PRINCIPLES OF DRUG THERAPY MANAGEMENT OF THE SYMPTOMATIC COVID-19 PATIENT

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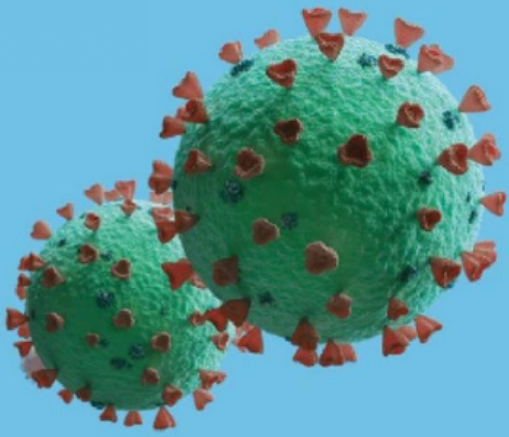

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In the circular dated Nov. 30, 2020, "Home Management of Patients with SARS-Cov-2 Infection," the mode of pharmacological treatment of symptomatic patient with COVID-19 is addressed. [1]

The first critical issue that can be highlighted concerns the definition of a "confirmed" case: *a case with laboratory confirmation for SARS-CoV-2 infection, regardless of clinical signs and symptoms* (WHO 07/08/2020).
Since the confirmation of potential infection is done by the method in real time RT-PCR, it is well documented that the presence of false positives and negatives is currently not quantifiable[2] , unless a validation of the method by culture+NGS or Nanopore sequencing and study of the replication kinetics of SARS-Cov-2 is carried out and that the laboratory diagnostic test can in no way be used for clinical diagnosis[3] . It is therefore **incorrect to frame any case with RT-PCR positivity as a COVID-19-confirmed case** because it is the study of clinical manifestations and the results of the diagnostic tests that allow us to define the pathology the person has. This approach during the pandemic has led to an inevitable overestimation of cases, the most difficult interpretation of data and, most seriously, the inappropriate management of patients who are not

[1] Home management of patients with SARS-Cov-2 infection
https://www.trovanorme.salute.gov.it/norme/renderNormsanPdf?anno=2020&codLeg=77456&part=1%20&series=null

[2] Feng W, Newbigging AM, Le C, et al.
Molecular Diagnosis of COVID-19: Challenges and Research Needs. Anal Chem. 2020;92(15):10196-10209. doi:10.1021/acs.analchem.0c02060
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7346719/

[3] Afzal A.
Molecular diagnostic technologies for COVID-19: Limitations and challenges [published online ahead of print, 2020 Aug6]. JAdv Res. 2020;10.1016/j.jare.2020.08.002. doi:10.1016/j.jare.2020.08.002
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7406419/

COVID-19 but positive in the test.

Clinical management of asymptomatic or paucisymptomatic subjects.

The circular suggests the following directions:

- watchful waiting;
- Periodic measurement of oxygen saturation by pulse oximetry;
- Symptomatic treatments (e.g., acetaminophen);
- appropriate hydration and nutrition;
- Do not modify ongoing chronic therapies for other conditions (e.g., antihypertensive, hypolipidemic, anticoagulant or antiplatelet therapies), as this would risk causing aggravation of pre-existing conditions;
- individuals undergoing chronic immunosuppressive treatment because of a previous solid organ transplant rather than because of immune-mediated pathogenesis diseases will be allowed to continue current drug treatment unless otherwise indicated by the treating specialist;
- Do not routinely use corticosteroids;
- the use of corticosteroids is recommended in individuals with severe COVID-19 disease who require oxygen supplementation. The use of these drugs at home may be considered only in those patients whose clinical picture does not improve within 72 hours, in the presence of worsening pulse oximetry parameters requiring oxygen therapy;
- do not use heparin. The use of this medication is indicated only in the following
  Subjects immobilized by ongoing infection;
- Do not use antibiotics. Their possible use should be reserved only when there is persistent febrile symptomatology for more than 72 hours or whenever the clinical picture raises a well-founded suspicion of bacterial overlap, or, finally, when bacterial infection is demonstrated by microbiological examination;
- Do not use hydroxychloroquine whose efficacy has not been confirmed in any of the controlled clinical studies conducted so far;
- Do not administer drugs by aerosol when in isolation with other cohabitants because of the risk of spreading the virus in the environment.

