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REVIEW ARTICLE

The Risk of Latent Tuberculosis Reactivation in COVID-19 Therapy

Risiko Reaktivasi Tuberkulosis Laten pada Terapi COVID-19

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ABSTRACT

The high mortality rate among COVID-19 patients in the acute respiratory distress syndrome (ARDS) phase led to the administration of immunosuppressive drugs. Corticosteroids could block inflammation caused by cytokine storm, and prevent pneumonia, edema, fibrosis, and ARDS. Even though it was believed to have beneficial effects, corticosteroids can suppress T CD4+ and CD8+ cell-mediated immunity reaction through decreased IFNγ production thus leading to reactivation of latent Tuberculosis (LTBI). Therefore, the usage of corticosteroids in the ARDS phase of COVID-19 patients should be carefully given; pre-screening of LTBI may be done to avoid Tuberculosis reactivation.

Keywords: COVID-19, corticosteroid, immunosuppressant, LTBI, TB reactivation.

ABSTRAK

Kematian yang tinggi pada pasien COVID-19 pada fase acute respiratory distress syndrome (ARDS) dapat dicegah dengan pemberian obat imunosupresif. Kortikosteroid sebagai salah satu obat imunosupresif dapat memblokir peradangan yang disebabkan oleh badai sitokin dan mencegah terbentuknya pneumonia, edema, fibrosis, dan ARDS pada kasus COVID-19 parah. Walaupun demikian, mekanisme kerja kortikosteroid dengan menurunkan produksi IFNγ dan menekan produksi sel T CD4+ dan CD8+ menimbulkan risiko terjadinya reaktivasi Tuberkulosis laten (LTBI) pada pasien. Oleh karena itu, penggunaan kortikosteroid pada pasien COVID-19 berat perlu diperhatikan dan uji pre-skrining terhadap status infeksi laten tuberculosis pada pasien dapat direkomendasikan untuk mencegah terjadinya reasktivasi Tb.

Kata kunci: COVID-19, kortikosteroid, imunosupresan, LTBI, reaktivasi TB.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the cause of COVID-19 infection.[1,2] The virus attacks the respiratory system, causing respiratory disorders, from light to chronic lung infections, and even death. Indonesia was one of the countries affected by COVID-19, with an extremely high number of cases. It was recorded that in the middle of August 2021, the average number of cases may reached 27.704 cases a week.[3]

Immunosuppressive drugs are common medical treatments used to treat COVID-19 patients, which are believed to have beneficial effects in the ARDS (Acute Respiratory Distress Syndrome) phase in COVID-19 patients. However, the use of immunosuppressive drugs may increase the risk of reactivation or new *M. tuberculosis* infection.[4]

Tuberculosis (TB) is an infectious disease and one of the 10 causes of death in the world.[5–7] The number of TB cases in Indonesia reached approximately one million cases per year.[8] Indonesia was reported to be the country with the third highest TB cases, after India and China.[9]

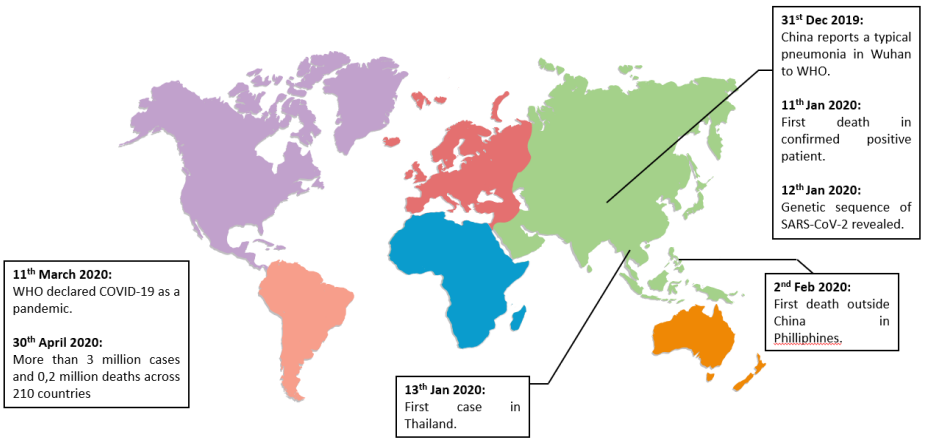
TB is primarily caused by *Mycobacterium tuberculosis* which attacks the lungs (pulmonary TB) but can also attack other body parts (extrapulmonary TB). TB is transmitted when the patients release the bacteria into the air, for example by coughing.[6] Clinical manifestations resulting from this can be active or latent lesions.[10]

