ICU

MANAGEMENT & PRACTICE

INTENSIVE CARE - EMERGENCY MEDICINE - ANAESTHESIOLOGY

VOLUME 20 - ISSUE 1 -2020

COVID-19 Challenges

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COVID-19 and the History of Pandemics

How are we dealing with the COVID-19 pandemic and the lessons we can learn from similar diseases over the last few centuries.

The face of human history has always been pockmarked by disease, in more ways than one. In our current privileged world of technology, gene sequencing and micro RNA, the possibility of a new disease that kept us inside our houses seemed an impossible dystopia. However it has proved inevitable and recurrent across Europe and the wider world, for disease to bring disaster in a sudden and unwelcome wave. Mass graves silently bear forensic evidence of societies past, as they will this one.

The novel coronavirus COVID-19 was first presented to the world in the embers of December 2020 (Wang et al. 2020), and the world looked on, intrigued as China drafted in the military, barricaded the city of Wuhan and built new hospitals. From February through March 2020, the domino effect left Italy, Spain, France, the UK and the US reeling, with their own medical services drowning, a significant lack of ventilators, new hospitals and vast re-organisation of services required, such as cancelling elective operations and outpatient clinics. This was all accompanied by an enemy vanguard of PPE shortages, amidst ever-fluid guidance from public health bodies.

What do we know about this version of coronavirus? It belongs to a family of viruses that have often infected mammals, especially bats, and is known to cause a mild respiratory illness such as the common cold in humans. This particular strain however, can prove lethal. It seems to have originated in Wuhan, China, possibly from a live animal market (Wang et al. 2020). It shares many convincing genomic features with bat coronaviruses, and this animal host is known for fairly virulent, highly mutating viruses due to a rather impenetrable immune system, which the host can withstand potentially due to anti-oxidant and mitochondrial adaptations that have arisen for the necessities of flight (O'Shea et al. 2014).

In humans it was first described as a highly contagious airborne and droplet-spread pathogen causing fever, dry cough and pneumonia in some, but not all, afflicted individuals.

From an epidemiology standpoint it seemed to have an R0 number of 3 (in contrast to SARS which was less), affect men more than women (Sun et al. 2020) [consistently 60-80% for UK ICU data (ICNARC 2020)], possibly because of gendered behaviour or X-chromosome conferred immunity (Schurz 2019), for the main part did not produce symptoms in children [which remain less than 1% of cases and minimal fatality (Kelvin and Halperin 2020)] and could be carried asymptomatically (Sun et al. 2020). Although it can attack the young and apparently healthy, the majority of victims are >65 years when it comes to mortality rates. Those with diabetes and hypertension seem to be particularly affected, as do smokers (Jordan et al. 2020). There have been cautious questions of whether non-Caucasian ethnicities seem to be a greater risk for lethality, however this remains hypothetical and the reasons are unexplored as yet (Science Media Center 2020). Postulates are socioeconomic, urban living probability – at least in the UK, and potentially genetic/MHC subtypes, as MHC class has significant variability on antigen presentation/strength of T cell activation (Wieczorek 2017).

It is from the family coronaviruses, and contains a particular spike protein for invasion. Though it bears resemblance to past MERS and SARS viruses, it uses the ACE2 receptor to enter cells (Wang et al. 2020). ACE 2 is, in many ways, the yang to ACE's yin; it is a separate receptor, unaffected by traditional ACE inhibitors, that has a vasodilatory effect on vasculature. COVID-19 then goes on to replicate inside cells as all viruses have a wont to do, and has been found in both lung and capillary epi/endothelium, alongside biopsy findings of pulmonary oedema, pus, hyaline surfactant disruption, microthrombosis and pulmonary infarction (Xu et al. 2020).

