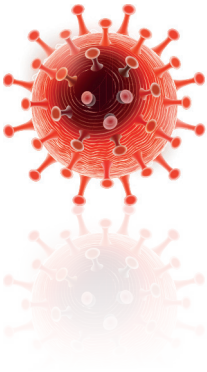

13. Bölüm

COVID-19 ve Romatoloji

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COVID enfeksiyonu SARS-CoV-2 virüsünün yaptığı klinik bir tablodur. Bu virüsün hızlıca tüm dünyaya yayılması nedeni ile 11 Mart 2020'de Dünya Sağlık Örgütü (DSÖ) tarafından pandemi ilan edilmiştir. Bunun üzerine yapılan birçok çalışma ile bu enfeksiyon açısından riskli popülasyonlar belirlenmeye çalışılmıştır. Şu an hala tüm riskli popülasyonlar belirlenemese de kazanılan deneyimle beraber bazı kesin risk faktörleri tespit edilmiştir. Bu risk faktörleri ileri yaş, obezite, kardiyovasküler hastalık varlığı, akciğer ve böbrek hastalıkları varlıklarıdır. (1)

Romatolojik hastalık varlığı ikincil enfeksiyonlar için risk faktörüdür(2). Romatolojik hastalık tedavisinde kullanılan hidroksiklorokin, metilprednizolon, IL 6 inhibitörü gibi ilaçlar COVID-19 enfeksiyon tedavisinde kullanıldığı da bilinmektedir (2, 3). Romatolojik hastalık tedavisinde kullanılan ilaçlar artmış enfeksiyon riski ile beraber olmasına rağmen bu ilaçların herhangibirinin artmış COVID-19 enfeksiyon riski veya komplikasyonu ile ilişkili olduğu saptanmamıştır (4, 5). Az sayıda yapılan gözlemsel çalışmalarda da veriler kafa karıştırıcıdır. Bir kısmı sistemik romatolojik hastalık tedavi alan hastalarda artmış COVID-19 enfeksiyon olduğu tespit edilmişken bir kısmında riskin aynı veya düşük olduğu gözlenmiştir (6, 7, 8, 9). 600 hastanın dahil olduğu bir çalışmada glukokortikoid ≥10mg/g kullanan hastaların hastane yatış oranının arttığı ve anti-TNF tedavi kullanımının hastaneye yatış riskini azalttığı saptanmış konvansiyonel hastalık modifiye edici tedaviler (DMARD), JAK inhibitörü ve non steroid anti-inflamatuar ilaç kullanımının hastaneye yatış riski ile ilişkili olmadığı gözlenmiştir (10).

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KAYNAKLAR

1. Reilev M, Kristensen KB, Pottega° rd A et al. Characteristics and predictors of hospitalization and death in the first 11 122 cases with a positive RT-PCR test for SARS-CoV-2 in Denmark: a nationwide cohort. Int J Epidemiol 2020;49:1468–81.
2. Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. Rheumatology 2013;52:53–61.
3. Lauper K, Bijlsma JWJ, Burmester GR. Trajectories of COVID-19 information in the Annals of the Rheumatic Diseases: the first months of the pandemic. Ann Rheum Dis 2021;80:26–5.
4. Atzeni F, Masala IF, di Franco M, Sarzi-Puttini P. Infections in rheumatoid arthritis. Curr Opin Rheumatol 2017; 29:323.
5. Sepriano A, Kerschbaumer A, Smolen JS, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2020; 79:760.
6. Haberman R, Axelrad J, Chen A, et al. COVID-19 in Immune-Mediated Inflammatory Diseases - Case Series from New York. N Engl J Med 2020; 383:85.
7. Bachiller-Corral J, Boteanu A, Garcia-Villanueva MJ, et al. Risk of severe coronavirus infection (COVID-19) in patients with inflammatory rheumatic diseases. J Rheumatol 2021.
8. Monti S, Balduzzi S, Delvino P, et al. Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. Ann Rheum Dis 2020; 79:667.
