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Seven immediate, low-cost management strategies for Covid. Exploiting viral Thermolabity: Possible, immediate solutions

Giovanni Belcaro[1]*, Umberto Cornelli[1], Maria Rosaria Cesarone[1], Beatrice Feragalli[2], Ezio Bombardelli[1], Mark Dugall[1], Sandeep Shah[1], Marcello Corsi[1], Roberto Cotellese[1], Shu Hu[1] and Morio Hosoi[1]

[1]*Darwin Lab & Irvine3 Labs and the OOLEX C-Virus project, Italy*

[2]*Radiology, Dip SMO Biotec, D'Annunzio University, Italy*

***Corresponding author:** Giovanni Belcaro, Darwin Lab & Irvine3 Labs and the OOLEX C-Virus project, Pescara, ITALY

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SYNOPSIS

Seven strategies are proposed - and are under evaluation - to control the disrupting effects of COVID on our medical and social structures:

Home/pre-hospital strategies

a) Diagnostic kit & sensor

b) whv: warm-humid vaporization

c) low-cost home ventilator

Pre-intensive care

d) Pge1 to increase bronchial perfusion

e) Optimization of anticoagulants

Post-intensive, long-term follow-up

f) Prevent pulmonary fibrosis

g) Screen with ultrasound, new protocols.

The focus of these simple, low-cost strategies is on early, before-hospital (and before ICU) management. Life losses, social disruption and costs may be greatly reduced, and the hospital burden may be shifted to homecare and prevention.

Introduction

A 'war' consensus document has been produced by a group of clinical research physician on the pandemics with special suggestions usable in a short term for patients at risk or affected by the Wuhan virus: 7 strategies may be used - at present - against the Wuhan virus (in association with what can be defined the standard management) to reduce its impact, morbidity and mortality. Each of these strategies is now in evaluation and more specific data will be available in days and analysed as separate observations or globally. However, there is no time. War is now. They may be used according to the patients' best interest if the situation is adequate and if it is technically possible. Often the patient at risk is a physician. We do not have a magic bullet for this new virus (vaccination or a specific antiviral); we may suggest different strategies to reduce its impact: one will decrease morbidity, for instance, of a factor of 20%; another may reduce viral replication of some 20%; one will reduce the inflammatory, respiratory response of some 25%; one strategy may avoid the side effects produced by drugs by 30-60% by local, direct administration into the bronchial tree. Anticoagulants (particularly LMWH, defibrotide), may reduce the occurrence of most thrombotic events in most of these patients both in the early phases and more during the hospitalization. All subjects with pneumonia should receive antithrombotic prophylaxis as indicated by several (consensus) documents and now became a normal procedure.

All these apparently 'minor' steps may induce a decrease in morbidity and mortality with a great impact on costs, on the

community and decreasing hospital load. Most patients should be managed (not abandoned) at home or in specific institutions to avoid viral spreading. One of the major problems of our health care system was the focus on hospitals, neglecting home care and GP-managed defences. Hospitals are now castles without a moat but also without a wall. No sentinels of course (a soldier or guard whose job is to stand and keep watch; like the WHO). No defenders too. In November there was a significant cluster in Wuhan with some 57 deaths (data difficult to find and verify) in days and linked to the wet market (Figure 1). It is possible that in this occasion several drugs were used without completely killing the virus but selecting more resistant and infective strains with a mechanism comparable to the creation of MRSA (methicillin resistant Staphylococcus aureus). MRSA infection is caused by a super-selected type of staph bacteria that has become resistant to many of the antibiotics used to treat staph infections. The over-selection of a resistant strain may have produced the COVID 19 virus. Most MRSA infections occur in patients who've been in hospitals or other health care settings (nursing homes, dialysis centres).

