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COMMENTARY

The need to step away from conventional thinking: the unprecedented global and clinical challenges of an unprecedented virus

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The role of the scholar is to destroy chimeras....
Gustave Le Bon

Overview

On December 31, 2019, the Wuhan Municipal Health Commission in Wuhan City, Hubei Province, China, reported a cluster of pneumonia of unknown etiology. In January 2020, China reported a novel corona virus (2019-nCoV), and the genome sequence showed a new virus related to severe acute respiratory syndrome (SARS)-CoV class that presented with clinical features such as fever, dyspnea, bilateral lung infiltrate, on chest radiographic imaging, similar to previous severe virus such as avian influenza, adenovirus, SARS, and Middle East respiratory syndrome [1–5]. Within weeks, the transmission from human to human appeared to be of similar magnitude of SARS-CoV and other pandemic influenza, indicating a global risk of spread. Thus, the new coronavirus 2 became SARS CoV-2 [6]. Due to the rapid spread, the World Health Organization (WHO) declared that SARS CoV-2 was a public health emergency internationally, just a month later [7].

By then, not only many citizens infected but also an unusually high number of healthcare workers and many of whom later succumbed [8,9]. In short, it was highly contagious, and its infectivity was enhanced by a large percentage of persons who were either asymptomatic or were shedding virus 1 day or 2 days before their first symptom appeared [4]. Within 90 days, SARS CoV-2 had spread globally with more well over 100,000 known cases in 114 countries [10]. At the same time, the spread of COVID-19 has been insidious, first appearing to be fairly invisible and unimposing in a given population but then suddenly overwhelming healthcare systems within weeks. In the United States (U.S.), for example, which currently has the largest number of reported cases compared to other countries, the first patient was identified as early as January 19, 2020, in Washington state. This report led to the U.S. Centers for Disease Control and Prevention (CDC) releasing an interim guideline "person under investigation for COVID-19 testing recommendation" [11,12]. However, by March 1, there were only two reported deaths in the U.S. with 89 confirmed cases [13]. Accordingly, at the time, it was also promulgated that the disease was somewhat mild illness for most (80% of cases) and that it would mostly harm the older populations with underlying health conditions. Within days, the referred equivalence did not match what was indeed beginning to happen with frontline healthcare workers in hot zones such as New York City, who were being stretched to theirs limits by a short supply of mechanical ventilators and personal protective gear [personal protective equipment (PPE)]. The degree of shortage had not been seen in the U.S., even during the worst of any influenza season over the past 50 years [14,15].

In fact, within another 90 days, more than 100,000 U.S. citizens had died despite ambitious attempts to impose physical distancing and stay-at-home policies for the majority of citizens [16]. While the elderly living in congregate living facilities did indeed have a higher probability of getting severe disease, many deaths were also among the young and healthy, including frontline first responders, doctors, nurses, and many other healthcare colleagues [17–19].

Even before its dramatic promulgation began in the U.S., countries such as Iran, Italy, and several others outside of China were already experiencing severe hardships with thousands of casualties. It was not until March 11, 2020, that the WHO officially declared COVID-19

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to be a pandemic [20]. It was emphasized that, at the time, COVID-19 was a major threat that could cause the severe acute respiratory failure in about 20% of patients with a high case fatality rate. It was also disseminated that the virus was being transmitted via infectious respiratory droplets, and therefore, precautions usually recommended for influenza epidemics were strongly advised [4,5].

In response, unprecedented worldwide messages of "social" (physical) distancing, conscientious hand washing, and avoiding large group gatherings were communicated through unparalleled mass media attention to an infectious agent. "Stay at home" orders, already being enforced in some countries, were soon executed across the world [21]. By April 2020, it was being predicted that, without such measures, COVID-19 mortality could eventually surpass the death toll from the 1918 influenza pandemic that resulted in almost 50 million deaths worldwide [3].