COVID-19 originally was said to present with a cough and fever, and potentially GI upset, leading towards pneumonia. Now we are further into the outbreak (3-4 months), we are aware of presentations such as rashes (Recalcati 2020), ophthalmic complications (Wu et al. 2020), anosmia (Iacobucci 2020), neurological complications (Mao et al. 2020) and peri/myocarditis (Fried et al. 2020). Critically ill patients appear to have a high rate of mortality [50% of ICU admissions in

ICNARC data (2020)], suffering from cytokine storm, haemodynamic collapse and a significant proportion have renal failure. In the UK roughly 1/5 of hospital admissions require critical care, but without mass testing it is unclear what the true fatality rate is, given the likely presence of asymptomatic infection. Whilst initially focus was on an ARDS like development of pneumonia, which some do yet display, it was clear there were different phenotypes of disease when it came to lung pathology (Gattinoni 2011). Some do not have the classic stiff, wet lung characteristic of bacterial ARDS, though biopsy findings have described very similar features shared by both (Xu et al. 2020).

It is of particular note that the microthrombosis and hyper-coagulable state of COVID-19 patients is a rather novel component of its natural history. D-dimer was early on reported as a poor prognostic marker in these patients (Jordan et al. 2020), representing clot turnover. This fits with the clinical picture that is consistent with widespread microthrombosis such as renal failure, apparent pulmonary shunting, and certain skin changes. If heparin yields little effect in some, it suggests that part of the pathology is related to platelet dysfunction, a feature of other viruses (Lope da Silva 2011) such as dengue (Rossi et al. 2010) ADAMTS13 is a molecule that affects the cleavage of vWF. Auto-antibodies against it are commonly provoked by numerous viruses, and defects with it are the cause of complaint in thrombocytopaenic thrombotic purpura, which has a similar constellation of coagulopathy signs, including renal failure (Zheng 2013). Clotting is very much married to the immune cascades both evolutionarily, for example a species of snail secretes immunoglobulins that are attached to fibrinogen (Janeway 2001). This enables trapping and scavenging of pathogens. In humans too, we are aware of the effect of cytokine activation on clotting and recognise DIC for example as a consequence of profound sepsis. Even the 1665 physician Nathaniel Hodges, recognises DIC in bubonic plague (Hodges 2012). Other significant issues in these patients are the high rate of adverse cardiac features (Fried et al. 2020), arrhythmias and right heart failure. It is unclear if this is secondary to cytokines, direct viral attack on ACE2, viral myocarditis, hypoxic vasoconstriction causing right heart failure and so on.

Investigations obviously are testing – both antigen PCR and antibody testing are available, although of limited sensitivity and specificity. FBC shows lymphopaenia, U&Es may show renal dysfunction, LFTs are often elevated, and a high D-dimer is a poor prognostic sign.

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X-ray/CT imaging (Soldati et al. 2020) will show bilateral opacities, concentrating predominantly in the peripheries, and CT describes bilateral ground glass opacities and consolidation. ECHO may demonstrate any of a hyperdynamic circulation, Takotsubo-like cardiomyopathy, reduced cardiac function and in particular, right ventricular dysfunction (Peng et al. 2020). Lung ultrasound reveals consolidation, subpleural thickening and less frequently, effusions (Soldati et al. 2020). These patients can in some circumstances, be notably hypoxic without appropriate respiratory distress.

Management of COVID-19 typically involves supplementary oxygen and CPAP, ideally prone which improves VQ mismatch (Gattinoni 2011). These patients respond to proning rather well. Their fluid balance should be managed to avoid exacerbating either pulmonary oedema or AKI; dehydration from febrile illness can cause them to be underfilled on presentation. They may require renal replacement therapy. NIV is used with appropriate staff precautions such as filters, negative pressure rooms and staff PPE. HFNC is not globally advised given the high oxygen demands and potential aerosol dangers, although it is popular in the US (Poston et al. 2020). Ventilation strategies appear to be causing controversy given ventilator associated lung injury and the fact these patients have compliant lungs in some phenotypes, however these patients can be profoundly hypoxic, deteriorate fast and can be hard to extubate, so naturally intubation and ventilation is a step that must be taken in some patients, abiding by lung protective strategies such as low tidal volumes and minimal oxygen titration to limit iatrogenic exacerbation of disease (Gattinoni 2011).