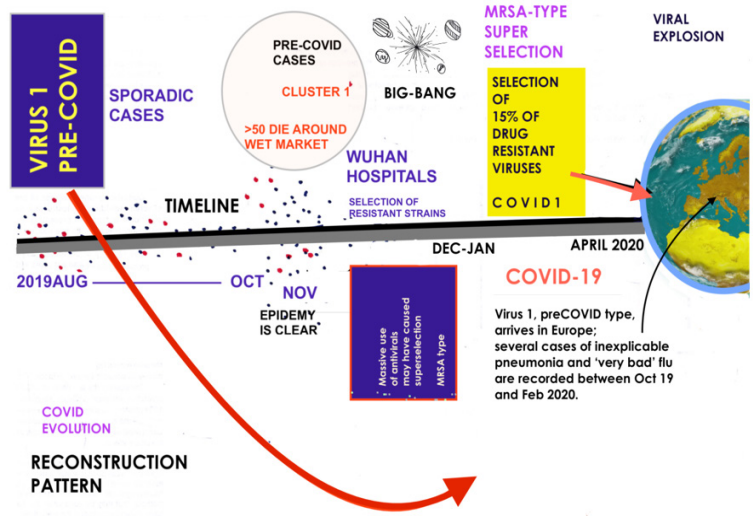

Figure 1: The reconstruction of the possible viral evolution in Wuhan is shown in this image. An original coronavirus (Virus 1, less aggressive, minimally lethal) probably started the outburst.

Health care-associated MRSA (HA-MRSA). Infections are associated with invasive procedures (surgeries, intravenous tubing, artificial joints et cet.). The selected COVID may have found its way into Wuhan and into the rest of the world in a few weeks. The Virus 1 strain may have separately found its way into Europe causing a great number of atypical (inexplicable) pneumonia cases (however not very deadly) before the arrival of the super selected COVID virus. There is some limited evidence that subjects who had these atypical pneumonia episodes did not get the COVID.

Seven, low-cost, available strategies can be applied even in places where the healthcare system does not have many resources. A study with Predictive Analytics is in progress to evaluate the relative impact of each strategy of morbidity and mortality.

A. Home/Pre-Hospital Strategies

1. Diagnostic kit & sensor
2. Whv: warm-humid vaporization
3. Low-cost home ventilator

B. Pre-Intensive Care

1. Pge1 to increase bronchial perfusion
2. Optimization of anticoagulants

C. Post-Intensive, Long-Term Follow-Up

1. Prevent pulmonary fibrosis
2. Screen with ultrasound, new protocols

Diagnostic Kit & Sensor

A diagnostic kit or a sensor should be able to diagnose the presence of an infections even with minimal symptoms. The association of flu-like symptoms, including fever, cough, fatigue, and shortness of breath is generally clinically diagnostic and indicates the need for early treatment. A nasopharyngeal swab may be negative or positive. It could be negative today (and positive tomorrow) but treatment should be considered based on symptoms. These tests are practically not available for everybody. A compact sensor could give in seconds temperature, variations or irregularities in breathing and variations in heart rate. This is faster than a swab and indicates (unless the patient is proven negative) the need for treatment and isolation. Several companies are working at this sensor now. In some cases, the sensor can be connected to a network and pass information to a medical hub. In case of fever, cough, fatigue subjects should not go on transports and need to be carefully supervised. The temperature is increased in almost 90% of patients with symptoms and cough is present in more than 38%. Even without a swab we must presume that the patients have

COVID and should be managed for this condition. The use of swabs is still not widespread, and tests are difficult to obtain; often it has been impossible to get even in symptomatic patients with a large variability in different nations and regions. For the swab, close contact is needed; they may expose to some contamination both of operators and other patients and require materials that are often unavailable. The swab, as a clinical diagnostic solution is not optimal at the moment. A sensor (not specific for COVID) could be an easier and possible solution to detect symptoms without contacts.