Paracetamol:

In the case of symptomatic treatment of fever or joint or muscle pain from potential SARS-Cov-2 infection, **acetaminophen (PAC) is to be avoided** because PAC and its metabolites reduce GSH levels, even when administered at relatively low doses in healthy volunteers, and in elderly people 3 g of PAC for 14 days resulted in a significant reduction in sulfur amino acids. Plasma levels of PAC may increase beyond expected concentrations, exacerbating thiol consumption, under conditions of intestinal dysbiosis, another common state in the COVID- 19 risk population.
PAC in the absence of adequate physiological levels of GSH may give rise to genotoxic quinon-imine metabolites, and therefore should be administered with caution, especially in subjects with severe GSH depletion who, again, are those at highest risk of developing a severe form of COVID-19. The quinon-imine metabolite is also the major contributor to the hepatic and renal toxicity of PAC, and 97% of acute drug-induced liver failure has been attributed to PAC itself. Finally, it is important to consider that PAC has the ability to reduce fever and pain, as well as NSAIDs, and may mask symptoms by delaying the framing of disease severity, but lacks the anti-inflammatory and antiplatelet activities of NSAIDs that could be critical in containing the exacerbation of COVID-19. [4]
PAC consumption in at-risk groups is particularly high especially in Western countries, which may have made this population group even more susceptible to SARS-CoV-2 at the time of its spread.

[4] Sestili P, Fimognari C.
Paracetamol-Induced Glutathione Consumption: Is There a Link With Severe COVID-19 Illness?
Front Pharmacol. 2020;11:579944. Published 2020 Oct 7.
doi:10.3389/fphar.2020.579944
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7577213/

Drugs that can be used only at specific stages of the disease

Corticosteroids

In COVID-19, some of the early respiratory symptoms are nasal congestion, coughing and wheezing, features due to excessive inflammation and cytokine activation. [5]

In acute inflammatory states, early treatment with immunomodulators offers greater benefit. [6] It follows that early use of corticosteroids is a rational intervention for patients with COVID-19 with symptoms associated with cytokine activation, but keeping in mind the risks associated with their excessive and improper use.[7]

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[5] Han H, Ma Q, Li C, et al.
Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors.
Emerg Microbes Infect. 2020;9(1):1123-1130. doi:10.1080/22221751.2020.1770129
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7473317/

[6] Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S.
Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment.
Clin Rheumatol. 2020;39(7):2085-2094. doi:10.1007/s10067-020-05190-5
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7260446/

Lam S, Lombardi A, Ouanounou A.
COVID-19: A review of the proposed pharmacological treatments.
Eur J Pharmacol. 2020;886:173451. doi:10.1016/j.ejphar.2020.173451
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7406477/

Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB.
Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review.
JAMA. 2020 May 12;323(18):1824-1836. doi: 10.1001/jama.2020.6019. PMID: 32282022.
https://jamanetwork.com/journals/jama/fullarticle/10.1001/jama.2020.6019

[7] Yang JW, Yang L, Luo RG, Xu JF.
Corticosteroid administration for viral pneumonia: COVID-19 and beyond [published online ahead of print, 2020 Jun 27]. Clin Microbiol Infect. 2020;26(9):1171-1177. doi:10.1016/j.cmi.2020.06.020
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7320691/

Drugs not recommended for the treatment of COVID-19

Antibiotics

"The lack of solid rationale and the absence of evidence of efficacy in the treatment of patients with SARS-CoV- 2 viral infection alone do not allow us to recommend the use of antibiotics, either alone or in combination with other drugs with special reference to hydroxychloroquine."

