



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

# Inflammaging at the Time of COVID-19



Maria Beatrice Zazzara, MD<sup>a,1</sup>, Andrea Bellieni, MD<sup>a,1</sup>, Riccardo Calvani, PhD<sup>a,\*</sup>, Hélio Jose Coelho-Junior, PhD<sup>a,b</sup>, Anna Picca, PhD<sup>a</sup>, Emanuele Marzetti, MD, PhD<sup>a,b</sup>

## KEYWORDS

- Inflammation • Immunosenescence • Cytokines • Older adults • SARS-CoV-2
- Long COVID • Physical activity • Diet

## KEY POINTS

- Inflammaging, a state of chronic, low-grade inflammation that accompanies aging, plays a major role in the pathogenesis of most geriatric syndromes.
- Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection unleashes an abnormal inflammatory response that contributes to severe coronavirus disease 2019 (COVID-19) and, possibly, long-term sequelae.
- Inflammaging and SARS-CoV-2 infection interact in an interplay that involves acute and chronic inflammation, which predisposes older adults to severe (COVID-19).
- Medications targeting inflammation pathways have proved to be effective in reducing morbidity and mortality associated with acute COVID-19.
- Lifestyle interventions (eg, physical activity and diet) can reduce chronic inflammation and may therefore counteract long-term symptom persistence.

## INTRODUCTION

With more than 400 million confirmed cases and over 6 million deaths,<sup>1</sup> the coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has significantly affected everyone's life. Most people infected with SARS-CoV-2 have a self-limiting infection and do recover; others experience more severe disease, with 10% of patients requiring intensive care unit (ICU) admission.<sup>2</sup> The case-fatality rate of COVID-19 is approximately 1.5% (<https://covid19.who.int/>). Most COVID-19-related deaths have occurred in those 60 years and older, and an even higher mortality was registered among the oldest old (ie,

<sup>a</sup> Fondazione Policlinico Universitario A. Gemelli IRCCS, L.go F. Vito 1, Rome 00168, Italy;

<sup>b</sup> Department of Geriatrics and Orthopedics, Università Cattolica del Sacro Cuore, L.go F. Vito 1, Rome 00168, Italy

<sup>1</sup> Equal contribution

\* Corresponding author. Center for Geriatric Medicine (Ce.M.I.), Fondazione Policlinico Universitario A. Gemelli IRCCS, L.go F. Vito 1, Rome 00168, Italy.

E-mail address: [riccardo.calvani@policlinicogemelli.it](mailto:riccardo.calvani@policlinicogemelli.it)

≥80 years).<sup>3</sup> The presence of a least 1 underlying chronic condition (eg, cancer, diabetes, hypertension, obesity, cardiovascular disease, cerebrovascular disease) is a major risk factor for death.<sup>4–6</sup> Older adults are more susceptible to SARS-CoV-2 infection, more prone to develop severe COVID-19, and more frequently admitted to ICUs, with consequent increased mortality.<sup>3,5</sup>

An extraordinary proliferation of studies suggests that SARS-CoV-2 infection unleashes an abnormal inflammatory response, the so-called cytokine storm. Indeed, severe COVID-19 in hospitalized patients is characterized by high circulating levels of C-reactive protein (CRP), interleukin (IL)-6, tumor necrosis factor alpha (TNF- $\alpha$ ), and lymphopenia.<sup>7</sup> The abnormal inflammatory response, along with hypercoagulability and defective viral clearance, contributes to the development of severe pneumonia and acute respiratory distress syndrome (ARDS), with subsequent end-organ damage, multiorgan system failure, and eventually death.<sup>8</sup> Although severe COVID-19 disproportionately affects older people, systemic inflammation during SARS-CoV-2 infection is detected in patients of all ages, including children, in whom a severe multi-system inflammatory syndrome with features of Kawasaki has been described.<sup>9</sup> This implies that COVID-19–induced inflammation is not per se sufficient at inducing negative health outcomes. This article provides a pathophysiologic view of COVID-19 in older adults within the frame of inflammaging, with a focus on antiinflammatory treatments for acute and postacute disease.