Latent Tuberculosis Infection (LTBI) is a condition where a person is infected by *M. tuberculosis* but does not have any clinical symptoms as in TB patients.[10] It was approximated that one-third of the world's population has latent TB. In terms of reactivation, patients with LTBI might have around a 5-10% chance of bearing the lifetime risk of reactivation. Moreover, most patients may develop TB in the first five years, not long after the initial infection.[11]

In the COVID-19 pandemic period, the risk of reactivation of latent TB increased, due to the weakened immunity caused by SARS CoV-2 infection and the use of immunosuppression drugs to treat COVID-19 patients with ARDS.

The Epidemiology of COVID-19

In early December 2019, the COVID-19 epidemic occurred and spread widely from Wuhan to many countries outside of China.[1] On January 13, 2020, Bangkok became the first country outside



of China to have a COVID-19 case detected. Furthermore, it was reported that on March 2, 2020, there were 8,565 COVID-19 cases with 132 deaths in 67 countries outside of China. In addition, there was a significant transmission in several countries around the world, for example in Iran and Italy. Due to its major transmission and infection, COVID-19 was immediately declared a global pandemic. It was announced by WHO on March 11, 2020.[2]

Figure 1. COVID-19 Epidemiology Timeline.

The Characteristics of SARS-CoV-2

SARS-CoV-2, a virus belonging to the family Coronaviridae, causes Coronavirus disease 2019 (COVID-19). The coronavirus particles are round, with 80-160 nm in diameter. Coronavirus is composed of spike protein (S), membrane protein (M), and envelope protein (E). Inside the envelope, there is a genomic RNA and phosphorylated nucleocapsid protein (N), forming a spiral nucleocapsid.[12]

The coronavirus genome is composed of single-stranded positive-sense RNA, with 26-32 Kb length, has a 5' cap structure, 3' polyadenylate tail structure, and six open reading frames (ORF), where ORF 1 is located near the 5' terminus which encodes 16 non-structural proteins (nsp 1-16) involved in viral replication, while other ORF encodes four major structural proteins (S, M, N, and P protein), and eight accessory proteins (3a, 3b, p6, 7a, 7b, 8b, 9b, and ORF14) which hold an important role in viral assembly process.[12]

The Pathogenesis of COVID-19

SARS-CoV-2 passes through the mucous membrane, such as nasal mucous membranes or larynx. Through the respiratory tract, the virus enters the lungs. It then attacks the target organs, such as the lungs, the heart, renal system, and the gastrointestinal tract which express angiotensin converting 2 enzymes (ACE2). Its ability to enter the target cells is influenced by TMPRSS2.[2]

The COVID-19 incubation period is between 3-14 days. This period is marked by normal or a slightly decreased lymphocyte and leukocyte count. Furthermore, the patients will not have experienced any symptoms yet. After this incubation period, through the blood vessels, the virus will spread to organs that express ACE 2, and the patients will experience mild symptoms. Their condition will worsen in four to seven days after early symptoms appear, marked by low

lymphocyte count, worsened lung lesions, and dyspnea. Acute Respiratory Distress Syndrome (ARDS) occurs when this phase cannot be controlled.[2,13]

