Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

than with walking. The authors speculated that differences in body posture, functional residual capacity, and/or hemodynamics probably caused these findings. The ability to fix the arm position with the handlebars may improve accessory muscle use in a manner that improves respiratory efficiency on the bicycle. The authors concluded that "cycling may not reflect precisely their ventilatory and metabolic requirements for daily activities such as walking."

The current study and another recent investigation[12] confirm that arterial desaturation is more likely to occur with the 6MWT than with maximal cycling. Whether walking or cycling more correctly demonstrates the physiologic abnormalities with exercise in severe COPD really does not matter. Most patients with COPD do not ride a bicycle, but they nearly all walk.

In summary, Turner et al have added to our understanding of the evaluation of dyspneic COPD patients by comparing the 6MWT, ISWT, and cycle ergometry tests in a group with substantial airflow obstruction. In this population, all three act as maximal tests. The walking tests are more likely to identify oxygen desaturation, and the 6MWT is the easiest to perform. For many situations, it is an adequate test, although treadmill testing may be necessary for specific applications such as those mentioned above.

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Treatment of Severe Acute Respiratory Syndrome

Severe acute respiratory syndrome (SARS) is a newly emerged infectious disease that has posed an enormous threat to international health. During the global outbreak in 2003, the most severely affected countries were China (*ie*, mainland China, Hong Kong,[1] and Taiwan[2]), Vietnam, Canada,[3] and Singapore.[4] On July 5, 2003, the World Health Organization announced that the last known chain of human-to-human transmission of SARS had been broken in Taiwan.[5] This brought an end to the initial outbreak of SARS that had begun in mid-November 2002 in southern China and had spread internationally in late February 2003. Genetic analysis showed that the SARS coronavirus (CoV) isolates from Guangzhou shared the same origin with those in other countries, with a phylogenetic pathway that matched the spread of SARS to other parts of the world.[6] As of July 31, 2003, 8,098 probable cases had been reported in 29 countries and regions with a death toll of 774 (9.6%).[5]

Due to the limited knowledge about this newly emerged disease, the treatment of SARS was empiric during the outbreak in 2003. Apart from supportive care, the appropriate treatment for SARS is unknown at present. No prospective, randomized, placebo-controlled study of any intervention has been reported. Respiratory failure is the major complication of SARS. Hypoxemia develops in almost half of affected adults, and 20 to 36% of adults may require

ICU admission, whereas 13 to 26% of adults may progress into ARDS, necessitating the use of invasive ventilatory support.[1,7–10]

Anecdotal reports have indicated that noninvasive positive-pressure ventilation (NPPV) was effective in SARS patients with respiratory failure.[11,12] In the current issue of *CHEST* (see page 845), Cheung et al report on the efficacy and safety of NPPV in the treatment of acute respiratory failure, which occurs during phase 2 of SARS.[7,10] NPPV was applied via face mask to 20 patients who developed severe acute hypoxemic respiratory failure without preexisting COPD in a hospital environment with adequate airflow, full personal protective equipment, and the addition of a viral-bacterial filter to the exhalation port of the NPPV device. Endotracheal intubation was avoided in 14 patients (70%), who had a much shorter length of stay in the ICU than did those who were intubated. Health-care workers (HCWs) were particularly vulnerable to SARS-CoV as viral loads increased to peak levels on days 8 to 10 from disease onset.[7] Thus, the major concern with the use of NPPV was whether there was any clinical or subclinical SARS-CoV infection among the HCWs involved in the management of the 20 patients. None of the 105 HCWs involved had developed clinical evidence of SARS, whereas 102 HCWs (97%) had negative SARS serology. As there were still three HCWs who had refused SARS serology testing, one cannot entirely eliminate the possibility of subclinical SARS infection that was related to the use of NPPV, although it seems highly unlikely. However, it has been reported[13] that wild animal handlers in southern China may develop positive antibodies to SARS-CoV without any symptoms. Despite the retrospective nature of this study, the small sample size, and the lack of a control group, the authors are to be commended for adding more evidence for the application of NPPV in respiratory failure related to community-acquired pneumonia (CAP). Confalonieri et al[14] have reported that NPPV lowered the intubation rate, the length of ICU stay, and the 2-month mortality rate in patients with severe CAP, but these beneficial actions were confined to those patients with underlying COPD. In a prospective observational study that excluded patients with underlying COPD, Jolliet et al[15] showed that NPPV improved oxygenation and respiratory rate in 22 of their 24 patients with CAP during the initial trial, but 66% of patients needed intubation after an average of 1.3 days, mainly because of worsening respiratory failure. NPPV was well-tolerated by SARS patients, probably because sputum production was uncommon in patients with SARS-CoV pneumonia.[1–4,10,16] Nevertheless, NPPV should be applied only if there is adequate protection for the HCWs (*ie*, adequate air exchange, contact and droplet precaution, plus full personal protective equipment) because of the potential risk of viral transmission via mask leakage and flow compensation causing dispersion of a contaminated aerosol. Cheung et al have shown that NPPV may reduce the intubation rate and the number of ICU admissions when applied early in SARS patients with severe acute hypoxemic respiratory failure. The addition of a viral-bacterial filter to the exhalation port of NPPV or oxygen mask[17] may reduce the risk of nosocomial transmission of SARS.