The Insidious and Unprecedented Chimeric Viral Disease

Not only was the disease's exponential evolution and epidemiology insidious but also was the clinical picture. Early on, COVID-19 was primarily described as a severe respiratory illness characterized by cough, fever, and "flu-like" symptoms. Those seeking hospital care was generally described as having severe dry (non-productive) cough, dyspnea, fever, and pleuritic chest pain or tightness [2,22]. Somewhat confusingly, many were also found to have arterial oxygen desaturation, even in the absence of dyspnea. Some patients remained minimally symptomatic, but others had shown that they could rapidly decompensate into a severe respiratory failure requiring ventilator support, with a radiographic picture often resembling adult respiratory distress syndrome (ARDS) [23,24]. As often seen in ARDS, the severe lung disease cases were also frequently associated with renal demise, liver enzyme elevations, myocardial dysfunction, and other general signs of so-called "cytokine storm." Thus, this multiorgan failure has been widely accepted as a secondary complication of the more overt pulmonary symptoms and hypoxemia [25].

As weeks passed and experience grew with clinical presentations and the clinical course of the disease, it became apparent that the novel virus was also causing a novel disease that was often chameleon in nature and chimeric in terms of presentation.

Besides those many patients who were infectious yet entirely asymptomatic (or simply dismissing relatively mild constitutional symptoms), data were surfacing with respect to variable new signs and symptoms. In an early study from Iceland, when testing the population as a whole for COVID-19 by ribonucleic acid polymerase chain reaction (PCR) molecular assays, 43% of those testing positive reported to have no symptoms [26]. The CDC in the U.S. also estimated that at least 12% of those infected were asymptomatic without discrete symptoms, but more recently evidence suggests that nearly half of the infected patients are without symptoms [27,28]. Even before they felt the full brunt of the pandemic, the European colleagues began to report an unusual number of young and healthy persons presenting with anosmia or dysgeusia (alone), who later were found to be positive for COVID-19 by molecular testing [29]. Most of those patients recovered and remained otherwise well. Many other patients presented with gastrointestinal cramping and diarrhea, often associated with diffuse myalgias, that eventually resolved despite the positive PCR tests [23,29].

Overall, the majority of persons with milder disease most often complained on the onset of diffuse malaise, significant weakness, and myalgia and sometimes associated with low-grade fever usually occurring for about 4 or 5 days after the likely exposure. For some, the fever would appear for several hours in the evening and rise as high as 38°C or more. In other cases, there were also dry cough and occasional chest tightness or a loss of appetite or autonomic chills and systemic vasoconstriction that would last for several minutes [23]. There simply were no pathognomonic signs or symptoms.

While the disease course was unpredictable with onsets as early as 2 or 3 days after exposure and perhaps up to 2 weeks, the median reported incubation period was 4.5–5.8 days with symptoms starting at 4 or 5 days of exposure. Those patients with predominant respiratory issues often would sense a mild improvement on day 5 or 6 of their illness but then have a sudden evolution of severe cough and a sense of dyspnea mostly characterized by restriction in breathing and occasionally accompanied by some desaturation on pulse oximetry. Over the next 2 days, those patients either recovered remarkably well or deteriorated rapidly. At this point, they generally presented to healthcare workers with the well-publicized respiratory failure based on that most common presentation to healthcare facilities [3,23].

Not Just Lung Failure

To add to the chameleon nature of the disease, the more moderate or severe COVID-19 illnesses may not only be primarily a pulmonary problem but also rather a broad systemic infection that involves a spectrum of widespread inflammation and highly unusual vascular disorders. The vascular disorders themselves may not only contribute to respiratory dysfunction but also create many other pathological findings.

Specifically, in many affected patients, the virus seems to cause widespread clotting of capillaries and smaller blood vessels, accompanied by concomitant inflammatory processes that further damage previously healthy tissues. In some patients, clotting in larger vessels may result in deep vein thrombosis, pulmonary embolism, stroke, and even myocardial injury. Patients found dead at home during the COVID-19 crisis are suspected to be the victims of such hypercoagulable processes [30].

As has been emphasized more recently with respect to children, a widespread systemic inflammatory response with resulting vasculitis can occur with COVID-19 and sometimes occur late into the disease process without significant pulmonary involvement. Typically occurring a little later in the clinical course of symptomatology, this complication is also characterized as a so-called "cytokine storm," usually marked by the high levels of inflammatory proteins in the bloodstream as is often seen in the pulmonary cases and other forms of ARDS [25].