Although overuse and misuse of antibiotics is to be discouraged because of the risk of antibiotic resistance, **their timely use in the treatment of pulmonary complication is supported by several clinical studies** in the literature **and their antiviral mechanism of action toward** SARS-Cov-2, anti-inflammatory and antibiotic toward bacterial overinfection. [8]

In particular, for **azithromycin,** this effect is closely dependent on **timing**: prophylactic or therapeutic administration at an early stage may prevent viral entry and therapeutic intervention, whereas at an advanced stage it may cause a deleterious effect due to worsening immunopathology[9] .
In support of the antiviral efficacy of antibiotics used to treat SAR-Cov-2, preliminary results[10] show that the

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[8] Sultana J, Cutroneo PM, Crisafulli S, Puglisi G, Caramori G, Trifirò G.
Azithromycin in COVID-19 Patients: Pharmacological Mechanism, Clinical Evidence and Prescribing Guidelines.
Drug Saf. 2020;43(8):691-698. doi:10.1007/s40264-020-00976-7

[9] Channappanavar R, Fehr AR, Vijay R, et al.
Dysregulated Type I Interferon and Inflammatory Monocyte-Macrophage Responses Cause Lethal Pneumonia in SARS-CoV-Infected Mice.
Cell Host Microbe. 2016;19(2):181-193. doi:10.1016/j.chom.2016.01.007
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4752723/

[10] Petrillo, Mauro, Brogna, Carlo, Cristoni, Simone, Querci, Maddalena, Piazza, Ornella, & Van den Eede, Guy.
Increase of SARS-CoV-2 RNA load in faecal samples prompts for rethinking of SARS-CoV-2 biology and COVID-19 epidemiology
(Version v1). Zenodo. (2020, October 14). http://doi.org/10.5281/zenodo.4088208
https://zenodo.org/record/4088208#.X7m1wqpKjjA

virus replicates efficiently in a bacterial growth medium and that replication follows bacterial growth, leading to the hypothesis that SARS-Cov-2 is able to colonize intestinal bacteria with a bacteriophage-like mechanism of action. A further study by the same group,[11] found the production of specific toxin-like peptides * associated with virus replication in intestinal bacteria and potentially responsible for extrapulmonary manifestations peculiar to COVID-19.

Hydroxychloroquine

"AIFA confirms the suspension of the authorization for off-label use of hydroxychloroquine in clinical practice for both therapeutic (hospital and territorial) and prophylactic use"

As reviewed by the regulatory agencies[12] , it appears that retrospective studies and currently completed randomized trials have generally shown these results:

1) **if started late** in the hospital course and for short periods of time, antimalarials appear to be **ineffective**,
2) **when started earlier** in the hospital course, for progressively longer durations, and in outpatients, **antimalarials can reduce disease progression, prevent hospitalization, and are associated with reduced mortality**.

It follows that the timing of HCQ therapy (administration within 1 day of admission) could explain the discrepancies between the different studies. In the RECOVERY study, the median time between symptom onset and randomization was 9 days and a

[11] Brogna, Carlo, Petrillo, Mauro, Cristoni, Simone, Querci, Maddalena, Piazza, Ornella, & Van den Eede, Guy.
Detection of toxin-like peptides in plasma and urine samples from COVID-19 patients (Version v1). Zenodo. (2020, October 27). http://doi.org/10.5281/zenodo.4139341 https://zenodo.org/record/4139341#.X7m2sqpKjjA

[12] https://www.aifa.gov.it/aggiornamento-sui-farmaci-utilizzabili-per-il-trattamento-of-disease-covid19

substantial percentage of patients (16.7%) were already on mechanical ventilation at the time of randomization, and the dosages used were also higher than in the other studies that reported favorable results without reports of serious adverse reactions[13] . Indeed, CQ/HCQ have narrow therapeutic ranges and toxic effects are closely related to the dose ingested. A one-time dose of 20 mg/kg of CQ has been described as toxic and doses of 30 mg/kg of CQ have resulted in deaths,[14] while the use of the prescribed dosages for home treatment and the short duration of therapy has a very favorable benefit/risk ratio.