## DISCUSSION

### *The Aging Process and Inflammaging*

---

Aging is a complex phenomenon characterized by numerous changes that result from environmental, stochastic, genetic, and epigenetic events in different cell types and tissues.<sup>10</sup> One of the most accredited hypotheses on the pathogenesis of aging stems from the observation that older organisms tend to develop a proinflammatory status reflected by increased circulating levels of inflammatory biomolecules.<sup>10,11</sup> Inflammation is instrumental to combat infections or other exogen pathogens; however, when it becomes sustained and prolonged, it can be detrimental to health. The state of chronic, sterile, inflammatory process that accompanies aging is termed inflammaging<sup>11</sup> and is associated with a decline in the efficiency of the immune system, named immunosenescence.<sup>12</sup> Hence, immunosenescence and inflammaging are 2 separate but highly intertwined entities that combine to progressively reduce the immune system's ability to trigger an effective antibody and cellular response to infections and vaccinations, and are associated with increased incidence of cancer and autoimmune diseases.<sup>13</sup> Immunosenescence and inflammaging can be accelerated by different factors, such as persistent tissue damage, environmental stressors, unhealthy lifestyles, and social and psychological stress, and could explain differences in resistance to SARS-CoV-2 infection between younger and older adults, and genders.<sup>14</sup> In this complicated picture, centenarians are outliers characterized by high circulating levels of antiinflammatory biomarkers that protect them against common age-related conditions and possibly from severe COVID-19.<sup>14</sup> Inflammaging plays a pivotal role in most geriatric conditions, such as sarcopenia, frailty, disability, and multimorbidity, and is a major risk factor for several age-associated chronic diseases (eg, cardiovascular disease, metabolic syndrome, diabetes, cancer, autoimmune disorders, dementia),<sup>11,15,16</sup> all of which are linked to increased COVID-19 fatality.<sup>4</sup>

The mechanisms underlying this chronic inflammatory response are difficult to decipher and are still under intense investigation. The accumulation of senescent cells is one of the mechanisms implicated in the pathogenesis of chronic inflammation.<sup>17</sup>

Several factors contribute to cellular senescence, including oxidative stress, genomic instability, metabolic derangement, and altered proteostasis.<sup>10</sup> Senescence is characterized by the arrest of cell proliferation and secretion of senescence-associated secretory phenotype factors, including proinflammatory cytokines and chemokines.<sup>11</sup> In addition, damaged cellular and organellar components are recognized by a network of sensors and trigger further secretion of inflammatory biomolecule.<sup>18</sup> Other sources of inflammaging are harmful products of commensal microbes, such as oral and gut microbiota.<sup>19</sup> During aging, the composition of gut microbiota changes, with reduced diversity and enrichment in proinflammatory bacteria.<sup>20</sup> This age-related gut dysbiosis may alter the morphology and barrier properties of the intestinal mucosa with increased permeability (so-called leaky gut).<sup>20</sup>

Age-related changes in both the innate and adaptive immune systems play an important role in the pathophysiology of inflammaging. Declines in the number, function, and activation of cells involved in the immune response, along with the depletion of hematopoietic stem cells and alteration in the coagulation system, are major phenotypes of immunosenescence.<sup>12</sup> Adaptive immunity declines with age, whereas innate immunity undergoes more subtle changes that could result in mild hyperactivity.<sup>12</sup> Defective regulation of the complement pathways and increased activation of the coagulation system can also determine local inflammatory reactions and lead to the development of degenerative diseases.<sup>12</sup>

Chronic inflammation involves several cytokines, molecular pathways, effector cells, and tissue responses that appear to be shared across age-related diseases. Clinically, it is characterized by moderately increased serum levels of several inflammatory biomarkers, including CRP, IL-6, IL-18, and TNF- $\alpha$ .<sup>11,21</sup> IL-6 is considered to be the most prominent cytokine that is shared across age-related disease conditions.<sup>21</sup> IL-6 serum levels also predict incident disability and frailty,<sup>22</sup> with a risk of developing mobility disability increasing linearly for concentrations higher than 2.5 pg/mL.<sup>23</sup> As such, IL-6 is hallmark of chronic morbidity and a commonly used biomarker of inflammaging.<sup>21</sup>