This pathological development is now well associated with processes such as myocarditis, encephalitis, and diffuse vasculitis. It is speculated, therefore, that the vasculitis could potentially trigger widespread clotting. However, for many other reasons, including the observation of clotting problems in the absence of distinct systemic inflammatory complications, the precise cause still remains unclear. In fact, it is also speculated that the clotting and associated microinfarcts in various body tissues could be, in turn, a key contributor to the inflammatory processes including those in the lung leading to respiratory failure.

To date, investigators point to Angiotensin-converting enzyme 2 receptors in the nose, lung, intestines, and endothelium primarily as target receptors [31]. The inoculum hitting those sites is a large determinant of disease manifestation and severity. Whatever may be the factors contributing to the degree of illness, its severity, presentation, and clinical course in a given individual remain difficult to predict. The basic overview is that SARS CoV-2 is not only a unique, highly contagious virus with a multitude of non-uniform clinical signs and symptoms but also a complex pathophysiology that has defied traditional experience and thinking. In turn, COVID-19 has proven to require non-conventional thinking and management as discussed throughout the following discussion.

Complications of Combating a Complicated Chimeric Disease Process

By early April 2020, the reports about COVID-19 were indicating a catastrophic disease with a mortality rate varying from 50% to 88% [3,8,22,32]. Besides, the spread of the virus seemed to be accelerating more rapidly than initially reported. The combination of a catastrophic mortality rates, full intensive care units (ICUs), rapid transmission of the disease, and the direct impact on healthcare workers created an unprecedented race for governments to obtain PPE and mechanical ventilators to manage the onslaught of respiratory failure cases [4]. Healthcare workers were quickly consuming available supplies of appropriate PPE. The supply chain that once produced most of the PPEs came to a complete halt as a main source, China, had shutdown [4,15].

The fear and concerns over the supply chain breakdown were not only applicable to PPE but also it included all the other conventional tools and equipment required to manage sick patients with severe respiratory failure. Amplified by the resulting escalation of death and the daily fear and uncertainty of letting patients and their families down, practitioners were faced with making last minute, uncertain but compassionate-care decisions were largely based on a understandable sense of duty, ethics, and caring [15].

Miracle Drug or a Snake Oil Solution

The renowned Latin phrase, primum non nocere (first, do no harm) often became a secondary ideation in the face of having to deal with many so patients' agony, acute distress, and likely demise. With the novel virus rapidly disseminating and the unprecedented pathophysiology challenging conventional wisdom, usually well-intentioned anecdotal observations, concepts, and often rudimentary medical reports emerged worldwide. However, these reports only instilled further confusion and apprehension about appropriate actions to take. Those fears eventually laid a rocky foundation for the early adoption of a myriad of proposed therapies to mitigate the disease.

In February 2020, Professor Raoult Didier, Director of the Research Unit in Infectious and Tropical Emergent Diseases, at l'Institut Hospitalo-Universitaire Méditerranée Infection in Marseille, France, announced, in a widely circulated video, that the known antimalarial drug, hydroxychloroquine, was a cure for COVID-1 [5]. This proposed therapy was based on early work that he had previously conducted on another coronavirus, and a publication from China shows the positive results with the *in vitro* activity of chloroquine against SARS CoV-2 [6]. Both chloroquine and hydroxychloroquine are widely used as antimalarial drugs. In a preliminary publication, Dr. Raoult reported a significant reduction in infection (measured viral load as compared to the control group) when hydroxychloroquine was administered 200 mg three times a day for 10 days in a small sample study of 26 patients and 16 in the control group. Adding azithromycin to the treatment arm reportedly decreased viral loads even further [7]. However, six of the 26 patients were lost to follow up for unclear reasons.

Anxious to solve their related national problems and escalating loss of life, world leaders and non-medical professionals alike were quick to adopt hydroxychloroquine and azithromycin as a "holy grail" against SARS CoV-2. Although the overall safety profile of hydroxychloroquine is relatively acceptable, there are also well-known side effects including significant cardiac arrhythmias (e.g., twisting of peaks), prolonged QT syndrome, and even death. This concern resulted in interim guidelines and debate on inpatient versus outpatient use and recommendations for large clinical trials [8]. The double-blind randomized trials were emphasized, but the pressing issues of extreme loss of life were cited by those endorsing this approach. Other publications, though limited, consistently pointed to no benefits or a threat of risk in vulnerable patients [33,34]. While others went as far as stating that hydroxychloroquine should be used prophylactically for persons exposed to COVID-19, a

recent randomized double-blind, placebo controlled trial demonstrated that hydroxychloroquine did not prevent illness with COVID-19 [33].