Whv, Warm-Humid Vaporization

Bronchial-tracheal surface cells work at a specific temperature. At their ideal range (37-38 °C) their response to viruses and bacteria tend to be optimal and mucus tends to have the specific grade of fluidity to contrast infections [1,2]. With a decrease of 3-4 °C or more, these cell layers may be less protected, less active and not ready to fight infections. Most viruses may work and replicate only at lower temperatures (i.e. 34-35°C). There is an evolutionary reason for the survival of most respiratory viruses (RVs): it is possible that the ideal replication-diffusion temperature for RVs is lower than the ideal temperature at which the human, respiratory tract layers work most effectively to produce the best anti-viral/bacterial response. Exposure to cold/dry air lowers the temperature of the upper respiratory tract (URT) and the tracheal-bronchial epithelium layers in minutes. This offers a better field for viral diffusion-replication as the superficial respiratory cells are stoned by cold and become unable to respond at their maximum antiviral efficiency. Within minutes, exposure to lower temperatures may also cause important vasoconstriction of the superficial respiratory layers, blocking blood flow, altering microcirculatory responses and regular mucin production and, generally, anti-viral responses. Increasing the temperature of the air, keeping the bronchial temperature higher, may stop the replication and diffusion of most respiratory viruses. Thermoregulatory response is often altered in older people while children very quickly develop a higher body temperature that may halt viral replication. From an evolutionary point of view, individuals able to quickly increase their temperature may have a better chance of fighting infections.

A. Preventive Implications: warmer/humid air inhalation - i.e., by warm humid vaporization (WHV) 3-4 times daily - may prevent viral contamination, replication and quickly kill most RVs. The use of eucalyptol aerosol may help the antiviral activity of most terpenes. Therapeutic implications: a warmer aerosol (vapor, 40° C) in the early phases may stop viral replication in hours. In later cases, the use of warmer-humid air (40-41° C) in artificial respiratory systems may kill viruses or halt their replication in the respiratory tree and help the recovery process [1,2]. The correlation between lower air/environmental temperatures and respiratory infections (particularly acute viral infections) is one of the pillars of hygiene and medicine: 80% of respiratory viral infections happen in the colder months and are related to the low, average levels of temperature, particularly at night. They tend to decrease when the average minimum daily temperatures increase to >10°C.For the same reasons, most viruses may die when exposed to warmer/humid air; even a hairdryer may be effective in reducing bacterial-viral charges on surfaces. At the moment, there are no specific antiviral drugs licensed by FDA to treat patients with COVID-19. In the USA, the National Institutes of Health (NIH) is working to develop vaccines and therapeutics for COVID-19. In-vitro or in-vivo studies suggest some therapeutic activity of compounds against related coronaviruses, with minimal data from trials in humans at the moment. Remdesivir seems has an activity against SARS-CoV-2 and some patients with COVID-19 are treated with intravenous remdesivir. An NIH trialCOVID-19 is in progress as the first investigational therapeutic with remdesivir. Other trials with Remdesivir for COVID-19 patients in the U.S. are available (subjects with severe external and moderate external coronavirus disease). Some COVID-19 patients have received uncontrolled treatment with other investigational antivirals. The innovation of WHV allows to use antivirals (as a dose 1/50 to 1/80 of the systemic dose) directly in the upper respiratory tract (URT) and into the bronchial tree where the virus causes its damage and replicates.

B. New Indications: it is possible that local ventilation or instillation of study products, i.e., Remdesivir or other antiviral, directly into the bronchial tree (via warm vaporization) may be much more effective than systemic doses and may reduce side effects. Local vaporization of antivirals with warmer-humid air (>40 C°) may significantly decrease viral replication in 2-3 days in the initial phases of the respiratory disease. The quantity of product needed could be minimal and very cost-effective. Vaporization with warmer air - considering minimal side effects and low costs - may also have a preventive role (low dose, in non-symptomatic, high-risk subjects). It is also important to observe that smoking is the most important cause of bronchospasm and bronchial epithelial vasoconstriction. Vasoconstriction - as for cold - may significantly impair the reaction to a RVs. All smokers should be advised to avoid smoking in this situation. The evolution of COVID (Figure 2) shows long periods - before the respiratory insufficiency phase (RIP) - usable for management. However, so far, all efforts or most management methods have been focused on assisted respiration in ICUs. It is not possible to manage a disease, involving millions of subjects with ICUs. We need to focus on medical preventive methods particularly in higher-risk subjects and we need aggressive management methods of early symptoms, out of hospitals. Our management targets are shown in Figure 3: hot and humid air with vaporizers may reduce viral spread and replication within the bronchial spaces. Antivirals, even with limited activity, may locally affect viral replication. Anti-inflammatory agents may locally control the inflammatory response due to the viral spread. Reconstitution of the mucin layers (and surfactants) may block the

