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Aan: Advisory panel for COVID-19 Innovative treatments

Subject: vitamine C therapy for COVID-19

- *Prevent damage, do not wait* -

Dear members of the Advisory Panel,

We would like to draw your attention to the importance of accelerated application of vitamin C therapy to prevent (organ) damage in COVID-19 patients. The role of vitamin C is sufficiently substantiated and justified. Severely ill COVID-19 patients have been shown to be deficient in this important micronutrient, leading to an unequal fight against this serious infection. As has also been shown with regard to vitamin D and was recently underlined by several professors and in the media, a deficiency in COVID-19 patients poses a greater risk of a serious course, while administration has been shown to be safe in all studies. In this situation, "waiting for full evidence to be obtained" can seriously hinder the chances of recovery for current and future patients. The recent publications and the clinical expertise of the physicians who have provided us with the key to the effectiveness of this therapy (viz. Through very rapid and adequate administration), show us not only a beckoning but also a proven perspective. Given the urgency, it is important to give this safe therapy, which can alleviate the impact of COVID-19 in the short and long term, more space as soon as possible.

We would like to explain this further below.

We would like to draw your attention to the publications published this autumn about the role of vitamin C in combating COVID-19. The previous research on vitamin C in the prevention and treatment of pneumonia and sepsis has laid an important foundation for translation to the situation of patients with COVID-19. Precisely in view of the fact that some RCTs do not appear to reproduce the results of Fowler's Phase I study, while other RCTs and the clinical practice of the FLCCC show a positive reality, a better examination of the details of large importance.

Vitamin C in the fight against COVID-19

At the end of October, Carr and Rowe's article was published, entitled: "The Emerging Role of Vitamin C in the Prevention and Treatment of COVID-19" In it, the authors provide a clear overview of the properties of COVID-19. vitamin C and the results so far. Vitamin C can reduce the severity and duration of the clinical picture in patients with pneumonia. A Chinese study (still under peer review) that had to stop prematurely because the number of IC admissions of patients with COVID-19 decreased, showed a significant effect on IC mortality in the more severely ill patients (baseline SOFA score of ≥ 3). Although this trial did not show a reduction in the number of ventilation days or days of vasopressor treatment, oxygenation improved and IL-6 in the intervention group showed a significant decrease on day 7. In addition, it is a given that critically ill patients received intravenous doses at grams to normalize their 'vitamin C plasma level'. It is known from the basic sciences and a great deal of research that vitamin C strengthens, among other things, the defenses of white blood cells that must clear the virus, reduces the inflammatory response in the lung and scavenges oxygen radicals.

Oxygen radicals play a role in the immune system but are produced in excess during a violent infection and then cause damage in the lung and other organs. Vitamin C captures them and is then recycled. It now appears that the vitamin C level in sepsis is severely reduced. There is a great need and recycling is inadequate. As a result, vitamin C cannot do what it could do; playing a protective, essential role in modifying the "pathway" of viral sepsis (such as a severe COVID-19 infection) that leads to organ failure requiring intensive care treatment. Timely, adjuvant treatment with a high dose of Vitamin C via the IV drip can limit damage in the lung and promote recovery of the patient. Carr and Rowe provide an overview of all current investigations in their article, on page 5. They conclude the article with these telling words: "Optimization of the intervention protocols in future trials, e.g., earlier and sustained administration, is warranted to potentially improve its efficacy. Due to the excellent safety profile, low cost, and potential for rapid upscaling of production, administration of vitamin C to patients with hypovitaminosis C and severe respiratory infections, eg, COVID-19, appears warranted." Carr previously published a study showing that critically ill patients, despite intravenous nutrition, had a greatly reduced vitamin C level. This was recently underlined by Chiscano-Camón et al. in another publication, specifically with regard to COVID-19 patients.

The conditions for the effectiveness of vitamin C therapy

Vitamin C plays a central role in the "metabolic resuscitation of the patient", when administered early and at a high dose and with sufficient duration. This has been described in many scientific publications (see the review by Holford et al.), by the doctors who have achieved positive results with this in practice (see, among others, the FLCCC) and, in various emphases, in various studies such as the CITRIS-ALI trial (which was revised positively afterwards), the ORANGES trial, the study by Long et al. (which demonstrated the importance of timely administration, on a par with the sepsis bundle, in septic shock) and the recent Chinese study. It is very plausible that the effect of vitamin C does not emerge in a number of RCTs because the conditions for a maximum effect of vitamin C are not or insufficiently present. The "time-critical" aspect deserves more attention. Vitamin C, a substance that we naturally need but cannot produce ourselves, has many essential functions and also acts as a stress hormone (as Holford et al. also describe in their recent paper entitled: *Vitamin C — An Adjunctive Therapy for Respiratory Infection, Sepsis and COVID-19*). Fighting a viral infection without the timely support of this substance is an uneven battle. And the need for speed is not only emphasized in the aforementioned article by Long et al.¹⁴, but also in the practice of the FLCCC. The duration of therapy is also an important aspect. De Grooth et al. conclude in their study entitled *Vitamin C Pharmacokinetics in Critically Ill Patients* (published in *Chest* in 2018) that "Sustained therapy is needed to prevent hypovitaminosis." Holford et al. say about this in the aforementioned article: "There is concern, however, that these study designs limit the use of vitamin C to a maximum of four days, which may be inadvisable in acutely ill patients due to the potential return of symptoms, if the inflammation is not resolved. This issue was illustrated by the CITRIS-ALI trial, which showed a maximum reduction in mortality compared to placebo on day 4, the final day of vitamin C administration, but a decreased difference between the groups after 28 days". Last but not least the level of the dosage is important: research has shown that supra-physiological dosage enhances the positive properties of vitamin C on all fronts.

