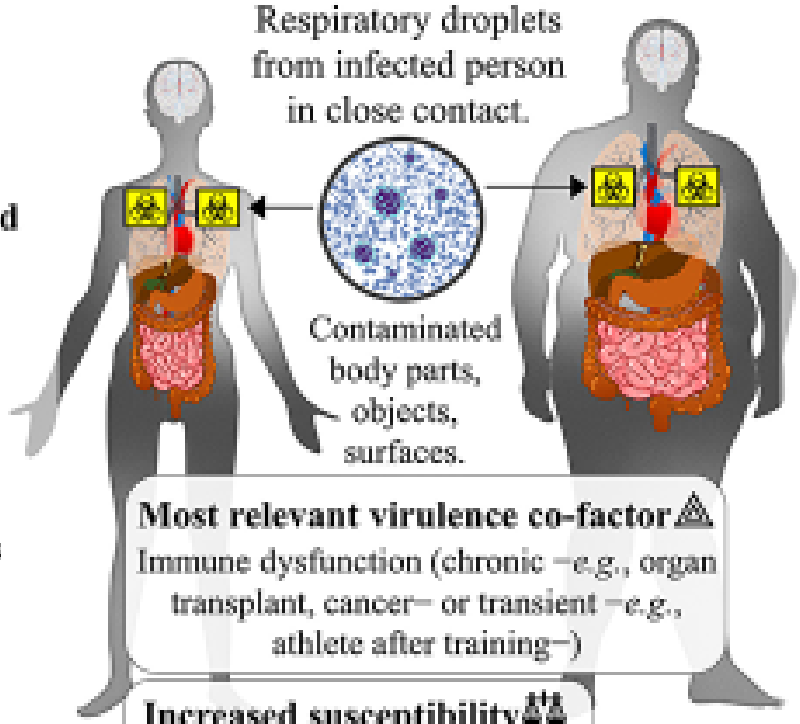
Malnutritional statuses as virulence factor for the SARS-CoV-2

Hyponutrition

Mainly protein-energy malnutrition

Conditions possibly associated with increased virulence

Shortage diseases
Low body proteins (low intake)
Low immunoreactivity
Reduced T cell function
Increased IL-4 and IL-10
Vitamin A, D, and E deficiencies
Vitamin B deficiencies
Iron-deficiency anemia
Micronutrient deficiencies



Most relevant virulence co-factor

Immune dysfunction (chronic –e.g., organ transplant, cancer– or transient –e.g., athlete after training–)

Increased susceptibility

Older age, comorbid conditions, polypharmacotherapy

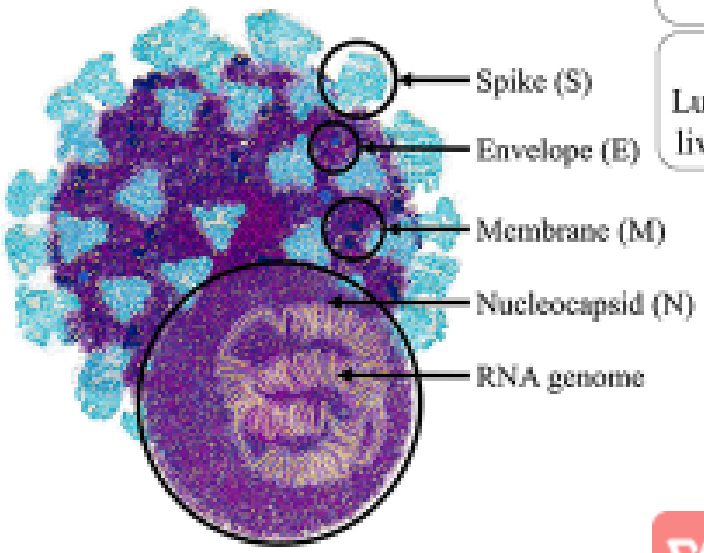
Hypernutrition

Mainly sarcopenic obesity

Conditions possibly associated with increased virulence

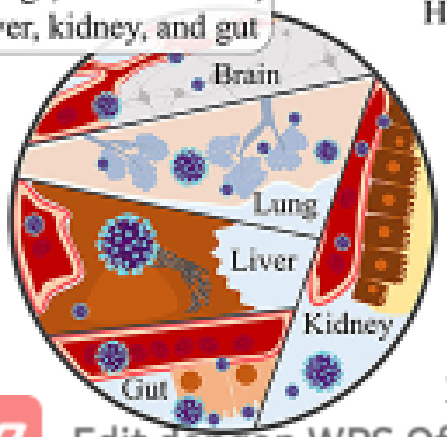
Wellness diseases
Low body proteins (high sedentary)
Low-grade inflammation
Increased immunoreactivity
Exhaustion of T cells
Reduced IL-4 and IL-10
Vitamin A, D, and E deficiency
Vitamin B deficiencies
Iron, zinc, and selenium deficiencies

