Review Article

The Immunologic Basis of COVID-19: a Clinical Approach

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Abstract

The novel severe acute respiratory syndrome coronavirus (SARS-CoV2) has leaded to a global infection and a pandemic afterwards. This pandemic is one of the greatest global challenges for the health system. In this review, the immunologic basis of the human body response after infection with SARS-CoV2 has been reviewed with discussions on both innate and adaptive immunity. Due to the relatively short time after appearance of the problem, the currently available evidence exclusively dealing with SARS-CoV2 and the disease, coronavirus diseases 2019 (COVID-19) are scant; especially in the field of cellular and molecular medicine; however, previous studies especially focusing on SARS-CoV and MERS are available. At the final part of the manuscript, involvement of the main human organs with COVID-19 is briefed.

Keywords: SARS-CoV2, COVID-19, immunologic response, innate immunity, adaptive immunity

Please cite this article as: Rajaei S, Dabbagh A. The immunologic basis of COVID-19: a clinical approach. J Cell Mol Anesth. 2020;5(1):37-42.

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Introduction

Coronavirus disease 2019 (COVID-19) has appeared since December, 2019, is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) (1, 2). This pandemic outbreak has challenged not only the global health care system but also the majority of life aspects all over the world.

How could human being fix the problem? An exact and vivid understanding of the viral effects on the body and the human responses would be undoubtedly among the first steps of finding a solution.

How does the human body interact with the SARS-CoV2? Here we discuss the response of the immune system towards SARS-CoV2 infection. In general, two types of intermingled immune responses are reported to be involved during any viral infection including, SARS-CoV2 infection; innate and adaptive immunity.

We first discuss the innate immune response and then the adaptive one. Throughout the text, the author should remember that due to the novelty of SARS-CoV2 in the world, many of the studies, both in vivo and in vitro, are related to the two other members of the *Coronaviridae* family, SARS-CoV and Middle East respiratory syndrome (MERS-CoV), which caused known epidemics in the world throughout two recent decades. However, there are studies directly related to SARS-CoV2.

The study proposal was assessed and approved by Research Ethics Committee, Tehran University of Medical Sciences, Tehran, Iran; coded: IR.TUMS.VCR.REC.1399.155.

Mechanism of viral entry to the human body

SARS-CoV2 binds to Angiotensin converting enzyme 2 (ACE2) through spike (S) glycoproteins and enters to the host cells by endocytosis. S glycoprotein is composed of two components, S1 and S2, the first one is responsible for attachment of the virus to ACE2 and the latter induces fusion of viral body with the target cell membrane (3). In SARS-CoV2, a furin cleavage site is existed between S1 and S2. This area is unique to SARS-CoV2 and is not presented in earlier pathogenic members of the *coronaviridae* family (3). In addition, priming of S protein by a serine protease, named TMPRSS2, is obligatory for entrance of the virus into target cells (4). ACE2 presents in many tissues; however, surface protein expression is more restricted to lung alveolar epithelial cells and enterocytes of small intestine (5, 6); viral attachment to ACE2 would ultimately result in respiratory and gastrointestinal symptoms. On the other hand, ACE2 inactivates angiotensin II and functions as a vasodilator. In a controversial finding in mice models, ACE2 could protect mice from acute respiratory distress syndrome (ARDS) (7). Similar protective roles for ACE2 were proposed for COVID-19 indeed (8).

Innate immune responses against Coronaviruses

Viruses could invade to different types of immune and non-immune cells in the upper and the lower respiratory tract. Pattern recognition receptors (PRRs) in cytosol or endosomal membranes of infected cells sense viral nucleic acids and initiate signaling pathways; a gate keeping process that mainly results in production of type 1 interferons (IFN-α and β) (9).

Retinoid-inducible gene (RIG) like receptors (RLRs) are the main members of PRRs; they recognize cytosolic viral RNA and trigger antiviral responses. RIG1 detects RNA molecules with triphosphate groups at 5′ end. On the other hand, melanoma differentiation-associated gene 5 (MDA5) identifies longer temporary viral double stranded RNAs (dsRNAs) formed in cytosol during replication of RNA viruses. TLR3 and TLR7, which are endosomal membrane receptors, could be involved in recognition of dsRNA, which are produced throughout viral replication, and single stranded RNA (ssRNA) of coronaviruses, respectively. Following recognition of viral RNA by these PRRs, other adaptor molecules will be recruited; finally resulting in transcription of nuclear factor κB (NF-κB) and interferon regulatory protein 3 (IRF3) which in turn induce production of pro-inflammatory cytokines and type I interferons (9-11), as a protective innate immune response in initial phase of viral infection.