This was supported by an international vote of 6227 physicians from 30 countries and regions released by the SERMO Global Medical Voting Society found that of the 15 treatment alternatives, 37% of physicians rated HCQ as "the most effective treatment for COVID-19."[15] .

The numerous mechanisms of action of hydroxychloroquine and associated drugs/phytotherapeutics (chloroquine, quinine, active ingredients *of Artemisia annua* and *Nigella sativa*) against SARS-Cov- 2 and SARS-Cov-1 **support the rationale for use for this drug.** [16]

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[13] RECOVERY Collaborative Group, Horby P, Mafham M, et al.
Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19.
N Engl J Med. 2020;383(21):2030-2040. doi:10.1056/NEJMoa2022926
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7556338/

[14] Taylor WR, White NJ.
Antimalarial drug toxicity: a review.
Drug Saf. 2004;27(1):25-61. doi: 10.2165/00002018-200427010-00003. PMID: 14720085.
https://link.springer.com/article/10.2165%2F00002018-200427010-00003

[15] Sermo.Com (2020)
Breaking Results: Sermo's COVID-19 Real Time Barometer Study.
Available at Sermo's COVID-19-Barometer Web
https://public-cdn.sermo.com/covid19/c8/be4e/4edbd4/dbd4ba4ac5a3b3d9a479f99cc5/wave-i-sermo-covid-19-global-analysis-final.pdf. Accessed 27 Mar 2020.

[16] Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R.
Effects of chloroquine on viral infections: an old drug against today's diseases?
Lancet Infect Dis. 2003;3(11):722-727. doi:10.1016/s1473-3099(03)00806-5

Drugs not evaluated in the circular for treatment of the symptomatic patient

Intravenous infusion of immunoglobulins (IVIG and hyperimmune/convalescent plasma)

The results of clinical research still remain inconclusive, due to critical issues related to the planning of study protocols, regarding the efficacy of hyperimmune or convalescent plasma therapy in COVID-19,[17] despite the fact that positive findings published especially by Italian teams are particularly encouraging. [18] Clinical feedback from physicians who have used it during the course of the outbreak shows that **early administration is strongly recommended, is optimal within the first 7 days, efficacy remains good within 14 days, while it is not indicated beyond three weeks after disease onset. It is also important to perform therapy during the viral replication phase**.

Ozone therapy

The SIOOT (INTERNATIONAL SOCIETY OF OXYGEN OZONOTHERAPY, www.ossigenoozono.it), published the results of the employment

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7128816/

Gies V, Bekaddour N, Dieudonné Y, et al.
Beyond Anti-viral Effects of Chloroquine/Hydroxychloroquine.
Front Immunol. 2020;11:1409. Published 2020 Jul 2. doi:10.3389/fimmu.2020.01409
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7343769/

[17] Wooding DJ, Bach H.
Treatment of COVID-19 with convalescent plasma: lessons from past coronavirus outbreaks.
Clin Microbiol Infect. 2020;26(10):1436-1446. doi:10.1016/j.cmi.2020.08.005
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7417293/

[18] Perotti C, et al
Covid-19 plasma task force. Mortality reduction in 46 severe Covid-19 patients treated with hyperimmune plasma. A proof-of-concept single arm multicenter trial. Haematologica. 2020 Jul 23:haematol.2020.261784. doi: 10.3324/haematol.2020.261784. Epub ahead of print.
https://haematologica.org/article/view/9826

of ozone therapy on treated COVID-19 patients in 15 Italian hospitals, with a significantly better clinical course than untreated patients. Patients treated simultaneously with drugs and ozone had an even more favorable course and a clear reduction in side effects seen in patients treated with drugs alone.[19]

Ozone simultaneously performs the following main functions:

- Reduces tissue acidity, hypoxia and inflammation;
- Improves microcirculation and oxidative phosphorylation;
- Increases the production of ATP;
- is a powerful Antibiotic and Virustatic (so far no resistant virus or bacteria have been found).

and the reducing action carried out by ozone therapy regarding inflammation, thrombi, hypoxia, asthenia and pain is decisive.