Antibiotics should be given for secondary infection and be guided by biomarkers, potentially procalcitonin, and clinical features. Anti-coagulating these patients may extend renal filter life, and potentially assist disease recovery (Tang et al. 2020). Heparin infusions are the most commonly used. ECMO is an option for countries with available beds (Poston et al. 2020).

Multiple agents are in use with respect to trials – hydroxychloroquine, azithromycin, kaletra, remdesivir, vitamin C, IL-6 antagonist agents, convalescent plasma and steroids are all under trial surveillance, with some nominally interesting results, none of which have robust RCT evidence. Registered trials in Europe are available on the clinical trials register (EU Clinical Trials Register). Steroids have been used to attempt to control the cytokine storm, however there are concerns they could enhance mortality/viral progression and enable secondary infection. Randomised

trials are awaited. Many trials are compassionate use-based.

Most measures have focused on public health interventions such as hand-washing, isolating the afflicted, limiting travel, shop and public space closure, social distancing, working from home/furloughing staff and school shut down. There have been and will be profound economic effects, with secondary health consequences. COVID-19 truly is the plague of our time.

As we do with law, in our own personal lives, we find ourselves reflecting on precedent to predict the future in medicine. The medical response throughout past epidemics has proved both predictable, humorous and sorrowful at once. As a profession we have witnessed Ebola, Influenza, Cholera, Typhus, Syphilis, Malaria, Dengue. Our bones have joined those of patients, riddled with the same disease. Some have chosen to assist, head on, others have chosen to direct from the rear. We can all sympathise with everything the ghosts of history experienced, and wonder how they coped, acted, and died. In many ways, infectious disease was a more familiar creature to the medics of the past and perhaps more bearable. Alternatively lack of explanation, the wrath of religious figures, and the inevitable socioeconomic chasm led to dissolution of order that was only partly bridged by the moral conscience of individuals. You will recognise shut downs, rationing and neighbourly kinship in the narratives of plague history.

When it comes to how our forebears managed the moral maze of self preservation amidst epidemics, I have sourced material from literature, diary entries, and commentators at the time, including information published by the Church and clergy concomitant with outbreaks. Plagues have been a perpetual shadow over human societies – whether it be the Justinian plague in 542 BC, the Black Death between 1348 AD and the late 17th century, or others such as those mentioned in Ancient Greece and Egypt, for which we have less information. I will start by explaining the role of medical practitioners within their historical framework.

Traditionally, the identifying feature of physicians was a university degree (Mellinger 2006). There was much time dedicated to studying the liberal arts – theology, philosophy, logic, rationality – and even astrology, in addition to basic sciences. This forms the basis for the Oxbridge science degree as a Bachelor of The Arts accreditation. Anatomy was something more prevalently studied in the Middle East. Much of European early study focused on Galen and Hippocrates, however there were limited translations available of Greek texts during the Middle Ages. Indeed, many Islamic texts were more accessible, and Ibn Sina (Avicenna) around the 9th/10th century had a lot of influence over European medicine.

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Most theories focused on the idea of humours as we are familiar with – but uroscopy (Eknoyan 2007), in compact with astrology, was often used. Uroscopic kits were actually rather popular! The consistency, appearance, odour and even taste of urine was examined. The pulse too, was a source of information for the ancient physician. Descriptions were rather poetic - gazelle, worm or ant-like pulses are described (Boylen 2007).

Universities therefore generally managed medicine, as they do today. One of the first putative medical schools was in Salerno, Italy (originating in 9th Century AD, formally recognised in 1231). Ideas from Greece and the Middle East, generally spread across to Italy, France, and England, although various cultures flavoured the exact form of medicine that was applied, and of course religious direction cultivated certain theories. Again it is notable that anatomy and physiology flowed from the Middle East (Mellinger 2006).

