As in the June 2020 issue, 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/q_BFCFzEAD0).

**COVID-19: MANAGEMENT AND THERAPEUTIC CONSIDERATIONS**

Two companion papers on COVID-19, in concert, summarize key epidemiologic and clinical aspects of this disease, outline an approach to management, and provide an overview of drugs and other approaches currently considered and/or investigated for their therapeutic efficacy. Beginning with an overview of the essential features of SARS-CoV-2, how the virus infects cells, and how it spreads, Razonable et al broadly outline the consequences of such infection that range from an asymptomatic state in a relatively large number of individuals to the spectrum of symptoms observed in COVID-19; approximately 20% of symptomatic patients develop moderate to severe pneumonia and require hospitalization. Along with commonly observed laboratory findings, the initial patient evaluation is reviewed, and this is followed by a discussion of the diagnostic role of polymerase chain reaction (PCR) testing, the significance of serologic findings, and the radiologic features observed in COVID-19. The basic management involves antipyretics, analgesia, attention to fluid and electrolyte balance, and oxygen supplementation. Razonable et al emphasize the importance of a team-based approach in managing hospitalized COVID-19 patients and sequentially address major complications and how they are broadly managed including: the hyperinflammatory syndrome; respiratory failure; cardiovascular complications; hepatic dysfunction; acute kidney injury and other renal complications; and the propensity to venous thromboembolic disease and disseminated intravascular coagulation. The need to consider the possibility of coexisting infection with other pathogens is emphasized, and isolation procedures are broadly reviewed including settings when aerosol-generating procedures are performed. The companion paper by Vijayvargiya et al discusses repurposed drugs with antiviral properties (eg, chloroquine/hydroxychloroquine, lopinavir/ritonavir, ribavirin), novel antiviral compounds (eg, favipiravir, remdesivir), immunomodulatory drugs (eg, inhibitors of IL-6 and GM-CSF), and the use of convalescent plasma and neutralizing antibodies. As underscored by Vijayvargiya et al, none of these agents is of proven efficacy in the management of COVID-19 as of this writing, and they should be employed as part of institutionally approved clinical trials. These authors provide an algorithm for the management of COVID-19 depending on the severity of the illness: in general, supportive care and close clinical monitoring are provided for asymptomatic individuals or those with mild illness, while for moderate-severe illness, enrollment in approved clinical trials with specific agents may be considered; if ineligible for such trials, consideration may be given to the US Food and Drug Administration emergency use authorization of hydroxychloroquine or chloroquine. The paper by Razonable et al returns to the patient recovering from a...
moderate-severe illness, and broadly outlines criteria to be met for appropriate hospital dismissal, requirements for home quarantine, and the importance of telemedicine and remote monitoring in the follow-up of patients. These two companion papers by Razonable and colleagues provide an invaluable, up-to-date synthesis of key considerations in COVID-19 and its management, recognizing, however, that the latter will likely evolve as the understanding of COVID-19 advances and current therapeutic questions are resolved.

Razonable RR, Pennington KM, Meehan AM, et al. A collaborative multidisciplinary approach to the management of coronavirus disease-19 in the hospital setting. Mayo Clin Proc. 2020;95(7):1467-1481.

Vijayvargiya P, Esquer Garrigos Z, Castillo Almeida NE, Gurram PR, Stevens RW, Razonable RR. Treatment considerations for COVID-19: A critical review of the evidence (or lack thereof). Mayo Clin Proc. 2020;95(7):1454-1466.

