COVID-19: self care for the vulnerable

An open access review from the College of Medicine
Dietary and Lifestyle advice. 31st March 2020
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Summary

- **The evidence from the early months of the SARS-CoV-2 virus (COVID-19) pandemic is that this coronavirus harms mostly people with more than one other health problems. The highest risks have been identified and include cardiovascular problems.**

- **It is possible to identify realistic, safe and healthy measures that could reduce the risk of harm for people with these vulnerabilities. These are positive and non-contentious measures that should be widely shared as self-care recommendations.**

Introduction to COVID-19 progression

Incubation period

This begins after coronaviruses have been inhaled (from someone coughing nearby) or transferred by contact from contaminated hands to mouth or nose. The viruses move into the mucosa lining the airways and start genetically engineering the host cells to replicate more viruses to bud off and infect other cells and tissues.

The incubation period is five days on average but varies widely. There will be no symptoms at this stage. With good primary defences many infected remain well, although the proportion is not yet known. Of those who progress to overt infections 80% have mild infections. **Each stage of severity is determined by the extent of immune system response**.

Mild infection

80% of sufferers >

Symptoms are mostly a fever and a cough. Body aches, fatigue and a headache are all possible as well. Recent reports from countries with large numbers of sufferers indicate that some can get upper respiratory symptoms like runny nose and sore throat, and loss of smell and taste.

These symptoms are the result of the body's **healthy immune response** to the virus, which includes the release of inflammatory cytokines: chemicals that provoke fever, aching and general malaise. There is also a drop in white blood cells (lymphocytes) and T-cells.

As the viruses irritate the airway mucosa they induce a dry cough. A lack of protective mucus can lower the barriers to secondary infection and in this case the cough may become productive, with a thick sputum.

This is a good time to get to bed. Dehydration is a threat and more fluid intake is important.

This phase can last about a week and most recover without any further trouble. 20% go further **>>**

Severe infection

14% >

This occurs when the **immune system overreacts to the virus** and generates increased and destructive inflammation and higher levels of cytokines. White blood cell levels are further depressed.

Inflammation of the lungs is called pneumonia. This is often marked by a dry cough, but also by fluid infiltration into the microscopic air sacs, which increasingly causes shortness of breath and difficulty breathing. Some people will need a ventilator to help them breathe. Around a third with severe infection (6% of total infected) go further **>>**

6%

Critical infection

By this point **the immune system is now spiralling out of control** and causing damage throughout the body. There is a massive increase in inflammatory cytokines ('cytokine cascade') and major depletion in important white blood cells. This leads first to 'acute respiratory distress syndrome' (ARDS) with a critical reduction in the oxygen the body needs to survive. Pneumonia turns into a form of sepsis. Septic shock follows and the blood pressure drops to dangerously low levels. The kidneys no longer clean the blood and there is damage to intestinal lining. Multi-organ failure follows and death follows in between 1-3% in total of those who show signs of infection.

Treatment by this stage will be highly invasive and can include extra-corporeal membrane oxygenation (ECMO) where an artificial lung takes the blood out of the body to oxygenate it.

COVID-19 risk factors

Among the first 44,672 confirmed cases to be monitored in China, those who are most damaged were most often with other health conditions. Fatality rates have been particularly high among patients with **cardiovascular disease** (4 times the average), and then in decreasing order **diabetes**, **lung disease**, **high blood pressure** and **cancer**.[1] A later more detailed study among fewer subjects supported the conclusion that those with more than one of the conditions of high blood pressure, cardiovascular disease and diabetes were most at risk of critical outcomes or death.[2] Such multiple co-morbidities are predominantly suffered by the elderly. This is different from seasonal flu infections where immune-compromised patients, including the very young, and pregnant women are most at risk.[3]