The structure of SARS-CoV-2



War sites

Lungs, but also brain, liver, kidney, and gut



The nutritional implications that may experience patients with SARS-CoV-2

Symptom/sign	Nutritional effect
High body temperature	Increased energy needs
Tachypnea	Increased energy expenditure
Cytokine storm	Loss of body constituents
Diarrhea	Malabsorption
Abdominal pain	Lack of appetite
Lethargy, anorexia	Reduced food supply
Social isolation	Reduced food security
Mental distress	Lack of desire to feed
Reduced movement	Loss of lean mass

Front Med (Lausanne). 2020; 7: 146

IMMUNONUTRITON

- Nutrition that modulate immune systems, considerably influence immune function and inhibiting inflammatory responses, improve metabolic and nutritional indices

Greater Effects :

- Glutamine
- Arginine
- ω-3 (PUFA)

Lesser Effects :

- Nucleotide
- Vitamin A, C, E
- Zinc
- Taurine

GLUTAMINE

- Asam amino >> dalam plasma, skeletal dan seluruh tubuh (sintesis utama di skeletal)
- ”Bahan bakar” oksidasi
- “sinyal” kondisi injuri
- Prekursor nukleotidan dan glutathione
- Substrat untuk gluconeogenesis hepatic dan ureagenesis
- Mengatur dan menjaga fungsi pencernaan pada kondisi injuri *(gut barrier protection)*
- Menurunkan produksi sitokin proinflamasi

→ Mengurangi inflamasi pada infeksi akut & regulasi imun

GLUTAMINE *cont...*

- Kadar Glutamin rendah pada pasien ICU, <0.42 mmol/L
- Pasien dengan kondisi kritis → kadar glutamin <<< ~ perburukan *outcome*
  - PRODUKSI < KEBUTUHAN

IN COVID-19??

Kim, H. (2011). Yonsei medical journal, 52(6), 892-897.

Glutamine supplementation for critically ill adults

Kun-Ming Tao[1], Xiao-Qian Li[2], Li-Qun Yang[1], Wei-Feng Yu[1], Zhi-Jie Lu[1], Yu-Ming Sun[1], Fei-Xiang Wu[1]

[1]Department of Anesthesiology, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China. [2]Department of Traditional Chinese Medicine, Changhai Hospital, Second Military Medical University, Shanghai, China

Authors' conclusions

This review found moderate evidence that glutamine supplementation reduced the infection rate and days on mechanical ventilation, and low quality evidence that glutamine supplementation reduced length of hospital stay in critically ill or surgical patients. It seems to have little or no effect on the risk of mortality and length of ICU stay, however. The effects on the risk of serious side effects were imprecise. The strength of evidence in this review was impaired by a high risk of overall bias, suspected publication bias, and moderate to substantial heterogeneity within the included studies.

Tao KM, et al. *Cochrane Database of Systematic Reviews.* 2014, Issue 9.