In fact, the universal physician philosophy, which had tended to focus on prevention rather than cure through agency via a good diet, and avoidance of certain foods or behaviours (usually sexual ones), was that flight was the only method of managing plague (Wallis 2006). To flee, flee far, and return late (Bocaccio 1886). This was a consistent approach, and their rational one – in an era whereby death was common and cures minimal, this was not considered morally inept. However for the clergy and the churchmen – flight was not considered appropriate and edicts from the Church authorities stated this. This was partly due to the fact that an early death, though tragic, was not as eternally damning as death before confessing one's earthly sins (Wallis 2006).

Bishop of Gloucester and Worcester, John Hooper, wrote, there were 'such officers of trust … [who] for no cause may flee:' the bishop, parson, vicar, and curate…Such also as have places and offices of trust for the commonwealth, as the captains of soldiers in the time of war, judges and justices in the time of peace"(Wallis 2006).

Physicians therefore were often absent from plagues, tended chiefly the rich, and left a vacuum for plague doctors. These varied from 'second rate' unsuccessful physicians, apprentices, barbers, herbalists…right through to fruit salesmen (Mellinger 2006). The characteristic beaked appearance of a plague doctor did not really represent a traditional physician. Practitioners were those, without a university degree, who had dabbled, or

received a little training, and doubtless varied in their efficacy.

Two popular commentators, Martin Luther and Beza had opposing views on flight (Wallis 2006). Luther argued it was immoral to desert one's family/leave the poor in harm's way, whilst Beza felt people had a moral obligation to leave and not 'tarry' recklessly, where they might tempt the condemnation of God. Indeed most commentary towards the end of the pandemics did not oppose flight, although charity and concern for one's kin was highly regarded, there was no 'state obligation' for the greater common wealth (Wallis 2006). Flight discussions were targeted more towards clergy and other public offices, and frankly physicians earned little notice, at odds with commentary of today. A lot of discourse swirled around the state of people's souls, poverty, social inequality, dissolution of order and the physical consequences. Magistrates and governance were heavily scrutinised.

The only exception to the absence of physician scrutiny was specifically employed 'city physicians' who were employed for the purpose of the epidemic, and swore an oath. Which suggests that magistrates should provide the common wealth "of Phisitions, Chirurgians, and such as they commonlye call Apothecaries, such as for yeares, fame, experience, honestie of manners, virtue, and the feare of God, they shall iudge to bee best liked and fitte." Furthermore such individuals 'should be 'hyred for a convenient stipend, & bound by oath unto the common wealth, that they take no occasion to start away, for feare of the sickness greatly increasing' (Wallis 2006).

What is interesting is that in such times, to be a physician was a rather ordinary calling, but had little spiritual overtone, so the weight of moral obligation was perhaps not quite so profound – either by the standard of society, or by personal conscience. One commentator, a vicar called Balmsford, rather meekly attempted to criticise physicians with the argument that their ability to do good, fortified their duty to provide it. He was, of course, criticised for not visiting the sick himself (Wallis 2006).

It is notable that in 1630, members of the College of Physicians were criticised because they "did not go out in their gowns in the street" to avoid public recognition (Wallis 2006). I'm sure we can all draw our own parallels to contemporaneous behaviour.

It would be remarkably improper not to use the diary of our favourite naval officer, Samuel Pepys to help us reflect on this time. I managed to find this incredible passage:

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"Dr. Goddard did fill us with talke, in defence of his and his fellow physicians going out of towne in the plague-time; saying that their particular patients were most gone out of towne, and they left at liberty; and a great deal more, &c. But what, among other fine discourse pleased me most, was Sir G. Ent about Respiration; that it is not to this day known, or concluded on among physicians, nor to be done either, how the action is managed by nature, or for what use it is. Here late till poor Dr. Merriot was drunk, and so all home, and I to bed."(Pepys 1666)

Physician's own musings on the subject also favoured flight, whether mentioned in books such as 'The Touchstone for the Physik" by William Walwyn, and "The Chymical Galenist" by George Castle, or by individual physicians. A supporter of the College of Physicians, Kemp stated firmly "Think well then of your Doctor, and oblige him whilst you are in health, to venture his life to preserve you when you are sick" (Wallis 2006), meanwhile the head of the College, Nathaniel Hodges, was very clear that when duties to neighbours and existing patients disbarred, many of whom had indeed left, flight was advisable. It was felt however, that the College had also ever been reluctant to provide city physicians during epidemics.

