This month’s feature highlights five articles on COVID-19 that appear in the current print and online issue of Mayo Clinic Proceedings. These articles are also featured on the Mayo Clinic Proceedings’ YouTube Channel (https://youtu.be/MT3ZFDAOKYU).

SAFETY OF CONVALESCENT PLASMA IN COVID-19

With the current absence of a vaccine against SARS-CoV-2 and the ongoing search for therapies for COVID-19, the therapeutic potential of convalescent plasma in COVID-19 is now under active investigation. This therapeutic strategy in infectious diseases, based on passive immunization, reaches back more than 100 years to its use during the influenza pandemic of 1918 and to the award of the inaugural Nobel Prize in Physiology or Medicine in 1901 to Emil von Behring for demonstrating its efficacy in diphtheria. Passive immunization relies on neutralizing antibodies that bind to proteins on the surface of infectious agents, thereby neutralizing these agents and interrupting processes that drive the infectious disease; other constituents in convalescent plasma may also exert beneficial effects. Neutralizing antibodies are engendered in the course of recovery from an infectious disease, and those that target SARS-CoV-2 are present in convalescent plasma in variable amounts in patients recovering from COVID-19. To study the potential efficacy of convalescent plasma in COVID-19, Joyner and collaborators set the stage in early 2020 for a multicenter investigation of this question, recognizing at the very onset that a fundamental requirement would be the collection of convalescent plasma and its distribution to regional medical centers caring for patients with COVID-19. This goal was successfully achieved by a national Expanded Access Program created by the US Food and Drug Administration in partnership with Mayo Clinic and blood banking centers nationwide. In the present issue of Mayo Clinic Proceedings, Joyner et al provide a safety analysis in 20,000 patients with severe COVID-19 or at risk for developing severe COVID-19 who were administered convalescent plasma; this study is a follow-up to their prior safety analysis of the first 5000 patients so treated, all of whom are included in the present analysis. Convalescent plasma was administered to participants as clinically decided by the managing physician and as part of a modified clinical trial design. Within 4 hours of transfusion, less than 1% of transfusions were attended by serious adverse events, the latter including circulatory overload, acute lung injury, and severe allergic reactions. Of the 63 fatalities that occurred at this timepoint, 12 possibly, 1 probably, 0 definitely were linked to the plasma transfusion. At 7 days after transfusion, cardiac events and thromboembolic/thrombotic events occurred in approximately 3% and less than 1% respectively, but the overwhelming majority of these events were not ascribable to transfusion with convalescent plasma. The seven-day mortality averaged 8.6% and was higher in those subsets of patients either in the intensive care unit, requiring ventilator support, with septic shock, or with multi-organ dysfunction. Interestingly, in their prior report of 5000 patients with COVID-19 treated with convalescent plasma, the mortality rate was higher at 12%. Joyner et al offer 3 possible explanations for this decline in mortality in the present analysis: 1) general improvement in US health care systems in managing ill patients with...
COVID-19; 2) earlier administration of convalescent plasma to patients; and 3) more expeditious recruitment of donors recovering from COVID-19 and obtaining their plasma, thereby increasing the likelihood that their convalescent plasma would be more enriched with neutralizing antibodies. The reassuring and important finding of the present study is the relative safety of administering convalescent plasma to hospitalized patients with COVID-19. Joyner and collaborators are to be congratulated for their perspicacity in envisioning the need for this study and their herculean accomplishment in rapidly organizing and spearheading this logistically challenging study. Their forthcoming study on the efficacy of convalescent plasma in COVID-19 is anxiously awaited.

Joyner MJ, Bruno KA, Klassen SA, et al. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. Mayo Clin Proc. 2020;95(9):1888-1897.

PRIMARY CARE IN THE COVID-19 ERA AND BEYOND: QUO VADIS?