Preliminary results from Italy[4] are that men make up 70% of fatalities. The median age of deceased patients (80.5 yrs) is more than 15 years higher than that of patients who contracted the infection (63 yrs). From 355 of the first 2003 deaths the average number of pathologies observed was 2.7. Overall, less than 1% of fatalities had no prior pathologies, almost a half had three or more:

3+ pathologies	2 pathologies	1 pathologies	0
48.50%	25.60%	25.10%	

The most common pre-existing chronic pathologies (diagnosed before contracting the infection - cardiovascular-related conditions highlighted) in deceased patients were:

Arterial hypertension	76.1
Diabetes mellitus	35.5
Ischaemic heart disease	33
Atrial fibrillation	24.5
Cancer within last 5 years	20.3
Kidney failure	18
COPD	13.2
Stroke	9.6
Dementia	6.8
Chronic liver disease	3.1

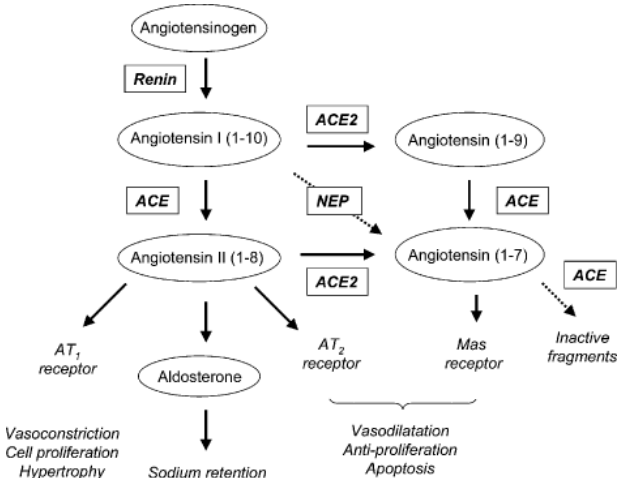
Why are fatalities related to cardiovascular problems?

Terminal circulatory failure. Those who are most harmed by COVID-19 infection undergo a second dangerous hyper-reactive phase to the virus that leads to a 'cytokine cascade' and widespread organ failure. The first casualty is usually considerable lung damage, leading to the need for ventilators, which in turn puts major strain on the heart and circulation. Pre-existing circulatory disease would make this more likely to be terminal.[5]

Prescriptions for cancer and diabetes; alcohol and recreational drugs. Cardiovascular vulnerability can also be linked to prescriptions for cancer and diabetes. Some of these are more likely disturb the mitochondria in heart cells. Alcohol and recreational drugs can have similar effects.[6] This is not unusual: in recent decades cardiotoxicity has been the reason for almost half of drug withdrawals from the market.

Antihypertensive medication? Patients with hypertension, diabetes and cardiovascular disease often take prescriptions to inhibit or block the hypertensive effects of a natural metabolite angiotensin II. Hypertension often involves an increase in the angiotensin converting enzyme (ACE) system that generates angiotensin II: this narrows blood vessels, retains water and in other ways increases blood pressure. ACE inhibitors like ramipril, and angiotensin receptor blockers (ARBs) like candesartan, are commonly prescribed to block this process. Moreover the body produces its own moderator of angiotensin II, ACE2 (*see chart*) and these prescriptions also increase the cell production of ACE2.[7]

ACE2 is particularly important in protecting the lungs. However cells producing ACE2 have been found to be targeted by the SARs coronavirus,[8] and it is now demonstrated that this is also the case for COVID-19.[9,10] (However unlike SARs COVID-19 may also engage with other receptors in the upper respiratory system as well[11]) It has been suggested that patients taking ACE-inhibitor or ARB prescriptions may be increasing routes of infection by this coronavirus.[12] However an early review did not see the link[13] and a paper circulated ahead of peer review found the opposite, that taking ACE-inhibitors protected hypertensives from serious consequences.[14] Instead it is possible that co-morbidities themselves, especially hypertension and diabetes,[15] may lead to dangerously increased expression of ACE 2.[16]