Through RIG-I-like receptors, NOD-like receptors, and TLR, RNA virus can be detected by the innate immunity system. This will induce interferon (IFN) production, and make $CD8^+$ cells, NK cells, and macrophages appear as antiviral receptors. In COVID-19 cases, delayed secretion of cytokines and chemokines by innate immunity cells is the result of non-structural protein blockade from the virus. This condition causes an increase in the number of chemokines and pro-inflammatory cytokines (IL-8, IL-6, IL-1β-, TNF-α, CCL2, CCL5, MCP-1, and IFN) through lymphocytes and macrophages activation. This cytokine release activates adaptive immune cells simultaneously, for example, T cells, neutrophils, and NK cells, by the continuous production of pro-inflammatory cytokines. The rise in the number of pro-inflammatory cytokines causes inflammation infiltration by the lung tissues, leading to epithelial and endothelial damage. This can cause ARDS and many organ failures which leads to instantaneous death.[2]

In asymptomatic infections, there is no specific incubation due to the absence of clinical signs. However, detected viral load in an asymptomatic population, similar to those found in symptomatic patients, shows that asymptomatic infection has the potential to transmit virus in initial infection.[14]

COVID-19 Therapy with Corticosteroid

The high severity level of COVID-19 is caused by hyper-inflammation, marked by immune dysregulation, cytokine storm or cytokine release, and pro-inflammatory chemokines related to Th-1, including IL-1β, IL-6, TNF-α, IFN-γ, monocyte chemoattractant protein-1 (MCP-1) and CXCL10.[15,16]

The ARDS phase is the result of the host's overactive immune response, known as cytokine storm. Research conducted by Monreal and the team showed that immunosuppressed COVID-19 patients or those with autoimmune disease (AD) significantly had a smaller chance of developing into ARDS.[17] Thus the consideration of immunosuppressive drugs may be beneficial in this COVID-19 ARDS phase.[15]

Corticosteroid (CST) has many anti-inflammation and immunomodulatory effects, such as inhibiting pro-inflammatory cytokines, inducing T-lymphocyte apoptosis, and, reducing leukocyte migration.[17,18] Therapy using CST can block inflammation caused by cytokine storm and prevent pneumonia, edema, fibrosis, and ARDS from developing in severe COVID-19 cases.[19]

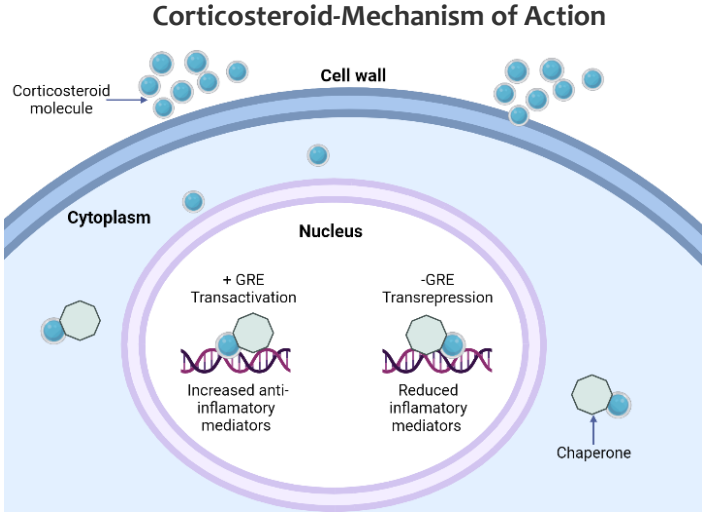


Figure 2. Mechanism of action of corticosteroid.

Corticosteroid works on numerous cells, specifically on immune cells.[20] CST molecules will pass the host's cell membranes and bind with glucocorticoid receptor (GR), leading to conformational changes in the receptors. The GR-CST complex will then translocate to the nucleus. In the nucleus, the GR-CST complex experiences dimerization and binding with Glucocorticoid Response Elements (GRE).[19,21] GRE associates with genes that suppress or stimulate transcription, producing ribonucleic and protein synthesis, where each of them is called transrepression and transactivation. Finally, the agents hinder the transcription factors involved in pro-inflammatory mediator synthesis, such as macrophages, eosinophils, lymphocytes, mast cells, and dendritic cells. In addition, phospholipase A2, which was involved in the production of multiple inflammatory mediators, will be inhibited.[21]