Good care is harmed by waiting

As patient organizations, Hersenletsel.nl and Sepsis and thereafter find it objectionable that good care is equated with "waiting for full evidence to be obtained" while patients remain vitamin C deficient in the meantime. There are great risks associated with vitamin C deficiency, while the safety of vitamin C administration has been demonstrated. We are also surprised that only other means that do carry safety risks in the ICU in the context of 'compassionate use' have so far been deployed and some of them were even considered 'as treatment options', while the collected evidence of the effect of vitamin C and its effects in practice (see also the FLCCC) are not inferior to these agents. In our opinion, public health does not benefit from giving vitamin C therapy no space in the search for what can support patients in their fight against the

virus. This is in line with the conclusion of Kashiouris et al. who stated in their review on sepsis (January 2020): "With further study, vitamin C may become standard of care for the treatment of sepsis, but given its safety profile, current treatment can be justified with compassionate use. " In view of the fact that the next results of a large RCT with regard to vitamin C therapy cannot be expected before 2022/2023, we do not think waiting is a realistic option. It is unacceptable to us that critically ill COVID-19 patients are denied optimization of their vitamin C status in the meantime.

Breaking the vicious circle through collaboration

In our view, the available evidence is not just the result of the "scientific evidence" in the highest category; it is also necessary to reflect on the basis of ethical considerations on the basis of which evidence may be regarded as "sufficient" and application as justified under the given circumstances. The proposed adjuvant treatment is the sum of scientific evidence, clinical expertise and patient values and preferences. The last 2 should also be taken into account proportionally, certainly in a situation in which we continue to have to deal with the major impact of this virus on human lives, our society and healthcare. See also the aforementioned statement by Carr 2, a scientist highly respected for her expertise in this field. We would like to add to that: Let's use the evidence we have, to prevent the impact we can. We would like to break the vicious circle and work with you to explore the possibilities of using vitamin C in a controlled context so that, with a joint effort of several hospitals, an accelerated route is created to offer patients a chance on this safe therapy and in collect valuable data in the meantime. In our view, this would fit within the framework of the advisory panel to "help develop specific promising treatments." In its "Roadmap COVID-19", the WHO also takes vitamin C as an adjuvant therapy very seriously.¹⁷ In order to guarantee the voice of the patient as the 'first stakeholder' in our country, we as patient organizations are happy to discuss this with you.

We look forward to your response,

Yours sincerely and with kind regards, on behalf of

Chairman directeur Hersenletsel.nl

Sepsis en daarna, patiëntenplatform

Plaats: Velp

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- ⁴ Spoelstra–de Man, A.M.E. et al. Adjuvant vitamin c for sepsis: mono or triple? Critical Care (2019) 23:425 doi: 10.1186/s13054-019-2717-x
- ⁵ Oudemans-van Straaten, H.M. et al. Vitamin C revisited. Crit Care, 2014 Aug 6;18(4):460. doi: 10.1186/s13054-014-0460-x.
- ⁶ SepsisNet (met steun van VWS gelanceerd op 11-9-2020), <https://www.sepsisnet.nl/patienten>
- ⁷ Carr, A.C. et al. Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes, Crit Care, 2017 Dec 11;21(1):300. doi: 10.1186/s13054-017-1891-y
- ⁸ Chiscano-Camón, L. et al. Vitamin C levels in patients with SARS-CoV-2-associated Respiratory Distress Syndrome, Crit Care, 2020 Aug 26;24(1):522. doi: 10.1186/s13054-020-03249-y
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- ¹¹ Fowler, A.A. et al. Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure, JAMA, 2019;322(13):1261-1270. doi:10.1001/jama.2019.11825
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- ¹³ Iglesias, J. et al. Outcomes of Metabolic Resuscitation Using Ascorbic Acid, Thiamine, and Glucocorticoids in the Early Treatment of Sepsis: The ORANGES Trial, Chest 2020 Jul;158(1):164-173. doi: 10.1016/j.chest.2020.02.049. Epub 2020 Mar 17
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- ¹⁷ WHO, A coordinated global research roadmap: 2019 novel coronavirus, March 2020 https://www.who.int/blueprint/priority-diseases/key-action/Coronavirus_Roadmap_V9.pdf, p. 37