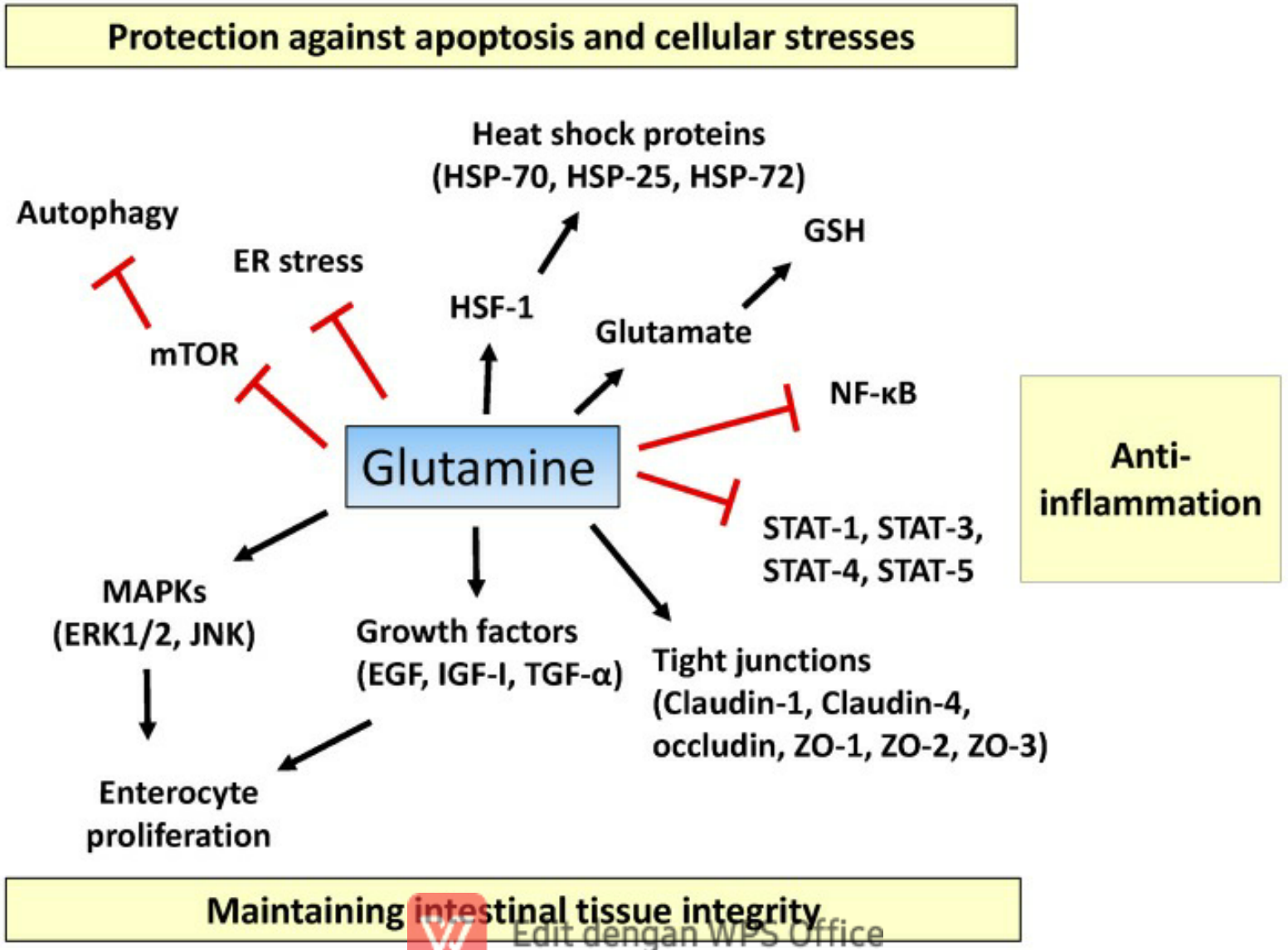
BIOMEDICAL REPORTS 6: 576-584, 2017

Therapeutic benefits of glutamine: An umbrella review of meta-analyses

MARC P. McRAE

11 meta-analyses. Glutamine supplementation for critically ill or surgical patients through parenteral or enteral routes appears to reduce the rate of hospital acquired infectious complications and shortening of the length of stay in hospital. Furthermore, glutamine supplementation appeared to reduce the rate of in-patient mortality, but the majority of meta-analyses did not reach statistical significance. However, researchers must

Glutamine & Intestinal Barrier



Int J Mol Sci. 2017 May; 18(5): 1051.