Nathaniel Hodges, this erstwhile head of the College, wrote a book called "Loimologica: An Historical Account of the Plague in London" published in 1665. I am hard pressed not to quote all of it, simply for the writing.

"Disputes are raised about the use of Alexipharmicks, Fumigations, Fires and other general Topics, which have little Foundation, than a wilful misapprehension, for it cannot be imaged, that these are either good or bad in all Circumstances but that they require the Conduct and Discretion of able Judges, as Particular Occasions or Symptoms demand them."

These words are not unwholly foreign to any of us who have attended many a discourse on new treatments. By the time of publication of his book in 1665, he was rather annoyed by people 'of mean thought' using astrology, and could not imagine that any conjunction of Saturn or Mars, had any bearing on the matter, other than to sink spirits and reduce resistance to 'the contagion.' He also goes into a great explanation about comets, for though they seem intimidating he states 'there is nothing strange about the ascension of heterogeneous particles into flame.' It is also notable however, that he laments a surfeit of cherries and grapes, which may have contributed to the pestilence and the body's disposition to it.

He himself does appear to have tended patients, for he describes that during Christmas Holy days he attended a young man with a fever, and risings on each thigh the size of a nutmeg, who had caught the plague. This patient recovered. He had received a two day course of Alexiterial medicines.

What is very heavy, throughout all accounts, is the reliance on neighbours for charity and aid. This is naturally a very biblical concept, but one commented upon even by the College of Physicians. Nathaniel Hodges in his accounts, expresses worry over magistrates shutting people in their houses and painting a red cross – he feels, though trying to be impartial, that this doesn't work and drives the neighbours away, who could otherwise deliver food and medicine. He feels more died than necessary, due to the abandonment of neighbours. Curiously in his reflections, he strongly advocates for accommodation to be made outside the City Walls for those with infected families, as he finds it 'abhorrent to religion and humanity' to shut up the sick and unafflicted together. I am not sure, this is something even now, we have quite grasped.

It is clear in many ways, that although flight is somewhat less acceptable now that it was to the people of the 17th Century, many of the ethical problems we address about the role of healthcare workers in epidemics were actually less problematic and also better solved, in a historical reference frame. I have drawn heavily on concepts from an incredible reference by Malm et al. (2008) for understanding 'moral theory' in relation to the role of medics in plagues. Please attribute most of the following concepts to their paper, although I have tried to apply their principles to the current pandemic.

Firstly, moral theory argues there are at least two categories of good deed. One is a General Good – helping someone frail with shopping or rescuing someone trapped, with an obvious answer and little skill required, and we all as people are morally obligated to do so. The other is a Special Good – one has skills or training to be of particular benefit, such as a trauma surgeon. Lots of arguments through history, including during plagues, have suggested that doctors do have a duty to perform 'Special Good' deeds. An easy example is a call to aid on public transport for a deteriorating patient, and even the GMC have a position on this. Other Special Good deeds might relate to the position between carer and dependent – parent and child. Moral decency extends to slightly more investment in action.

However, Special Good does not always logically conclude that we must risk life, to save life. We would expect a lifeguard to save a drowning person. We would not necessarily expect them to get in and fight a shark, unless trained or equipped to do so. And this comes down to five key arguments regarding 'duty to treat' at risk of harm. This is a seriously topical subject, given the nature of not only an infectious corona epidemic, but the call to arms from retired and potentially vulnerable health care workers.

1. **Consent**: We are all familiar with consent, and many of us sign job contracts. None of us have signed a contract to say we accept we are risking our life, and have not necessarily got any compensation for doing so – unlike someone in the armed forces for example. Gaining a medical degree and working in the NHS is not informed consent for pandemic office. The magistrates in the plague epidemics therefore specifically hired city physicians in these outbreaks, who took oaths, who acknowledged the danger and CHOSE employment.