Pneumocyte type II as the main target of SARS-CoV2 has essential role in innate immunity by providing barrier effect and sensing the pathogen and inducing production of anti-viral cytokines (12, 13).

Uptake of SARS-CoV by dendritic cells (DCs) has been shown by electron microscopy in vitro. It seems that the process is not mediated by ACE2 and other molecules involved in virus entry to cells. Coronaviruses are replicated inside DCs; although this replication seems to be incomplete. Replication of virus in immature DCs, does not induce maturation or apoptosis of these cells. SARS-CoV infected DCs produce lower amount of anti-viral cytokines e.g. IFNs and IL-12, while moderate amount of tumor necrosis factor α (TNF- α) and IL-6 and higher amount of chemokines (14). On the other hand, Cheung et al confirmed that monocyte derived macrophages can fetch SARS-CoV in vitro. Transcription of virus genes, and thereafter synthesis of viral proteins begin inside the macrophages; however, this process halts and complete virus is not produced finally. At the same time, production of chemokines, including interferon gamma-induced protein 10 (IP-10) and monocyte chemoattractant protein 1 (MCP1), was upregulated while synthesis of IFN-β was decreased (15). Based on the above evidences, SARS-CoV triggers chemokine production while prevents interferon production; this leads to more accumulation and recruitment of the immune cells in situ.

Plasmacytoid dendritic cells are the main source of interferon type 1 (IFN-α and β), in contrast to conventional dendritic cells which are not able to produce large amount of type 1 interferons upon contamination with SARS-CoV (16, 17). These interferons induce different interferon stimulated genes (ISGs) which in turn ensue to anti-proliferative and antiviral state (16).

Virus Evade mechanisms from innate immunity

The initial response against viruses is mediated by production of type 1 interferons; meanwhile, previous studies have shown that coronaviruses could bypass both production and function of these interferons by at least three IFN-I antagonists, including open reading

frame (ORF)3b, ORF6 and nucleocapsid proteins (N proteins) (18). In addition, ORF6 has the ability to antagonize transportation of STAT1 to the nucleus and in this way, inhibits host antiviral responses (19). It was shown that coronaviruses escape from being recognized by cytosolic PRRs through creation of double membrane vesicles, where replication of virus happens (20). In addition, viral nucleocapsid proteins can interfere with ubiquitination and therefore activation of RIG1 (21). In spite of all these diverse evasion mechanisms of SARS-CoV, plasmacytoid dendritic cells as the main sources of type 1 interferons provide anti-viral immunity (17, 22-24).

Adaptive immune responses against Coronaviruses

For long-lasting immunity, adaptive immune responses are mandatory. Specific T and B-lymphocytes mediate acquired immunity. Like other viral infections, cytotoxic T lymphocytes (CTLs) seem to play an important role in elimination of infected cells. Zhou et al. identified a decameric epitope of S protein which could be presented by HLA-A*0201 and stimulate IFN-γ production by CTLs (25). A delayed and disturbed T cell response has been reported in SARS-CoV infections, which could be related to disrupted competency of DCs in processing and presenting antigens to T lymphocytes. In addition, abundant IFN type I production could induce apoptosis of T cells (26). Peng et al. demonstrated persistence of memory CD4+ and CD8+ T cells two years after recovery of SARS-CoV infected patients. These memory cells were specific for a nucleocapsid protein epitope. The authors suggested that some epitopes of N proteins could be presented more frequently by antigen presenting cells and thus and consequently are able to induce more robust T cell responses. However, these epitopes are not necessarily the ones that stimulate strong B cell responses (27). Also, Zhao et al. emphasized on importance of T cell responses in clearance of SARS-CoV and confirmed that insufficient T cell responses could play a significant role in pathogenesis of ARDS (28).

Antibodies as the main product of B lymphocytes play an important role in neutralizing corona viruses; however, this neutralizing role is not inclusive for all human antibodies produced in response to the virus; in other words, a specific profile of produced antibodies could work as neutralizing agents against the virus. The role of CD4+ T cells is essential for creation of these antibodies (29).

Antibodies presented in convalescent plasma of COVID-19 patients are able to decrease the titer of virus in critically ill patients, even to undetectable amounts. This seems to be related to the presence of neutralizing antibodies in plasma of recovered patients (30). These beneficial effects were reported previously in studies regarding SARS-CoV and MERS-CoV (31-34). Neutralizing antibodies need to act against nucleocapsid and spike proteins. These antibodies begin to be produced nearly ten days after symptom onset and are composed of IgM (mainly in the initial phase); after a while, these antibodies are predominantly converted to IgG (35, 36).

