This month’s feature highlights four 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/2Q8aQJMz7II).

WAITING AND HOPING: EFFECTIVE AND SAFE SARS-CoV-2 Vaccines
Desired vaccines elicit targeted and durable immunologic stratagems that prevent infectious agents from causing clinical diseases, and confer, and safely so, lasting individual and population-based herd immunity. In the current COVID-19 pandemic, attempts to develop effective and safe vaccines against SARS-CoV-2 are intense and multitudinous and involve initiatives that are regional, national, and global. In the present issue of Mayo Clinic Proceedings, Poland et al provide a comprehensive and masterful overview of the current landscape of vaccine development against SARS-CoV-2. In setting the stage for this discussion, and in delineating as a backdrop the ideal attributes of a SARS-CoV-2 vaccine, Poland et al underscore the spectrum of manifestations of this infection, ranging from an asymptomatic state to a life-threatening illness, and identify those subpopulations that are more vulnerable to this infection and its complications. They then highlight the essential steps in the pathobiology of SARS-CoV-2 infection which sequentially involve priming of the S-protein of the virus by the serine protease TMPRSS2; the engagement of the primed S-protein via its receptor binding domain to ACE2, the surface receptor on host cells that incorporates the virus into the intracellular compartment; attendant viral replication and ensuing cell injury and death; and the instigation of regional and systemic proinflammatory responses. In addition to ACE2, the authors point out recent data that intracellular entry may also occur in certain host cells via the CD147-S protein engagement pathway. Poland et al cover a number of areas relevant to vaccine development including, among others: knowledge of the genome of SARS-CoV-2 and mutations recognized thus far; prior literature on SARS and MERS and attempts to develop relevant vaccines against these infections; the need for a fuller understanding of the innate, humoral, and cellular immune responses to SARS-CoV-2; and the adjunctive strategy provided by computational biology. The authors then succinctly summarize current clinical trials, identifying in tabular form the type of vaccine, the known/likely target antigen, the sponsor, and where the trial is conducted. This is followed by an in-depth discussion of the assorted strategies used to produce vaccines, and these include DNA and RNA vaccines; live vaccines; inactivated whole virus vaccines; subunit vaccines that target either the S-protein, the receptor binding domain of the S-protein, or the N protein; vectored vaccines (using, for example, vesicular stomatitis virus, adenovirus, measles, others), and peptide-based vaccines. The authors discuss the strengths, challenges, and weaknesses of each approach, as well as providing salient examples utilizing that particular strategy. The Review builds to an “Expert Commentary/Look Ahead” as the penultimate section that spotlights unresolved issues surrounding vaccine development, including those that are biologic, immunologic, methodologic and
delivery-related, ethical, and health care policy-related in nature. Notably, and harking back to the emphasis earlier in their review on the need to understand the heterogeneity of responses to SARS-CoV-2 and at-risk populations, Poland et al point out that not just one vaccine is needed, but rather several, including those targeting specific populations that are either immunoimmature, immunosenscet, immunocompromised, or involve pregnant patients. Achieving desired vaccines against SARS-CoV-2 in an accelerated time frame is essential, even though the challenges are so daunting. However, as the history of human crises tells us, humanity so often fully measures up with the requisite innovation that enables crisis resolution, and the same will indubitably be true for the COVID-19 pandemic. The great French writer Alexandre Dumas wrote that human wisdom can be distilled into two words - wait and hope. Poland et al are to be warmly commended for providing this superb overview of the current landscape regarding SARS-CoV-2 vaccine development and for leaving with us that vital message of waiting and hoping while in the midst of the angst caused by the current COVID-19 pandemic.


