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PERSPECTIVE

Applying the Lessons of Influenza to COVID-19 During a Time of Uncertainty

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In late January 2020, the 3 of us were consulted by the American College of Cardiology to assist in developing expert guidance to inform our colleagues regarding potential cardiac implications of a novel coronavirus epidemic in Wuhan, China, now known as coronavirus disease 2019 (COVID-19). We are not infectious disease experts, nor do we have specific expertise in coronaviruses, but we have been studying the effects of influenza on the cardiovascular system and investigating ways to lower the risk of influenza-related complications in our high-risk patients. As information emerges from this new pandemic, it is becoming abundantly clear that, as is the case with influenza, patients with cardiovascular disease are especially vulnerable to the ravages of this virus, which may have unique effects on the cardiovascular system. The lessons we have learned from influenza and past coronavirus outbreaks can be especially informative during this time of limited evidence on this new threat.

The association between viral respiratory illness and risk for subsequent cardiovascular events has been well established; acute infections, particularly influenza, have been linked temporally to subsequent myocardial infarction and heart failure decompensation.[1,2] Viral infection increases metabolic demand, which can unduly decompensate individuals with heart failure who have limited reserve. Some viral infections, such as influenza or coxsackie, have direct toxic effects on the myocardium and can cause myocarditis. Influenza has been associated with destabilization of atherosclerotic plaques, leading to acute coronary syndrome, and higher rates of ventricular arrhythmias.

The extent to which, and mechanisms by which, coronaviruses may contribute to increased cardiovascular risk in the general population or in high-risk individuals remains unclear, but early reports suggest that an individual's risk, including for death, is directly related to his or her degree of comorbidity. Among 72 314 patients in Wuhan (of whom 44 672 had laboratory-confirmed COVID-19), the case-fatality rate was 10.5% among those with underlying cardiovascular disease and confirmed infection, compared with 2.3% in the cohort overall.[3] Whereas the exact mortality rates of this disease have been difficult to assess accurately, may vary regionally, and may be lower than originally estimated given limited testing and unknown number of asymptomatic cases, there is almost certainly a multifold increased relative risk associated with preexisting cardiovascular disease, a finding that is consistent with the Middle East Respiratory Syndrome experience.

Chronic conditions influencing severity of illness for coronaviruses are analogous to factors influencing risk related to other respiratory viruses, including seasonal influenza. Older adults and those with multiple medical conditions are more susceptible to infection-related complications because of a less robust immune system and are more likely to develop secondary bacterial infections. Shared pathogenic mechanisms between cardiovascular disorders and infectious diseases include endothelial

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dysfunction and inflammation, which can attenuate innate immune function. Immune dysregulation and cytokine storm appear to be key components of progression to critical disease in COVID-19. Individuals with heart failure exhibit attenuated immune response to influenza viruses and most certainly will have similar altered immune responses to COVID-19.

Even among those without underlying cardiac disease, the prior coronavirus outbreaks have been associated with adverse cardiovascular effects. Both transient cardiomegaly and decreases in left ventricular ejection fraction, observed during acute illness with improvement after recovery, were reported during the 2002 to 2003 severe acute respiratory syndrome (SARS) epidemic. SARS coronavirus 2 (SARS-CoV-2) shares 79.5% sequence identity with SARS coronavirus (SARS-CoV), and the point of entry of SARS-CoV-2 into the host cell is also analogous to SARS-CoV, through the angiotensin-converting enzyme 2 receptor, which is expressed on airway epithelial cells. Whereas the majority of severe morbidity associated with COVID-19 has been pulmonary, reports are emerging of cardiac injury, left ventricular dysfunction, and myocarditis associated with severe COVID-19,[4] and the molecular similarities of SARS-CoV-2 and SARS-CoV make cardiac effects similar to those reported with SARS likely.

Whereas COVID-19 shares similarities with seasonal influenza, it appears to be more transmissible and more virulent than any influenza since the 1918 influenza pandemic. Estimates from China indicate that the COVID-19 basic reproductive number (secondary cases generated by a primary case of infection in a susceptible population) is ≈1.94, which is higher than that of influenza, estimated at 1.3 for most years and 1.8 for the 1918 influenza pandemic. Accumulating data indicate higher mortality rates for COVID-19 compared with the 2009 H1N1 pandemic. Although most individuals with COVID-19 do not experience severe symptoms, evidence of asymptomatic transmission and substantial community spread suggest that this virus will infect a larger number of people and lead to more deaths than SARS and Middle East respiratory syndrome.[5]

Current strategies for COVID-19 management focus on minimizing transmission and spread of infection and providing supportive care for individuals who experience airway compromise or other adverse clinical sequelae. Because severity of illness with COVID-19 can be highly variable, with some individuals displaying no or minimal symptoms, and with restricted testing available in most places, individuals at high risk should avoid contact with people with even mild respiratory infections. Other strategies for minimizing risk of exposure include delaying routine, in-person medical appointments and elective procedures. In the absence of an effective vaccine or targeted antiviral therapies, management options are limited. Several pharmacological treatments are under investigation, and we need to be vigilant in considering how they may affect the cardiovascular system. For example, use of chloroquine and hydroxychloroquine, for which limited data exist, can cause QT prolongation.

For patients with underlying cardiovascular disease, other opportunities for minimizing complications from infection include remaining up to date on other immunizations, including influenza vaccine, which is available and effective, and pneumococcal vaccine, as secondary bacterial infections often lead to hospitalizations among those with primary viral infections.

Because viral illness has been shown to exacerbate underlying cardiac illness and can lead to acute events such as acute myocardial infarction or decompensated heart failure, efforts should be made to optimize guideline-directed treatment strategies that have been shown to improve clinical status in high-risk patients, and thus reduce the risk of worsening symptoms or acute events in case of infection. In patients without known or suspected COVID-19, this includes all evidence-based therapies in cardiovascular disease, such as aspirin, statins, and β-blockers for secondary prevention in patients with coronary disease, and guideline-directed medical therapy in those with heart failure. Keeping patients out of the hospital is an essential component to reducing infection. The use of guideline-directed medical therapy is also warranted in patients with known or suspected COVID-19. One area of uncertainty is the influence of angiotensin receptor enzyme inhibitors and angiotensin receptor blockers on this disease, because coronaviruses gain entrance to cells by the angiotensin-converting enzyme 2 receptor, which might be upregulated by use of these therapies. The American Heart Association, the American College of Cardiology, the Heart Failure Society of America, and the European Society of Cardiology recommend not withdrawing renin-angiotensin system inhibitors on the basis of the available data unless warranted clinically.

The rapid spread of COVID-19 is testing healthcare systems around the world profoundly and likely will continue to do so before this pandemic abates. The increased vulnerability of patients with cardiovascular disease at risk for adverse cardiovascular outcomes, in conjunction with patients' reduced access to healthcare services while the healthcare system is stressed, underscores the importance of understanding COVID-19 and its implications for all practitioners of cardiovascular medicine.

ARTICLE INFORMATION

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