The Hydra-Headed Coronaviruses: Implications of COVID-19 for Homeopathy

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Abstract

Successful homeopathic prescriptions are based on careful individualization of symptoms, either for an individual patient or collectively in the case of epidemic outbreaks. The ongoing COVID-19 pandemic was initially represented as a severe acute respiratory illness, with eventual dramatic complications. However, over time it revealed to be a complex systemic disease with manifestations derived from viral-induced inflammation and hypercoagulability, thus liable to affect any body organ or system. As a result, clinical presentation is variable, in addition to variations associated with several individual and collective risk factors. Given the extreme variability of pathology and clinical manifestations, a single, or a few, universal homeopathic preventive medicine(s) do not seem feasible. Yet homeopathy may have a relevant role to play, inasmuch as the vast majority of patients only exhibit the mild form of disease and are indicated to self-care at home, without standard monitoring, follow-up, or treatment. For future pandemics, homeopathy agencies should prepare by establishing rapid-response teams and efficacious lines of communication.

Keywords
- coronavirus diseases
- homeopathy
- therapeutic approaches
- complex pandemics

Introduction

If coronavirus disease 2019 (COVID-19) has a striking characteristic, it is its puzzling nature. As in the Hydra myth, when experts believe to have taken hold of its head, a new and unexpected one seems to appear in its place.

Curious findings for a flu-like, viral pneumonia, such as indicators of hypercoagulability (elevated activated partial thromboplastin time, fibrinogen, and d-dimer levels), were reported among the earliest cases. By the end of April 2020, it had become clear that thrombo-inflammation is a striking feature of the pathophysiology of COVID-19.[1–3] A patient admitted to our hospital by this time provides good illustration. A 3-month-old infant, she was one of only four children who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at the Shaare Zedek Medical Center throughout the high-transmission period of the pandemic. She had started with a high fever 5 days prior to admission, without any other symptoms, not even loss of appetite. Since the fever had not receded 3 days later, she was taken to a primary care provider and the due work-up was done which, given the times, also included the polymerase chain reaction (PCR) for SARS-CoV-2 RNA (ribonucleic acid). She was found to have a simple urinary tract infection, was prescribed oral antibiotics, and discharged. The following day, her parents received a telephone call and were informed their daughter had tested positive; thus they brought her back to hospital. On admission she had moderate fever (38.2°C), normal vital signs and oxygen saturation, no abnormal findings on physical examination, leukocytosis (36.4 cells/μL) with neutrophilia, moderate thrombocytosis, and C-reactive protein 13.96 (0–0.5 mg/mL). By this time, *Escherichia coli* had grown in the urine sample culture. But "odd" findings were also identified: on admission fibrinogen was 976 mg/dL (normal range, 200–500 mg/dL) and d-dimer 1,076 ng/mL (0–500 ng/mL). These are indicative of blood clotting and are characteristically increased in many COVID-19

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patients. The child was treated with intravenous antibiotics and discharged 2 days later to ambulatory follow-up.

A few days later, media worldwide were reporting that SARS-CoV-2 in children had been associated in the United Kingdom with an inexplicably high incidence of clinical manifestations resembling Kawasaki disease and/or toxic shock syndrome (TSS), with similar cases reported in Italy, France and Belgium.[4,5] According to an Italian pediatric cardiologist, colleagues in Spain and Portugal had mentioned a similar situation to him.[6] Naturally, the first thing to do was to look for references in the literature. To our utter surprise and shock we found a paper in *The Journal of Infectious Diseases* entitled: "Association between a Novel Human Coronavirus and Kawasaki Disease".[7] Obviously, it concerned children, as Kawasaki is a childhood disease. But the odd aspect is that this paper had been published 15 years earlier (this novel coronavirus was HCoV-NH [human coronavirus-New Haven], not the current coronavirus). We recalled that during the height of the pandemic, we had seen at our hospital several children with typical or atypical Kawasaki or undiagnosed Kawasaki-like conditions, as well as one case of TSS in an otherwise healthy child. An expert from New York City, Dr. Dyan Hes, stated on television, "I'm not surprised, because children who get a common cold, which is often caused by coronaviruses—the *non*-COVID-19—can get Kawasaki disease…. What we're learning more and more is that COVID-19 can cause just about any symptom and attack any part of the body but particularly in the vasculature—it causes a lot of inflammation".[8] To be sure, very early in the course of the pandemic, many doctors had observed that COVID-19 evoked the macrophage activation syndrome.[9]