9. Conticini E, Bargagli E, Bardelli M, et al. COVID-19 pneumonia in a large cohort of patients treated with biological and targeted synthetic antirheumatic drugs. Ann Rheum Dis 2021; 80:e14.
10. Gianfrancesco M, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, Izadi Z, Jacobsohn L, Katz P, Lawson-Tovey S, Mateus EF, Rush S, Schmajuk G, Simard J, Strangfeld A, Trupin L, Wysham KD, Bhana S, Costello W, Grainger R, Hausmann JS, Liew JW, Sirotich E, Sufka P, Wallace ZS, Yazdany J, Machado PM, Robinson PC; COVID-19 Global Rheumatology Alliance. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis. 2020 Jul;79(7):859-866. doi: 10.1136/annrheumdis-2020-217871. Epub 2020 May 29. PMID: 32471903; PMCID: PMC7299648.
11. Mikuls TR. Co-morbidity in rheumatoid arthritis. Best Pract Res Clin Rheumatol 2003;17:729.
12. Nurmohamed MT, Heslinga M, Kitas GD. Cardiovascular comorbidity in rheumaticdiseases. Nat Rev Rheumatol 2015; 11:693.
13. Bichile T, Petri M. Prevention and management of co-morbidities in SLE. Presse Med2014; 43:e187.
14. Perez-Chada LM, Merola JF. Comorbidities associated with psoriatic arthritis: Review andupdate. Clin Immunol 2020; 214:108397.
15. Burner TW, Rosenthal AK. Diabetes and rheumatic diseases. Curr Opin Rheumatol 2009; 21:50.
16. Queiro R, Lorenzo A, Tejón P, et al. Obesity in psoriatic arthritis: Comparative prevalenceand associated factors. Medicine (Baltimore) 2019; 98:e16400.
17. Panoulas VF, Metsios GS, Pace AV, et al. Hypertension in rheumatoid arthritis. Rheumatology (Oxford) 2008; 47:1286.
18. Gianfrancesco M, Yazdany J, Robinson PC. Epidemiology and outcomes of novelcoronavirus 2019 in patients with immune-mediated inflammatory diseases. Curr OpinRheumatol 2020; 32:434.
19. People Who Need to Take Extra Precautions. https://www.cdc.gov/coronavirus/2019- ncov/need-extra-precautions/index.html. Page last reviewed: June 2, 2020.

20. Who's at higher risk from coronavirus. UK National Health service. 2020. https://www.nhs.uk/conditions/coronavirus-COVID-19/people-at-higher-risk-from-coronavirus/whos-at-higher-risk-from-coronavirus/. Accessed 25 Apr 2020
21. Ren YR, Golding A, Sorbello A, ji P, Chen j, Bhawana S,et al. A Comprehensive updated Review on SARS-CoV-2 and COVID-19. J Clin Pharmacol. 2020;10.1002/jcph.1673.
22. Lai CC, Shih TP, Ko wC et al. Severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int j Antimicrob Agents. 2020;55:105924.
23. Mao L, jin H, wang m, Hu Y, Chen S, He Q, Chang j, Hong C, zhou Y, wang D, miao X, Li Y, Hu B. Neurologic manifestations of Hospitalized Patients with Coronavirus Disease 2019 in wuhan, China. jAmA Neurol .2020 Apr 10;77(6):1-9.
24. Guan wj, Ni zY, Hu Y et al. Clinical characteristics of Coronavirus Disease 2019 in China. N Engl j med. 2020. doi: 10.1056/NEjmoa2002032.
25. Lippi G, Plebani m, michael B. Thrombocytopenia Is Associated with Severe Coronavirus Disease 2019 (COVID-19) Infections: A meta-Analysis. Clin Chim Acta. 2020;506:145-8.
26. Qin C, zhou L, Hu z, zhang S, Yang S, Tao Y, et al. Dysregulation of Immune Response in Patients with COVID-19 in wuhan, China. Clin Infect Dis. 2020;ciaa248.
27. Ackermann m, Verleden SE, Kuehnel m, Haverich A, welte T, Laenger F, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in COVID-19. N Engl j med. 2020 may 21. doi: 10.1056/NEjmoa2015432
28. Abobaker A, Raba AA, Alzwi A. Extrapulmonary and Atypical Clinical Presentations of COVID-19. j med Virol. 2020 jun 10.