### ***Inflammaging and Coronavirus Disease 2019***

---

Bacterial or viral infections and/or vaccinations usually cause an immune response that confers an immunologic memory. The history of the individual exposure to different antigens shapes people's so-called immunobiography and influences the degree and characteristics of the inflammatory response to a new stimulus.<sup>24</sup> This trained immunity often results in a more active and functional immune system.<sup>24</sup> Immunosenescence and inflammaging negatively affect the immune response to pathogens, including SARS-CoV-2, which explains, at least partly, the development of more severe clinical manifestations in older adults.<sup>25,26</sup> In the early phases of COVID-19, infected cells release damage-associated molecular patterns (DAMPs), such as ATP and nucleic acids, which are recognized by lung epithelial and endothelial cells, and alveolar macrophages. This process triggers the production of various proinflammatory cytokines and chemokines, allowing recruitment of innate and acquired immune cells to the site of infection.<sup>27</sup> The activation of virus-specific CD4+ and CD8+ T cells kills infected cells. However, in the case of a dysfunctional immune response, the accumulation of immune cells in the lungs leads to the overproduction of proinflammatory cytokines, especially IL-6, causing damage to local cells and tissue, with subsequent systemic implications.<sup>28</sup> In older adults, a more robust activation of innate proinflammatory pathways is thought to increase the risk of severe disease.<sup>23,26,28</sup> In older men, IL-6 is chronically upregulated, with a higher rate of inflammaging, which might help explain the greater risk of death by COVID-19 compared

with women.<sup>28,29</sup> Pathophysiologic pathways in COVID-19 and risk factors for negative outcomes in individuals affected by SARS-CoV-2 share several underlying mechanisms that regulate inflammation, which might affect the clinical course of COVID-19, from flulike syndrome to severe respiratory failure and death.<sup>30</sup> Moreover, an acute COVID-19 episode may induce accumulation of subclinical damages that predisposes to a chronic proinflammatory state, even when the episode is mild and clinically resolved with no apparent immediate consequences.<sup>30</sup> Indeed, a substantial share of COVID-19 survivors experience symptom persistence for weeks or months after viral clearance.<sup>31</sup> This condition, known as postacute COVID or long COVID, is an increasingly recognized public health issue.<sup>32</sup> Common long-lasting signs and symptoms include cough, fever, dyspnea, fatigue, musculoskeletal (myalgia, joint pain) and gastrointestinal complaints, and anosmia/dysgeusia.<sup>33</sup> In the postacute phase, some patients show an accelerated decline in physical, cognitive, and functional abilities that resembles age-related long-term impairments.<sup>31</sup> Evidence shows that cytokine levels are still increased in patients with long COVID and the maintenance of a low-grade chronic inflammation could be one of the mechanisms that might explain symptom persistence.<sup>30,34,35</sup> From this perspective, long COVID bears resemblance with postintensive care syndrome (PICS). Patients with PICS present with cognitive, psychological, and physical disabilities, and some never fully recover.<sup>36</sup> Physical impairment in PICS often involves muscle weakness and fatigability, and symptoms of deconditioning,<sup>36</sup> all cardinal features of age-related frailty and sarcopenia.<sup>15,37</sup> In addition, it is worth mentioning that the long-term effects of COVID-19 on health, functional status, and quality of life may be further worsened by social distancing, isolation, and financial difficulties,<sup>38</sup> which indicates that the management of long COVID requires comprehensive approaches similar to those developed based on the paradigm of comprehensive geriatric assessment.<sup>39</sup>

### ***Inflammation as a Therapeutic Target in Coronavirus Disease 2019***

---

Since the beginning of the pandemic, studies on COVID-19 treatments have mostly focused on quenching the uncontrolled inflammatory response. The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial has been a cornerstone in the field by showing that dexamethasone significantly reduces mortality in patients with severe COVID-19 who require supplemental oxygen.<sup>40</sup> Dexamethasone is a synthetic glucocorticoid with broad immunosuppressive properties, which downregulates the differentiation of B and T cells and inhibits the production of proinflammatory cytokines and chemokines.<sup>41</sup> Other agents targeting specifically IL-1 and IL-6 have become routinely used in the management of critical ill patients with COVID-19. Tocilizumab and sarilumab are IL-6 receptor blockers that have proven to be lifesaving in patients with COVID-19 who are severely or critically ill and are now recommended by the World Health Organization (WHO), especially when administered along with corticosteroids.<sup>42–44</sup> More recently, the European Medicines Agency (EMA) approved the use of anakinra, a recombinant IL-1 receptor antagonist (IL-1Ra), in patients with COVID-19 at increased risk of disease progression to respiratory failure identified by early elevation of soluble urokinase plasminogen activator receptor serum levels.<sup>45,46</sup> However, the use of immunosuppressants in older adults is associated with several adverse effects and can expose frail individuals to increased risk of secondary bacterial and fungal infection during hospitalization.<sup>47–49</sup>