Schematic diagram of the renin–angiotensin–aldosterone system which shows the role of ACE and ACE2 (after Hamming et al)

Endothelial dysfunction. Recent articles have confirmed that compared with those with few symptoms of mild infections,[17] critically ill patients with COVID-19 generally have low lymphocyte counts (lymphopenia),[18,19,20] T-lymphocytes ($CD4^+$T and $CD8^+$ T)[21] rather the B-cells, combined with high levels of inflammatory cytokines[22] particularly levels of interleukin-2 receptor (IL-2R), IL-6[23] and IL-10 and TNFα, at the extreme leading to a catastrophic 'cytokine cascade'. This combination was also evident in critical patients with coronavirus Severe Acute Respiratory Syndrome (SARS-CoV).[24,25] as well as a particularly virulent form of pneumonia,[26] both which can lead to similar **sepsis**-like organ failure.

Endothelial dysfunction is a central element in these processes,[27] is well understood as crucial generally to the development of cardiovascular diseases and diabetes,[28] and is also an inherent feature of high blood pressure.[29] It includes a breakdown in intercellular junctions, enhanced movement of white blood cells out into surrounding tissues, and consequent lymphopenia. Disturbed endothelia generate endothelins that are powerful macrophage activators[30] and can help precipitate cytokine storms. Such combined features have been postulated as contributing to COVID-19 mortality.[31]

Other factors that may increase vulnerability

Gut and microbiome disruption. A detailed Chinese clinical review of the COVID-19 outbreak indicates that some patients have gastrointestinal symptoms (such as abdominal pain and diarrhoea) due either to direct viral infection of the intestinal mucosa, or antiviral and anti-infective drugs. There have been reports of dysbiosis, manifesting as a significant reduction of Lactobacillus and Bifidobacterium. The authors call for probiotic measures to help maintain wider immune functions.[32]

Obesity. Official communications in the UK point to increased risks for people with body-mass index (BMI) levels of greater than 40 – in other words those who are significantly obese. Early

UK data[33] has indicated the death rate is twice higher in people with BMI 30+ versus BMI 25-. It is understood that adipocytes are potent generators of inflammation and macrophage activation,[34] and higher BMI is also associated with insulin resistance and endothelial stress.[35,36]

What can we do to help the most vulnerable?

Reducing endothelial dysfunction. A priority should be to **reduce refined carbohydrate** in the diet with attendant glycaemic load on the circulation, and the endothelial stress associated with insulin resistance. Associated **weight loss**, with reduced adipocytic inflammatory pressures would be an extra bonus.

There is evidence that **polyphenol-rich foods** such as black and red berries, cocoa, [37] nuts,[38] (and cocoa with nuts) [39,40] green and black teas, and omega-3 fatty acids protect endothelial cells,[41,42,43] including with potential benefits on blood pressure.[44] Positive changes with cocoa have been seen in days.[45]

Taking **Asian spices** like turmeric, ginger and cinnamon has also been shown to have positive benefits for endothelial function,[46] even when combined with fatty foods.[47] A useful demonstration is that these effects can be extremely quick, with positive changes observed after one meal.[48]

A number of these foods have also been shown to help reduce blood pressure, often through similar vascular effects.[49]

Vitamin D can reduce blood pressure by downregulating renin at the outset of the ACE pathway (see chart),[50] and by further modulating ACE2, appears to exert additional protective effects on inflammatory lung injury.[51] If Vitamin D is deficient blood pressure can rise.[52]

In the light of the complicating factors surrounding high blood pressure and cardiovascular disease above, and especially for those taking certain medicines for blood pressure[53] it makes sense to increase Vitamin D levels, if necessary by supplementation. Low levels of sunshine has been implicated in exacerbating many viral infections and one could also aim to take moderate levels when possible.