29. Parry AH, wani AH, Yaseen m. Acute mesenteric Ischemia in Severe Coronavirus-19 (COVID-19): Possible mechanisms and Diagnostic Pathway. Acad Radiol. 2020;S1076-6332(20)30292-0.
30. Richardson s, et al. "Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area." Jama (2020).
31. Wu j, wu X, zeng w, et al. Chest CT Findings in Patients with Corona Virus Disease 2019 and its Relationship with Clinical Features. Invest Radiol. 2020.
32. Gomez-Arbelaez D, Ibarra-Sanchez G, Garcia- Gutierrez A, Comanges-Yeboles A, Ansuategui-Vicente m, Gonzalez-Fajardo jA. COVID-19-Related Aortic Thrombosis: A Report Of Four Cases. Ann Vasc Surg. 2020;S0890-5096(20)30438-6.
33. Jin-jin Z, et al. "Clinical characteristics of 140 patients infected with sARs_CoV_2 in Wuhan, China." Allergy (2020).
34. COVID, C. D. C., et al. "Preliminary estimates of the prevalence of selected underlying health conditions among patients with coronavirus disease 2019-United states, February 12- March 28, 2020." Morbidity and Mortality Weekly Report. 2020;69 (13) :382.
35. Wang B, et al. "Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis." Aging (Albany NY) 2020;12(7):6049.
36. Tinku J, Moslehi MA. "International Pulmologists Consensus on COVID19." (2020).
37. Simonnet, Arthur, et al. "High prevalence ofobesity in severe acute respiratory syndrome coronavirus_2 (sARs_CoV_2) requiring invasive mechanical ventilation." Obesity (2020).
38. Jia, Xiaodong, et al. "Two things about COVID-19 might need attention." (2020).
39. Mikuls TR, Johnson SR, Fraenkel L, Arasaratnam RJ, Baden LR, Bermas BL, et al. American College of Rheumatology Guidance for the Management of Rheumatic Disease in Adult Patients During the COVID-19 Pandemic: Version 2. Arthritis Rheumatol. 2020.
40. Special Expert Group for Control of the Epidemic of Novel Coronavirus Pneu- monia of the Chinese Preventive Medicine Association An update on the epi- demiological characteristics of novel coronavirus pneumonia (COVID-19). *Chin J Epidemiol* 2020:41.
41. Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. *Seminars Immunopathol* 2017; 39 (5):517–28 2017/07/01 .

42. Channappanavar R, Fehr AR, Vijay R , Mack M , Zhao J , Meyerholz DK , et al. Dys- regulated Type I Interferon and inflammatory monocyte-macrophage re- sponses cause lethal pneumonia in SARS-CoV-Infected Mice. *Cell Host Microbe* 2016; 19 (2):181–93 PubMed PMID: 26867177. Eng.
43. Davidson S, Maini MK, Wack A . Disease-promoting effects of type I interferons in viral, bacterial, and coinfections. *J Interf Cytokine Res Offic J Int Soc Interf Cy- tokine Res* 2015; 35 (4):252–64 PubMed PMID: 25714109. Epub 2015/02/25. Eng.
44. Shaw AC, Goldstein DR, Montgomery RR. Age-dependent dysregulation of innate immunity. *Nature Rev Immunol* 2013; 13 (12):875–87 PubMed PMID: 24157572. Epub 2013/10/25. Eng.
45. Law HKW, Cheung CY, Ng HY, Sia SF, Chan YO, Luk W, et al. Chemokine up-reg- ulation in SARS-coronavirus-infected, monocyte-derived human dendritic cells. *Blood* 2005; 106 (7):2366–74 PubMed PMID: 15860669. Epub 2005/04/28. Eng.
46. Cheung CY, Poon LLM, Ng IHY, Luk W, Sia S-F, Wu MHS, et al. Cy- tokine responses in severe acute respiratory syndrome coronavirus-in- fected macrophages in vitro: possible relevance to pathogenesis. *J Virol* 2005; 79 (12):7819–26 PubMed PMID: 15919935. Eng .