In patients with long COVID, lifestyle interventions can effectively counteract chronic inflammation independent of underlying chronic conditions, and may therefore be proposed as strategies to mitigate long-term symptom persistence.<sup>50</sup> Physical activity and specific nutritional strategies may be especially suitable for older adults for

their potential of reducing inflammaging and supporting successful immune aging.<sup>50,51</sup> Indeed, regular physical activity has been associated with enhanced innate and adaptive immune functions, thereby attenuating mechanisms linked to immune-senescence.<sup>51,52</sup> Studies have shown that physical activity improves natural killer and neutrophil function, as well as T-cell proliferation.<sup>51,53</sup> Furthermore, aerobic physical exercise may induce cell death in apoptosis-resistance senescent T lymphocytes and increase the pool of naive T cells.<sup>53</sup> Notably, physical activity reduces the expression of toll-like receptors, transmembrane glycoproteins that initiate an immune response following recognition of DAMPs or other endogenous agents, with consequent reduced secretion of proinflammatory cytokines.<sup>51</sup> Furthermore, physical activity promotes the secretion of controlled levels of IL-6, which stimulates the production of immune-regulatory mediators such as IL-1ra, IL-8, and IL-10, thereby regulating the balance between proinflammatory and antiinflammatory factors and contributing to the immune homeostasis.<sup>54,55</sup> Similar to physical activity, dietary habits play an important role in shaping the immune system, and appropriate nutritional interventions have been shown to attenuate inflammation.<sup>51,56</sup> Proinflammatory diets characterized by insufficient consumption of fruits, vegetables, and whole grains, and excessive use of saturated fats, meat, processed foods, and refined sugars can induce a chronic increase in inflammatory cytokine levels even in younger adults.<sup>57</sup> In contrast, healthy eating patterns, such as the Mediterranean diet and vegetarian diets, may ameliorate the inflammatory process and oxidative stress, maintain gut microbial eubiosis, and decrease circulating levels of inflammatory biomarkers.<sup>56,58,59</sup> The New Dietary Strategies Addressing the Specific Needs of the Elderly Population for Healthy Aging in Europe” (NU-AGE) project has demonstrated the feasibility of a tailored Mediterranean-like dietary pattern, specifically designed to meet dietary needs of older adults aged 65 years old and older as a comprehensive dietary strategy to reduce inflammaging and improve health and quality of life in older adults.<sup>60</sup> Whether such an approach may help reduce the burden of symptom persistence in older COVID-19 survivors warrants exploration.

## SUMMARY

Inflammaging and SARS-CoV-2 infection interact in an interplay that involves both acute inflammation and low-grade chronic inflammation, predisposing older adults to severe COVID-19. During the acute phase, the precipitating factor is represented by an aberrant immune response characterized by the overproduction of proinflammatory cytokines. Increased cytokine levels may persist long after viral clearance and are potentially responsible for the installment of low-grade chronic inflammation and long-lasting persistence of COVID-19 symptoms. Therapeutic approaches targeting inflammation have proven to be effective in reducing mortality during an acute COVID-19 episode. However, at the time of writing, no standard treatment is available for the postacute phase. Although further research is needed, lifestyle interventions (physical activity and specific nutritional strategies) can effectively counteract chronic inflammation and may therefore be proposed as strategies to mitigate long-term symptom persistence.

## CLINICS CARE POINTS

- Inflammaging along with the abnormal inflammatory response to SARS-CoV-2 predisposes older adults to severe COVID-19.

- Targeting inflammation is key during the acute phase and reduces COVID-19 lethality.
- Behavioral interventions such as physical activity and optimal diet should be recommended to counteract symptom persistence following acute COVID-19.

## DISCLOSURE

The authors have nothing to disclose.