The crisis of COVID-19 redirects so much of the health care system to the necessity of detecting, treating, and limiting the spread of the disease. This abrupt redeployment of health care resources to such exigencies created by an unanticipated pandemic impacts aspects of the health care system in at least two major ways: First, such diversion interrupts attention to and conduct of the primary mission of aspects of health care; and, second, the stress of COVID-19 lays bare and exacerbates their pre-existing inadequacies. In the present issue of Mayo Clinic Proceedings, two perspectives discuss the latter consideration as it applies to primary care and broadly outline how to address this issue. As pointed out by Lin et al, long before the COVID-19 era, primary care faced numerous challenges including insufficient time afforded to patients because of the number of patients needed to be seen; insufficient or inconsistent attention to chronic care and preventive services; limitations and disparities in capacity and access; uneven quality of care; affordability; the importance accorded to primary care; and the reimbursement for primary care. In envisioning the path ahead, Lin et al note that the constraints of the COVID-19 crisis necessitated and enabled the rapid growth of telemedicine, and this powerful and versatile technology (with a more supportive reimbursement environment) has become an indispensable component in primary care now and into the future. Lin et al emphasize the importance of patient-generated data through an expanding menu of technology-based tools, the advisability of preventive care undertaken between visits, and the importance of population health management. With these essential components, Lin et al propose an integrated and sequential process that incorporates pre-scheduling, pre-visit planning, the medical visit, and inter-visit care management, all shaped and directed by human governance aided by the remarkable power of artificial intelligence. In an accompanying perspective, Sinsky agrees with the transformative potential of telemedicine, but emphasizes that the optimism surrounding telemedicine should be tempered by recognition of its potential risks and limitations. Sinsky draws an analogy to the advent and incorporation of the electronic health record (EHR) in primary care some 20 years ago, an advance similarly met with high expectations. But, for all its indubitable benefits, the mixed blessings of the EHR became readily apparent, including its substantiated role in contributing to physician burnout. Sinsky underscores that telemedicine should be incorporated in primary care within a framework that is cognizant of the importance of teamwork and relationships in patient care, the risks of multitasking, the importance of a faithful accounting of all time that is spent, and the need to decide which patients are more suited for virtual care. Sinsky concludes with a perspective that differs from the one provided by Lin et al on workflows and processes in primary care, and how preventive care should be organized. Both perspectives, however, are united in the view that now is the time to address and heal the ills that afflict primary care, in part by the judicious incorporation of telemedicine and other technological innovations. Primary care is a cornerstone in health care, and insightful discussions such as those provided by Lin et al and Sinsky enable the informed restructuring and strengthening of primary care and the fuller realization of its indispensable mission.
CELLULAR ENTRY OF SARS-COV-2 VIA ACE2 AND TMPRSS2: THERAPEUTIC IMPLICATIONS

A critical event in the development of COVID-19 is cellular entry of SARS-CoV-2. For this to occur the viral spike proteins must bind to the ACE2 receptor on cellular surfaces. An obligatory prior step is the priming of the spike protein as it is cleaved at specific sites, a function in which another surface receptor, TMPRSS2 (a proteolytic enzyme), is instrumental. Viral entry into cells then ensues after which the virus proliferates and kills cells, thereby incurring local and systemic inflammatory responses; interestingly, after viral cell entry occurs, the ACE2 receptor is downregulated. Two articles in the present issue of *Mayo Clinic Proceedings* discuss the therapeutic implications surrounding the involvement of ACE2 and TMPRSS2 in cellular entry of SARS-CoV-2. Poland et al point out that while ACE2 expression enables viral entry, ACE2 exerts cytoprotective effects in tissues. Such beneficial effects occur because ACE2 degrades angiotensin II to angiotensin 1-7, the latter representing a vasodilating, anti-inflammatory, and anti-fibrotic peptide, and thus one that opposes the recognized vasoconstricting, proinflammatory, and profibrotic actions of angiotensin II; ACE2 expression, through angiotensin 1-7, thus mitigates angiotensin II-dependent inflammation and other adverse effects on tissues. As further pointed out by Poland et al, divergent effects may also surround the use of angiotensin II receptor blockers (ARBs). On the one hand, ARBs increase plasma concentrations of angiotensin II which serves to increase expression of ACE2 and thus, theoretically, increasing cellular entry of SARS-CoV-2; on the other, such increased expression of ACE2 exerts cytoprotective effects in tissue via its anti-inflammatory and other salutary actions. These latter effects of ARBs serve as the basis, in part, for the clinical trials of these agents in COVID-19. Another approach involves blocking the virus in the extracellular space by recombinant ACE2 protein, a soluble form of ACE2 that acts as a decoy and diverts SARS-CoV-2 away from the membrane bound ACE2. The other surface receptor involved in SARS-CoV-2 entry, TMPRSS2, is also a potential therapeutic target in COVID-19 for multiple reasons, as clearly delineated by Baughn et al in the same issue of *Mayo Clinic Proceedings*. First, preclinical studies indicate that as tissues are inflamed and injured, TMPRSS2, unlike ACE2, does not appear to exert a cytoprotective role; thus inhibiting the function of TMPRSS2 may not exert adverse effects. Second, rodent models with genetic deficiency of TMPRSS2 exhibit less severe disease when infected by SARS-CoV; extrapolating from these preclinical findings to COVID-19 raises the possibility that suppressing the expression/action of TMPRSS2 may be beneficial. Third, agents that inhibit TMPRSS2 activity are currently undergoing clinical trials in COVID-19. Fourth, the TMPRSS2 gene can be induced by androgen-dependent pathways, and thus its expression may be suppressed by androgen deprivation therapy or antiandrogens. The TMPRSS2 gene is expressed in diverse tissues, and highly so in the prostate. Androgen deprivation therapy and/or antiandrogens are established approaches in the treatment of prostate cancer and thus represent a plausible therapeutic strategy in COVID-19. In sum, therapeutic strategies targeting receptors for SARS-CoV-2 may offer clinical benefit in COVID-19, and the results of relevant ongoing studies are thus of considerable interest.

Poland GA, Bass J, Goldstein MR. SARS-CoV-2 infections: An ACE in the hole and systems biology studies — a research agenda. *Mayo Clin Proc*. 2020;95(9):1838-1841.

Baughn LB, Sharma N, Elhaik E, Sekulic A, Bryce AH, Fonseca R. Targeting TMPRSS2 in SARS-CoV-2 infection. *Mayo Clin Proc*. 2020;95(9):1989-1999.