47. Lau SKP, Lau CCY, Chan K-H, Li CPY, Chen H, Jin D-Y, et al. Delayed induc- tion of proinflammatory cytokines and suppression of innate antiviral response by the novel Middle East respiratory syndrome coronavirus: implications for pathogenesis and treatment. *J Gen Virol* 2013; 94 (Pt 12):2679–90 PubMed PMID: 24077366. Epub 2013/09/28. Eng.
48. R C, AR F, J Z, C W-L, JE A, M M, et al. IFN-I response timing relative to virus replication determines MERS coronavirus infection outcomes. *J Clin Invest* 2019; 130 :3625–39 PubMed PMID: 31355779 .
49. Herold S, Steinmueller M, von Wulffen W , Cakarova L , Pinto R , Pleschka S , et al. Lung epithelial apoptosis in influenza virus pneumonia: the role of macrophage-expressed TNF-related apoptosis-inducing ligand. *J Exper Med* 2008; 205 (13):3065–77 PubMed PMID: 19064696. Epub 2008/12/08. Eng.
50. Högner K, WolffT, Pleschka S, Plog S, Gruber AD, Kalinke U, et al. Macrophage–expressed IFN- βcontributes to apoptotic alveolar epithelial cell injury in se- vere influenza virus pneumonia. *PLoS Pathogens* 2013; 9 (2) e1003188-e. PubMed PMID: 23468627. Epub 2013/02/28. Eng.
51. Rodrigue-Gervais IG, LabbéK, Dagenais M, Dupaul-Chicoine J, Champagne C, Morizot A, et al. Cellular inhibitor of apoptosis protein cIAP2 protects against pulmonary tissue necrosis during influenza virus infection to promote host sur- vival. *Cell Host Microbe* 2014; 15 (1):23–35 PubMed PMID: 24439895. Eng.
52. Chen L, Liu H-G, Liu W, Liu J, Liu K, Shang J, et al. Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia. *Chin J Tuberc Respir Dis* 2020; 43
53. ForceTADT Acute respiratory distress syndrome: the berlin definition. *JAMA* 2012; 307 (23):2526–33.
54. Parsons PE, Eisner MD, Thompson BT, Matthay MA, Ancukiewicz M, Bernard GR, et al. Lower tidal volume ventilation and plasma cytokine markers of inflam- mation in patients with acute lung injury. *Critical Care Med* 2005; 33 (1):1–232 PubMed PMID: 15644641. Eng .
55. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med* 2006; 3 (9) e343-e. PubMed PMID: 16968120. Eng.
56. Arabi YM, Shalhoub S, Mandourah Y, Al-Hameed F, Al-Omari A, Al Qasim E, et al. Ribavirin and interferon therapy for critically ill patients with middle east respiratory syndrome: a multicenter observational study. *Clinical Infect Diseas Offic Publ Infect Diseases Soc Am* 2019 ciz544. PubMed PMID: 31925415. Eng.
57. Falzarano D, de Wit E, Rasmussen AL, Feldmann F, Okumura A, Scott DP, et al. Treatment with interferon- α2b and ribavirin improves outcome in MERS–CoV-infected rhesus macaques. *Nature Med* 2013; 19 (10):1313–17 PubMed PMID: 24013700. Epub 2013/09/08. Eng.

58. Omrani AS, Saad MM, Baig K, Bahloul A, Abdul-Matin M, Alaidaroos AY, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syn- drome coronavirus infection: a retrospective cohort study. *Lancet Inf Diseases* 2014; 14 (11):1090–5 PubMed PMID: 25278221. Epub 2014/09/29. Eng.
59. Davidson S, McCabe TM, Crotta S, Gad HH, Hessel EM, Beinke S, et al. IFN λis a potent anti-influenza therapeutic without the inflammatory side effects of IFN αtreatment. *EMBO Molecul Med* 2016; 8 (9):1099–112 PubMed PMID: 27520969. Eng.