The medical world was left with more questions than answers regarding hydroxychloroquine. COVID-19 task force coalitions all across the U.S., usually formed by physicians on the front line, were still trying to navigate the many conflicting recommendations. Exacerbating this situation, the Lancet, one of the world's top medical journals, retracted that a study, which had published, had raised alarms about the safety of the experimental chloroquine and hydroxychloroquine. On the same day, the New England Journal of Medicine retracted another study focused, in this case, on blood pressure medication use in the era of COVID-19. According to media reports, the retractions came at the request of the authors of the studies whose data had come under scrutiny. In one case, the lead author conceded that he was not directly involved with the data collection and analysis. Confidence in the science was teetering [35–37].

More recently, conflicting information about the antiviral drug, Remdesivir^{R}, has added to the confusion. A recent study supported by the U.S. National Institutes of Health appeared to have positive results, but second-guessing of those findings has since arisen [38]. Moreover, drug availability has been limited to the sickest patients when most would believe that the earlier the intervention, the better the results would be.

In like manner, numerous other interventions have been promoted, but a plausible and evidence-based panacea has yet to be found.

Stepping Away from Conventional Thinking

If the therapeutic world has been confusing, recommendations regarding the respiratory management of the sickest patients with this chimeric and chameleon disease entity have also been just as challenging. It has prompted us to step away from the conventional wisdom and to perhaps adopt a "novel" wisdom.

Soon after the outbreak, an "expert opinion" paper by Cheung et al. [39] recommended that clinicians should not use high-flow nasal cannula or non-invasive ventilation until there is viral clearance, a recommendation that resulted in additional confusion for practitioners wishing to protect themselves, their colleagues, and their patients.

Several studies reported alarming mortality rates for mechanically ventilated patients. Yang et al. [40] reported that ICU patients receiving invasive ventilation had a mortality rate of 79%, questioning its ineffectiveness. In another publication, ICU patients who required mechanical ventilation had a mortality rate of 86% [41]. In an investigation of over 5,700 patients on mechanical ventilators, 81% were dead or discharged with COVID19, with the large majority of patients on invasive mechanical ventilation remained in hospital at the time of the publication [32]. In the United Kingdom COVID 19 database, mortality for (endotracheal) intubated patients on mechanically ventilation exceeded 60% [42]. However, in Boston-based study, among 66 intubated COVID-19 patients, 56 met the Berlin criteria for mild or moderate ARDS. Eventually, 62.1% were successfully extubated, and 16.7% died [43].

While the reported mortality rates with intubated patients were initially accepted as simply reflecting a malevolent disease process, there soon were growing conflicts about non-invasive versus invasive ventilation or management. In terms of the conventional approaches for respiratory failure, early radiological reports showed that computer-assisted tomography (CT) provided an additional perspective concerning the disease. In the sicker patients, there was a presentation of diffuse infiltrates, especially in the peripheral lung zones. Occasionally, the infiltrates were localized at first, but, in most presentations, they appeared to be similar to a traditional ARDS picture. In turn, in the face of hypoxemia, this familiar finding drove the inclination to use traditional methods to manage such a process such as endotracheal intubation and mechanical ventilation with the addition of positive end-expiratory pressure (PEEP).

However, COVID-19 is unprecedented disease with an unusual pathophysiology. In another early (March 2020) publication, from Dr. Luciano Gattinoni, the author wrote an editorial admonishing that COVID-19 was not only "typical" ARDS but also an "atypical ARDS" [44,45]. Gattinoni et al. had observed a near normal pulmonary compliance in many cases, a finding that is not seen in classic ARDS. Accordingly, they described a time-related diseased spectrum within two primary "phenotypes:" (1) type L (high compliance) with low elastance, low ventilation-to-perfusion ratios, low lung weight, and low "recruitability" and (2) type H (diminished compliance) which is characterized by high elastance, high lung weight, and high recruitability. The group recommended that the type L should be treated with non-invasive options such as high flow nasal cannula or continuous positive airway pressure (CPAP). They also stated that if the type L patients were to be intubated, they should be deeply sedated and ventilated with tidal volumes > 6 ml/kg (which is the traditional "ARDS net" approach) and, instead, recommended 8–9 ml/kg with reduced PEEP levels about 8–10 cmH_2O. On the contrary, the type H patients would be treated as the usual severe ARDS with tidal volumes of 4–6 ml/kg but also high PEEP with prone positioning (PP) [44,45]. In other words, in many cases, the lungs were not as stiff as one would expect in traditional ARDS cases, thus implying a need for modification in management. Once again, COVID-19 provided a new challenge for uncharted medical therapy.