Like Dr. Hes, none of us should be surprised. But we are all surprised because from the very onset of the pandemic, the prevailing representation of COVID-19 was essentially that of an extremely aggressive flu-like, viral pneumonia with potentially dramatic complications, including acute respiratory distress syndrome (ARDS), septic shock, refractory metabolic acidosis, coagulation dysfunction, and multiple organ failure.[10]

This is also the representation of the disease adopted by homeopaths worldwide in their attempts to find not a cure for individual patients, but a universal preventive medicine, that is, the so-called *genus epidemicus* (GE).[11–13]

Historia Magistra Vitae

There is no need to delve here too deeply into the history of homeopathy in epidemics—the apparent success cases are repeated as a mantra by the global homeopathy community,[14] from Hahnemann's treatment of scarlet fever in 1799,[15] to the more recent prevention of dengue fever in Brazil,[16,17] and leptospirosis in Cuba in the 2010s.[18] Therefore, it is worth looking closer into the "secret" of their success.

Hahnemann emphasized that the preventive remedy is the one able to quickly check a disease at its onset, not the remedy that cures it once it is fully developed. To illustrate, in the 1799 scarlet fever epidemic, he identified two forms of disease, a "mild" and a "severe", to be treated with opium and ipecacuanha respectively. In turn, patients with early, incipient (we would say prodromal) symptoms and healthy contacts were to be prescribed belladonna.[19] The first lesson, therefore, is that the GE of COVID-19—or of any other disease for that matter—should be obtained from the earliest manifestations, that is, before pneumonia and the more severe complications set in. Whether in the present time we should also include laboratory data, such as liver function and coagulation profile for COVID-19, we leave it open for debate (our view is favorable—liver and thrombo-inflammation are already present and perceptible, albeit through means other than the human senses). The later stages (pneumonia and complications) should be regarded as a different disease, which should be analyzed separately for the corresponding curative (no longer preventive) treatment. However, the available data correspond exclusively to hospitalized, that is, severe and critical patients. This information does not serve to identify a homeopathic preventive remedy.

Going back to Hahnemann, each and every outbreak, he noted, should be fully investigated *de novo*,[20] regardless of whether it or anything similar had ever previously appeared anywhere. Case definitions (suspect, probable, and confirmed cases) serve for epidemiological purposes, for example, to determine who should be tested, transmission rates, reproductive rates, and to plan the response. They also serve to distinguish between similar conditions. The following illustrates the point.

The history of the COVID-19 pandemic began in December 2019, when doctors in Wuhan, Hubei province, China, noticed *clusters of viral pneumonia of unknown etiology*.[10] The causative agent was soon identified as a novel coronavirus; therefore attention focused on its similarities to and differences from two other coronaviruses that had recently triggered severe epidemic *respiratory diseases*, the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS).[21,22] This led to the idea of COVID-19 as essentially a *respiratory disease*, a form of pneumonia, to the extent that it is still called "COVID-19 pneumonia".[10,23]

According to Hahnemann, this approach is not at all useful in homeopathy: now we know that pneumonia develops later in the course of the disease and not in all the affected patients—approximately 80% of infections are mild, while some may be altogether asymptomatic,[24] and the vast majority of those infected do not develop pneumonia. Thus, it cannot be considered in the investigation of preventive GE medicine(s). What we know of SARS and MERS is not only unhelpful, but a confounding factor for homeopathy. We transcribe here an extremely elucidating warning by Hahnemann: "A careful examination will show that every prevailing disease is in many respects a phenomenon of a unique character, differing vastly from all previous epidemics, to which certain names have been falsely applied—with the exception of those epidemics resulting from a contagious principle that always remains the same, such as smallpox, measles, etc".[20] As the most elementary literature search reveals, diseases by coronaviruses are pleiomorphic, and in no hypothesis can they be considered as "always remaining the same".