## REFERENCES

1. World Health Organization. WHO coronavirus (COVID-19) dashboard. Available at: <https://covid19.who.int/>. Accessed February 15 2022.
2. Sun P, Qie S, Liu Z, et al. Clinical characteristics of hospitalized patients with SARS-CoV-2 infection: a single arm meta-analysis. *J Med Virol* 2020;92:612–7.
3. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *JAMA* 2020;323:1775–6.
4. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708–20.
5. Du RH, Liang LR, Yang CQ, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. *Eur Respir J* 2020;55:2000524.
6. Wang L, He W, Yu X, et al. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. *J Infect* 2020;80:639–45.
7. Fajgenbaum DC, June CH. Cytokine storm. *N Engl J Med* 2020;383:2255–73.
8. Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. *Lancet Respir Med* 2020;8:e46–7.
9. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet* 2020;395:1771–8.
10. López-Otín C, Blasco MA, Partridge L, et al. The hallmarks of aging. *Cell* 2013;153:1194–217.
11. Franceschi C, Bonafè M, Valensin S, et al. Inflamm-aging: an evolutionary perspective on immunosenescence. *Ann N Y Acad Sci* 2000;908:244–54.
12. Pawelec G. Age and immunity: what is “immunosenescence”. *Exp Gerontol* 2018;105:4–9.
13. Oh SJ, Lee JK, Shin OS. Aging and the immune system: the impact of immunosenescence on viral infection, immunity and vaccine immunogenicity. *Immune Netw* 2019;19:e37.
14. Domingues R, Lippi A, Setz C, et al. SARS-CoV-2, immunosenescence and inflammaging: partners in the COVID-19 crime. *Aging (Albany NY)* 2020;12:18778–89.
15. Ferrucci L, Fabbri E. Inflammaging: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat Rev Cardiol* 2018;15:505–22.
16. Franceschi C, Garagnani P, Parini P, et al. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol* 2018;14:576–90.
17. Campisi J, D’Adda Di Fagagna F. Cellular senescence: when bad things happen to good cells. *Nat Rev Mol Cell Biol* 2007;8:729–40.

18. Picca A, Calvani R, Coelho-Junior HJ, et al. Cell death and inflammation: the role of mitochondria in health and disease. *Cells* 2021;10:537.
19. Biagi E, Candela M, Franceschi C, et al. The aging gut microbiota: new perspectives. *Ageing Res Rev* 2011;10:428–9.
20. Ragonnaud E, Biragyn A. Gut microbiota as the key controllers of “healthy” aging of elderly people. *Immun Ageing* 2021;18:2.
21. Maggio M, Guralnik JM, Longo DL, et al. Interleukin-6 in aging and chronic disease: a magnificent pathway. *J Gerontol A Biol Sci Med Sci* 2006;61:575–84.
22. Soysal P, Stubbs B, Lucato P, et al. Inflammation and frailty in the elderly: a systematic review and meta-analysis. *Ageing Res Rev* 2016;31:1–8.
23. Ferrucci L, Harris TB, Guralnik JM, et al. Serum IL-6 level and the development of disability in older persons. *J Am Geriatr Soc* 1999;47:639–46.
24. Franceschi C, Salvioli S, Garagnani P, et al. Immunobiography and the heterogeneity of immune responses in the elderly: a focus on inflammaging and trained immunity. *Front Immunol* 2017;8:982.
25. Gensous N, Bacalini MG, Pirazzini C, et al. The epigenetic landscape of age-related diseases: the geroscience perspective. *Biogerontology* 2017;18:549–59.
26. Müller L, Di Benedetto S. How immunosenescence and inflammaging may contribute to hyperinflammatory syndrome in COVID-19. *Int J Mol Sci* 2021;22:12539.
27. Tay MZ, Poh CM, Rénia L, et al. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020;20:363–74.
28. Mojtavavi H, Saghadzadeh A, Rezaei N. Interleukin-6 and severe COVID-19: a systematic review and meta-analysis. *Eur Cytokine Netw* 2020;31:44–9.
29. Bonafè M, Olivieri F, Cavallone L, et al. A gender-dependent genetic predisposition to produce high levels of IL-6 is detrimental for longevity. *Eur J Immunol* 2001; 31:2357–61.
30. Bektas A, Schurman SH, Franceschi C, et al. A public health perspective of aging: do hyper-inflammatory syndromes such as COVID-19, SARS, ARDS, cytokine storm syndrome, and post-ICU syndrome accelerate short- and long-term inflammaging? *Immun Ageing* 2020;17:23.
31. Kim Y, Bitna-Ha, Kim S-W, et al. Post-acute COVID-19 syndrome in patients after 12 months from COVID-19 infection in Korea. *BMC Infect Dis* 2022;22:93.
32. World Health Organization. Coronavirus disease (COVID-19): post COVID-19 condition. Available at: [https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-\(covid-19\)-post-covid-19-condition](https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-(covid-19)-post-covid-19-condition). Accessed 15 February 2022.
33. Carfi A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020;324:603–5.
34. Maltezou HC, Pavli A, Tsakris A. Post-COVID syndrome: an insight on its pathogenesis. *Vaccines* 2021;9:497.
35. Crook H, Raza S, Nowell J, et al. Long covid - mechanisms, risk factors, and management. *BMJ* 2021;374:n1648.
36. Rawal G, Yadav S, Kumar R. Post-intensive care syndrome: an overview. *J Transl Intern Med* 2017;5:90.
37. Wilson D, Jackson T, Sapey E, et al. Frailty and sarcopenia: the potential role of an aged immune system. *Ageing Res Rev* 2017;36:1–10.
38. Galea S, Merchant RM, Lurie N. The mental health consequences of COVID-19 and physical distancing: the need for prevention and early intervention. *JAMA Intern Med* 2020;180:817–8.



