JCI The Journal of Clinical Investigation

Does common cold coronavirus infection protect against severe SARS-CoV2 disease?

David K. Meyerholz, Stanley Perlman

J Clin Invest. 2020. https://doi.org/10.1172/JCI144807.

Commentary In-Press Preview

The coronavirus disease 2019 (COVID 19) pandemic continues to cause morbidity and mortality. Since severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was identified as the cause for COVID 19, some have questioned whether exposure to seasonal common cold coronaviruses (CCCs) could provide tangible protection against SARS-CoV-2 infection or disease. In this issue of the *JCI*, Sager, et al. examined SARS-CoV-2 infections and outcomes from patients previously tested for CCC as part of a comprehensive respiratory panel using PCR and were segregated into negative (CCC–) or positive (CCC+) exposure. No differences were seen between groups in terms of susceptibility to SARS-CoV-2 infection. However, hospitalized patients with a documented history of CCC+ infection had lower rates of ICU admissions and higher rates of survival than hospitalized CCC– patients. While these findings are associative and not causative, they highlight evidence suggesting that previous CCC+ infection may influence the disease course of SARS-CoV-2 infection.

Does common cold coronavirus infection protect against severe SARS-CoV2 disease?

David K. Meyerholz[1] and Stanley Perlman[2,3]

[1]Department of Pathology, University of Iowa, Iowa City, Iowa, USA

[2]Departments of Microbiology and Immunology and [3]Pediatrics, University of Iowa, Iowa City Iowa USA

Address correspondence to:
David K. Meyerholz
Department of Pathology, 1165ML
University of Iowa
500 Newton Road
Iowa City, Iowa 52242
Phone: 319-353-4589
E-mail: david-meyerholz@uiowa.edu

or

Stanley Perlman
Department of Microbiology and Immunology, BSB 3-712
University of Iowa
51 Newton Road
Iowa City, IA, 52242
Phone: 319-335-8549
E-mail: Stanley-perlman@uiowa.edu

Conflicts of interest.
SP has received funding under a sponsored research agreement from Eli Lilly. DKM declares no conflict of interest.

Abstract

The coronavirus disease 2019 (COVID 19) pandemic continues to cause morbidity and mortality. Since severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was identified as the cause for COVID 19, some have questioned whether exposure to seasonal common cold coronaviruses (CCCs) could provide tangible protection against SARS-CoV-2 infection or disease. In this issue of the *JCI*, Sager, et al. examined SARS-CoV-2 infections and outcomes from patients previously tested for CCC as part of a comprehensive respiratory panel using PCR and were segregated into negative (CCC-) or positive (CCC+) exposure. No differences were seen between groups in terms of susceptibility to SARS-CoV-2 infection. However, hospitalized patients with a documented history of CCC+ infection had lower rates of ICU admissions and higher rates of survival than hospitalized CCC- patients. While these findings are associative and not causative, they highlight evidence suggesting that previous CCC+ infection may influence the disease course of SARS-CoV-2 infection.

Common cold coronaviruses

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged in 2019 and continues to cause the worldwide pandemic known as coronavirus disease19 (COVID 19) (1, 2). Clinical symptoms typically emerge within 2-14 days of exposure and include fever, fatigue, cough/shortness of breath, and sensory (smell/taste) deficits, and in some cases clinical disease can extend to a variety of other organs including brain, heart, kidney and gastrointestinal tract (3). SARS-CoV-2 infection commonly causes asymptomatic infection to mild/moderate respiratory disease in the majority of cases, but in about 10% of cases the clinical disease is severe requiring hospitalization with a case mortality rate of 0.5-1.0% (4). Predisposition to

severe COVID 19 is generally skewed to specific subpopulations such as the elderly or those with comorbidities including diabetes, cardiovascular disease, and lung disease. There is substantial interest in better understanding the immune response to SARS-CoV-2 to illuminate mechanisms for disease predisposition, disease pathogenesis and in the development of vaccines and targeted therapies (5, 6).