Exercise. In spite of social isolation and often confinement it is important to maintain or even increase levels of daily activity. Almost all parameters of immune and cardiovascular health will benefit from a new routine of sustained exercises, with daily walks or more active exercise outdoors if at all possible.

Probiotics and prebiotics. Signs of particular disturbances in the microbiome from COVID-19 infections highlight a growing consensus that the gut is the largest part of the body's immune defences.

For a public summary of these findings the College of Medicine has an updated COVID-19 page on its Our Health Directory site.

Conclusions

People who are vulnerable to COVID-19 because they have cardiovascular disease, hypertension and diabetes can usefully be advised to ensure their diet is predominantly made up of plant foods like fruit and vegetables, cocoa, seeds, nuts and teas, to add Asian spices where possible, and to consider supplementation with Vitamin D. Increased exercise and reduced carbohydrate consumption will add to a regime that could help others too.

References

1 Wu Z, McGoogan JM. (2020) Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72,314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA*. Published online February 24, 2020.
Full Text

2 Guan WJ, Liang WH, Zhao Y, et al. (2020) Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. *Eur Respir J*. 2000547
Abstract and Full Text

3 WHO. (2012) Vaccines against influenza WHO position paper –November 2012. Wkly Epidemiol Rec 47: 461–76

4 Istituto Superiore di Sanità (2020) Report sulle caratteristiche dei pazienti deceduti positive a COVID-19 in Italia Il presente report è basato sui dati aggiornati al 17 Marzo 2020. https://tinyurl.com/wbplmwf

5 Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19in China. *Clin Res Cardiol*. 2020;10.1007 [online ahead of print]
Abstract

6 Varga ZV, Ferdinandy P, Liaudet L, Pacher P. (2015) Drug-induced mitochondrial dysfunction and cardiotoxicity. *Am J Physiol Heart Circ Physiol*. 309(9): H1453–H1467
Full text

7 Ferrario CM, Jessup J, Chappell MC, et al. (2005) Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation*. 111(20): 2605–2610
Full Text

8 Hamming I, Cooper ME, Haagmans BL, et al. (2007) The emerging role of ACE2 in physiology and disease. *J Pathol*.212(1):1–11
Full Text

9 Zhou P, Yang XL, Wang XG, et al (2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 579 (7798): 270-273

10 Hoffmann M, Kleine-Weber H, Schroeder S, et al. (2020) SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor [online ahead of print]. *Cell*. S0092-8674(20) 30229-4
Full Text

11 Woelfel R, Corman VM, Guggemos W, et al (2020) Clinical presentation and virological assessment of hospitalized cases of coronavirus disease 2019 in a travel-associated transmission cluster medRxiv 2020.03.05.20030502
Abstract and Full Text

12 Sommerstein R and Gräni C. (2020) Rapid response to Preventing a COVID-19 pandemic: ACE inhibitors as a potential risk factor for fatal Covid-19, BMJ 368:m810.
Full Text

13 Peng YD, Meng K, Guan HQ, et al. (2020) *Zhonghua Xin Xue Guan Bing Za Zhi*. 2020;48(0):E004 (in Chinese)
English Abstract

14 Liu Y, Huang F, Xu J, et al (2020) Anti-hypertensive Angiotensin II receptor blockers associated to mitigation of disease severity in elderly COVID-19 patients. medRxiv 2020.03.20.20039586
Abstract and Full Text

15 Chen X, Hu W, Ling J, et al (2020) Hypertension and Diabetes Delay the Viral Clearance in COVID-19 Patients. medRxiv 2020.03.22.20040774
Abstract and Full Text

16 Pinto BGG, Oliveira AER, Singh Y, et al. (2020) ACE2 Expression is Increased in the Lungs of Patients with Comorbidities Associated with Severe COVID-19. medRxiv 2020.03.21.2004026.
Abstract and Full Text