The antibodies work by several different mechanisms. Some of them can function as neutralizing antibodies which prevent attachment of the virus to its receptor on the target tissues; however, some others can opsonize the virus and facilitate its elimination by phagocytes, induce the recruitment of other immune cells or collaborate in deposition and activation of complement components (37). Whichever of these mechanisms is involved in omitting the virus, it should be considered that antibody production requires the assistance of CD4+ helper T cells.

Host HLA type play an important role in presenting viral protein antigens and shaping the immune responses (38). Recognition of immune-dominant epitopes of SARS-CoV2 by techniques such as epitope mapping seems to be an important part of vaccine development (39, 40).

Role of cytokines in pathogenesis of COVID-19

Large amount of cytokines are produced and released by different types of infiltrated immune cells in respiratory tract upon viral infection. Huang et al. reported higher amount of Interleukin (IL)2, IL7, IL10, Granulocyte-colony stimulating factor (GCSF), IP10, MCP1, macrophage inflammatory protein 1 (MIP1) and TNF-α in Covid-19 patients who were admitted to ICU compared to non-admitted ones (41).

Although these cytokines are released initially as a defense response, uncontrolled production and release of the cytokines, which is known as cytokine storm, finally lead to a severe proinflammatory condition in critically ill patients (38).

A summary of COVID-19 main organ involvement

Pulmonary involvement

The pathologic findings in lungs during COVID-19 are much similar to SARS and MERS and include a combination of the following findings (42-44):

- pulmonary edema and hyaline membrane formation (early stages of ARDS)
- proliferation and enlargement of pneumocytes associated with amphophilic granular pattern in the cytoplasm and enlarged nucleoli indicating cytopathic pneumocyte changes which finally lead to desquamation of pneumocytes into the alveoli (later stages of ARDS)
- diffuse and bilateral alveolar injury and fibroid cellular exudates in alveoli with accumulation of mononuclear inflammatory infiltrates, dominated by lymphocytes added with myriads of type II pneumocytes and clustering of CD68-positive macrophages in the alveolar spaces
- interstitial infiltration of mononuclear cells especially lymphocytes (mostly CD3-positive and CD20-negative)

Cardiovascular involvement

The underlying inflammatory nature of COVID-19 has direct detrimental effects on the cardiovascular system; not only because of the immune system disturbances and inflammatory responses but also due to the abundancy of ACE2 in the cardiovascular system; on the other hand, underlying cardiovascular disease is an important mortality risk factor in COVID-19 patients (45). Add to the above the finding that myocardial damage due to SARS-CoV2 is among the challenging pathologic features of the disease; which could be seriously associated with widespread damage to the myocardial tissue. In the latter patients, often the serum levels of "high-sensitivity cardiac troponin I" and "Creatine-Kinase-MB: CK-MB" surged dramatically. Even though, a minority of COVID-19 patients may be involved with cardiovascular problems as their presenting illness. However, in COVID-19 patients with underlying heart failure, hypertension, or myocardial infarction, ACE inhibitors should not be abstained (46-48).

Renal involvement

ACE2 is expressed on kidney cells and acute kidney injury was reported as a comorbidity in COVID-19. Despite previous studies that have not been able to show the presence and replication of SARS-CoV directly in the kidney cells (49), novel SARS-CoV2 has been found in kidney tubular cells and was able to induce acute tubular damage (50). In addition, kidney could be involved during cytokine storm. Dialysis in patients with chronic kidney disease could demonstrate beneficial effects in reduction of lung inflammation (51). In a recent study, it was shown that COVID-19 is not a provoking factor for acute kidney injury (52); however, other study contrary indicated worsening of acute kidney injury during hospitalization in Covid-19 admitted patients (53) .

Gastrointestinal involvement

Gastrointestinal symptoms were reported in COVID-19 cases including anorexia, nausea, vomiting and diarrhea (54, 55). SARS-CoV2 RNA was reported in stool specimens; Also ACE2 was highly expressed on the surface of enterocytes (5). These evidences implicate active replication of virus in gastrointestinal epithelial cells (56).

Neurological involvement

ACE2 is expressed on the surface of neurons and glial cells. Two ways were proposed for CNS involvement with SARS-CoV2; first by systemic distribution of virus and the second one, by local transmission through ethmoidal bone. The circulatory virus can attach to ACE2 on the surface of capillary endothelial cells and enter the cells. Following viral egression, endothelial cells would be damaged and this causes accessibility of virus to the brain which contain numerous neurons with ACE2. The direct arrival of virus through cribriform plate might result in disturbed sense of smell (57). Different symptoms of central and also, peripheral nervous system have been reported in COVID-19 patients (58). Furthermore it was reported that SARS-CoV2 has the potential to engage respiratory center in brain stem which may lead to respiratory failure in patients with COVID-19 (59).