What must be done is to observe as many cases as needed until becoming familiar with the totality of signs and

symptoms of any novel epidemic outbreak. Obtaining a characteristic portrait of the disease is the indispensable condition to find a suitable homeopathic medicine. Moreover, Hahnemann observes that clusters of patients infected from the same source exhibit similar clinical characteristics, but do not represent the full extent of the disease.[25] Nunes' experience in Macaé, Rio de Janeiro, Brazil, with dengue fever provides appropriate confirmation.[16]

From 2007 to 2012, the Macaé municipal health secretariat included homeopathy in its standard management of epidemic and endemic dengue fever, through distribution of homeopathic medicines gratis to the entire city population with preventive intent. Outbreaks occurred in 2007 and 2010. In the first year (2007) the selected medication was a three-component formula derived from a pilot trial in São José do Rio Preto, São Paulo. For the following 5 years, medicines were selected based on careful analysis of the characteristic signs and symptoms of each outbreak *at the local level*. With this, in the second year (2008) for instance, incidence dropped 71% in Macaé, while it increased 273% to 3454% in the neighboring municipalities and 315% in the state of Rio de Janeiro as a whole. Mortality rate fell in 2010 to 0.68, versus 1.86 to 4.76 for neighboring municipalities and 2.18 for the state as a whole.

In the case of COVID-19, instead, we find premature recommendations based on symptom descriptions taken from conventional doctors and national and international health agencies. These, as mentioned earlier, are biased toward influenza-like and respiratory symptoms, case definitions and, more seriously, they were obtained from severe and critical hospitalized patients (stages 2 and 3). A case in point is that of the recommendations by the International League of Homeopathic Doctors.[11]

Premature conclusions were drawn also in the first reports of attempts at homeopathic characterization of COVID-19. As an example, the unpublished study by Kasariyans and Sankaran of 18 patients (only eight described, only three reported as confirmed cases) rapidly travelled across the global community of homeopathic practitioners.[26] For instance, the municipal secretariat of health of Itajaí, Santa Catarina, Brazil, has been offering the remedy suggested by these authors at primary care facilities since April 29, 2020.[27]

Yet these authors were neither imprudent nor negligent: their conclusions were based on a construction of GE attributed to Kent—who never reported having treated a single epidemic outbreak of any disease, but was merely commenting on the indispensable need to individualize cases, both singly and collectively. Chapter 3 of the notes compiled by Kent's students and published as *Lectures on Homeopathic Philosophy* reads that observing just *twenty* patients suffices to obtain the image of any epidemic outbreak as it affects the entire "human race".[28] In stark contrast, in the next section we discuss the extreme variability of COVID-19's clinical manifestations.

A Kaleidoscopic Disease

The ground-laying reports are those by Huang et al,[29] Chen et al,[30] Guan et al,[31] and Wang et al.[32] The pattern they described is characterized by fever and dry cough, variable rates of fatigue, and characteristic abnormal findings on chest computed tomography. In turn, upper respiratory tract symptoms are almost negligible (►**Table 1**).

With reports increasing, the China National Health Commission published a guideline,[10] which has been periodically updated. We had access only to the 7th and last edition, published on March 4, 2020, but as per citations in the literature the core seems practically unchanged with regard to clinical aspects. According to this document, the main manifestations of COVID-19 are fever, dry cough and fatigue. Other relevant symptoms include nasal obstruction, runny nose, sore throat, myalgia and diarrhea. Severely ill patients present dyspnea and/or hypoxemia 1 week after onset. The Commission comments that, remarkably, some severely ill patients present only mild- to moderate-grade fever throughout the course of disease, and some show no fever at all. Children and newborns present atypical symptoms, such as vomiting, diarrhea, and other gastrointestinal discomfort, or drowsiness and shortness of breath. Mild cases present low-grade fever and slight fatigue, without evident pneumonia.