The Epidemiology of Tuberculosis

Tuberculosis (TB) is not only infectious, but also it is fatal, as it entered the top 10 list of global causes of death, following ischemic heart disease, stroke, chronic obstructive pulmonary disease, lower pulmonary tract infection, Alzheimer and other dementia diseases, tracheal cancer, bronchial and pulmonary diseases, mellitus diabetes, walking injury, and diarrhea.[5–7] While in Indonesia, TB cases reached approximately one million cases per year.[8] Indonesia was reported to be the country with the third highest TB cases, after India and China.[9]

Specifically, tuberculosis agents are transmitted through mucous droplets which are suspended in the air. Tubercle bacilli can live for 8 weeks on smooth aerosol particles. In addition, there are some factors affecting people's vulnerability to tuberculosis, for instance, malnutrition, weak immune system, lung injury, and genetic factors.[22]

The Characteristics of *Mycobacterium tuberculosis*

M. tuberculosis is a bacterium that belongs to the family of Mycobacteriaceae, from the phylum Actinobacteria. Actinobacteria have a high guanine and cytokines content on their DNA. Moreover, they are one of the biggest bacterial phyla, spreading in various ecosystems, both in aquatic and terrestrial ecosystems. *Mycobacterium* is closely related to other pathogenic bacteria, such as *Corynebacterium, Nocardia, Propionibacterium,* and *Tropheryma*, all belong to the phylum Actinobacteria. [23–25]

M. tuberculosis is a rod-shaped and acid-resistant bacteria. *Mycobacterium's* acid-resistant ability comes from its high lipid content. It has a complex layered structure, and not only contains wax but also contains mycolic acid in its high lipid content. Thus, *Mycobacterium* can survive desiccation and germicide.[22]

The Pathogenesis of Tuberculosis

TB infection can occur when a person inhales droplet nuclei containing tubercle bacilli which then reach the alveoli. In 2-8 weeks, the tubercle bacilli will be digested by the macrophages and are commonly destroyed, while some of them will reproduce intracellularly. And then, when the macrophages are going to be released, the remaining bacilli will spread to deeper tissues and organs through the blood vessels or the lymphatic channels.[10]

The macrophages that have been infected will release cytokines and chemokines, attracting other phagocytes, including monocytes, neutrophils, and other alveolar macrophages which then form a nodular granulomatous structure known as a tubercle. If the bacterial replication is uncontrolled, the tubercle will grow, and the bacilli enter the local lymph nodes. This causes lymphadenopathy, the typical clinical manifestation of primary TB. The expansion of the tubercle into the lungs parenchyma and lymph node involvement will result in a lesion named Ghon complex. Bacteremia may accompany primary infection.[26]

Bacilli will continuously reproduce until an effective cell-mediated immunity response develops, usually two to six weeks after infection. The host's failure to overcome effective cell-mediated immunity response and tissue repair causes the lungs to experience progressive damage. Tumour Necrosis Factor (TNF)-alpha, reactive oxygen and nitrogen intermediates, and cytotoxic compounds (granzyme and perforin) may be involved in the development of caseous necrosis which is characteristic of tuberculosis lesion.[26]

Latent Tuberculosis Infection (LTBI) is a condition where *M. tuberculosis* is detected in the body of a person who does not suffer from TBC. LTBI starts when extracellular bacilli are digested by macrophages and presented to other white blood cells. That will stimulate the immune response, in which the white blood cells will kill a large number of bacilli, and lead to the process of granuloma formation. In this state, LTBI has been formed. Tuberculin Skin Test (TST) or Interferon-Gamma Release Assay (IGRA) can be taken to detect LTBI.[10]

In LTBI patients, TB bacteria will be inactive for a lifetime without causing any diseases. However, it is different for people with immune system disorders or those who have anti-TNFα antibody or corticosteroid medical treatment. It can cause reactivation of LTBI, reactivate and make the bacteria reproduce, causing TBC disease.[10,19]