Common cold coronaviruses (CCCs) are endemic viruses that cause upper respiratory infections with mild to moderate severity (i.e. colds) and include HCoV-229E, HCoV-OC43, HCoV-HKU-1, and HCoV-NL63 (6, 7). This combined group of four CCCs cause about 15% of the seasonal colds and host immunity against these viruses is often short-lived, so reinfection is not uncommon. Most individuals become infected one or more times by the time that adulthood is reached. Since the onset of the pandemic, some have raised questions as to whether previous exposure to CCCs could influence the disease course or severity of COVID 19. In this issue of the *JCI,* Sager et al. (8) report a possible protective link between prior CCC infection and SARS-CoV-2 disease course. Since most people should have been exposed to CCC over their lifetime, this report assessed the potential role of more recent CCC infection in COVID-19 outcomes. The authors identified patients previously tested for CCCs and these were grouped as CCC+ and CCC- exposures. The two groups were studied for SARS-CoV-2 infection and development of severe disease or death. SARS-CoV-2 infection rates were similar between the two exposure groups. However, among hospitalized SARS-CoV-2 patients, the study identified significantly reduced admission rates to the intensive care unit (ICU) for those with prior exposure to CCC+ infection. Furthermore, hospitalized SARS-CoV-2 patients with prior CCC+ infection had an increased survival rate compared with the CCC- group (Figure 1). This finding offers some preliminary clinical evidence that prior CCC+ infection could impact severity of SARS-CoV-2

infection (8). We speculate that adaptive immune responses, innate immune responses and other various factors could explain this apparent protective effect.

Adaptive immune response

Cross-reactive adaptive immune responses from previous CCC infections is one of the most tangible explanations for this apparent conferred protective effect; and recent reports in the literature support and corroborate the idea of cross-reactivity, at least to a limited extent.

In animal models, T cells (both $CD4^+$ and $CD8^+$) have been shown to provide effective and protective immunity against coronavirus infection (9, 10). In humans, recent studies point to the possibility of cross-reactive T cell epitopes (especially $CD4^+$) between SARS-CoV-2 and CCCs, presumptively from previous seasonal infections (11-14). As an example, a recent assay of individuals without SARS-CoV-2 exposure detected cross-reactive $CD4^+$ T-cells that were developed against homologous epitopes in CCC. These cross-reacting cells were present in low amounts and reacted to epitopes that differed from those targeted in COVID-19 patients. The authors of the study speculated that this cross-reactivity could explain, in part, the varied clinical disease spectrum of COVID 19 (11).

Neutralizing antibodies are widely used as a diagnostic marker of previous SARS-CoV-2 infection and serve as COVID 19 therapies (convalescent serum or monoclonal antibody therapies). Their generation at protective levels is the chief goal of many candidate COVID19 vaccines (15-18). Following SARS-CoV-2 infection in naive individuals, neutralizing antibodies are generated although they begin to diminish after several months (19). Interestingly, one recent study found that during this same convalescent time period, a concurrent synchronous expansion of cross-reactive antibodies to CCCs (HCoV-OC43 and HCoV-HKU1) spike S2, but not spike

S1, was generated (16). Antibodies against seasonal CCC are often short lived, but this report (16) suggests expansion of a preexisting memory response against partially homologous antigens of a related pathogen is possible; whether this memory response provides protection or enhancement of disease remains unknown.

Innate immune response

In humans, severe SARS-CoV-2 disease is reportedly associated with expansion of innate immune cell lineages along with concurrent reduction in T cell numbers, and protracted to sustained cytokine expression (20). Previous microbial infection or antigenic exposure has been reported to influence innate immune cell function, such as cytokine production and antigen presentation, that can, in some situations, modulate later infections from another pathogen, part of a process called heterologous immunity (21). In experimental studies, dysregulated or impaired immune responses have been reported as a result of severe coronavirus infection. Specifically, delayed type I interferon (IFN-I) signaling early in a mouse model of SARS-CoV infection can lead to expansion of inflammatory monocyte-macrophages and elevated lung cytokine/chemokine levels with vascular leakage and impaired virus-specific T cell responses (22).

Indirect factors

Several factors have been proposed to influence the susceptibility and severity of SARS-CoV-2 infection, often indirectly influencing the immune system. For example, the SARS-CoV-2 virus utilizes angiotensin-converting enzyme-2 (ACE2) as a primary receptor for cellular entry and the protease, transmembrane serine protease 2, TMPRSS2 serves as a co-factor for this

process. Regulation and expression of both ACE2 and TMPRSS2 have been studied as a possible explanation for enhanced SARS-CoV-2 susceptibility and severity in prone populations (23, 24). Similarly, neuropilin-1 was recently shown to bind the cleaved SARS-CoV-2 S1 protein to stabilize virus/receptor interaction for enhanced virus entry and possibly to serve as a co-receptor for the virus (25). Could recent CCC infection dampen the expression of one or more of these factors to diminish severity of clinical SARS-CoV-2 disease?