60. Blazek K, Eames HL, Weiss M, Byrne AJ, Perocheau D, Pease JE, et al. IFN- λresolves inflammation via suppression of neutrophil infiltration and IL-1 βproduction. *J Exper Med* 2015; 212 (6):845–53 PubMed PMID: 25941255. Epub 2015/05/04. Eng.
61. Zumla A, Chan JFW, Azhar EI, Hui DSC, Yuen K-Y. Coronaviruses —drug dis- covery and therapeutic options. *Nature Rev Drug Discov* 2016; 15 (5):327–47 2016/05/01
62. Auyeung TW, Lee JSW, Lai WK, Choi CH, Lee HK, Lee JS, et al. The use of cor- ticosteroid as treatment in SARS was associated with adverse outcomes: a ret- rospective cohort study. *J Infect* 2005; 51 (2):98–102 PubMed PMID: 16038758. Eng.
63. Ho JC, Ooi GC, Mok TY, Chan JW, Hung I, Lam B, et al. High-dose pulse ver- sus nonpulse corticosteroid regimens in severe acute respiratory syndrome. *Am J Resp Crit Care Med* 2003; 16 8 (12):144 9–56 PubMed PMID: 12947028. Epub 2003/08/28. Eng.
64. Yam LY-C, Lau AC-W, Lai FY-L, Shung E, Chan J, Wong V, et al. Corticos- teroid treatment of severe acute respiratory syndrome in Hong Kong. *J Infect* 2007; 54 (1):28–39 PubMed PMID: 16542729. Epub 2006/03/15. Eng.
65. Chen R-c, Tang X-p, Tan S-y, Liang B-l, Wan Z-y, Fang J-q , et al. Treatment of Severe Acute Respiratory Syndrome With Glucosteroids: The Guangzhou Expe- rience. *Chest* 2006; 129 (6):1441–52 2006/06/01/ .
66. Zhao J-p, Hu Y, Du R-h, Chen Z-s, Jin Y, Zhou M, et al. Expert consensus on the use of corticosteroid in patients with 2019-nCoV pneumonia. *Chin J Tuberc Respir Dis* 2020(00) E007-E. Chi.
67. Zhou Y-H, Qin Y-Y, Lu Y-Q, Sun F, Yang S, Harypursat V, et al. Effectiveness of glucocorticoid therapy in patients with severe novel coronavirus pneumonia: protocol of a randomized controlled trial. *Chin Med J* 2020(00) E020-E. Chi.
68. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clini- cal characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; 395 (10223):507–13 2020/02/15.
69. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, Stemmler HJ, Schlößer HA, Schlaak M, et al. Cytokine release syndrome. *J ImmunoTherapy Cancer* 2018; 6 (1):56 2018/06/15.
70. Shakoory B, Carcillo JA, Chatham WW, Amdur RL, Zhao H, Dinarello CA, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior phase III trial. *Critical Care Med* 2016; 44 (2):275–81 PubMed PMID: 26584195. Eng.
71. Biggioggero M, Crotti C, Becciolini A, Favalli EG. Tocilizumab in the treatment of rheumatoid arthritis: an evidence-based review and patient selection. *Drug Design, Devel Therapy* 2018; 13: 57–70 PubMed PMID: 30587928. Eng.
72. Tanaka T, Narazaki M, Kishimoto T. Immunotherapeutic implications of IL-6 blockade for cytokine storm. *Immunotherapy* 2016; 8 (8):959–70 PubMed PMID: 27381687. Eng
73. Qiu P, Cui X, Sun J, Welsh J, Natanson C, Eichacker PQ. Antitumor necrosis factor therapy is associated with improved survival in clinical sepsis trials: a meta–analysis. *Critical Care Med* 2013; 41 (10):2419–29 PubMed PMID: 23887234. Eng.
74. McDermott JE, Mitchell HD, Gralinski LE, Eisfeld AJ, Josset L, Bankhead A, et al. The effect of inhibition of PP1 and TNF αsignaling on pathogenesis of SARS coronavirus. *BMC Syst Biol* 2016; 10 (1):93 -. PubMed PMID: 27663205. Eng.