ARGININE

- Termasuk asam amino non-esensial pada kondisi normal
- Banyak berpengaruh pada fungsi imun dan penyembuhan luka
- Respons baik pada kondisi stress (injuri)
- Mengaktivasi Sel T naïve
- Prekursor Nitric Oxide (NO) → ↓tonus vascular, berperan pada eradikasi bakteri dan sel tumor oleh sel fagosit

→<u>Memperbaiki sistim imun</u>

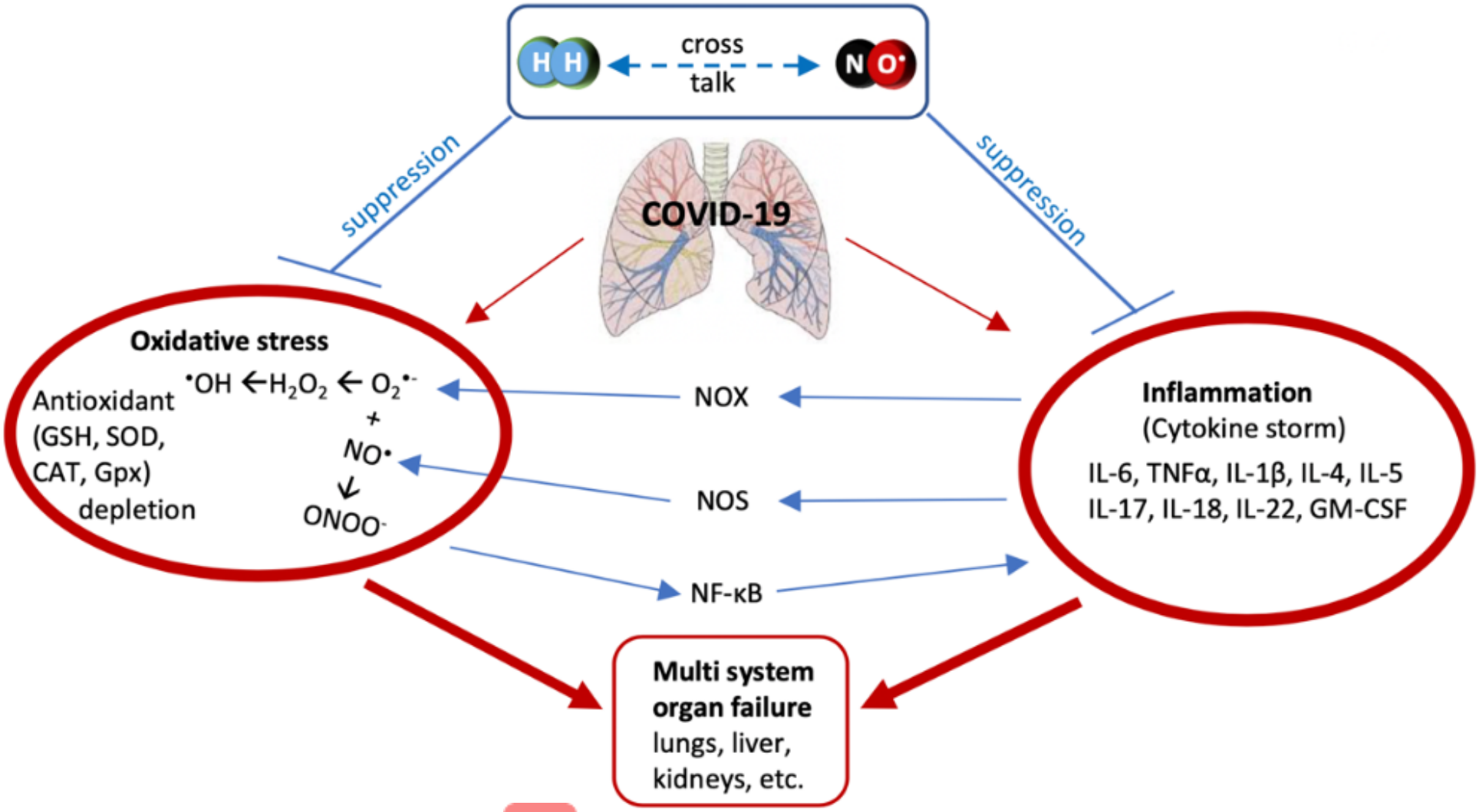
ARGININE *cont...*

Kontradiktif

- Pada banyak penyakit paru dikaitkan dengan PENINGKATAN aktivitas arginase tetapi DEFISIENSI arginin
- Arginin defisiensi pada sepsis : intake << dan kerusakan sintesa endogen

Davis JS, et al. 2011. Critical care medicine, 39(2), 380-385.