viral passage directly into cells. Minor quantities of drugs can be used for bronchial vaporization, avoiding side effects and reducing costs. The initial infection is a local viral spread and not a systemic disease. Even with limited antiviral, anti-inflammatory activity and mucin-reconstituting action, a warm-humid atmosphere may produce lower spread and limited symptoms. The graph in Figure 4 shows that daily hot-humid vaporization (WHV) can stop most of the winter respiratory viral infections (associated to fever) in a 3-month follow-up (the graph was obtained during the previous winter).

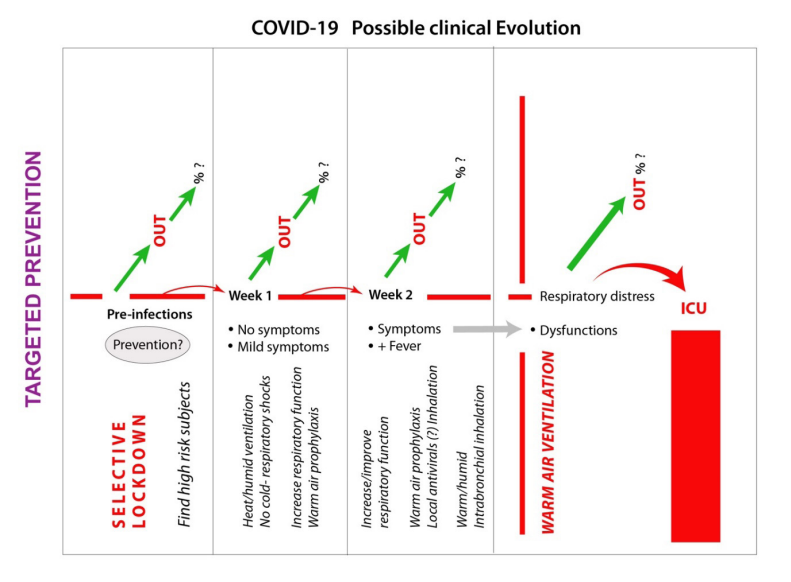

Figure 2: COVID evolution. The syndrome shows long periods – before the respiratory insufficiency phase (RIP) - usable for management. So far most management methods have been focused on assisted respiration in ICUs. It is not possible to manage a disease, possibly involving millions of subjects, with ICUs. We may to focus on medical preventive methods (not only lockdown) particularly in higher-risk subjects and we need management methods of early symptoms, out of hospitals.