Future directions

The study by Sagar et al. (8) potentially opens the door to new avenues of COVID 19 research, but it is important to recognize that the results are still preliminary in nature. Larger, multicenter, prospective studies from diverse populations are needed to reproduce and validate the results, and to clarify the mechanisms involved. Little is known about the T cell response that occurs after CCC infections and this arm of the immune response could contribute to anamnestic (or recall) immune responses. Future studies could distinguish whether there are specific CCCs that differentially contribute to protection, and determine how the temporal relationship between CCC and SARS-CoV-2 infections contributes to protection or pathogenicity. Furthermore, the CCC+ group had more frequent and recent diagnostic testing relative to the CCC- group suggesting that patients had more clinical respiratory infections (8). These increased episodes prior to SARS-CoV-2 infection could suggest a role for heterologous immunity, where previous infection with one pathogen can protect against infection of another pathogen (21). In summary, the connection between previous CCC infection and possible protection against severe SARS-CoV-2 disease is interesting for clinicians and researcher alike. Further validation and

mechanistic studies will be required to learn how (or if) this knowledge has feasible use in prophylactic and/or therapeutic applications.

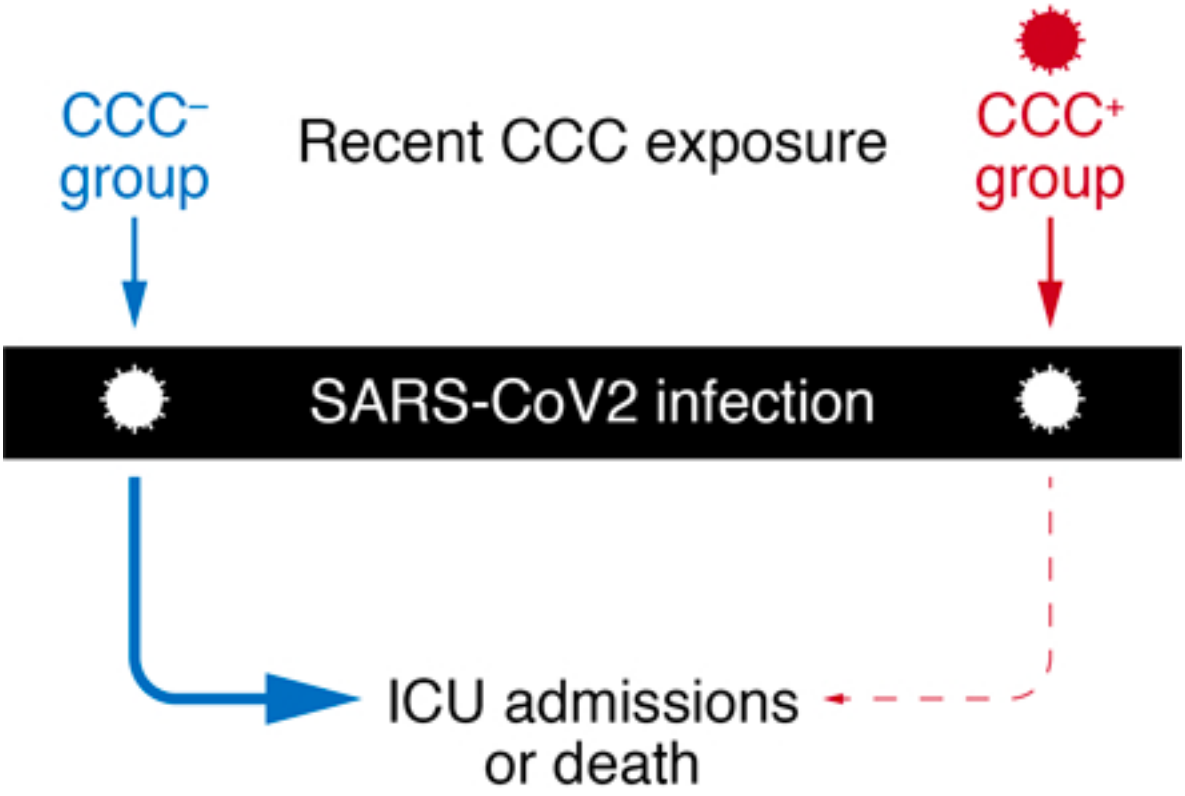

Figure 1. Exposure to the common cold coronavirus (CCC) infection may influence the disease course of SARS-CoV-2 infection. Sagar et al. (8) grouped COVID-19 patients according to documented common cold coronavirus (CCC- and CCC+). Patients with subsequent SARS-CoV2+ infection were studied to see if CCC exposure influenced SARS-CoV2 disease severity. Previous CCC+ diagnosis was associated with reduced ICU admissions and death in hospitalized patients.

Acknowledgments

We would like to acknowledge support from the following NIH grants: PO1 AI060699 (DM and SP) and RO1 AI129269 (SP).