17 Pedersen SF, Ho YC. (2020) SARS-CoV-2: A Storm is Raging. *J Clin Invest*. 137647
Abstract and Full Text

18 Yang X, Yu Y, Xu J, et al. (2020) Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study *Lancet Respir Med*. S2213-2600(20)30079-5
Full Text

19 Wang D, Hu B, Hu C et al. (2020) Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. 2020
Full Text

20 Li LQ, Huang T, Wang YQ, et al. (2020) 2019 novel coronavirus patients' clinical characteristics, discharge rate and fatality rate of meta-analysis. *J Med Virol.* [online ahead of print]
Abstract

21 Chen G, Wu D, Guo W, et al. (2020) Clinical and immunologic features in severe and moderate Coronavirus Disease 2019. *J Clin Invest*. 137244
Abstract and Full Text

22 Huang C, Wang Y, Li X et al. (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*. 395 (10223); 497-506
Full Text

23 Chen L, Liu HG, Liu W, et al. *Zhonghua Jie He He Hu Xi Za Zhi*. 2020;43(0nline ahead of print -in Chinese)
English abstract

24 Lee N, Hui D, Wu A, et al. (2003) A major outbreak of severe acute respiratory syndrome in Hong Kong. *N Engl J Med*. 348: 1986–1994
Full Text

25 Cameron MJ., Ran L, Xu L, et al. (2007) Interferon-mediated immunopathological events are associated with atypical innate and adaptive immune responses in patients with severe acute respiratory syndrome. *J Virol.* 81: 8692–8706
Full Text

26 Méndez R, Menéndez R, Amara-Elori I, et al. (2019) Lymphopenic community-acquired pneumonia is associated with a dysregulated immune response and increased severity and mortality. *J Infect*. 78: 423–431
Full Text

27 Bermejo-Martin JF, Martín-Fernandez M, López-Mestanza C, et al. (2018) Shared Features of Endothelial Dysfunction between Sepsis and Its Preceding Risk Factors (Aging and Chronic Disease). *J Clin Med*. 2018; 7
Full Text

28 Daiber A, Chlopicki S. (2020) Revisiting pharmacology of oxidative stress and endothelial dysfunction in cardiovascular disease: Evidence for redox-based therapies. *Free Radic Biol Med* [online ahead of print]
Full Text

29 Saka B, Oflaz H, Erten N, et al. (2005) Non-invasive evaluation of endothelial function in hypertensive elderly patients. *Arch Gerontol Geriatr*. 40(1): 61–71
Full Text

30 Gonsalves C, Kaira VK (2010) Endothelin-1–Induced Macrophage Inflammatory Protein-1β Expression in Monocytic Cells Involves Hypoxia-Inducible Factor-1α and AP-1 and Is Negatively Regulated by microRNA-195. J Immunol 185 (10) 6253-6264
Full Text

31 Bermejo-Martin JF, Almansa R, Menéndez R, et al. (2020) Lymphopenic community acquired pneumonia as signature of severe COVID-19 infection: Lymphopenia in severe COVID-19. *J Infect*. [Online ahead of print]
Full Text

32 Liang T ed. (2020) Handbook of COVID-19 Prevention and Treatment. First Affiliated Hospital, Zhejiang University School of Medicine.
Full Text

33 Intensive Care National Audit and Research Centre. Report on 775 patients critically ill with COVID-19: 27th March 2020
Report link

34 Russo L, Lumeng CN. (2018) Properties and functions of adipose tissue macrophages in obesity. *Immunology*. 155(4):407–417
Full Text

35 Agabiti-Rosei C, Paini A, De Ciuceis C, et al. (2018) Modulation of Vascular Reactivity by Perivascular Adipose Tissue (PVAT). *Curr Hypertens Rep*. 20(5): 44.
Abstract