This Gattinoni's perspective and similar observations by other clinician investigators led to very divisive opinions regarding the topic of early endotracheal intubation and mechanical ventilation with PEEP. Even in the presence of a significant degree of oxygen desaturation that would conventionally prompt intubation and invasive ventilation, deferring the invasive approach was becoming

a mainstream topic. This evolving management paradigm was counter to the traditional criteria for intubation, and it emphasized that the clinician follows the patient's clinical condition and not simply treat the "numbers" (oxygen saturation levels), especially if the patients had good mental status, lacked acidosis, and had reasonably tolerable dyspnea or respiratory distress. Leanings toward this less-invasive approach were augmented by the fear of dispersion of particles during intubation.

Accordingly, this evolving perspective also led to an assimilated secondary recommendation that if endotracheal intubation was indeed to be attempted, it should involve: (1) full PPE by all in attendance (in limited numbers), (2) the most experienced person to perform the procedure, (3) indirect methods such as video laryngoscopy or fiberoptic scope placement preferred over direct laryngoscopy intubation, (4) use of a transparent box or clear plastic cover as a means of improved barrier protection, and (5) supplemental oxygen flow (but avoidance of bag-valve mask ventilation) [46–49].

Counter arguments to deferred intubation included the concern over dispersal of viral droplets by high flow oxygen. In that respect, Leonard et al. investigated the dispersion of aerosols and droplets during high-velocity nasal insufflation (HVNI) therapy using a single surgical mask. Their goal was to assess the leakage of particles around the mask. They studied the dispersion of the particles by using Vapotherm, a HVNI, at 40 l/minute. Their results revealed a very low dispersion of molecules with the use of the face mask as compared to none (see Figure 1) [49]. Furthermore, in a recent systematic review and meta-analysis of 25 randomized clinical trials, the authors concluded that in patients with acute hypoxemic respiratory failure, treatment with non-invasive compared with standard therapy was associated with a lower risk of death [50].

Taking a Different Position on COVID-19 Hypoxemia

If non-invasive ventilation is to be advocated, clinicians have also explored additional adjuncts to improve oxygenation. PP was one option. PP has become a well-recognized and effective line of therapy in patients with the most severe forms of ARDS when used in conjunction with mechanical ventilation. Munshi et al. [51] found that PP is likely to reduce mortality in patients with ARDS if it is used at least 12 hours daily. They reached this conclusion after conducting a study that focused on four patients with hypoxemic respiratory failure, who, by that definition, met criteria for mechanical ventilation. However, measuring blood gas results before and after, the team used PP with oxygen supplementation and found that patients had a rapid improvement in their arterial O_2 levels (PaO_2) and thus avoided mechanical ventilation in all four patients [52].

Besides, Scaravilli et al. [53] conducted a large retrospective study that evaluated 15 non-intubated ARDS patients who were being treated with PP. It was found that these 15 patients had improved oxygenation, starting with a mean PaO_2/FiO_2 of 124 ± 50 mmHg before PP, 187 ± 72 mmHg during PP, and then 140 ± 61 mmHg when returned to supine positions; $p < 0.01$). Of these 15 ARDS patients, 12 were discharged from the hospital without requiring intubation using this tactic.

Another strategy now being recommended in COVID-19 hypoxemia is a regular rotational change in position that involves turning the patient into the right lateral, prone, and left lateral positions (or the other direction), with a change in position occurring every few hours (or some variation on that theme) while monitoring the effects closely considering the logistics and that some patients may not respond so well.

Advocating Scientific Collaboration

It should be emphasized that the combined use of HVNI and PP (or rotational positions) in patients with COVID-19 has not been well documented. However, during the COVID-19 outbreak, several collaborating emergency medicine and critical care physicians from New York and Florida, along with other colleagues across the globe, discussed the benefit of HVNI and positioning. These discussions were based on their own actual direct observations, not on formal peer-reviewed studies. Sharing their observations on social media, podcasts, and even in the media, there appeared to be a *de facto* shared observation about the benefits with this strategy, particularly after late adopters found the same positive results [54,55].

