Scientific Review of COVID-19 and MATH+

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On August 18, 2020, a shortened version of this scientific review was published in “Expert Review of Anti-Infective Therapy” on Taylor & Francis online:

MATH+ protocol for the treatment of SARS-CoV-2 infection: The scientific rationale
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On December 14, 2020, the FLCCC Alliance peer-reviewed paper
Clinical and Scientific Rationale for the “MATH+” Hospital Treatment Protocol for COVID-19
was published in the **Journal of Intensive Care Medicine** (a shorter but more up-to-date version of this page). The MATH+ protocol potentially offers a life-saving approach to the management of hospitalized COVID-19 patients. The MATH+ protocol offers an inexpensive combination of medicines with well-known safety profiles based on strong physiologic rationale and an increasing clinical evidence base.

Abstract
In December 2019, COVID-19, an illness characterized by pneumonia associated with the new coronavirus SARS-CoV-2 (COVID-19) emerged in Wuhan, China. On March 13, 2020, the United States declared a national emergency in response to the pandemic. The greatest impact that COVID-19 had was on intensive care units (ICUs), given that approximately 20% of hospitalized cases developed acute respiratory failure (ARF) requiring ICU admission. Based on the assumption that COVID-19 represented a viral pneumonia and no anti-coronaviral therapy existed, nearly all national and international health care societies advocated a primary focus on supportive care with avoidance of other therapies outside of randomized controlled trials, and with specific recommendations to avoid the use of corticosteroids.

However, several early studies of COVID-19-associated ARF reported inexplicably high mortality rates, with frequent prolonged durations of mechanical ventilation (MV), even from centers expert in such supportive care strategies. These reports led the authors to form a clinical expert panel that collaboratively reviewed the emerging clinical, radiographic, and pathological reports of COVID-19 and held multiple discussions among a wide clinical network of front-line clinical ICU experts from initial outbreak areas in China, Italy, and New York. Based on the shared early impressions of “what was working and what wasn’t working” from these colleagues along with the insights derived from increasing publications and the panel members rapidly accumulating personal clinical experiences and investigations into the pathophysiology of COVID-19 patients, a treatment protocol named “MATH+” was created to guide the treatment of hospitalized patients. This manuscript reviews the scientific and clinical rationale behind MATH+ based on published in-vitro, pre-clinical, and clinical data in support of each medicine, with a special emphasis of studies involving patients with viral syndromes. The review concludes with a comparison of published multi-national mortality data with MATH+ center outcomes.

The Pathophysiology of COVID-19

Rationale for the MATH+ Hospital Treatment Protocol

Evidence based scientific reviews supporting MATH+ components:

Methylprednisolone
Ascorbic Acid
Thiamine
Heparin
Melatonin
Zinc
Vitamin D

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Abstract
Vitamin D deficiency is a major global public health problem in all age groups and it has been estimated that in excess of one billion people world- wide have vitamin D deficiency. Although it has been quickly recognized that number of factors, including age, co-morbidities, race, access to healthcare and genetic factors (and the complex interactions between these factors), determine the clinical course after exposure to SARS-CoV-2, in the below section, the physiologic importance of vitamin D, the implications of Vitamin D deficiency, and the impacts of Vitamin D supplementation in influencing the risk of dying from SARS-CoV-2 will be reviewed.

Vitamin D and COVID-19

Vitamin D is obtained via the diet or produced in the skin by UVB light. Aside from its known role in calcium metabolism and bone health it also has important roles in the immune system including support of endothelial barriers, and innate and adaptive immunity.[133] The innate immune system in COVID-19 produces both pro-inflammatory and anti-inflammatory cytokines while vitamin D reduces the production of pro-inflammatory Th1 cytokines such as tumor necrosis factor α and interferon γ and increase the expression of anti-inflammatory cytokines by macrophages.[134–136]

Given it's important roles in immune function, many have hypothesized that vitamin D deficiency increases susceptibility to infections and that supplementation may improve outcomes, particularly in COVID-19.[137,138] Data supportive of the theory that deficiency leads to infections largely rest on the fact that seasonal influenza infections generally peak in conjunction with times of the year when 25(OH)D concentrations are lowest.[139] Further, the onset of the epidemic and higher case load in countries during the winter season also raises the possible association with low vitamin D status.[140] Rhodes et al first identified this link by comparing the mortality of COVID-19 in relation to country latitude and found that, even after adjusting for age, there was a 4.4% increase in mortality for each degree latitude north of 28 degrees. Further, ethnic minorities in both the United States and the United Kingdom have high rates of Vitamin D deficiency, potentially explaining why the mortality rates in these populations are much higher.[141]

Given the strong associations of Vitamin D deficiency with higher rates of viral infections, multiple studies have tested whether vitamin D supplementation can reduce this risk. Although studies have conflicted in their findings, a recent meta-analysis from 2018 found that regular supplementation with vitamin D decreased the risk of acute respiratory tract infections, with the most profound effects in patients with severe vitamin D deficiency.[142]

In the critically ill, the benefits of supplementation are even more profound. First, vitamin D deficiency in the ICU is common and levels decrease rapidly after admission.[143,144] Deficiency has strong negative correlations with poor outcomes, namely higher mortality.[145,146] Overall, less than 800 patients have been included in RCTs worldwide, but a meta-analysis of these studies found that supplementation in the ICU, largely using high doses, improved survival.[147,148] Currently there are two large RCT's together enrolling over 5000 patients which will provide more definitive evidence to guide therapy.

The available data suggest that high-dose vitamin D supplementation is beneficial not only in the prevention of viral infections but also in improving outcomes of the critically ill. Although the impact of supplementation varies by deficiency status as well as severity of illness, vitamin D supplementation is safe; one meta-analysis of healthy patients found no adverse events, while in the critically ill, mild hypercalcemia was the most common adverse effect.[142,149]

Levels greater than 50nmol/L (20ng/mL) are thought sufficient for protection against acute respiratory tract infections.[142] One report mentioned that "doses up to 10,000 IU/day is safe, although well above what is needed" and that "only 1,000–2,000 IU may be needed to obtain optimal effects on bone and immunity".[150] Thus to reduce the risk of infection, one expert recommended that people at risk of COVID-19 consider taking 10,000 IU/d of vitamin D3 for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000 IU/d. The goal should be to raise 25(OH)D concentrations above 40–60 ng/mL (100–150 nmol/L).[150]

In the critically ill, the doses used from published RCT's ranged from 200,000–600,000 IU.[147] Han et al gave either 50,000 or 1000,000 IU for 5 days straight while in the largest trial, Amrein et al gave a single enteral dose of 540,000 IU then monthly doses of 90,000 IU for 5 months.[151,152]

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