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[19] Valdenassi L, Franzini M, Ricevuti G, Rinaldi L, Galoforo AC, Tirelli U.
Potential mechanisms by which the oxygen-ozone (O2-O3) therapy could contribute to the treatment against the coronavirus COVID-19.
Eur Rev Med Pharmacol Sci. 2020 Apr;24(8):4059-4061. doi: 10.26355/eurrev_202004_20976. PMID: 32374009.
https://www.europeanreview.org/article/20976

Franzini M, Valdenassi L, Ricevuti G, et al.
Oxygen-ozone (O2-O3) immunoceutical therapy for patients with COVID-19. Preliminary evidence reported. Int Immunopharmacol. 2020;88:106879. doi:10.1016/j.intimp.2020.106879
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7414302/

Menendez-Cepero S, Marques-Magallanes-Regojo JA, Hernandez-Martinez A, Hidalgo Tallón FJ, Baeza-Noci J
Therapeutic Effects of Ozone Therapy that Justifies Its Use for the Treatment of COVID-19.
J Neurol Neurocrit Care Volume 3(1): 1-6. (2020)
https://clinalgia.com/JNNC-3-304_AC.pdf

Gavazza A, Marchegiani A, Rossi G, et al.
Ozone Therapy as a Possible Option in COVID-19 Management.
Front Public Health. 2020;8:417. Published 2020 Aug 25. doi:10.3389/fpubh.2020.00417
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7477102/

Home ozone therapy, practiced by USCA or other appropriately trained and equipped medical teams, could thus significantly reduce the recovery time and the need for hospitalization of symptomatic patients.

Antihistamines

Coronaviruses develop special mechanisms to invade the body and immune cells, including mast cells, which when activated by the virus produce histamine, prostaglandin D2 (PGD2) and leukotriene C_4 (LTC_4) that induce acute bronchoconstriction and lung inflammation. (mast cell activation syndrome)
[20]

Currently, there are few studies examining the use of antihistamine products in patients with COVID-19, however, the results to date are particularly significant[21] . In a study of ten consecutive patients with COVID-19 who self-administered high-dose oral famotidine (80 mg three times daily (n = 6) for a median of 11 days (range: 5-21 days)) all 10 patients had marked improvement in COVID-19 symptoms. [22]

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[20] Afrin LB, Weinstock LB, Molderings GJ.
Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome.
Int J Infect Dis. 2020;100:327-332. doi:10.1016/j.ijid.2020.09.016
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7529115/

[21] Efficacy of Famotidine for COVID-19: A Systematic Review and Meta-analysis
Rahul Sethia, Manya Prasad, Soumya Jagannath, Neeraj Nischal, Manish Soneja, Pra mod Garg, Shalimar
medRxiv 2020.09.28.20203463; doi: https://doi.org/10.1101/2020.09.28.20203463
https://www.medrxiv.org/content/10.1101/2020.09.28.20203463v1.full.pdf

Malone RW, Tisdall P, Fremont-Smith P, et al.
COVID-19: Famotidine, Histamine, Mast Cells, and Mechanisms.
Preprint. Res Sq. 2020;rs.3.rs-30934. Published 2020 Jun 22. doi:10.21203/rs.3.rs-30934/v2
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7336703/

[22] Janowitz T, Gablenz E, Pattinson D, et al.
Famotidine use and quantitative symptom tracking for COVID-19 in non-hospitalized patients: a case series.
Gut. 2020;69(9):1592-1597. doi:10.1136/gutjnl-2020-321852

Nutritional and functional medicine therapy

"There is, to date, no solid and incontrovertible evidence (i.e., from controlled clinical trials) of efficacy of vitamin supplements and dietary supplements (e.g., vitamins, including vitamin D, lactoferrin, quercitin), the use of which for this indication is, therefore, not recommended."