Both the Commission's and later the World Health Organization's[33] definitions of suspect cases emphasize epidemiological history (travel to or residence in communities with documented COVID-19-positive cases or contact with COVID-19 patients within 14 days prior to the onset of symptoms) and the presence of acute *respiratory* illness (fever and respiratory symptoms). The Chinese also consider imaging features of COVID-19 pneumonia and normal or decreased leukocyte and lymphocyte counts. Confirmed cases are those with positive laboratory testing, particularly real-time PCR for SARS-CoV-2 RNA. Thus, any patient who does not present fever and/or respiratory symptoms/abnormal chest imaging is not considered a suspect case and is not included for targeted testing.

Yet, there is one intriguing aspect. The Chinese guidance lists the main differential diagnosis as being upper respiratory tract infection for mild cases, pneumonia by other causes (influenza, adenovirus, respiratory syncytial virus, *Mycoplasma pneumoniae*), and organizing pneumonia. However, according to the guidance, this stage of disease should also be distinguished from vasculitis syndromes (reasonable in light of the aforementioned considerations) and dermatomyositis, which seems inexplicable.

Published case series are too numerous to be individually analyzed (we retrieved all those included in PubMed and in the medRχiv database of articles under peer-review until April 28, 2020). Results are extremely variable, besides the fact they mainly report signs and symptoms of flu-like and respiratory illnesses, as expected from the definitions of the suspect case. Yet, after 4 months, there is a considerable number of systematic reviews with meta-analysis of cases inside and outside China. All, however, relate exclusively to hospitalized (severe and critical) patients—which represent the smallest proportion, approximately 20%. In any case, these reviews (published until April 23, 2020) corroborate the original descriptions: only fever and cough are present in more than half of the patients, with fatigue closely following (30.4–42.0%).[34–37] Abnormal findings on chest imaging compatible

Table 1 Symptoms at onset of the earliest COVID-19 patients

	Huang et al[28]	Chen et al[29]	Wang et al[31]	Guan et al[30]
Symptom	$n = 41$	$n = 99$	$n = 138$	$n = 1{,}099$
Time frame	Until January 2	January 1–20	January 1–28	Until January 29
Fever	**98%**	**83%**	**98.6%**	On admission 43.8% During hospitalization **88.7%**
Cough	**76%**	**82%**	**59.4%**	**67.8%**
Myalgia/fatigue	44%	11%	34.8%/**69.6%**	3.8%/38.1%
Sputum production	28%	NR	26.8%	33.7%
Headache	8%	8%	6.5%	13.6%
Hemoptysis	5%	NR		38.1%
Diarrhea		2%	10.1%	3.5%
Shortness of breath	None on admission **55%** during stay at hospital	31%	31.2%	18.7%
Confusion		9%		
Sore throat		5%	17.4%	13.9%
Rhinorrhea		4%		
Chest pain		2%		
Nausea and/or vomiting		1%	10.1%/3.6%	4.6%
Conjunctival congestion				0.8%
Nasal congestion				4.8%
Chills				11.5%
Anorexia			39.9%	
Dizziness			9.4%	
Abdominal pain			2.2%	
Pneumonia on imaging	**100%**	**75%** bilateral 25% unilateral	**100%**	**86.2%**

Abbreviations: COVID-19, coronavirus disease-2019; NR, not reported.
Note: bold > 50%.

with COVID-19 were reported for 88.2 to 96.6% of patients. According to a recent summary, most patients present more than one symptom on admission, but the combination of fever, cough, and shortness of breath is rare.[38]