75. J G, Z T, X Y. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends* 2020; 14 (1):72–3 PubMed PMID: 32074550.
76. Mahevas M, Tran V-T, Roumier M, Chabrol A, Paule R, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial. medrxiv. 2020.
77. Yeh KM, Chiueh Ts, siu L, Lin jC, Chan PK, et al. Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital. Journal of Antimicrobial Chemotherapy. 2005;56(5):919-22.
78. Ko j-H, seok H, Cho sY, Ha YE, Baek jY, et al. Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. Antiviral therapy. 2018;23(7):617-22.
79. H W, B L,Y T, P C , L Y , B H , et al. Improvement of sepsis prognosis by Ulinas- tatin: a systematic review and meta-analysis of randomized controlled trials. *Frontiers Pharmacol* 2019; 10:1370 PubMed PMID: 31849646
80. Maceyka M, Harikumar KB, Milstien S, Spiegel S. Sphingosine-1-phosphate sig- naling and its role in disease. *Trends Cell Biol* 2012; 22 (1):50–60 PubMed PMID: 22001186. Epub 2011/10/14. eng.
81. Walsh KB, Teijaro JR, Rosen H, Oldstone MBA. Quelling the storm: utilization of sphingosine-1-phosphate receptor signaling to ameliorate influenza virus-in- duced cytokine storm. *Immunol Res* 2011; 51 (1):15 2011/09/08.
82. Teijaro JR, Walsh KB, Cahalan S, Fremgen DM, Roberts E, Scott F, et al. Endothe- lial cells are central orchestrators of cytokine amplification during influenza virus infection. *Cell* 2011; 146 (6):980–91 PubMed PMID: 21925319. Eng.
83. Uccelli A, de Rosbo NK. The immunomodulatory function of mesenchymal stem cells: mode of action and pathways. *Ann NY Acad Sci* 2015; 1351 (1):114–26.
84. Ben-Mordechai T, Palevski D, Glucksam-Galnoy Y, Elron-Gross I, Margalit R, Leor J. Targeting macrophage subsets for infarct repair. *J Cardiovascular Phar- macol Therapeut* 2014; 20 (1):36–51 2015/01/01 .
85. Lee JW, Fang X, Krasnodembskaya A, Howard JP, Matthay MA. Concise review: Mesenchymal stem cells for acute lung injury: role of paracrine soluble factors. *STEM CELLS* 2011; 29 (6):913–19.
86. K X, H C, Y S, Q N, Y C, S H, et al. Management of corona virus dis- ease-19 (COVID-19): the Zhejiang experience. *Zhejiang da xue xue bao Yi xue ban* 2020; 49 (1):0 PubMed PMID: 32096367.
87. Schrezenmeier E, Dörner T (2020) Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat Rev Rheumatol 16:155–166. https://doi.org/10.1038/s41584-020-0372-x
88 Page F. Treatment of lupus erythematosus with mepacrine. Lancet 1951;2:755–8.
89. Wallace DJ. Antimalarial drugs in the treatment of rheumatic diseases, 2020. Available: https://www.uptodate.com/contents/antimalarial-drugs-in-the-treatment-ofrheumatic-disease?search=hydroxychloroquine&source=search_result&selectedTitle=2~148&usage_type=-default&display_rank=1#H7
90. Abdulaziz N, Shah AR, McCune WJ. Hydroxychloroquine: balancing the need to maintain therapeutic levels with ocular safety: an update. Curr Opin Rheumatol 2018;30:249–55.
91. Taylor WRJ, White NJ. Antimalarial drug toxicity: a review. Drug Saf 2004;27:25–61.
92. 7 Ben-Zvi I, Kivity S, Langevitz P, et al. Hydroxychloroquine: from malaria to autoimmunity. Clinic Rev Allerg Immunol 2011;42.
93. Sperber K, Quraishi H, Kalb TH, et al. Selective regulation of cytokine secretion by hydroxychloroquine: inhibition of interleukin 1 alpha (IL-1-alpha) and IL-6 in human monocytes and T cells. J Rheumatol 1993;20:803–8.