It is first noted that **in the Indications** for Clinical Management of Asymptomatic or Paucisymptomatic Subjects, **reference is made to "*appropriate hydration and nutrition,*"** and therefore, nutritional therapy and nutraceuticals, which can be taken through diet and supplementation with dietary supplements, are indispensable for proper management of COVID-19.

Because SARS-Cov-2 is a virus that interacts with and alters the gut and lung microbiota, the validity of the nutritional approach for prevention and therapy during the acute viral infection phase is widely demonstrated,[23] therefore **it is neither understandable nor**

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7299656/

[23] Infusino F, Marazzato M, Mancone M, et al.
Diet Supplementation, Probiotics, and Nutraceuticals in SARS-CoV-2 Infection: A Scoping Review.
Nutrients. 2020;12(6):1718. Published 2020 Jun 8. doi:10.3390/nu12061718
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7352781/

Count L, Toraldo DM.
Targeting the gut-lung microbiota axis by means of a high-fiber diet and probiotics may have anti-inflammatory effects in COVID-19 infection.
Ther Adv Respir Dis. 2020;14:1753466620937170. doi:10.1177/1753466620937170
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7328354/

Antunes AEC, Vinderola G, Xavier-Santos D, Sivieri K.
Potential contribution of beneficial microbes to face the COVID-19 pandemic.
Food Res Int. 2020;136:109577. doi:10.1016/j.foodres.2020.109577
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7378002/

Santos HO, Tinsley GM, da Silva GAR, Bueno AA.
Pharmaconutrition in the Clinical Management of COVID-19: A Lack of Evidence- Based Research But Clues to Personalized Prescription.
J Pers Med. 2020;10(4):145. Published 2020 Sep 25. doi:10.3390/jpm10040145

justified a denialist approach by the ministry, in clear contradiction to its recommendations for healthy eating during the COVID-19 emergency[24] .

In particular, the positive effects in both prevention and treatment of COVID-19 of **Vitamin D3**[25] in combination with **Vitamin K2**[26] and **zinc** especially in the elderly age group predisposed to severe/fatal complications are well documented, so such supplementation is indispensable[27] .

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7712662/

Alschuler L, Weil A, Horwitz R, et al.
Integrative considerations during the COVID-19 pandemic.
Explore (NY). 2020;16(6):354-356. doi:10.1016/j.explore.2020.03.007
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7270871/

[24] What to eat in the time of isolation
http://www.salute.gov.it/portale/nuovocoronavirus/dettaglioNotizieNuovoCoronavirus.jsp?language=italian&menu=news&p=frommministry&id=4262

Power supply during emergency COVID-19
https://www.epicentro.iss.it/coronavirus/sars-cov-2-stili-vita-alimentazione

[25] Yılmaz K, Şen V.
Is vitamin D deficiency a risk factor for COVID-19 in children?
Pediatr Pulmonol. 2020;55(12):3595-3601. doi:10.1002/ppul.25106
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7675606/

Annweiler G, Corvaisier M, Gautier J, et al.
Vitamin D Supplementation Associated with Better Survival in Hospitalized Frail Elderly COVID-19 Patients: The GERIA-COVID Quasi-Experimental Study.
Nutrients. 2020;12(11):3377. Published 2020 Nov 2. doi:10.3390/nu12113377
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7693938/.