Conclusion

Overall, corona virus infections could involve both innate and adaptive immune responses. While in initial phases of the infection, production of type 1 interferons play more important role in defense against the virus, long-lasting immunity needs the activation of

adaptive immunity, through production of neutralizing antibodies by B lymphocytes with the assistance of T cells. Providing this type of immunity is essential in vaccine development.

Acknowledgment

This study was supported by Tehran University of Medical Sciences (TUMS); Grant No 99-1-101-47441.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

References

1. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579(7798):265-9.
2. Chen Y, Li L. SARS-CoV-2: virus dynamics and host response. Lancet Infect Dis. 2020.
3. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell. 2020.
4. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020.
5. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631-7.
6. Roncati L, Gallo G, Manenti A, Palmieri B. Renin-angiotensin system: The unexpected flaw inside the human immune system revealed by SARS-CoV-2. Med Hypotheses. 2020;140:109686.
7. Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature. 2005;436(7047):112-6.
8. Cheng H, Wang Y, Wang GQ. Organ-protective Effect of Angiotensin-converting Enzyme 2 and its Effect on the Prognosis of COVID-19. J Med Virol. 2020.
9. Goubau D, Deddouche S, Reis e Sousa C. Cytosolic sensing of viruses. Immunity. 2013;38(5):855-69.
10. Totura AL, Whitmore A, Agnihothram S, Schafer A, Katze MG, Heise MT, et al. Toll-Like Receptor 3 Signaling via TRIF Contributes to a Protective Innate Immune Response to Severe Acute Respiratory Syndrome Coronavirus Infection. mBio. 2015;6(3):e00638-15.
11. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res. 2020;7(1):11.
12. Iwasaki A, Foxman EF, Molony RD. Early local immune defences in the respiratory tract. Nat Rev Immunol. 2017;17(1):7-20.
13. Leiva-Juárez MM, Kolls JK, Evans SE. Lung epithelial cells: therapeutically inducible effectors of antimicrobial defense. Mucosal Immunol. 2018;11(1):21-34.
14. Law HK, Cheung CY, Ng HY, Sia SF, Chan YO, Luk W, et al. Chemokine up-regulation in SARS-coronavirus-infected, monocyte-derived human dendritic cells. Blood. 2005;106(7):2366-74.
15. Cheung CY, Poon LL, Ng IH, Luk W, Sia SF, Wu MH, et al. Cytokine responses in severe acute respiratory syndrome coronavirus-infected macrophages in vitro: possible relevance to pathogenesis. J Virol. 2005;79(12):7819-26.
16. Thiel V, Weber F. Interferon and cytokine responses to SARS-coronavirus infection. Cytokine Growth Factor Rev. 2008;19(2):121-32.
17. Cervantes-Barragan L, Zust R, Weber F, Spiegel M, Lang KS, Akira S, et al. Control of coronavirus infection through plasmacytoid dendritic-cell-derived type I interferon. Blood. 2007;109(3):1131-7.
18. Kopecky-Bromberg SA, Martínez-Sobrido L, Frieman M, Baric RA, Palese P. Severe Acute Respiratory Syndrome Coronavirus Open Reading Frame (ORF) 3b, ORF 6, and Nucleocapsid Proteins Function as Interferon Antagonists. J Virol. 2007;81(2):548.
19. Frieman M, Yount B, Heise M, Kopecky-Bromberg SA, Palese P, Baric RS. SARS-CoV ORF6 Antagonizes STAT1 Function by Sequestering Nuclear Import Factors on the rER/Golgi Membrane. J Virol. 2007.
20. Knoops K, Kikkert M, Worm SH, Zevenhoven-Dobbe JC, van der Meer Y, Koster AJ, et al. SARS-coronavirus replication is supported by a reticulovesicular network of modified endoplasmic reticulum. PLoS Biol. 2008;6(9):e226.
21. Hu Y, Li W, Gao T, Cui Y, Jin Y, Li P, et al. The Severe Acute Respiratory Syndrome Coronavirus Nucleocapsid Inhibits Type I Interferon Production by Interfering with TRIM25-Mediated RIG-I Ubiquitination. J Virol. 2017;91(8).
22. Scheuplein VA, Seifried J, Malczyk AH, Miller L, Höcker L, Vergara-Alert J, et al. High Secretion of Interferons by Human Plasmacytoid Dendritic Cells upon Recognition of Middle East Respiratory Syndrome Coronavirus. J Virol. 2015;89(7):3859.
23. Frieman M, Heise M, Baric R. SARS coronavirus and innate immunity. Virus Res. 2008;133(1):101-12.
24. Enjuanes L, Zuniga S, Castano-Rodriguez C, Gutierrez-Alvarez J, Canton J, Sola I. Molecular Basis of Coronavirus Virulence and Vaccine Development. Adv Virus Res. 2016;96:245-86.
25. Zhou M, Xu D, Li X, Li H, Shan M, Tang J, et al. Screening and identification of severe acute respiratory syndrome-associated coronavirus-specific CTL epitopes. J Immunol. 2006;177(4):2138-45.
26. Channappanavar R, Zhao J, Perlman S. T cell-mediated immune response to respiratory coronaviruses. Immunol Res. 2014;59(1-3):118-28.
27. Peng H, Yang LT, Wang LY, Li J, Huang J, Lu ZQ, et al. Long-lived memory T lymphocyte responses against SARS coronavirus nucleocapsid protein in SARS-recovered patients. Virology. 2006;351(2):466-75.
28. Zhao J, Zhao J, Perlman S. T cell responses are required for protection from clinical disease and for virus clearance in severe acute respiratory syndrome coronavirus-infected mice. J Virol. 2010;84(18):9318-25.
29. Zhou G, Zhao Q. Perspectives on therapeutic neutralizing