36 Thomas D, Apovian C. (2017) Macrophage functions in lean and obese adipose tissue. *Metabolism*. 72:120–143
Full Text

37 Gröne M, Sansone R, Höffken P, et al. (2020) Cocoa Flavanols Improve Endothelial Functional Integrity in Healthy Young and Elderly Subjects. *J Agric Food Chem*. 68(7):1871–1876
Abstract

38 Vinson JA, Cai Y. (2012) Nuts, especially walnuts, have both antioxidant quantity and efficacy and exhibit significant potential health benefits. *Food Funct*. 3(2):134–140
Full Text

39 Lee Y, Berryman CE, West SG, et al. (2017) Effects of Dark Chocolate and Almonds on Cardiovascular Risk Factors in Overweight and Obese Individuals: A Randomized Controlled-Feeding Trial. *J Am Heart Assoc*. 6(12): e005162
Full Text

40 Adamo M, Labate AM, Ferrulli A, et al. (2018) Effects of hazelnuts and cocoa on vascular reactivity in healthy subjects: a randomised study. *Int J Food Sci Nutr*. 69(2): 223–234
Abstract

41 Kashi DS, Shabir A, Da Boit M, et al. (2019) The Efficacy of Administering Fruit-Derived Polyphenols to Improve Health Biomarkers, Exercise Performance and Related Physiological Responses. *Nutrients*. 11(10): 2389
Full Text

42 Dimina L, Mariotti F. (2019) The Postprandial Appearance of Features of Cardiometabolic Risk: Acute Induction and Prevention by Nutrients and Other Dietary Substances. *Nutrients*. 11(9): 1963
Full Text

43 Serino A, Salazar G. (2018) Protective Role of Polyphenols against Vascular Inflammation, Aging and Cardiovascular Disease. *Nutrients*. 11(1): 53
Full Text

44 Maaliki D, Shaito AA, Pintus G, et al. (2019) Flavonoids in hypertension: a brief review of the underlying mechanisms. *Curr Opin Pharmacol*. 45: 57–65
Full Text

45 McFarlin BK, Venable AS, Henning AL, et al. (2015) Natural cocoa consumption: Potential to reduce atherogenic factors?. *J Nutr Biochem*. 26(6): 626–632
Full Text

46 Zahid Ashraf M, Hussain ME, Fahim M. (2005) Antiatherosclerotic effects of dietary supplementations of garlic and turmeric: Restoration of endothelial function in rats. *Life Sci*. 77(8):837–857
Full Text

47 Li Z, Henning SM, Zhang Y, et al. (2013) Decrease of postprandial endothelial dysfunction by spice mix added to high-fat hamburger meat in men with Type 2 diabetes mellitus. *Diabet Med*. 30(5): 590–595
Full Text

48 Nakayama H, Tsuge N, Sawada H, et al. (2014) A single consumption of curry improved postprandial endothelial function in healthy male subjects: a randomized, controlled crossover trial. *Nutr J*. 13: 67
Full Text

49 Ghaffari S, Roshanravan N. (2020) The role of nutraceuticals in prevention and treatment of hypertension: An updated review of the literature. *Food Res Int*. 128:108749
Full Text

50 Li YC, Qiao G, Uskokovic M, et al. (2004) Vitamin D: a negative endocrine regulator of the renin-angiotensin system and blood pressure. *J Steroid Biochem Mol Biol*. 2004;89-90(1-5):387–392.
Full Text

51 Xu J, Yang J, Chen J, et al. (2017) Vitamin D alleviates lipopolysaccharide-induced acute lung injury via regulation of the renin-angiotensin system. *Mol Med Rep*. 16(5): 7432–7438
Full Text

52 Andersen LB, Przybyl L, Haase N, et al. (2015) Vitamin D depletion aggravates hypertension and target-organ damage. *J Am Heart Assoc*. 4(2): e001417
Full Text

53 Garami AR (2020) Re: Preventing a covid-19 pandemic - Is there a magic bullet to save COVID-19 patients? We can give it a try! *BMJ* 2020;368:m810
Full Text