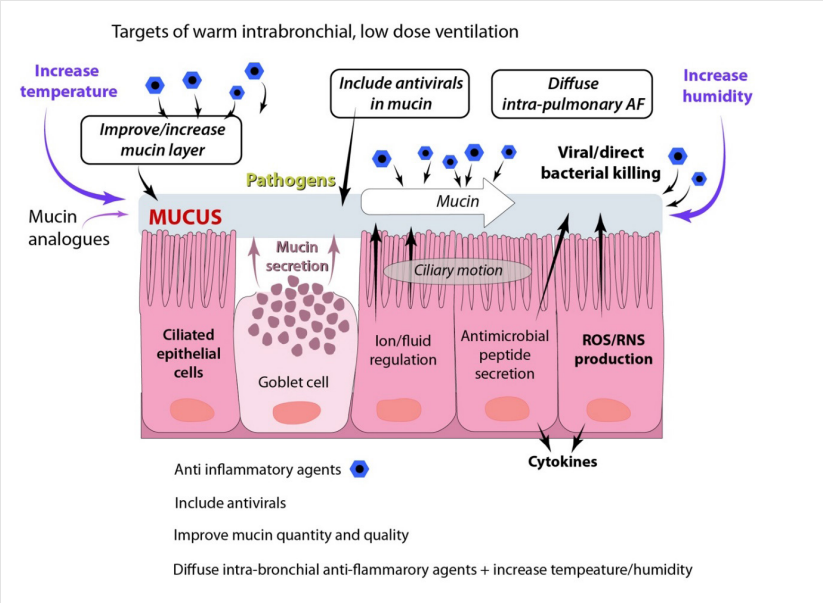

Figure 3: Targets of local, bronchial management: hot-humid vaporization:
improve the mucin layers
may use antivirals
may use anti-inflammatory agents.
This disease should be considered, at least the in early phases, a local respiratory disease that requires a local, low-dose, low-cost management, with minimal occurrence of side effects.

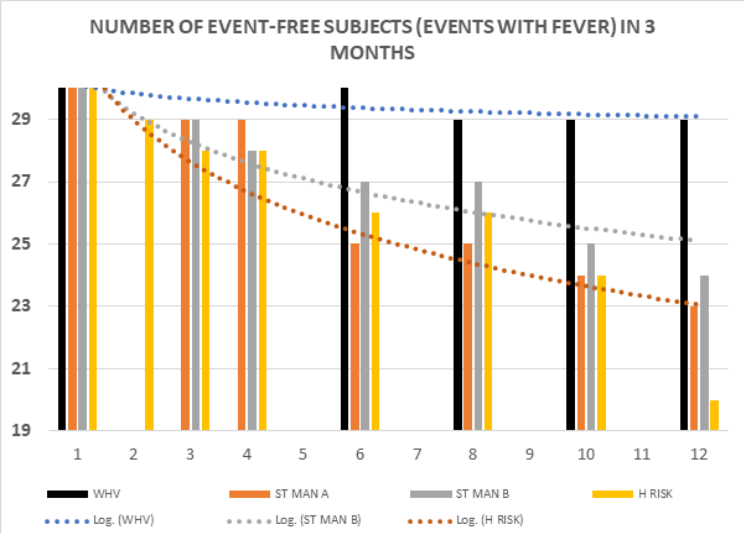

Figure 4: daily hot-humid vaporization (WHV) can stop most of the winter respiratory viral infections (associated to fever) in a 3 months follow-up. In this graph groups include 30 comparable subjects (age 50-75). WHC is compared to standard management (SM) A (vaccination, colustrum), only vaccination (SM B) and SM in high risk subjects (only vaccination). The trends for WHV, SM A and high-risk subjects are shown). The 97.7% of event-free subjects with WHV compares with the 66.67% ($p<0.05$) of high-risk subjects not having events

Symptomatic COVID subjects (mild-moderate symptoms) were managed at home with WHV (warm-humid ventilation), 3-4 times daily for 10 minutes. No drugs were added to the ventilation. Two comparable groups (22 subjects using WHV vs 22 controls using the standard management) had different evolutions; most symptoms (cough, throat and eye irritation, fever >38 °C and fatigue/malaise) were reduced at 10 days with WHV. This pilot study could be an indication of the potential of WHV that may be also associated to local, low-dose vaporization of antivirals, anti-inflammatory and mucin-protective or reconstituting products. Considering the evolution of initial signs/symptoms (7) predictive analytics suggests that a sample of 100 symptomatic patients (for 3 weeks) may be valid to evaluate the evolution in most (otherwise healthy) subjects with a relatively simple, low-cost model without considering hospital patients. The control of viral replication within the upper respiratory tract with WHV may also decrease the possible spreading of virus in the environment and achieve a significant community value to this method. Considering other methods of prevention for non-affected individuals, colostrum [3,4] has also shown a significant potential in preventing winter-related viral respiratory infections. Its role needs a larger investigation particularly in high-risk subjects.