94. Löffler BM, Bohn E, Hesse B, et al. Effects of antimalarial drugs on phospholipase A and lysophospholipase activities in plasma membrane, mitochondrial, microsomal and cytosolic subcellular fractions of rat liver. Biochim Biophys Acta 1985;835:448–55.
95. Lester RS, Burnham TK, Fine G, et al. Immunologic concepts of light reactions in lupus erythematosus and polymorphous light eruptions. I. The mechanism of action of hydroxychloroquine. Arch Dermatol 1967;96:1–10.
96. Cohen SN, Yielding KL. Spectrophotometric studies of the interaction of chloroquine with deoxyribonucleic acid. J Biol Chem 1965;240:3123–31.
97. Shukla AM, Wagle Shukla A, Shukla AW. Expanding horizons for clinical applications of chloroquine, hydroxychloroquine, and related structural analogues. Drugs Context 2019;8:2019-9-1.
98. van den Borne BE, Dijkmans BA, de Rooij HH, et al. Chloroquine and hydroxychloroquine equally affect tumor necrosis factor-alpha, interleukin 6, and interferon-gamma production by peripheral blood mononuclear cells. J Rheumatol 1997;24:55–60.
99. Li R, Lin H, Ye Y, et al. Attenuation of antimalarial agent hydroxychloroquine on TNF-α-induced endothelial inflammation. Int Immunopharmacol 2018;63:261–9.
100. Savarino A, Boelaert JR, Cassone A, et al. Effects of chloroquine on viral infections: an old drug against today's diseases? Lancet Infect Dis 2003;3:722–7.
101. Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J 2005;2:69.
102. Kwiek JJ, Haystead TAJ, Rudolph J. Kinetic mechanism of quinone oxidoreductase 2 and its inhibition by the antimalarial quinolines. Biochemistry 2004;43:4538–47.
103. Savarino A, Di Trani L, Donatelli I, et al. New insights into the antiviral effects of chloroquine. Lancet Infect Dis 2006;6:67–9.
104. Gao J, Tian Z, Yang X (2020) Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 14:72–73. https://doi.org/10.5582/bst.2020.01047
105. Multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia (2020) Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi Zhonghua Jiehe He Huxi Zazhi Chin J Tuberc Respir Dis 43:185–188. https://doi.org/10. 3760/cma.j.issn.1001-0939.2020.03.009
106. Efficacy of hydroxychloroquine in patientswith COVID-19: results of a randomized clinical trial | medRxiv. https://www.medrxiv.org/ content/10.1101/2020.03.22.20040758v2. Accessed 7 Apr 2020
107. Gautret P, Lagier J-C, Parola P et al (2020) Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an openlabel non-randomized clinical trial. Int J Antimicrob Agents 105949. https://doi.org/10.1016/j.ijantimicag.2020.105949
108. Hulme OJ, Wagenmakers E-J, Damkier P et al (2020) Reply to Gautret et al. 2020: a Bayesian reanalysis of the effects of hydroxychloroquine and azithromycin on viral carriage in patients with COVID-19 medRxiv 2020.03.31.20048777. https://doi.org/ 10.1101/2020.03.31.20048777
109. Tang W, Cao Z, Han M, et al (2020) Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial. medRxiv 2020.04.10.20060558. https://doi.org/10.1101/2020.04. 10.20060558
110. Elavarasi A, Prasad M, Seth T, Sahoo RK, Madan K, Nischal N, Soneja M, Sharma A, Maulik SK, Shalimar, Garg P. Chloroquine and Hydroxychloroquine for the Treatment of COVID-19: a Systematic Review and Meta-analysis. J Gen Intern Med. 2020 Nov;35(11):3308-3314. doi: 10.1007/s11606-020-06146-w. Epub 2020 Sep 3. PMID: 32885373; PMCID: PMC7471562..
111. Fiolet T, Guihur A, Rebeaud ME, Mulot M, Peiffer-Smadja N, Mahamat-Saleh Y. Effect of hydroxychloroquine with or without azithromycin on the mortality of coronavirus disease

2019 (COVID-19) patients: a systematic review and meta-analysis. Clin Microbiol Infect. 2021 Jan;27(1):19-27. doi: 10.1016/j.cmi.2020.08.022. Epub 2020 Aug 26. PMID: 32860962; PMCID: PMC7449662.