Arginine & Nitric Oxide



J Transl Sci, 2020. Volume 6: 1-6

JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Article

Cite This: J. Agric. Food Chem. 2019, 67, 4915−4922

pubs.acs.org/JAFC

Protective Effects of Functional Amino Acids on Apoptosis, Inflammatory Response, and Pulmonary Fibrosis in Lipopolysaccharide-Challenged Mice

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[†]State Key Laboratory of Animal Nutrition, Department of Animal Nutrition and Feed Science, China Agricultural University, Beijing 100193, China

[‡]Department of Animal Science, Texas A&M University, College Station, Texas 77843, United States

ABSTRACT: Lung injury is a complicated and lethal condition characterized by alveolar barrier disruption, pulmonary edema, enhanced inflammation, and apoptosis in alveoli. However, therapeutic strategies to ameliorate lung injury without exerting side effects are not available. Functional amino acids have been shown to have anti-inflammatory and anti-apoptotic effects under various conditions. The objective of this study was to test the hypothesis that arginine, glutamine, or glycine supplementation ameliorated lipopolysaccharide (LPS)-induced lung injury in mice. Mice pretreated with aerosolized arginine, glutamine, or glycine were exposed to aerosolized LPS to induce lung injury. Results showed that arginine or glycine pretreatment beneficially reduced LPS-induced collagen deposition, apoptosis of alveolar cells, expression of inflammatory cytokines and chemokines, and accumulation of neutrophils and macrophages in lung tissues of mice, thus contributing to improved alveolar integrity and function. Glutamine administration reduced LPS-induced collagen deposition and inflammatory cytokines without affecting any other parameters examined in the study. Our findings indicated that arginine or glycine pretreatment effectively alleviated LPS-induced lung injury by inhibiting the accumulation of lymphocytes, the release of inflammatory cytokines and chemokines, and the apoptosis of alveolar cells. Supplementation of arginine or glycine may be a novel nutritional strategy to reduce deleterious effects of bacterial infection on alveolar function.

KEYWORDS: *arginine, glutamine, glycine, lung injury, inflammation, fibrosis, apoptosis, leukocytes accumulation*

FACT : COVID-19 RESEARCH

"Thus, although there is no research to support evidence-based recommendations at this time, evidence to inform provision of additional micronutrients for individuals with COVID-19 infections may be available moving forward. "

"There were no registered trials found directly examining the effects of glutamine or arginine."

J Acad Nutr Diet. 2020; *ARTICLE IN PRESS*

RESEARCH *Glutamine*

Study	Population	Intervention	group	Outcomes reported	Major results
Glutamine					
Aydoğmuş et al 2012[22] RCT PMID 25207045	N = 40 in glutamine and comparison groups Patients on mechanical ventilator support for at least 7 d in the ICU Mean ± SD age: Nonglutamine group: 45 ± 18.2 y Glutamine group: 36.35 ± 16.37 y	Nutrient: glutamine Dose: 40 g/d Mode: TPN[k] Duration: 7 d	TPN without glutamine	Development of ventilator-associated pneumonia, CRP	There was no difference development of ventilator-associated pneumonia or CRP levels between groups.
Kaya et al 2017[17] RCT PMID 28096000	N = 88 Ventilated patients in neurosurgical ICU; expected to be ventilated at least 5 d Mean ± SD age: 48.57 ± 17.36	Nutrient: glutamine Concentration: 5% Mode: oral care Duration: 5 d	Oral care with 2% chlorhexidine gluconate solution	Ventilator-related pneumonia measured with Clinical Infection Score (chest x-rays; endotracheal aspirate cultures), acute APACHE II score	No difference between groups at day 1, 3, or 5 ($P > .05$)

OMEGA-3 (***ω***-3) & OMEGA-6 (***ω***-6)

- Menghambat dan mengatasi Inflamasi, mengefektifkan fungsi sel T
- Sebagai asam Linoleat dan linolenat berperan dalam menurunkan LDL , plasma Trigliserida dan pembekuan darah
- Sebagai immunomodulator