Nevertheless, similar to the discussion about promoted medications, clinicians and researchers must consider the paths taken to yield the given results and what, if any shortcuts were taken to deliver them, while weighing risks with benefit. Safety, not only for patients but also for the medical teams involved, should always remain a priority. The data and studies published to date have had limitations, and it is evident that the double-blind randomized clinical trials are needed. The certainty of thought should not routinely replace the scientific method. Nonetheless, this novel disease has been unprecedented in terms of it spread, its symptomatology, its pathophysiology, and even its immunology let alone its variable clinical course in any given person. It may require novel thinking led by improvization and willingness to explore the approaches beyond conventional thinking and particularly when done so in a conscientious, caring, and thoughtful manner.

Summary Perspectives

SARS CoV-2 is a chimeric viral illness with many chameleon presentations and a very complex pathophysiology that may not behave like similar

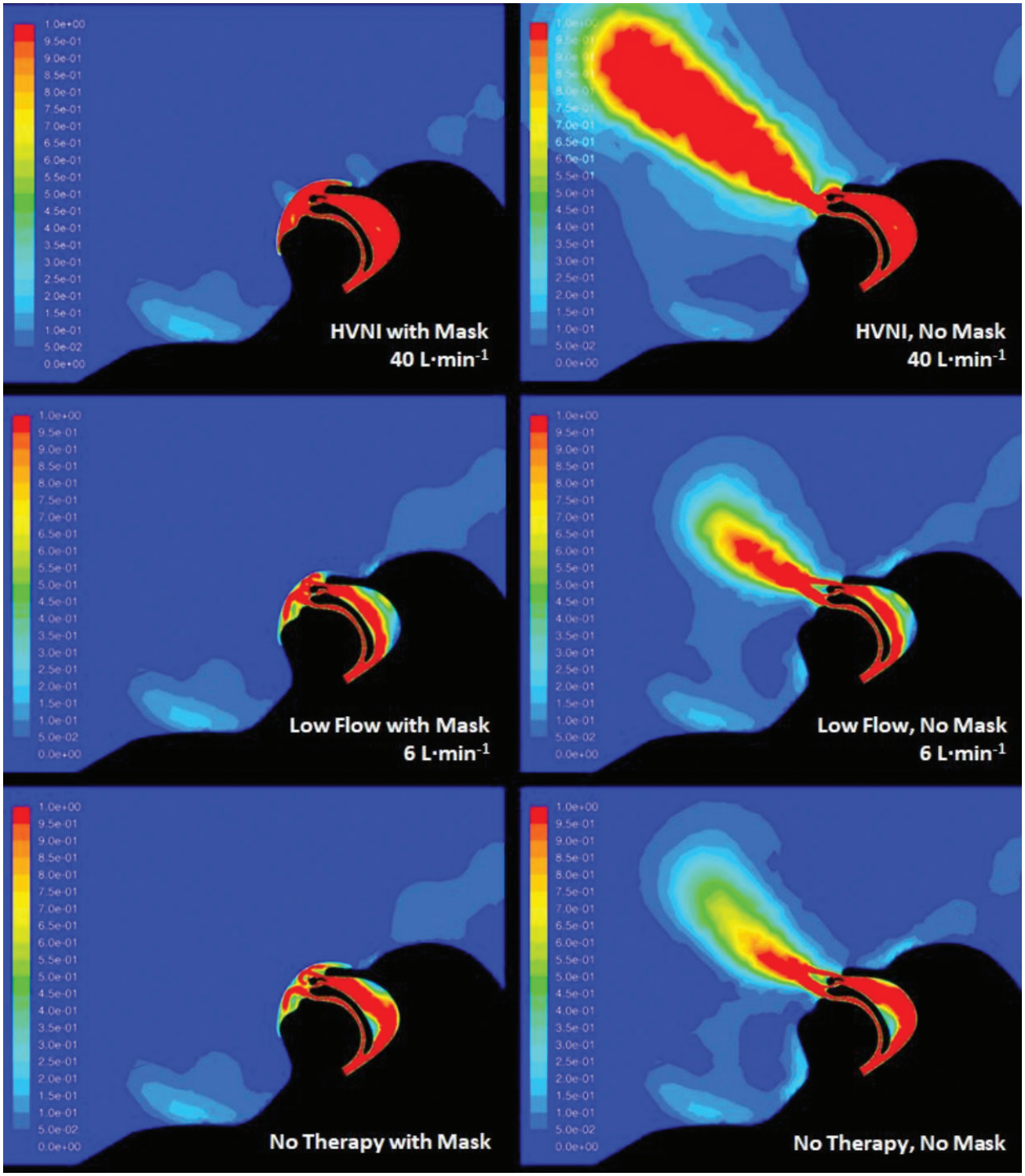

Figure 1. *Velocity map of gas flow for all tested settings. HVNI = high-velocity nasal insufflation. Source: WHO [20].*

maladies. It is likely that the traditional approaches to managing hypoxemia (low arterial oxygen tension/saturation) should be reconsidered in approaching COVID-19. Beyond its other diverse manifestations and complications, the respiratory illness of COVID-19 may present in three different phases, any of which may not appear at all. They may appear one at a time or even rapidly progress into the third phase depending on the individual and the time of presentation to medical personnel and hospitals.

COVID-19 hypoxemia is a part of a continuum of disease that may simply present with a "non-hypoxic hypoxemia" (so-called "silent hypoxemia"), in which there is no

dyspnea (maybe only some dyspnea on exertion), and with no accompanying lactic acidosis, no problem with intact mentation, and no other sign of organ failure. Other prodromal symptoms may be present, but there is no indication of pulmonary symptoms except possible paroxysms of non-productive cough. In this more occult type of hypoxemia (or phase of presentation), immediately treating the "number" (e.g., 65% SaO2) invasively should be discouraged. While it does not necessarily need to be ignored (use of supplemental oxygen/positioning), clinicians would be cautioned to focus on "treating the patient" and not the "number."