References

1. Coronaviridae Study Group of the International Committee on Taxonomy of V. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol.* 2020;5(4):536-44.
2. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature.* 2020;579(7798):270-3.
3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 2020;382(18):1708-20.
4. Salzberger B, Buder F, Lampl B, Ehrenstein B, Hitzenbichler F, Holzmann T, et al. Epidemiology of SARS-CoV-2. *Infection.* 2020.
5. Sariol A, and Perlman S. Lessons for COVID-19 Immunity from Other Coronavirus Infections. *Immunity.* 2020;53(2):248-63.
6. Channappanavar R, and Perlman S. Age-related susceptibility to Coronavirus infections: role of impaired and dysregulated host immunity. *J Clin Invest.* 2020.
7. Gorse GJ, Patel GB, Vitale JN, and O'Connor TZ. Prevalence of antibodies to four human coronaviruses is lower in nasal secretions than in serum. *Clin Vaccine Immunol.* 2010;17(12):1875-80.
8. Sager ea. Recent endemic coronavirus infection is associated with less severe COVID-19. *J Clin Invest.* 2020.
9. Zhao J, Zhao J, Mangalam AK, Channappanavar R, Fett C, Meyerholz DK, et al. Airway Memory CD4(+) T Cells Mediate Protective Immunity against Emerging Respiratory Coronaviruses. *Immunity.* 2016;44(6):1379-91.
10. Channappanavar R, Fett C, Zhao J, Meyerholz DK, and Perlman S. Virus-specific memory CD8 T cells provide substantial protection from lethal severe acute respiratory syndrome coronavirus infection. *J Virol.* 2014;88(19):11034-44.
11. Mateus J, Grifoni A, Tarke A, Sidney J, Ramirez SI, Dan JM, et al. Selective and cross-reactive SARS-CoV-2 T cell epitopes in unexposed humans. *Science.* 2020;370(6512):89-94.
12. Grifoni A, Weiskopf D, Ramirez SI, Mateus J, Dan JM, Moderbacher CR, et al. Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals. *Cell.* 2020;181(7):1489-501 e15.
13. Lipsitch M, Grad YH, Sette A, and Crotty S. Cross-reactive memory T cells and herd immunity to SARS-CoV-2. *Nat Rev Immunol.* 2020.
14. Braun J, Loyal L, Frentsch M, Wendisch D, Georg P, Kurth F, et al. SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19. *Nature.* 2020.

15. Zeng C, Evans JP, Pearson R, Qu P, Zheng YM, Robinson RT, et al. Neutralizing antibody against SARS-CoV-2 spike in COVID-19 patients, health care workers and convalescent plasma donors. *JCI Insight.* 2020.
16. Secchi M, Bazzigaluppi E, Brigatti C, Marzinotto I, Tresoldi C, Rovere-Querini P, et al. COVID-19 survival associates with the immunoglobulin response to the SARS-CoV-2 spike Receptor Binding Domain. *J Clin Invest.* 2020.
17. Wang Y, Zhang L, Sang L, Ye F, Ruan S, Zhong B, et al. Kinetics of viral load and antibody response in relation to COVID-19 severity. *J Clin Invest.* 2020;130(10):5235-44.
18. Pinto D, Park YJ, Beltramello M, Walls AC, Tortorici MA, Bianchi S, et al. Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. *Nature.* 2020;583(7815):290-5.
19. Seow J, Graham C, Merrick B, Acors S, Pickering S, Steel KJA, et al. Longitudinal observation and decline of neutralizing antibody responses in the three months following SARS-CoV-2 infection in humans. *Nat Microbiol.* 2020.
20. Lucas C, Wong P, Klein J, Castro TBR, Silva J, Sundaram M, et al. Longitudinal analyses reveal immunological misfiring in severe COVID-19. *Nature.* 2020;584(7821):463-9.
21. Sharma S, and Thomas PG. The two faces of heterologous immunity: protection or immunopathology. *J Leukoc Biol.* 2014;95(3):405-16.
22. Channappanavar R, Fehr AR, Vijay R, Mack M, Zhao J, Meyerholz DK, et al. Dysregulated Type I Interferon and Inflammatory Monocyte-Macrophage Responses Cause Lethal Pneumonia in SARS-CoV-Infected Mice. *Cell Host Microbe.* 2016;19(2):181-93.
23. Ortiz ME, Thurman A, Pezzulo AA, Leidinger MR, Klesney-Tait JA, Karp PH, et al. Heterogeneous expression of the SARS-Coronavirus-2 receptor ACE2 in the human respiratory tract. *EBioMedicine.* 2020;60:102976.
24. 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;181(2):271-80 e8.
25. Cantuti-Castelvetri L, Ojha R, Pedro LD, Djannatian M, Franz J, Kuivanen S, et al. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. *Science.* 2020.