

Protocol NAC-H2S-COVID -

preface

Here you will find a proposal protocol that aims to create "group viral immunity" within the population in a accelerated but milder way. No Lock-Down but limited & protected exposure.

Also we aim to modify the severity of the successive disease phases of the viral infection COVID19 to lessen the pressure on the hospital wards and the ICU.

This proposal is based on one human multicenter RCT trial and five preclinical animal studies.

Although this protocol is best performed as a double-blind RCT study, there are probably several factors that make it impossible. Time sets a pressure, After all, it concerns medicines OTC.

When the background study data will become publicly known, the drugstores will flock and availability of medication will be disrupted, e.g. for the health care workers, the fire brigade, the police and other crucial professions.

Therefore, a different experimental design is necessary, here a TwiC design is considered.

Operation:

By administration of N-acetylcysteine (and possibly also Taurine) endogenously the physiologically very useful H₂S is accelerated and strengthened in tissues.

Various studies show that increasing H₂S has an antiviral (decrease in virus replication) and anti-inflammatory (damping of leucocyte-endothelial traffic) effect.

H₂S itself does not have a virus-killing effect, but it can make the course of the disease milder, thus creating a time space for the gradual emergence of immunity naturally within the population.

H₂S is released during so-called redox reactions, which have not been clearly distinguished until 2018. Since the study by Ezerina et al (2018), the two different processes

1] generation of H₂S and 2] the actual antioxidant activity have been distinguished.

Also, after first using H₂S donor substances in *in vitro* studies, the role of

N-acetylcysteine (now abbreviated as NAC) has become known as a direct H₂S generator.

By administration of NAC, higher H₂S tissue concentrations are generated endogenously, among others in the lungs, where the virus-inhibiting and anti-inflammatory H₂S is intended.

NAC and Taurine are both substances without side effects and OTC available.

A safe dose range is known for a long time.

The arguments to include nebulization in this viral protocol : see below

Design of a study: Although a RTC double blind trial would be preferable, in this case a Trial within Cohort (TwiC) design can be considered for practical reasons (flexability in randomization and fast implementation)

Proposed Action Plan

The classification of treatment advice of CIB-RIVM (The Netherlands) will be followed. This current protocol is additive to the supportive care:

Disease phase	Treatment	Comments :
For disease phase 0: (healthy population)	useful NAC 2x 600 per os,	age > 18 years; n.d. after advice from a GP, .pref: not pregnant, anticoag, hepatic etc
	Vital professions : health care workers (and other crucial/vital professions , police , fire dpt, etc etc) will get the <u>guaranteed provision of the trial medications</u> by the government / employer.	
For disease phase 1: (seropos.* & Home isolation)	Added: Taurine 2x 2 grams per os, in addition to the NAC	
	Vital professions : health care workers (and other crucial/vital professions , police , fire dpt, etc etc) will get the <u>guaranteed provision of trial medications</u> by the government / employer.	
* ?Seropos or also strong suspicion COVID?	amendment	
For Disease Phase 2: (seropos. & Nursing ward)	In addition to NAC 2x 600 mg orally (i.v. if necessary parent. for nausea); Taurine 3x 2 grams per os; Start spray therapy 4-6 /d**	start spray **therapy especially after 3rd day after incubation. NB jet nebulizer with secure outlet protection as described below
For Disease phase 3	see ICU protocol .	Spray can integrated in ventilator circuit.

**))

start spray 4 - 6 x daily with 6 liters of compressed air (no oxygen!): with
1.5 cc Sodium Bicarbonas 4.2%
1.5 cc N-acetylCysteine 10%, [added just <3 min for starting inhalation]
0.5 cc Lidocaine 4%
0.5 cc Salbutamol 0.5%

-References:

- 1- argument for addition of Salbutamol [Ref PMID: 25632025]
 - a- prevents bronchospasm by NAC
 - b- stimulates lung liquid clearance
- argument for addition of N-acetylCysteine 10%
 - a- maximum saturation bronchial / mucous membrane / parenchyma for H₂S generation.
 - b- mucolytic on mucous plugs, especially after 2-3th day of illness
- argument for lidocaine = correction of bad taste of NAC, pH correction, mucolysis.

This spray combination is completely safe, without side effects and has been used for > 10-15 years on indications Bronchiectasia / Aspergillosis / Organizing pneumonia in Walcheren Hospital (1990-2005) without problems, also in seasons of influenza. Hospital Pharmacy Department did the preparation in 2 syringes apart.

Safety concerns about nebulization treatment

Everyone will be very concerned about the application of Nebulizer Therapy in COVID-19. Of course, extreme attention to PPE is needed to prevent ANY spread of virus particles in the environment through nebulization therapy in respiratory viral infections (nursing staff, paramedics and fellow patients). Yet the actual performed studies herein have proved reassuring: <https://doi.org/10.1086/502353> Wan et al 2004 and Tran 2012 DOI: [10.1371/journal.pone.0035797](https://doi.org/10.1371/journal.pone.0035797)

Moreover, as of 27 March 2020 the official guidelines of WHO and several national authorities have been adapted for a lower risk classification for nebulization.

Also in addition technically adjustments of the jet nebulizer setup are possible:

Safety Planning :

Virological in vitro contact examination beforehand:

1-Surface contact Safety : First of all, it must be ascertained whether the spray liquid may be virus-killing for [surface contact contamination](#) ; compared to alcohol 60% or 90% and strong bleach.

2-Aerogenic virological measurement /at first patient / or in a lab model.

3-In addition **Jet Nebulizer Adjustments** (Hudson type) by Dept Medical Technology:

-The outlet with a wide tube extends to the ground, to a BBB = covered bottom tray filled with a strong bleach solution; the branched pipe is submerged under the liquid surface; and on top of the liquid surface a multi-layer " bubble mattress " is placed for strong reduction of air bubbles coming up. (here at the start : aerogenic virological assessment)

-Ambulatory patients can nebulize sitting in a plastic tent setup [eg 1.5x 1.5 x 2.0 m (LxWxH)] in the room, wherein an air vacuum is created at 12 l / min [compared to the spray with 6 l / min compressed air from the nebulizer].

The exhaust air also goes to a BBB, preferably installed outdoors / next room.

-With a bedridden patient, a Hood half-over the patient's head that sucks the air away at > 12 l / min before, during and shortly after the spray session; also drain the exit-air to a BBB.

-Air quality: prevent from forming a "pool air" in the room...

In conclusion : H₂S

Hydrogen Sulfide (H₂S) have become recognized as an important gaseous signaling molecule with enormous pharmacological effects, therapeutic value, and central physiological roles.

All in all, here the picture emerges of a very useful endogenous pool of this gaseous modulator of H₂S that decreases with age and subsequently it is not sufficiently available for, among others, the acute defense against viral respiratory infections.

By supplementation of NAC and Taurine, this shortage in H₂S seems reversible.

The time frame in which sufficient H₂S will be supplemented is not yet exactly defined, but it can be estimated. More research is warranted.