Galen, Basic in Clinical Nutrition 3rd ed 2004

Rolandelli, Clnical Nutrition enteral Tube Feeding 4th ed 2005

Nutrients **2015**, *7*, 5572-5585; doi:10.3390/nu7075239

OPEN ACCESS

nutrients

ISSN 2072-6643

www.mdpi.com/journal/nutrients

Article

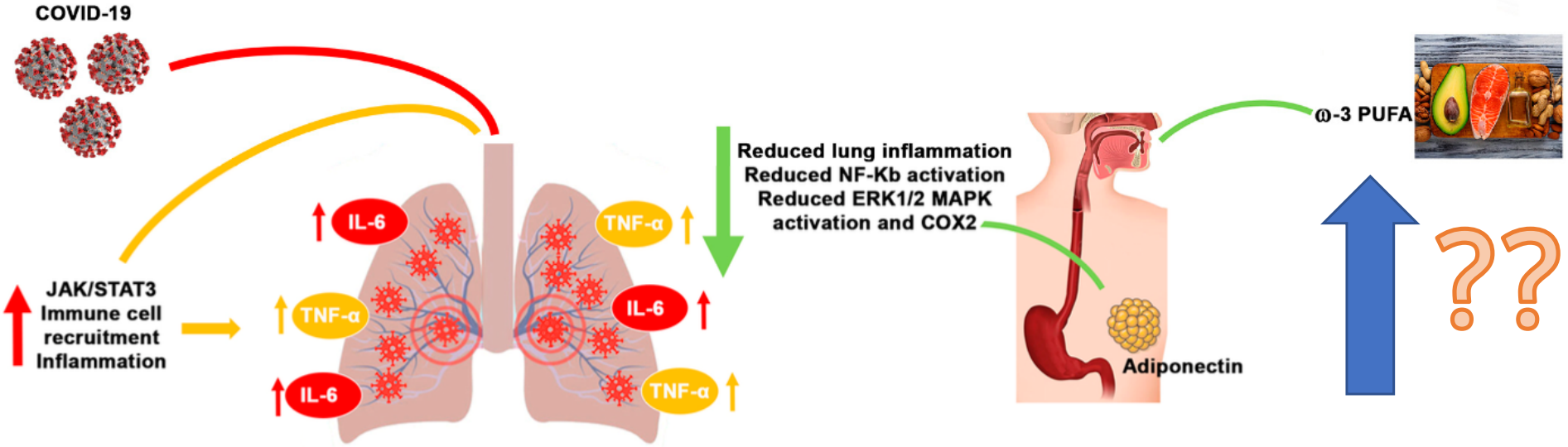
Enteral Immunomodulatory Diet (Omega-3 Fatty Acid, γ-Linolenic Acid and Antioxidant Supplementation) for Acute Lung Injury and Acute Respiratory Distress Syndrome: An Updated Systematic Review and Meta-Analysis

Congcong Li †, Liyan Bo †, Wei Liu, Xi Lu * and Faguang Jin *

Department of Respiratory and Critical Care Medicine, Tangdu Hospital, Fourth Military Medical University, Xinsi Road 1, Xi'an 710038, China; E-Mails: licong1988@hotmail.com (C.L.); boliyan@hotmail.com (L.B.); liuweilung@163.com (W.L.)

treatment. Conclusions: The enteral immunomodulatory diet could not reduce the severity of the patients with ALI/ARDS. Whereas, for ALI/ARDS patients with high mortality, this treatment might reduce the all-cause mortality, but its use should be treated with discretion.

Hypothesis of Diet Intervention to Improve Covid-19 outcomes



Int. J. Mol. Sci. 2020, *21*, 3104

VITAMIN C

- Berperan pada hampir seluruh aspek imunitas :
  - Fungsi pertahanan epitel
  - Pertumbuhan dan fungsi sel imun innate dan adaptive
  - Kemotaksis leukosit pada lokasi infeksi
  - Fagositosis dan *microbial killing*
  - Produksi antibody
  - Meningkatkan aktivitas neutrophil dan monosit
- Efek antioksidan +
- Meningkatkan produksi glutathione

Derbyshire E, Delange J. bmjnph 2020;0:1–6.

nutrients

MDPI

Review

Vitamin C and Infections

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Received: 31 January 2017; Accepted: 15 March 2017; Published: 29 March 2017

Abstract: In the early literature, vitamin C deficiency was associated with pneumonia. After its identification, a number of studies investigated the effects of vitamin C on diverse infections. A total of 148 animal studies indicated that vitamin C may alleviate or prevent infections caused by bacteria, viruses, and protozoa. The most extensively studied human infection is the common cold. Vitamin C administration does not decrease the average incidence of colds in the general population, yet it halved the number of colds in physically active people. Regularly administered vitamin C has shortened the duration of colds, indicating a biological effect. However, the role of vitamin C in common cold treatment is unclear. Two controlled trials found a statistically significant dose–response, for the duration of common cold symptoms, with up to 6–8 g/day of vitamin C. Thus, the negative findings of some therapeutic common cold studies might be explained by the low doses of 3–4 g/day of vitamin C. Three controlled trials found that vitamin C prevented pneumonia. Two controlled trials found a treatment benefit of vitamin C for pneumonia patients. One controlled trial reported treatment benefits for tetanus patients. The effects of vitamin C against infections should be investigated further.