Table 1. The Differences between an Individual with LTBI and an Individual with Active TB, According to CDC, 2019. [10]

An Individual with LTBI	An Individual with Active TB
Some TB bacteria inside the body, living but under control	There are TB bacteria inside the body
Does not transmit TB bacteria to other	Can possibly transmit TB bacteria to others Can possibly feel sick, and start to show symptoms. Such as cough, fever and weight loss
Asymptomatic, the bacteria turn active inside the body	
The result of a Tuberculin Skin Test (TST) or Interferon-Gamma Release Assay (IGRA) is usually positive	The result of Tuberculin Skin Test (TST) or Interferon-Gamma Release Assay (IGRA) is usually positive
Sputum smear and culture is positive	Sputum smear and culture is possibly positive
Does not need isolation	Need isolation

The Risk of Reactivation of Latent Tuberculosis by Corticosteroid

M. tuberculosis which infects the lungs of a person with weak protective immunity will cause active TB, while a person with strong immunity will cause LTBI. In an immunosuppressed host, corticosteroids may turn reactivation of LTBI into symptomatic or active TB. Coinfection between SARS-CoV-2 and *M. tuberculosis* causes the host's protective immunity deteriorate, leading to worsened active TB. Moreover, SARS-CoV-2 infection in LTBI cases will turn reactivation into active TB.[19]

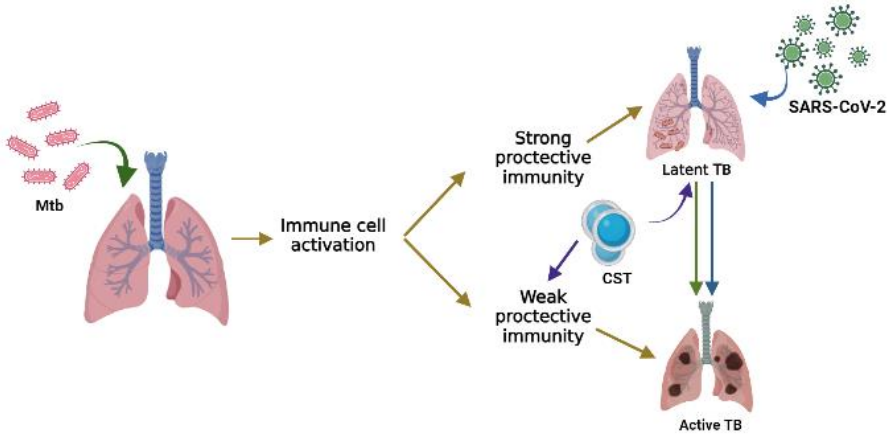


Figure 3. Effects of corticosteroids on *M. tuberculosis* infection.

Although immunosuppressive drugs are administered in limited amounts to COVID-19 patients with ARDS, they still have disadvantageous effects, for example, reactivation of TB both in the pandemic and post-pandemic period. (4) COVID-19 therapy using corticosteroids will surely cause the suppression of the host's immunity system, leading to the acceleration of active TB pathology, and in LTBI cases will cause reactivation.[19]

When *M. tuberculosis* infection occurs, the roles of innate immunity cells, such as signaling pathways and cellular functions are important in preventing the disease from developing, and function as potential regulators of antigen-specific adaptive immunity. Adaptive immunity cells determine the balance between protective immune response and pathogen on TB. Pattern recognition receptors (PRR) and cellular functions are the host's immunity cells which mainly contribute to protecting innate immune cells from *M. tuberculosis*. Innate immune cells (macrophages, dendritic cells, neutrophils, and NK cells) will recognize *M. tuberculosis* through PRRs, such as Toll-Like Receptors (TLR1, TLR2, TLR4, TLR7, TLR8, and TLR9), Nod-like Receptors (NOD1, NOD2, NLRP3, and NLRC4) and C-Type Lectin Receptors (MR, DC-SIGN, Mincle, Dectin-1 and Dectin-2, Dectin-3, CL-LK and DCIR). The host coordinates the signals from PRR and releases various cellular functions during TB infection, such as phagocytosis, autophagy, apoptosis, and inflammasome, so that *M. tuberculosis* can be controlled or removed.[27] As described previously, the use of CST as immunosuppression will inhibit the transcription factors involved in the synthesis of proinflammatory mediators, such as macrophages, eosinophils, lymphocytes, mast cells, and dendritic cells.[21] CST may cause reactivation will increase the risk of reactivation of TB due to the suppression of cell-mediated immunity and IFNγ production. Decreased production of