In the next phase (which may occasionally be the first manifestation when the first phase is not recognized), the patient may have some respiratory distress and a lot of coughing, but at this stage of the lung disease process, the condition often is still associated with relatively normal lung compliance (i.e., not a stiff lung), not requiring mechanical inflation. The symptoms may be reflecting an early pleuritis with persistent cough and "chest wall tightness" (plus/minus myocarditis) and with or without significant chest infiltrates on chest X-ray or any findings that, at this point, may only be seen on CT scan.

As discussed, most would still treat this phase with supplemental O_2 (as previously described with PP or rotating body positions) or with low-level CPAP/Bilevel positive airway pressure along with the rotating positions. In this phase, it is also recommended that the D-dimer, thromboelastographic study, ferritin, platelets, and other coagulation factors should be measured if a component of this presentation could be due to the formation of microvascular coagulopathy and microinfarctions. The clotting may be associated with concomitant inflammatory processes in the endothelial cells, thus affecting the lungs and suggesting the need for potential anticoagulant therapy as an adjunct therapy.

Accumulating experience has shown that each of these first two types of phases (or initial presentations) can begin to reverse and improve significantly and even do so quickly within the first or second week of illness. At the same time, many of these cases can also suddenly deteriorate, and most often after a week to 10 days of "prodromal" symptoms or any of the previously described pulmonary presentations. This phase, if it occurs, appears dramatically and is usually associated with low compliance (stiff) lung disease (more typical of classic ARDS and cytokine storm) with associated multiorgan failure. Failing the less invasive strategies, it may require more aggressive management. However, experience to date has clearly shown that outcomes may improve when the less invasive strategies are first implemented.

List of Abbreviations

ARDS	Adult respiratory distress syndrome
CoV	Coronavirus
CoV-2	Coronavirus 2
COVID-1	Coronavirus 1
COVID-19	Coronavirus 2019
CDC U.S.	Centers for Disease Control and Prevention
CPAP	Continuous positive airway pressure
CT	Computer tomography
ICU	Intensive care units
PaO^2	Arterial O^2 levels
PPE	Personal protective equipment
PEEP	Positive end-expiratory pressure
PP	Prone positioning
HVNI	High-velocity nasal insufflation
SaO^2	Saturation of oxygenation
US	United States
SARS	Severe acute respiratory syndrome
WHO	World Health Organization

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