VITAMIN D

- *Powerful Immunoregulator*
- Receptor Vit D diekspresikan oleh sebagian besar sel imun (Limfosit B, T, makrofag dan monosit)
- Berpotensi sebagai adjuvant dalam melindungi dan mengobati pasien dengan infeksi virus respirasi (def. Vit D)
- Metabolit vitamin D → memodulasi ekspresi dan sekresi Interferon tipe 1, sitokin pro inflamasi (misalnya TNF dan IL-6)

Derbyshire E, Delange J. bmjnph 2020;0:1–6.

REVIEW

Vitamin D modulation of innate immune responses to respiratory viral infections

Mihnea T. Zdrenghea[1†] | Heidi Makrinioti[2†] | Cristina Bagacean[1,3] | Andy Bush[4†] | Sebastian L. Johnston[2†] | Luminita A. Stanciu[1,2†]

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[2] Airways Disease Infection Section, National Heart and Lung Institute, Imperial College London, London, UK

[3] Laboratory of Immunology and Immunotherapy, University Hospital Brest, France

[4] Department of Paediatric Respiratory Medicine, Royal Brompton Hospital and Imperial College London, London, UK

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Email: mzdrenghea@umfcluj.ro

Summary

Vitamin D, in addition to its c d regulatory role in multiple process pithelial repair. Patients with respiratory disease are frequently deficient in vitamin D, implying that supplementation might provide significant benefit to these patients. Respiratory viral infections are common and are the main trigger of acute exacerbations and hospitalization in children and adults with asthma and other airways diseases. Respiratory monocytes/macrophages and epithelial cells constitutively express the vitamin D receptor. Vitamin D, acting through this receptor, may be important in protection against respiratory infections. Whether the in vitro findings can be translated into a substantial in vivo benefit still remains uncertain. Here we review the in vitro data on the role of vitamin D in antiviral innate immunity, the data concerning the deficient levels of vitamin D in lung diseases, and the in vivo role of supplementation as protection against respiratory viral infections in healthy individuals and in patients with chronic respiratory diseases. Finally, we suggest ways of improving the effectiveness of vitamin D as an adjuvant in the prevention and treatment of acute respiratory infections.

Vit D supplement might have NO effect for Healthy people

KEYWORDS
innate immunity, respiratory viruses, vitamin D

Rozga M, et al. J Acad Nutr Diet. 2020.

RESEARCH *Vit C & D*

Study	Population	Intervention	group	Outcomes reported	Major results
Ascorbic acid					
Fowler et al 2019[16] RCT[a] PMID[b] 31573637	N = 167 ICU[c] patients with sepsis and acute respiratory distress syndrome Plasma ascorbate levels at baseline were marginally deficient in both groups Mean ± SD[d] age: 54.8 ± 16.7	Nutrient: ascorbic acid Dose: 50 mg/kg in dextrose 5% in water Mode: intravenous infusion Duration: every 6 h for 96 h	Placebo (dextrose 5% in water only)	Organ failure (modified SOFA[e] score), C-reactive protein levels, thrombomodulin levels	Compared with placebo, ascorbic acid did not significantly improve reported outcomes.
Lin et al 2018[18] Retrospective case-control PMID 29931212	N = 80 Patients in burn shock resuscitation Baseline ascorbic acid status not reported Mean ± SD age: 41±15 (intervention group) and 42.4 ± 17 (comparison group)	Nutrient: high-dose ascorbic acid Dose: started at a dose of 66 mg/kg/h Mode: intravenous infusion Duration: mean time 4:01 ± 15 h	No treatment	Ventilator-associated pneumonia, mortality	There were no significant differences in the incidence of ventilator-associated pneumonia or mortality between the 2 groups.
Cholecalciferol					
Miroliaee et al 2017[21], 2018[19] RCT PMID 29248753 29201115	N = 49 Patients with ventilator-related pneumonia and cholecalciferol deficiency Mean ± SD age: 57.83 ± 18.84 (intervention group) and 56.45 ± 20.70 (comparison group)	Nutrient: cholecalciferol Dose: 300,000 U Mode: intramuscular Duration: N/A[f]	Placebo	IL-6[g], CRP[h], CPIS[i] score (pneumonia score), SOFA score, mortality	Compared with placebo, cholecalciferol group had significantly lower IL-6 levels and mortality, but not CRP level and SOFA or CPIS score.