Low-Cost Home Ventilator

A portable, low-cost ventilator (ACI Medical, San Marcos, California, USA), simple, to be used, mainly at home (with an AMBU device and mask) may solve most transient, respiratory blocks in minutes. Often, after a respiratory crisis and temporary respiratory support most subjects may be able to revert to spontaneous respiration even for days. This method and tool may reduce the number of acute admissions into hospitals and be used in pre-intensive or post-intensive management. This product can be a game changer saving possibly some 40% of patients to progress to ICU. The product is available and in further development.

A. Pre-Intensive Care: two management methods (Figure 5) must be refined or considered and will be discussed in a different more detailed article with our initial experiences.

Prostaglandin E1 (PGE1)

Infusion (around 1 microgram/kg in 100 ml in 20 minutes) increases bronchial perfusion. The increase in bronchial blood flow makes O2 and CO2 exchanges more dynamic, faster and may greatly improve the function of the residual bronchial surface. PGE1 has no significant side effects, does not require monitoring and may greatly improve respiratory function. Also, PGE1 relieves distal vasoconstriction and avoids peripheral necrosis (also seen in some COVID patients) in hypo perfused area.

The Optimization of Anticoagulants Needs to be evaluated in a more specific article

There a significant value in defining the right protocol for the different phases of the disease progression (i.e., home patients, home patient in bed, hospital patient et cet.). Patients immobilized in bed and with a catastrophic inflammatory and cytotoxic cascade need more specific anticoagulation protocols. However according

to international Consensus documents all subjects with pneumonia are at high risk for thromboembolic problems and should be managed as high-risk subjects, with LMWH or an equivalent method (i.e. defibrotide may be a candidate), and, if possible with anti-thrombotic (TED) stockings. In these conditions clinical trials are almost impossible and we physicians have to hit the virus and its complications with what we have and if we have it. The management should be made in the best-interest of single patients, in singular, individual situations. Most of these patients cannot give consent and a preliminary consent to a possible experimental trial does not have any legal value (as patients cannot refuse at any time and their tutors may be totally excluded or cannot be involved in management decisions). The speed of the disease has left very small margins of actions to try new products and any trial in this 'war' condition may be strongly biased [5-9].