THE ECG: THE SIXTH VITAL SIGN IN COVID-19 PATIENTS

The clinical course and outcomes in patients hospitalized with COVID-19 are heterogeneous, ranging from early demise due to acute respiratory distress syndrome and circulatory collapse on the one hand to rapid recovery and hospital dismissal on the other. Such heterogeneity in the tempo and severity of the disease requires varying levels of care, with sicker patients requiring admission to intensive care settings. Discerning which patients will likely exhibit rapid progression of COVID-19 when initially seen in emergency departments is thus a critical aspect of their evaluation. In the current issue of Mayo Clinic Proceedings, Elias et al demonstrate that attentiveness to the presenting vital signs and ECG remarkably improves such risk stratification in this patient population. These investigators analyzed the prognostic value of presenting vital signs (temperature, heart rate, systolic blood pressure, respiratory rate, oxygen saturation) and the presenting ECG in 1258 patients with COVID-19 seen in the emergency departments at 3 hospitals in New York. The primary composite outcome was the need for mechanical ventilation (excluding intubation during unsuccessful resuscitation) or death within 48 hours from diagnosis; an additional outcome was mortality at 30 days. Respiratory failure tended to occur early in the course of COVID-19 in these patients, with more than 50% of intubations necessitated within 48 hours. The primary composite outcome at 48 hours significantly correlated with respiratory rate greater than 20/min, oxygen saturation less than 95% (or the need for oxygen therapy), and the presence in the ECG of either atrial fibrillation/flutter, right ventricular strain, or ST segment changes. The primary composite outcome at this time point was increased more than 6-fold in patients with any of these ECG changes and either of these two abnormal vital signs as compared with patients without such findings (32% versus 5%). Furthermore, the concomitant presence of any of these 3 ECG abnormalities per se was associated with more than 2-fold increase in the primary composite outcome in patients with normal respiratory vital signs (12% versus 5%) and an almost 2-fold increase in this outcome in patients with abnormal respiratory vital signs (32% versus 17%). Analyses at 30 days showed on the multivariable regression model that these 5 abnormalities significantly associated with mortality. This study by Elias et al is important for several reasons. First, it shows how time honored and basic aspects of patient evaluation can significantly aid in the prognostication of these patients and inform the prudent triaging of care in these patients. Second, it shows that these 3 abnormalities in the ECG per se provide additive prognostic power, leading the authors...
to regard the ECG in the emergency department as a "sixth vital sign." Third, it underscores the increasing recognition of cardiac involvement in COVID-19 and that such involvement may serve as a determinant of outcomes in this disease.


SMOKING AND COVID-19
Few personal habits are as ruinous to one’s health as cigarette smoking, the latter adversely affecting virtually all major organs and tissues. In the present issue of Mayo Clinic Proceedings, two contributions discuss the adverse effects of smoking as they relate to the current COVID-19 pandemic. In a succinct Letter to the Editor, Lang and Yakhkind summarize common pathobiologic processes that are independently instigated by smoking and COVID-19 including the respiratory tract as the portal through which disease most commonly begins; the capacity of either smoking or COVID-19 to upregulate key proinflammatory transcriptional activators such as NF-kB, and downstream cytokines such as TNFa; the ability of both to increase the neutrophil to lymphocyte ratio; their fibrin-generating and prothrombotic effects as they both induce tissue factor, an activator of the extrinsic coagulation cascade; and the propensity of either to cause myocardial inflammation and disease. As these authors point out, smoking may not only upregulate the main receptor (ACE2) through which the virus invades cells, but also the other relevant surface receptor (TMPRSS2) that is essential in priming the spike protein of SARS-CoV-2 prior to its engagement of the ACE2 receptor. Given this congruency of effects independently exerted by smoking and COVID-19, the inevitable question is whether smoking predisposes to COVID-19 and worsens outcomes from this disease. These considerations are discussed by Hashmi et al in this issue of Mayo Clinic Proceedings, as they summarize the literature demonstrating that smoking predisposes to SARS-CoV-2 infectivity, severe COVID-19, and worse outcomes and mortality. Such effects likely occur as a consequence of the pathobiologic effects outlined above as well as smoking-induced increase in mucus production in the respiratory tract and compromised mucociliary clearance. Additionally, smoking may predispose to COVID-19 because of the increased risk of hand-to-mouth spread of SARS-CoV-2. Considerations that merit additional study include whether cigarette smoking predisposes to milder, reversible manifestations of COVID-19, and whether cessation of smoking decreases the risk of COVID-19, and if so, what duration of cessation is needed to convey this benefit. Hashmi et al also point out that the predisposition to COVID-19 by cigarette smoking may also apply to e-cigarettes, and smoking tobacco by shisha and hookah. Interest also centers on the effects of nicotine itself, and whether this constituent worsens or mitigates the risks of and outcomes in COVID-19. Other constituents and products of smoking on COVID-19 would be of interest including carbon monoxide, a gaseous product generated by cigarette smoking and one with effects on inflammatory processes. In concluding their perspective, Hashmi et al urge greater effort on the part of the medical community, local and national governmental agencies, the World Health Organization, and the World Trade Organization in strengthening tobacco control policies - for a potentially lethal disease with quite limited therapeutic options, smoking is not just a highly significant, but also a readily modifiable risk factor.