39. Gemelli Against COVID-19 Post-Acute Care Study Group. Post-COVID-19 global health strategies: the need for an interdisciplinary approach. *Aging Clin Exp Res* 2020;32:1613–20.
40. RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021;384:693–704.
41. Cain DW, Cidlowski JA. After 62 years of regulating immunity, dexamethasone meets COVID-19. *Nat Rev Immunol* 2020;20:587–8.
42. Lamontagne F, Agoritsas T, MacDonald H, et al. A living WHO guideline on drugs for covid-19. *BMJ* 2020;370:m3379.
43. Gupta S, Wang W, Hayek SS, et al. Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. *JAMA Intern Med* 2021;181:41–51.
44. World Health Organization. Therapeutics and COVID-19: living guidelines. Available at: <https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.1>. Accessed 15 February 2022.
45. Kyriazopoulou E, Poulakou G, Milionis H, et al. Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. *Nat Med* 2021;27:1752–60.
46. Huet T, Beauissier H, Voisin O, et al. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatol* 2020;2:e393–400.
47. Falcone M, Tiseo G, Giordano C, et al. Predictors of hospital-acquired bacterial and fungal superinfections in COVID-19: a prospective observational study. *J Antimicrob Chemother* 2020;76:1078–84.
48. Peng J, Fu M, Mei H, et al. Efficacy and secondary infection risk of tocilizumab, sarilumab and anakinra in COVID-19 patients: a systematic review and meta-analysis. *Rev Med Virol* 2021. <https://doi.org/10.1002/rmv.2295>.
49. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021;397:1637–45.
50. Woods JA, Hutchinson NT, Powers SK, et al. The COVID-19 pandemic and physical activity. *Sport Med Heal Sci* 2020;2:55–64.
51. Weyh C, Krüger K, Strasser B. Physical activity and diet shape the immune system during aging. *Nutrients* 2020;12:622.
52. Simpson RJ, Lowder TW, Spielmann G, et al. Exercise and the aging immune system. *Ageing Res Rev* 2012;11:404–20.
53. Tylutka A, Morawin B, Gramacki A, et al. Lifestyle exercise attenuates immunosenescence; flow cytometry analysis. *BMC Geriatr* 2021;21:200.
54. Scheller J, Chalaris A, Schmidt-Arras D, et al. The pro- and anti-inflammatory properties of the cytokine interleukin-6. *Biochim Biophys Acta* 2011;1813:878.
55. Starkie R, Ostrowski SR, Jauffred S, et al. Exercise and IL-6 infusion inhibit endotoxin-induced TNF-alpha production in humans. *FASEB J* 2003;17:884–6.
56. Santoro A, Pini E, Scurti M, et al. Combating inflammaging through a Mediterranean whole diet approach: the NU-AGE project's conceptual framework and design. *Mech Ageing Dev* 2014;136–7.
57. Cervo MMC, Scott D, Seibel MJ, et al. Proinflammatory diet increases circulating inflammatory biomarkers and falls risk in community-dwelling older men. *J Nutr* 2020;150:373–81.
58. Wawrzyniak-Gramacka E, Hertmanowska N, Tylutka A, et al. The association of anti-inflammatory diet ingredients and lifestyle exercise with inflammaging. *Nutrients* 2021;13:3696.

59. Haghghatdoost F, Bellissimo N, Totosy De Zepetnek JO, et al. Association of vegetarian diet with inflammatory biomarkers: a systematic review and meta-analysis of observational studies. *Public Health Nutr* 2017;20:2713–21.
60. Berendsen AAM, van de Rest O, Feskens EJM, et al. Changes in dietary intake and adherence to the NU-AGE diet following a one-year dietary intervention among European older adults—results of the NU-AGE randomized trial. *Nutrients* 2018;10:1905.