[26] Goddek S.
Vitamin D3 and K2 and their potential contribution to reducing the COVID-19 mortality rate.
Int J Infect Dis. 2020;99:286-290. doi:10.1016/j.ijid.2020.07.080
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7406600/

[27] Alexander J, Tinkov A, Strand TA, Alehagen U, Skalny A, Aaseth J.
Early Nutritional Interventions with Zinc, Selenium and Vitamin D for Raising Anti-Viral Resistance Against Progressive COVID-19.
Nutrients. 2020;12(8):2358. Published 2020 Aug 7. doi:10.3390/nu12082358

Added to these are the favorable results of using the:
-Vitamin **C**:[28] this vitamin revealed from the beginning its central role in the treatment of COVID-19, both for high-dose bolus therapy and in combination with other antioxidants (glutathione, N-acetylcysteine)
-lactoferrin,[29] particularly early viral clearance and rapid recovery of clinical symptoms in addition to a statistically significant reduction in blood levels of D-Dimer, Interleukin-6 and ferritin, as reported in a recent Italian study[30] .
-quercitin, which manifests selective actions against SARS- Cov-2 (inhibition of ACE2 and 3CL protease^{pro}) and immunostimulatory effects [31]

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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7468884/

[28] Feyaerts AF, Luyten W.
Vitamin C as prophylaxis and adjunctive medical treatment for COVID-19?
Nutrition. 2020;79-80:110948. doi:10.1016/j.nut.2020.110948
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7381407/

Farjana M, Moni A, Sohag AAM, Hasan A, Hannan MA, Hossain MG, Uddin MJ.
Repositioning vitamin C as a promising option to alleviate complications associated with COVID-19.
Infect Chemother. 2020 Nov 13. epub ahead of print. PMID: 33263242.
https://www.icjournal.org/DOIx.php?id=10.3947/ic.2020.52.e73

[29] Wang Y, Wang P, Wang H, et al.
Lactoferrin for the treatment of COVID-19 (Review).
Exp Ther Med. 2020;20(6):272. doi:10.3892/etm.2020.9402
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7664603/

[30] Pleiotropic effect of Lactoferrin in the prevention and treatment of COVID-19 infection: randomized clinical trial, in vitro and in silico preliminary evidences
Elena Campione, et al
bioRxiv 2020.08.11.244996; doi: https://doi.org/10.1101/2020.08.11.244996
https://www.biorxiv.org/content/10.1101/2020.08.11.244996v2.full.pdf

[31] Colunga Biancatelli RML, Berrill M, Catravas JD, Marik PE.
Quercetin and Vitamin C: An Experimental, Synergistic Therapy for the Prevention and Treatment of SARS-CoV-2 Related Disease (COVID-19).
Front Immunol. 2020;11:1451. Published 2020 Jun 19. doi:10.3389/fimmu.2020.01451
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7318306/

-melatonin: this hormone has numerous functions that make its use particularly important in the treatment of COVID-19 (antioxidant, anti-inflammatory, immunomodulatory, antiviral, cytoprotective, neuroprotective, ect). [32]
Finally, **immunoprobiotics** and **prebiotics** play a key role in the prevention and treatment of gut dysbiosis that occurs during infection. [33]

The Ministry of Health's precautionary approach may be justified by the fact that many clinical trials are still ongoing and do not allow the true benefit/risk ratio of various therapeutic strategies to be conclusively established, but it should in no way override or even prevent, as in this case, the physician from applying his or her own knowledge from clinical experience to decide which therapies are most appropriate for his or her patient.
The guidelines adopted and restrictions imposed were decided without any prior consultation with the physicians who used the suspended or unsuccessful drugs, and if applied as such make the management of COVID-19 patients on the ground particularly difficult with the inevitable result that hospitals will again be overburdened precisely because of the incorrect guideline imposed for home care.

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[32] Cardinals DP, Brown GM, Pandi-Perumal SR.
Can Melatonin Be a Potential "Silver Bullet" in Treating COVID-19 Patients?
Diseases. 2020;8(4):44. Published 2020 Nov 26. doi:10.3390/diseases8040044
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7709121/

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