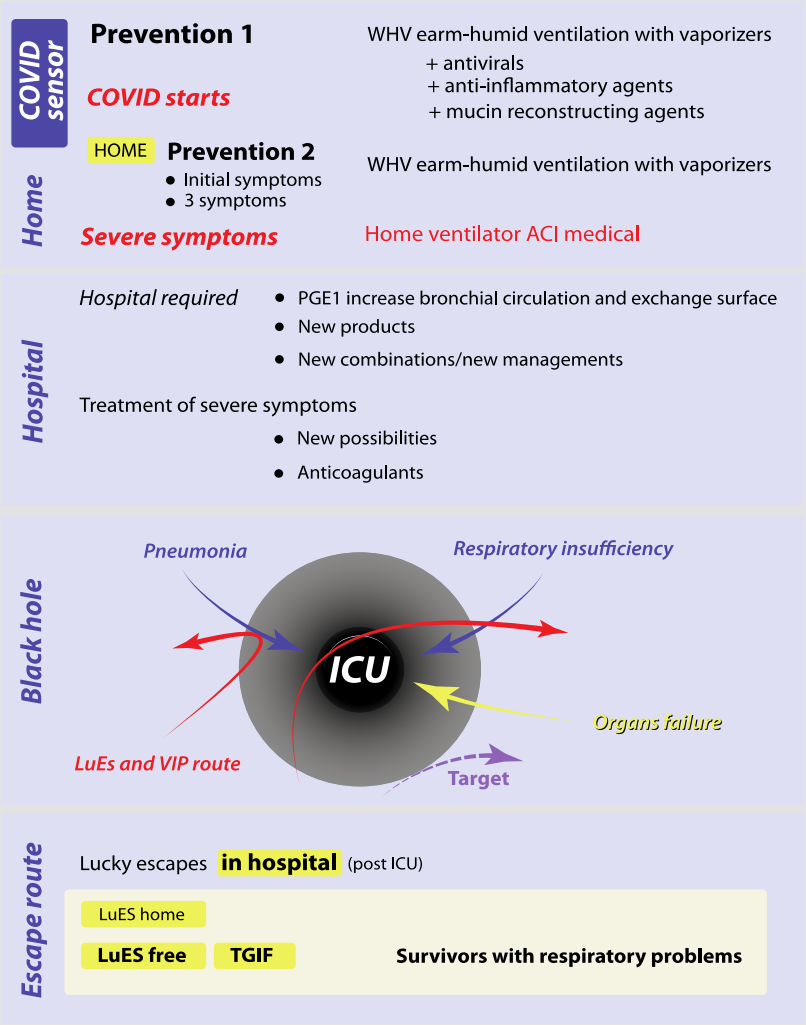

Figure 5: The different phases of the evolution of COVID. The 'black hole' is the passage into ICU. Before (and after) there are several strategies we may use to block the effects of this viral condition.
Most strategies should be used at home, before hospital admission and, possibly, instead of intensive hospital care. The target is to avoid the 'black hole'. LuEs are the lucky survivors, VIP have often a privileged management line.

A. Post-Intensive, Long-Term Follow-Up the Evolution of PCPF (POST-COVID PULMONARY FIBROSIS).

The last two long-term strategies involve post-COVID patients and are aimed at:

I. Preventing pulmonary fibrosis in ICU survivors.

II. Screening Lungs with Ultrasound, Defining New Protocols

These studies are now in progress. ICU survivors may have to deal with significant lung problems for the rest of their life. Specific drugs and products are being tested to avoid post COVID pulmonary fibrosis (PCPF). A long period of morphological and functional observation appears to be needed (5-10 years or more). Lung ultrasound is being specifically developed at this time to monitor these patients as CT scans and MRI would not be used (for costs and/or side effects) all the time for monitoring after COVID.

In conclusions the thermolability [10-11] of this virus may be a significant key weak point to attack by the virus - and thus local virus spread is preventable with relatively simple means, essential when the number of patients is of the present and future magnitude. Solutions must consider costs and simple methods that may be used when the healthcare systems have limited budgets and there are millions of patients. WHV is an important vector to develop to send targeted, low-dose therapies into the URT and into the bronchial tree from inside. In most patients the initial disease is largely a local viral condition of the bronchial tree without systemic complications. This condition may be managed with local treatments with very low doses of pharmaceuticals. Surfactants are also important in bronchial infusions and may be added with the WHV [12]. This is the place and the moment to respond, with all the tools we have, to the virus. Most clinical managements should be planned and made at home, before the intensive care phase (the black hole; Figure 5) with relatively simple, low-cost means to avoid more expensive treatments and possibly to decrease morbidity and mortality. Aim of the management is to keep the patients away from the 'black hole' as long as possible.

New possible managements options.

As no single antiviral is effective it is possible to suggest a management lasting 4 weeks based on 4 separate chemotherapeutic agents in sequence, each one, possibly active on a different aspect of viral replication. The cyclic use of the agents may limit side effects. The preventive dosage should be lower (50%) of the used therapeutic dose. Hydroxychloroquine, baicalein, colchicine, Lariam (mefloquine hydrochloride) can be used in this sequence. Other candidates may be evaluated but the present availability of antivirals is limited. All these products have been used for coronavirus. Baicalein has been extensively used in China even during the present Wuhan epidemy. This sequence (Figure 6) seems to have no side effects but large studies may be needed. However, there is no time and studies can be only organized for the next epidemy. Most patients use for prophylaxis (and even for minor symptomatic disease) what they have or what they think is right in a do-it-yourself plan, without telling their GPs, often busy with more serious patients.