112. Mitja O, Corbacho-Monne M, Ubals M, et al. Hydroxychloroquine for early treatment of adults with mild COVID-19: a randomized-controlled trial. Clin Infect Dis. 2020.
113. Remdesivir EUA letter of authorization. [updated 2020 May 1; cited 2020 Jul 19]. Available from: https://www.fda.gov/media/137564/ download
114. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19 - preliminary report. N Engl J Med. 2020. DOI:10.1056/NEJMoa2007764
115. Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, Skipper CP, Nascene AA, Nicol MR, Abassi M, Engen NW, Cheng MP, LaBar D, Lother SA, MacKenzie LJ, Drobot G, Marten N, Zarychanski R, Kelly LE, Schwartz IS, McDonald EG, Rajasingham R, Lee TC, Hullsiek KH. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for COVID-19. N Engl J Med. 2020 Aug 6;383(6):517-525. doi: 10.1056/NEJMoa2016638. Epub 2020 Jun 3. PMID: 32492293; PMCID: PMC7289276.
116. Mitjà O, Corbacho-Monné M, Ubals M, Alemany A, Suñer C, Tebé C, Tobias A, Peñafiel J, Ballana E, Pérez CA, Admella P, Riera-Martí N, Laporte P, Mitjà J, Clua M, Bertran L, Sarquella M, Gavilán S, Ara J, Argimon JM, Cuatrecasas G, Cañadas P, Elizalde-Torrent A, Fabregat R, Farré M, Forcada A, Flores-Mateo G, López C, Muntada E, Nadal N, Narejos S, Nieto A, Prat N, Puig J, Quiñones C, Ramírez-Viaplana F, Reyes-Urueña J, Riveira-Muñoz E, Ruiz L, Sanz S, Sentís A, Sierra A, Velasco C, Vivanco-Hidalgo RM, Zamora J, Casabona J, Vall-Mayans M, González-Beiras C, Clotet B; BCN-PEP-CoV2 Research Group. A Cluster-Randomized Trial of Hydroxychloroquine for Prevention of COVID-19. N Engl J Med. 2021 Feb 4;384(5):417-427. doi: 10.1056/NEJMoa2021801. Epub 2020 Nov 24. PMID: 33289973; PMCID: PMC7722693.
117. Blumentals WA, Arreglado A, Napalkov P, Toovey S. Rheumatoid arthritis and the incidence of influenza and influenza-related complications: a retrospective cohort study. BMC Musculoskelet Disord 2012;13:158.
118. Accortt NA, Lesperance T, Liu M, Rebello S, Trivedi M, Li Y, et al. Impact of sustained remission on the risk of serious infection in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken) 2018;70:679–84.
119. Favalli EG, Ingegnoli F, Lucia OD, Cincinelli G, Cimaz R, Caporali R. COVID-19 infection and rheumatoid arthritis: faraway, so close [review]! Autoimmun Rev 2020;19:102523.
120. Landewé RB, Machado PM, Kroon F, Bijlsma HW, Burmester GR, Carmona L, Combe B, Galli M, Gossec L, Iagnocco A, Isaacs JD, Mariette X, McInnes I, Mueller-Ladner U, Openshaw P, Smolen JS, Stamm TA, Wiek D, Schulze-Koops H. EULAR provisional recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2. Ann Rheum Dis. 2020 Jul;79(7):851-858. doi: 10.1136/annrheumdis-2020-217877. Epub 2020 Jun 5. PMID: 32503854.
121. Curtis JR, Johnson SR, Anthony DD, Arasaratnam RJ, Baden LR, Bass AR, Calabrese C, Gravallese EM, Harpaz R, Kroger A, Sadun RE, Turner AS, Anderson Williams E, Mikuls TR. American College of Rheumatology Guidance for COVID-19 Vaccination in Patients with Rheumatic and Musculoskeletal Diseases - Version 1. Arthritis Rheumatol. 2021 Mar 17. doi: 10.1002/art.41734. Epub ahead of print. PMID: 33728796.