As of late, it has been widely acknowledged that, despite very low oxygen saturations (as low as 50%), many COVID-19 patients are comfortable and do not exhibit dyspnea, as is the case of mountain climbers.[39] This condition, dubbed "silent hypoxia" or "happy hypoxia", is understandable when one considers that the basic lung injury is vascular microthrombosis:[3] that is, a disorder of the alveolar perfusion rather than of ventilation. It is thus not by chance that Italian intensivists learned to distinguish two populations of critical patients: a "silent" hypoxemia group with severe hypoxemia and near normal respiratory system compliance (a combination rarely seen in severe ARDS), and a remarkably dyspneic, normo/hypercapnic group.[40]

There is, however, far more to consider. A steadily increasing number of studies report potential transmission routes other than air droplets—among them, fecal-oral and tears—as well as extra-respiratory symptoms as initial manifestations of disease. This being the case, it can be inferred that when such patients do not present fever or respiratory problems, they are not considered for testing and are never diagnosed with COVID-19. On these grounds, Li et al estimated that up to 86% of cases in China may have been missed.[41]

Extra-Respiratory Manifestations

- *Neurological signs*: ischemic or hemorrhagic stroke, musculoskeletal disorders, impaired consciousness,[42,43] Guillain-Barré syndrome, acute hemorrhagic necrotizing encephalopathy,[44,45] acute meningoencephalitis,[46] and acute disseminated encephalomyelitis.[47] It is worth mentioning a recently reported striking series of young patients with large-vessel stroke as presenting feature of COVID-19.[48]
- *Ocular signs*: conjunctival hyperemia, chemosis, and increased secretion.[49,50]
- *Acute onset anosmia—a/hypo/dysgeusia*: incidence of up to 53%, and significantly higher than in control influenza cases.[51] These symptoms were included by the U.S. Centers of Disease Control as a suspect-case criterion on April 24, 2020.[52]
- *Cardiovascular symptoms*: myocardial injury,[53–55] myocarditis, myopericarditis,[56] arrhythmia, and heart failure.[53]

- *Gastrointestinal symptoms*: incidence of 3.0 to 79.0% appearing as initial or even single manifestation.[57–59]
- *Hepatic symptoms*: abnormal liver function in almost half of the cases, representing liver cell, rather than bile duct injury—despite the high expression of angiotensin-converting enzyme 2 (ACE2) in the latter.[60,61]
- *Spleen and lymphatic dysfunction*: direct infection via tissue-resident CD169+ macrophages—which express ACE2, with severe tissue damage.[62]
- *Dermatological signs*: reports are still contentious, while pernio (chilblains, "COVID toes") is currently discussed in the mass media. The American Academy of Dermatology has an open registry to collect data.

Vetter et al thus summarize the current picture: the working case definition to select people for viral testing imperfectly identifies patients without respiratory symptoms or with only very mild symptoms.[44] Tosato et al are even more daring: "COVID-19 is a multifaceted, chameleonic, and complex viral infection that can cause discordant features in its initial phase".[63]

Lessons Learned and Recommendations

Coronaviruses (sub-family *Coronavirinae*, family *Coronaviridae*, order *Nidovirales*) comprise four genera, *Alpha-*, *Beta-*, *Gamma-* and *Delta-coronavirus*, of which the former two are known to cause respiratory illness in humans and gastroenteritis in animals.[64] SARS-CoV-1 and MERS-CoV cause severe respiratory illness in humans, while the other four human coronaviruses (HCoV-NL63, HCoV-229E, HCoV-OC43, and HKU1) are associated with mild upper respiratory diseases, but eventually also lead to severe infections in infants, young children, and older adults. MERS-CoV uses dipeptidyl peptidase 4 (DPP4/CD26) as receptor, whilst SARS-CoV-1 uses ACE2, as do HCoV-NL63 and SARS-CoV-2.[65,66]

ACE2 is widely distributed throughout the human body. ACE2 messenger RNA is present in virtually all organs, and its protein is expressed mainly on lung alveolar epithelial cells and small intestine enterocytes, in addition to arterial and venous endothelial cells and arterial smooth muscle cells in at least the brain, skin, oral and nasal mucosa, nasopharynx, gastric cardia and corpus, spleen, thymus, lymph nodes, bone marrow, liver and kidneys.[66] It has been associated with the regulation of cardiac function and blood pressure, and is plentifully expressed in the placenta, indicating a role in the maternal–fetal interaction.[65] This widespread distribution of ACE2 may help explain the multifarious pathogenicity of SARS-CoV-2.