IFNγ causes T $CD4^+$ and $CD8^+$ count decline.[28,29] Based on research conducted in China, the prevalence of TB in COVID-19 patients ranged between 0,46%-4.47%, while patients with severe COVID-19 had a higher prevalence (1,47% vs 0,59%).[30]

CONCLUSION

The high severity level of COVID-19 was caused by hyper-inflammation, marked by immune dysregulation and cytokine storm or cytokine release, and pro-inflammatory chemokines. Corticosteroids had many anti-inflammatory and immunomodulatory effects, such as inhibiting pro-inflammatory cytokines, inducing T-lymphocyte apoptosis, and reducing leukocyte migration.

Corticosteroid (CST) therapy could lead to inflammation caused by blocked cytokine storm, and prevent pneumonia, edema, fibrosis, and ARDS from developing in severe COVID-19 cases. It was because CST could block transcription factors involved in the synthesis of pro-inflammatory mediators, such as macrophages, eosinophils, lymphocytes, mast cells, and, dendritic cells.

However, the use of immunosuppressive drugs on COVID-19 patients with ARDS might lead to reactivation of TB, since the cell-mediated immunity and IFNγ production were suppressed. Decreased production of IFNγ caused T $CD4^+$ and $CD8^+$ count decline. Thus, the risk of immunosuppression and reactivation of LTBI needed more attention in CST therapy, such as having LTBI screening before or along with COVID-19 screening and recording the patients' exposure history to *M. tuberculosis* in clinical tests that involved CST. This strategy will help manage TB and COVID-19 cases better.

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AUTHORS CONTRIBUTION

Idea owner of this literature review: GM. Abas, F. Sjatha; writing and submitting a manuscript: GM. Abas; editing and approval of final draft: GM. Abas, F. Sjatha, Y. Rosana.

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CONFLICT OF INTEREST

All authors declared no conflicts of interest.

REFERENCES

1. Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases from the Chinese Center for Disease Control and Prevention. JAMA - J Am Med Assoc. 2020;323(13):1239–42.
2. Di Gennaro F, Pizzol D, Marotta C, et al. Coronavirus diseases (COVID-19) current status and future perspectives: A narrative review. Int J Environ Res Public Health. 2020;17(8).