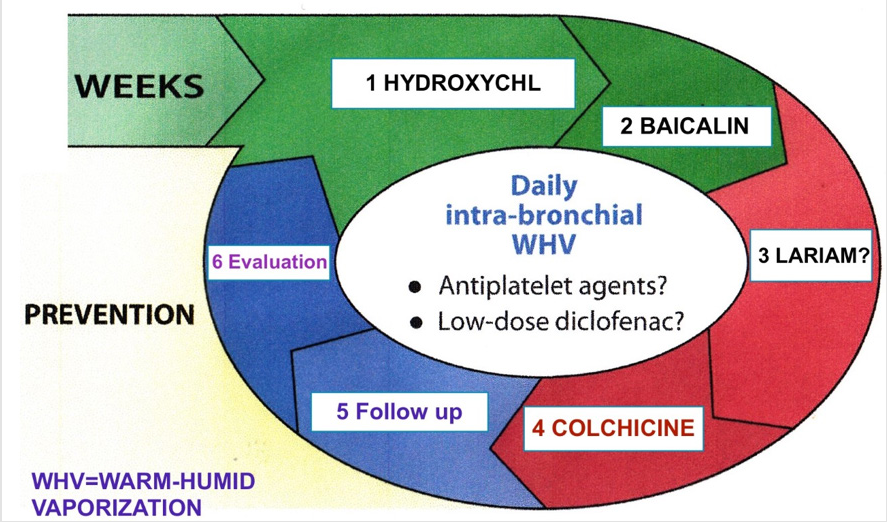

Figure 6: no single antiviral is definitely effective; it is possible to suggest a management lasting 4 weeks based on 4 separate chemotherapic agents in sequence, each one, possibly active on a different aspect of viral replication. The cyclic use of the agents may limit side effects. The preventive dosage should be lower (50%) of the used therapeutic dose. Hydroxychloroquine, baicalein, colchicine, Lariam (mefloquine hydrochloride) can be used in this sequence. Other candidates (and the sequence) may be evaluated but the present availability of antivirals is very limited. All these products have been used for coronavirus. Baicalein has been extensively used in China even during the present Wuhan epidemy. This sequence seems to have no side effects, but large studies may be needed. However, there is no time and studies can be only organized for the next epidemy.

Most GPs use their own prophylaxis when they can, as the NHS often did (and does) not provide most physicians with essential tools. In Italy more than 150 physicians have been killed (so far) by COVID in less than 2 months. This circular, sequential management requires refinement but at the moment it is what it is possible and available out of hospitals. Another important aspect to consider is that all countries able to fight back with efficacy have a very efficient wireless and internet system used to communicate fast to almost all the entire population. In Italy, internet connection is relatively poor, it does not cover all places; often, even phone lines are not usable in most of the territories outside the main centres. Most older people just have an ordinary phone for simple dialling and have no access to smartphones or sophisticated connections. Thinking of using Apps in Italy may leave out more than 50% of the

'weaker' population; they could be cut out. The same goes for home schooling, only possible if the connection is good and free and if there are instruments available.

In case of emergency all phone and web connection services should be made immediately available and free to all population. These studies are in progress and results should be available in days.

Comment

The antization of most oriental societies and nations (particularly China but excluding Japan that retains strong concepts of individuality) it is a time-bomb from an epidemiological point of view [13-14]. Shutting down an area of 60 million constitutes a minor block of a percentage of the population in China, while it is a whole country in Europe. With such a large population and its ant-like attitude the loss of 350 000 people is relatively bearable and less dramatic in proportion with the loss of the anthill. In Europe or in the Western cultures where 'no man is an island' even 300 deaths cause deep panic and sorrow. The ephemerality of the pandemics - which may go away without a real reason we can understand (as it happened in the past) - strongly conspires against a vaccine or a specific antiviral. Most companies do not like to invest in a treatment that may be useless in months. Anyway, we cannot wait. Simple, usable strategies may be useful during the war, now.

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