ACE2 EXPRESSION AND HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is a relatively prevalent condition, affecting approximately 0.2% of the population, and commonly has its origins in genetic abnormalities. For the majority of individuals afflicted by HCM, the course is relatively benign and indeed may be asymptomatic, while for a small number there is the risk of sudden cardiac death and heart failure. In the present issue of Mayo Clinic Proceedings, Bos et al analyzed the transcriptome in patients with HCM and controls, and found that 22% of the transcriptome was differentially expressed in these 2 groups; among genotypic groups of HCM, just 5% of the transcriptomic changes differ within the 3 largest genotypic subsets. A striking finding was that the most upregulated gene in HCM was the gene encoding for the angiotensin converting enzyme 2 (ACE2) protein, a finding confirmed by quantitative reverse transcription (qRT)-PCR, and corroborated by increased ACE2 protein expression. These latter findings are quite fascinating given the current interest in ACE2, as this protein, when bound to cell membranes, serves as a receptor for the cellular entry of SARS-CoV-2, thereby facilitating the disease that may ensue — COVID-19. ACE2 has distinct enzymatic actions as compared with ACE, the enzyme that cleaves angiotensin I to produce angiotensin II, a vasoconstrictive, hypertrophy-inducing, proinflammatory, profibrotic, and aldosterone-stimulating peptide. In contrast, ACE2 exerts countervailing effects because ACE2 converts angiotensin I and angiotensin II to peptides with actions that are, in the main, vasorelaxant, anti-inflammatory, and antifibrotic. Bos et al thus offer the plausible speculation that the markedly increased expression of ACE2 in the heart in HCM reflects an adaptive response that may mitigate cellular processes that drive HCM. This raises the exciting question regarding the extent to which such upregulation in ACE2 may also be observed in other cardiomyopathies. An additional speculation offered by Bos et al is how these findings may relate to the current COVID-19 pandemic. Because of its role as the receptor for viral entry, increased expression of ACE2 may predispose to infection with SARS-CoV-2 and thus COVID-19, and germane to this consideration is that cardiac disease is considered a risk factor for COVID-19. Interestingly, when cells are infected with SARS-CoV-2, expression of ACE2 decreases; such decrement in ACE2 expression reduces the countervailing salutary actions this enzyme offers, while allowing greater activation of the angiotensin II type 1 receptor (AT1R) because of higher levels of angiotensin II. Bos et al thus suggest the possibility that beneficial effects in COVID-19 may be accomplished by either blocking the AT1R or complexing SARS-CoV-2 in the extracellular space and thereby preventing its cellular entry. Indeed, they point out that there are clinical trials of angiotensin II receptor blockers that target the former pathway, and clinical trials of human recombinant soluble ACE2 that target the latter pathway. Bos et al are to be commended for their rigorous transcriptomic.
analysis of HCM which uncovered marked upregulation of ACE2 in HCM, a serendipitous scientific finding with an uncanny connection to the current COVID-19 crisis.

Bos JM, Hebl VB, Oberg AL, et al. Marked up-regulation of ACE2 in hearts of patients with obstructive hypertrophic cardiomyopathy: Implications for SARS-CoV-2-mediated COVID-19. Mayo Clin Proc. 2020;95(7):1354-1368.

SYNERGISM OF OBESITY AND SARS-CoV-2 IN PROMOTING POOR OUTCOMES IN COVID-19

Obesity is among the risk factors associated with poor outcomes in COVID-19. This association is consistently recognized in the current COVID-19 literature, and in this disease there appears to be no “obesity paradox” — the phenomenon whereby obese as compared with lean individuals may exhibit better short or medium term outcomes in certain cardiovascular and other diseases. Obesity generally predisposes to a number of diseases that themselves are associated with poor outcomes in COVID-19, including type 2 diabetes mellitus, hypertension, atherosclerosis, atrial fibrillation, chronic pulmonary disease, and chronic kidney disease. In the current issue of Mayo Clinic Proceedings, Sanchis-Gomar et al discuss the multiple pathogenetic mechanisms whereby obesity worsens outcomes in COVID-19. Adipose tissue possesses relatively high expression of the cell membrane receptor ACE2 which enables cellular entry and attendant replication of SARS-CoV-2 in adipocytes; adipose tissue, especially in obese individuals, may thus serve as a repository for the virus, from which viral spread may occur. Adipose tissue possesses the major components of the renin-angiotensin-aldosterone system and is a source of circulating angiotensin II. Angiotensin II fosters inflammation and vasoconstriction-dependent ventilation/pulmonary mismatch in the lungs, thereby exacerbating the pulmonary complications that may occur in COVID-19. Adipose tissue is a source of proinflammatory cytokines, including IL-6, and the systemic delivery of such cytokines to the lungs may drive acute lung injury in COVID-19. Adipose tissue promotes a prothrombotic state because of the prothrombotic adipokines it produces, and plasminogen activator inhibitor (PAI)-mediated impairment of fibrinolytic pathways; this contributes to venous thromboembolic disease that is prone to occur and worsens outcomes in COVID-19 patients. Finally, obesity predisposes to endothelial dysfunction in the systemic and regional vasculature; the dysfunctional endothelium not only exhibits a prothrombotic phenotype, but is also a source of systemic proinflammatory cytokines. In addition to these pathobiologic pathways emanating from adipose tissue and converging on the lungs and other organs in COVID-19, obesity impairs the mechanics and compliance of the respiratory system, with impaired ventilation, decreased functional residual capacity, and decreased expiratory reserve volume. Sanchis-Gomar et al comprehensively review and integrate such distant and direct effects of obesity in exacerbating pulmonary and other outcomes in COVID-19, and conclude with a call for heightened vigilance when managing COVID-19 in obese patients.

Sanchis-Gomar F, Lavie CJ, Mehra MR, Henry BM, Lippi G. Obesity and outcomes in COVID-19: when an epidemic and pandemic collide. Mayo Clin Proc. 2020;95(7):1445-1453.

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