Ribavirin, a nucleoside analog that has activity against a number of viruses *in vitro*, was widely used in the treatment of SARS last year.[1,3,4,7–11,18,19] After 2 weeks of ribavirin treatment, 59% of our patients experienced a fall in hemoglobin level of > 2 g/dL from baseline, whereas evidence of hemolytic anemia was documented in 36% of patients.[19] The use of ribavirin for the treatment of SARS in Toronto, based on a higher dosage that has been used for treating hemorrhagic fever virus, was associated with more toxicity, including elevated levels of transaminases, and bradycardia.[3] Nevertheless, ribavirin has no significant *in vitro* activity against SARS-CoV.[20–22]

Genomic analysis of the SARS-CoV has revealed several types of enzymatic targets, including the proteases.[23–25] Chu et al[26] have demonstrated *in vitro* activity against SARS-CoV for lopinavir and ribavirin at 4 and 50 μg/mL, respectively, after 48 h of incubation. Cytopathic inhibition was achieved down to a concentration of 1 μg/mL lopinavir combined with 6.25 μg/mL ribavirin, suggesting that this combination might be synergistic against SARS-CoV *in vivo*.[26] Two retrospective matched cohort studies[26,27] have compared the clinical outcome between patients who received lopinavir (400 mg)/ritonavir (100 mg) [LPV/r] (Kaletra; Abbott Laboratories; Abbott Park, IL) in addition to ribavirin, either as initial therapy within 5 days of the onset of symptoms or as rescue therapy after pulse methylprednisolone (MP) treatment for worsening respiratory symptoms, vs historical control subjects who received ribavirin alone as an initial antiviral therapy. The addition of LPV/r as initial therapy was associated with a reduced overall death rate (2.3%) and intubation rate (0%), when compared with a matched cohort that received standard treatment (15.6% and 11%, respectively).[27] Other beneficial effects included a reduction in MP use, fewer nosocomial infections, a decreasing viral load, and a rising peripheral lymphocyte count.[26] However, the subgroup that had received LPV/r as rescue therapy was no better than the matched cohort and received a higher mean dose of MP.[27] The improved clinical outcome in patients who received LPV/r as part of the initial therapy may

be due to the fact that both peak serum concentrations of lopinavir (9.6 μg/mL) and trough serum concentrations of lopinavir (5.5 μg/mL) could inhibit the virus.[28]

During phase 2 of SARS, when there is progression of pneumonia and hypoxemia, IV pulse MP (0.5 g daily) has been given to prevent immunopathologic lung injury,[1,7,10,12,18,19] with the rationale that progression of the pulmonary disease may be mediated by the host inflammatory response.[7] The use of pulse MP during clinical progression was associated with favorable clinical improvement with resolution of fever and lung opacities within 2 weeks.[1,10,19] Corticosteroids have been used as therapy because CT scans of the thorax have revealed radiologic features of bronchiolitis obliterans organizing pneumonia,[1,10,18,19,29] which is a steroid-responsive condition the presence of which is suggestive of an immunologic phenomenon.[30] The pulmonary pathologic features were dominated by diffuse alveolar damage,[1,31] with the presence of multinucleated pneumocytes, but bronchiolitis obliterans organizing pneumonia-like lesions in subpleural locations were also seen.[31] The use of high-dose pulse MP therapy aims to suppress the cytokine-induced lung injury in phase 2 of SARS.[1,7,10,12,18,19] Wong et al[32] have demonstrated a marked elevation of T helper type 1 cytokine interferon (IFN)-γ, inflammatory cytokines interleukin (IL)-1, IL-6, and IL-12 for at least 2 weeks after SARS onset. The chemokine profile demonstrated a significant elevation of IL-8, monocyte chemoattractant protein-1, and IFN-γ inducible protein-10. Corticosteroids significantly reduced IL-8, monocyte chemoattractant protein-1, and inducible protein-10 concentrations from 5 to 8 days after treatment. The data confirmed the T helper type 1 cell-mediated immunity and hyperinnate inflammatory response in patients with SARS through the accumulation of monocytes/macrophages and neutrophils.[32] In addition, in patients with fatal SARS, macrophages are the prominent leukocytes present in the alveoli, with evidence of hemophagocytosis in the lungs.[33] Hemophagocytosis has been attributed to cytokine dysregulation,[34] and intervention with steroids might modulate this cytokine response and prevent a fatal outcome, as has been proposed for other causes of ARDS.[35] However, a retrospective analysis[36] showed that the use of pulsed corticosteroids was associated with an increased risk of 30-day mortality, but the study could not establish whether a causal relationship exists between the use of pulsed corticosteroids and increased risk of death. Nevertheless, prolonged corticosteroid therapy could increase the risk of complications such as disseminated fungal disease[37] and avascular necrosis of bones. The optimal dose, timing, and duration of corticosteroid administration require further investigation.