Four months into the current pandemic, it is universally acknowledged that COVID-19 is no mere pneumonia or respiratory illness, but a complex polymorphic disease, with the potential to affect any body organ and system. Even when the same organ is involved, manifestations vary as a function of factors still to be elucidated. COVID-19 therefore does not seem to be a single disease, but a full range of pathological conditions having viral-induced inflammation and thrombosis in common. The manifestations exhibited by patients also vary as a function of age, which partially conditions their immune response, and at least mortality is known to be influenced by sex.[67] Outcomes further depend on several risk factors (hypotension, diabetes, coronary artery disease, and chronic respiratory diseases), with viral load an independent risk factor.[38] All these, in different combinations, paint numerous clinical pictures that are being gradually identified.

COVID-19 is nothing like the known epidemic diseases, characterized by typical (pathognomonic) signs, symptoms, and clinical course. Attempting to identify a single preventive GE medicine, or even a few, is therefore a Sisyphean task.

What, then, could be the role of homeopathy in future epidemics, especially when the microorganism is pleiomorphic? In COVID-19, homeopathy has played a very small part in population-based initiatives to date, except in India, Cuba and Brazil,[27,68–70] with still unknown outcomes, since data are still being collected.

From the research perspective, the gold standard is randomized clinical trials. At this moment, one is being conducted in India,[71] and another was granted ethical clearance in Brazil—investigators are currently dealing with recruitment issues (personal communication). These are trials of individualized homeopathy to measure clinical outcomes (progression to severe/critical stage, need of mechanical ventilation, death).

While this type of study is useful to measure effectiveness/efficacy, it is not helpful to guide practice. In the case of COVID-19, homeopathic practitioners worldwide are providing individual care to outpatients, a group that represents approximately 80% of all cases. Many registries are opened to gather this experience, which cannot be seen as dismissible, inasmuch as the group of mild COVID-19 patients usually remain in home isolation without medical monitoring, follow-up, or treatment other than over-the-counter drugs (fever reducers, etc.).

Homeopathy could contribute far more if its local, regional, national, and international bodies organize rapid-response teams and established lines of communication. At the same time, these bodies should strive to improve interaction with mainstream medicine to work together. A good point of departure could be the departments of integrative medicine already available at the best hospitals in the world, usually with focus on cancer patients. Through proactive dialogue, the Department of Complementary Medicine at Shaare Zedek Medical Center, in Jerusalem, was granted ethical clearance to treat hospitalized, severe, non-critical COVID-19 patients as a pilot study. Another interesting path of interaction is that of medical residency programs. There has been one since 2014 at the Regional Public Hospital of Betim, Minas Gerais, Brazil, where homeopathy has been part of the standard care provided in public health services since 1996 (personal communication). As part of the regular hospital medical staffing, homeopathy residents and their supervisors treat inpatients in all specialty wards, including adult and pediatric intensive care and the neonatology department. Treatment of COVID-19 patients thus

became a natural part of their tasks, which was extended to the local COVID-19 field hospitals. All these initiatives suggest that assimilation into the institutions of mainstream medicine seems a promising strategy to integrate homeopathy formally into health care systems.

Highlights

- COVID-19 was originally represented as an acute severe respiratory disease.
- In time it has proved to be a complex systemic condition liable to affect any body organ or system.
- As a result, it exhibits a complex scope of pathology and clinical manifestations.
- The complex nature of COVID-19 does not seem amenable to the *genus epidemicus* approach in homeopathy.

Conflict of Interest

None declared.

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