ZINC

- Dikenal sebagai 'Gatekeeper' fungsi imun, diperlukan agar imun bisa berfungsi
- Berperan pada regulasi *intracellular signaling pathway* sel imun innate dan adaptive
- Meningkatkan respons inflamasi
- Menginduksi imunitas seluler (CMI)
- Komponen kunci jalur transduksi eliminasi pathogen → membentuk *neutrophil extracellular trap*
- Pasien usia tua → ↓ stress biomarker & sitokin proinflamasi

→ Belum ada review atau meta analisis mengenai topik ini

Derbyshire E, Delange J. bmjnph 2020;0:1–6.

OPEN ACCESS Freely available online

PLoS PATHOGENS

Zn^{2+} Inhibits Coronavirus and Arterivirus RNA Polymerase Activity *In Vitro* and Zinc Ionophores Block the Replication of These Viruses in Cell Culture

Aartjan J. W. te Velthuis[1], Sjoerd H. E. van den Worm[1], Amy C. Sims[2], Ralph S. Baric[2], Eric J. Snijder[1]*, Martijn J. van Hemert[1]*

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Abstract

Increasing the intracellular Zn^{2+} concentration with zinc-ionophores like pyrithione (PT) can efficiently impair the replication of a variety of RNA viruses, including poliovirus and influenza virus. For some viruses this effect has been attributed to interference with viral polyprotein processing. In this study we demonstrate that the combination of Zn^{2+} and PT at low concentrations (2 μM Zn^{2+} and 2 μM PT) inhibits the replication of SARS-coronavirus (SARS-CoV) and equine arteritis virus (EAV) in cell culture. The RNA synthesis of these two distantly related nidoviruses is catalyzed by an RNA-dependent RNA polymerase (RdRp), which is the core enzyme of their multiprotein replication and transcription complex (RTC). Using an activity assay for RTCs isolated from cells infected with SARS-CoV or EAV—thus eliminating the need for PT to transport Zn^{2+} across the plasma membrane—we show that Zn^{2+} efficiently inhibits the RNA-synthesizing activity of the RTCs of both viruses. Enzymatic studies using recombinant RdRps (SARS-CoV nsp12 and EAV nsp9) purified from *E. coli* subsequently revealed that Zn^{2+} directly inhibited the *in vitro* activity of both nidovirus polymerases. More specifically, Zn^{2+} was found to block the initiation step of EAV RNA synthesis, whereas in the case of the SARS-CoV RdRp elongation was inhibited and template binding reduced. By chelating Zn^{2+} with MgEDTA, the inhibitory effect of the divalent cation could be reversed, which provides a novel experimental tool for *in vitro* studies of the molecular details of nidovirus replication and transcription.

IMMUNONUTRITION in COVID-19

Orang tua dan Px + komorbid
(HT, PPOK, DM and cardiovascular disease)

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Defisiensi Immunonutrisi (c/ Arginin, Glutamin, dll)
→ HIGH RISK untuk tertular
→ HIGH RISK sakit parah hingga meninggal

*Note : Arginine 41% ‹ pasien Non ICU

Huang C, et al. 2013. The Lancet, 395(10223), 497-506

RINGKASAN

- Efek immunonutrisi pada sistem imun sangat bervariasi dan belum sepenuhnya dipahami
  → Tetap dibutuhkan untuk meningkatkan respons imun dan mengendalikan infeksi, terutama pada kasus Covid-19
- Kombinasi immunonutrisi → efek sinergis atau lebih baik dibandingkan imunitas individual dan masing-masing efek fisiologis dari tiap nutrisi
- Penelitian lanjutan masih dibutuhkan terkait penggunaan immunonutrisi pada pasien

Thank You