Type I IFNs like IFN-α are produced early as part of the innate immune response to viral infections. Type I IFNs inhibit a wide range of RNA and DNA viruses[38,39] including SARS CoV *in vitro*.[22,40] In an uncontrolled study in Toronto,[41] the use of IFN alfacon-1 plus corticosteroids was associated with improved oxygen saturation, more rapid resolution of radiographic lung opacities, and lower levels of creatinine kinase. Complete inhibition of the cytopathic effects of SARS-CoV in culture was observed for IFN subtypes β-1b, α-n1, α-n3, and human leukocyte IFN-α.[22] In experimentally infected cynomolgus macaques with SARS-CoV, prophylactic treatment with pegylated IFN-α significantly reduced viral replication and excretion, viral antigen expression by type 1 pneumocytes, and pulmonary damage, compared with untreated macaques, whereas postexposure treatment with pegylated IFN-α yielded intermediate results.[42] These findings support clinical testing of approved IFNs for the treatment of SARS.

There are several other treatment modalities that deserve further investigation. Glycyrrhizin, an active component of liquorice roots, was active in inhibiting SARS- CoV *in vitro*.[21] Convalescent plasma, donated by patients who have recovered from SARS, contains neutralizing antibodies that may be clinically useful for treating other SARS patients.[43] An adenovirus-based vaccine can induce strong SARS-CoV-specific immune responses in rhesus macaques and holds promise for the development of a protective vaccine against SARS-CoV.[44] There is evidence that SARS-CoV infection is initiated through the binding of S1 protein to the angiotensin-converting enzyme-2 receptor.[45] A high-affinity human monoclonal antibody (huMab) has been identified for use against the SARS-CoV S1 protein termed *80R* that has potent neutralizing activity *in vitro* and *in vivo*.[46] huMab 80R efficiently neutralizes SARS-CoV and inhibits syncytia formation between cells expressing the S protein and those expressing the SARS-CoV receptor angiotensin-converting enzyme-2. huMab 80R may be a useful viral entry inhibitor for the emergency prophylaxis and treatment of SARS.[46]

Early laboratory confirmation of SARS can facilitate the early isolation of patients and can reduce the risk of nosocomial transmission. The detection rates for SARS-CoV on urine samples, nasopharyngeal aspirates, and stool specimens using conventional reverse transcriptase polymerase chain reaction (RT-PCR) are generally low in the first week of illness, whereas serology for confirmation may take 28 days to reach a detection rate of $> 90\%$.[7] By optimizing RNA extraction methods and applying quantitative

real-time RT-PCR techniques, the sensitivity of nasopharyngeal aspirate specimens for the early diagnosis of SARS can be enhanced to 80% for the first 3 days.[47] The quantitative measurement of blood SARS-CoV RNA with the real-time RT-PCR technique has been developed with a detection rate of 75 to 80% during the first week of infection.[48–50]

One year has elapsed since the global outbreak and spread of SARS through international traveling. Despite the reemergence of SARS involving laboratory personnel in Singapore[51] and Taiwan,[52] and more recently in four residents in Guangdong,[53,54] no major outbreak or secondary spread has occurred. However, one should never be complacent when dealing with emerging infectious diseases. Randomized placebo-controlled studies of different treatment modalities must be in place before SARS returns.

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The Evolving Paradigm of Hyperglycemia and Critical Illness

It is fascinating to observe how the approach to the diagnosis and treatment of a particular medical condition evolves over time. The treatment of hyperglycemia in the setting of critical illness represents one such example. It has been known for years that critically ill patients become hyperglycemic for a number of different reasons. Alterations in glucose metabolism including insulin resistance are common. There are numerous adaptive responses, such as increased catecholamine secretion, and elevations in serum cortisol and glucagon, that can also result in hyperglycemia. As a medical student some 20 years ago, hyperglycemia was viewed as more of an epiphenomenon. Though frequently observed in the ICU, most physicians did not think that it was directly pathogenic. This resulted in a *laissez fair* approach to treatment. In general, I was taught then to keep the blood glucose (BG) level at < 300 mg/dL with occasional doses of relatively small amounts of subcutaneous insulin.

As our knowledge base expands, this attitude is clearly changing. Data have gradually accumulated demonstrating that for specific medical and surgical diagnoses, a tighter control of hyperglycemia improves morbidity, mortality, and other outcome measures in both diabetic and nondiabetic patients. For example, a review article[1] concluded that the mortality risk increased 3.9-fold in a group of nondiabetic patients with acute myocardial infarction whose BG levels were in a range from ≥ 109.8 to 144 mg/dL. In a cardiac surgical model, mortality correlated with BG level in a dose-dependent manner with the lowest mortality occurring in the group with a mean postoperative BG level of < 150 mg/dL.[2] There is an increase in serious infections including sepsis, pneumonia, and wound infections in postoperative diabetic patients with elevated BG levels.[3] Mortality and functional recovery after acute stroke correlated with BG in a nondiabetic patient group.[4] In an important study, Van den Berghe et al[5]