2. **Implied consent**: Many of us are familiar with implied consent. There is an argument (although it is not very strong) that by choosing to be doctors or nurses or allied professionals, we accept this risk, and by continuing to be employed, we implicitly accept it. But this is not necessarily true, and also does not hold up vigorously in law. After all, consent relies on being able to weigh up information, be it on risks or mitigations such as PPE, that not all of us possess.

3. **Special good**: Here is probably the most prominent argument for me as an individual. Some of us, by dint of fortune or training, have special skills that either have special benefits for the situation or reduce the risk to ourselves. This is sacrifice for the greater good or common wealth argument.

4. **Reciprocity**: The above argument becomes particularly strong when we consider whether special skills have arisen due to public investment. For example whilst private physicians weren't much commented on during epidemics, city physicians (funded by magistrates) were. In the NHS certainly, we are mostly publically funded, although with the position of bursaries and loans etc, this may vary between professions, individuals and nationality. This argument is that society gives us special skills, training and equipment, including PPE (in some, not all hospitals of course!) and therefore we are morally obliged to give back to society.

5. **Oaths and codes**: There is no medical oath, or Hippocratic oath, performed at graduation in the West, that addresses the situation of risk to one's own life. "First do no harm " or primum non nocere, is the prevailing wind. This quote moreover, is not directly attributable to Hippocrates, despite assiduous efforts, although a similar vein is present in original texts. The closest I could find is "But I will keep pure and holy both my life and my art." In the context of biblical teachings in plague times, charity was very much salient, however suicide was not. Moreover, today, we are meant to consider separate our religious ideals and treatment of the unwell. Again, during plague outbreaks, magistrates used physicians who had sworn a very specific oath.

Overall it can be concluded that there is no obvious and easy moral answer to

the dilemma of medical assistance during epidemics. However I think many of us possess unease regarding the exposure, particularly of susceptible colleagues, to contagion. This is particularly prominent in the setting of insufficient PPE. Moral arguments regarding the continued provision of healthcare clearly vary by consent process, degree of training and protection, public investiture into funding and equipping healthcare, and one's own moral position on duty to treat – be it spiritual or otherwise. Is it a moral role to become a medic, or a scientific one? Do we have a public office that helps to sustain order? Even if these are true we also possess a moral obligation to our own families and neighbours, indisputably, to reduce harm to them.

As fascinating as historical precepts are – scientifically and sociologically, our knowledge now far exceeds that of the plagues of the past. Early 17th Century scientist Van Leeuwenhoek discovered 'animalcules' in dental plaque and onwards from there appeared discoveries about the agents and methods of infection, throughout the 17th-21st centuries. Our approach will have to evidentially differ from our forebears.

"The dogmas of the quiet past are inadequate to the stormy present. The occasion is piled high with difficulty, and we must rise with the occasion. As our case is new, so we must think anew and act anew." Abraham Lincoln

Absolutely. And with respect to one other controversy during this period – the onslaught of less-than-rigorous but rapid-turnover research, Nathaniel Hodges had very pointed suggestions about any perceived quackery, which he termed "Trash with pompous Titles" (Hodges 1665). ■

Key Points

- The novel coronavirus COVID-19 was first presented to the world in the embers of December 2020.
- From February through March 2020, the domino effect left Italy, Spain, France, the UK and the US reeling, with their own medical services drowning, a significant lack of ventilators, new hospitals and vast re-organisation of services required.
- COVID-19 originally was said to present with a cough and fever, and potentially GI upset, leading towards pneumonia. Now we are aware of presentations such as rashes, ophthalmic complications, anosmia, neurological complications and peri/myocarditis.
- Multiple agents are in use with respect to trials - hydroxychloroquine, azithromycin, kaletra, remdesivir, vitamin C, IL-6 antagonist agents, convalescent plasma and steroids are all under trial surveillance.
- Most measures have focused on public health interventions such as hand-washing, isolating the afflicted, limiting travel, shop and public space closure, social distancing, working from home/furloughing staff and school shut down.

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