antibodies against the Novel Coronavirus SARS-CoV-2. Int J Biol Sci. 2020;16(10):1718-23.
30. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. JAMA. 2020.
31. Ko JH, Seok H, Cho SY, Ha YE, Baek JY, Kim SH, et al. Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. Antivir Ther. 2018;23(7):617-22.
32. Arabi YM, Hajeer AH, Luke T, Raviprakash K, Balkhy H, Johani S, et al. Feasibility of Using Convalescent Plasma Immunotherapy for MERS-CoV Infection, Saudi Arabia. Emerg Infect Dis. 2016;22(9):1554-61.
33. Yeh K-M, Chiueh T-S, Siu LK, Lin J-C, Chan PKS, Peng M-Y, et al. Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital. J Antimicrob Chemother. 2005;56(5):919-22.
34. Cheng Y, Wong R, Soo YO, Wong WS, Lee CK, Ng MH, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis. 2005;24(1):44-6.
35. Chen Y, Li L. SARS-CoV-2: virus dynamics and host response. Lancet Infect Dis. 2020.
36. To KK, Tsang OT, Leung WS, Tam AR, Wu TC, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis. 2020.
37. Boudreau CM, Alter G. Extra-Neutralizing FcR-Mediated Antibody Functions for a Universal Influenza Vaccine. Front Immunol. 2019;10:440.
38. Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, et al. COVID-19 infection: the perspectives on immune responses. Cell Death Differ. 2020.
39. Ahmad TA, Eweida AE, Sheweita SA. B-cell epitope mapping for the design of vaccines and effective diagnostics. Trials in Vaccinology. 2016;5:71-83.
40. Ahmad TA, Eweida AE, El-Sayed LH. T-cell epitope mapping for the design of powerful vaccines. Vaccine Reports. 2016;6:13-22.
41. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet. 2020;395(10223):497-506.
42. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet Respiratory medicine. 2020.
43. Hsiao CH, Wu MZ, Chen CL, Hsueh PR, Hsieh SW, Yang PC, et al. Evolution of pulmonary pathology in severe acute respiratory syndrome. Journal of the Formosan Medical Association = Taiwan yi zhi. 2005;104(2):75-81.
44. Ng WF, To KF, Lam WW, Ng TK, Lee KC. The comparative pathology of severe acute respiratory syndrome and avian influenza A subtype H5N1--a review. Human pathology. 2006;37(4):381-90.
45. Turner A, Hiscox J, Hooper N. ACE2: from vasopeptidase to SARS virus receptor. Trends Pharmacol Sci. 2004;25(6):291-4.
46. Turner AJ, Hiscox JA, Hooper NM. ACE2: from vasopeptidase to SARS virus receptor. Trends Pharmacol Sci. 2004;25(6):291-4.
47. Kuster GM, Pfister O, Burkard T, Zhou Q, Twerenbold R, Haaf P, et al. SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19? Eur Heart J. 2020.
48. Zheng Y, Ma Y, Zhang J, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol. 2020.
49. Chu KH, Tsang WK, Tang CS, Lam MF, Lai FM, To KF, et al. Acute renal impairment in coronavirus-associated severe acute respiratory syndrome. Kidney Int. 2005;67(2):698-705.