3. Johns Hopkins University Center for Systems Science and Engineering. COVID-19 Data Repository by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University [Internet]. CSSEGISandData / COVID-19. 2021. Available from: https://github.com/CSSEGISandData/COVID-19
4. Visca D, Ong CWM, Tiberi S, et al. Tuberculosis and COVID-19 interaction: A review of biological, clinical and public health effects. Pulmonology. 2021;27(2):151–65.
5. World Health Organization. Global Tuberculosis Report 2018 [Internet]. 2018. Available from: https://apps.who.int/iris/handle/10665/274453
6. World Health Organization. Global Tuberculosis Report 2020 [Internet]. 2020. Available from: https://apps.who.int/iris/bitstream/handle/10665/336069/9789240013131-eng.pdf
7. Susilawati TN, Larasati R. A recent update of the diagnostic methods for tuberculosis and their applicability in indonesia: A narrative review. Med J Indones. 2019;28(3):284–91.
8. Amin M, Yanti B, Harapan H, et al. The role of Mycobacterium tuberculosis lineages on lung tissue damage and TNF-α level among tuberculosis patients, Indonesia. Clin Epidemiol Glob Heal. 2019;7(3):263–7. https://doi.org/10.1016/j.cegh.2018.11.002
9. World Health Organization. WHO global lists of high burden countries for tuberculosis (TB), TB / HIV and TB (MDR / RR-TB). 2021;2021–5. Available from: http://apps.who.int/bookorders.%0Ahttps://cdn.who.int/media/docs/default-source/hq-tuberculosis/who_globalhbcliststb_2021-2025_backgrounddocument.pdf
10. Centers for Disease Control and Prevention. Transmission and Pathogenesis of Tuberculosis [Internet]. Atlanta: Centers for Disease Control and Prevention; 2019. Available from: https://www.cdc.gov/tb/education/ssmodules/pdfs/module1.pdf
11. World Health Organization. Latent tuberculosis infection. The End TB Strategy [Internet]. 2015 Nov; Available from: http://www.who.int/tb/challenges/ltbi_factsheet_2014.pdf
12. Yang Y, Xiao Z, Ye K, et al. SARS-CoV-2: characteristics and current advances in research. Virol J. 2020;17(1):1–17.
13. Ayres JS. A metabolic handbook for the COVID-19 pandemic. Nat Metab. 2020;2(7):572–85. http://dx.doi.org/10.1038/s42255-020-0237-2
14. Gao Z, Xu Y, Sun C, et al. A systematic review of asymptomatic infections with COVID-19. J Microbiol Immunol Infect. 2021;54(1):12–6.
15. Monreal E, Sainz de la Maza S, Fernández-Velasco JI, et al. The Impact of Immunosuppression and Autoimmune Disease on Severe Outcomes in Patients Hospitalized with COVID-19. J Clin Immunol. 2021;41(2):315–23.
16. Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The experience of clinical immunologists from China. Clin Immunol. 2020;214:108393. https://doi.org/10.1016/j.clim.2020.108393
17. Schoot TS, Kerckhoffs APM, Hilbrands LB, et al. Immunosuppressive Drugs and COVID-19: A Review. Front Pharmacol. 2020;11.
18. Lansbury L, Rodrigo C, Leonardi-Bee J, et al. Corticosteroids as adjunctive therapy in the treatment of influenza. Cochrane Database Syst Rev. 2019;2019(2).
19. Gopalaswamy R, Subbian S. Corticosteroids for covid-19 therapy: Potential implications on tuberculosis. Int J Mol Sci. 2021;22(7).
20. Liberman AC, Budziñski ML, Sokn C, et al. Regulatory and mechanistic actions of glucocorticoids on T and inflammatory cells. Front Endocrinol (Lausanne). 2018;9:1–14.
21. Williams DM. Clinical pharmacology of corticosteroids. Respir Care. 2018;63(6):655–70.
22. Talaro KP. Foundation in Microbiolgy. 10th ed. New York: McGraw-Hill Education; 2018.
23. Barka EA, Vatsa P, Sanchez L, et al. Taxonomy, Physiology, and Natural Products of Actinobacteria. Microbiol Mol Biol Rev.2016;80(1):1–43.
24. Sharma NC, Efstratiou A, Mokrousov I, et al. Diphtheria. Nat Rev Dis Prim. 2019;5(1).

25. Bernard K. The Genus Corynebacterium☆. In: Reference Module in Biomedical Sciences [Internet]. Elsevier; 2016. Available from: https://www.sciencedirect.com/science/article/pii/B9780128012383992006
26. Serafino RL, Med T. Tuberculosis 2: Pathophysiology and microbiology of pulmonary tuberculosis. South Sudan Med J. 2013;6(1):10–2.
27. Liu CH, Liu H, Ge B. Innate immunity in tuberculosis : host defense vs pathogen evasion. Nat Publ Gr. 2017;14(12):963–75. http://dx.doi.org/10.1038/cmi.2017.88
28. Garg N, Lee YI. Reactivatiom TB With Severe COVID-19. Chest. 2020;158(4).
29. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. J Clin Invest. 2020;130(5):2620–9.
30. Gao Y, Liu M, Chen Y, et al. Association between tuberculosis and COVID-19 severity and mortality: A rapid systematic review and meta-analysis. J Med Virol. 2021;93(1):194–6.