Rising to the Challenge of COVID-19: Advice for Pulmonary and Critical Care and an Agenda for Research

The explosion of coronavirus disease (COVID-19), the illness related to the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had worldwide health implications, but it is a particular challenge to those of us who practice Pulmonary and Critical Care Medicine (PCCM) because of the high rate of respiratory tract involvement, the frequent presence of pneumonia in these patients, and the high mortality rate for those with respiratory failure, particularly in the ICU (1, 2). In China, although 80% had mild illness, approximately one quarter of those who were hospitalized for COVID-19 needed ICU care. For those in the ICU, mortality was 49%, whereas those with Acute Respiratory Distress Syndrome (ARDS) had a mortality of 52.4% (1, 3). As has become clear, many countries have not been able to contain COVID-19 spread because of unavailability of early widespread testing, undertesting of those at risk, failing to trace all contacts of infected patients, and in some overcrowded settings, nosocomial spread of the infection. There is concern about a shortage of ICU beds and ventilators, trained medical staff, adequate personal protective equipment (PPE), and ever-changing recommendations about management and supportive care, at a time when no definitive therapy for COVID-19 is available. All of these factors put great strain on PCCM clinicians, and we need to have a plan for meeting these challenges. In this editorial, we provide suggestions based on our experiences with this epidemic to guide our colleagues. We adhere to Benjamin Franklin's assessment that "by failing to prepare, you are preparing to fail."

Some important basic facts about COVID-19 are still being determined, most importantly the mortality rate. While some series report mortality rates as high as 3–4%, the rates vary widely by age, comorbidity, and severity of illness on presentation (4). Predictors of mortality have included older age, elevated D-dimer on admission, and higher degree of initial organ dysfunction (4). However, the calculated mortality rate is also a reflection of the degree of widespread diagnostic testing, because many infected individuals have minimal symptoms and may not be routinely evaluated. In South Korea, efforts have been made to test the broad population, and when a more accurate number of infected individuals is included, the overall mortality rate may be $<1\%$. However, this makes COVID-19 more deadly than seasonal influenza, which has a 0.1% mortality rate; this may reflect not only the natural history of influenza but also the favorable impact of vaccination and antiviral medication. Other coronaviruses, such as Middle East Respiratory Syndrome and SARS, have much higher mortality rates, estimated to be 40% and 10% respectively (5). COVID-19 does present unique challenges as we learn about its relatively long asymptomatic, but infectious, incubation period (5–7 d) during which community spread and the prolonged shedding of virus after symptom resolution (an additional 7–14 d) may occur (6). In a series of 181 cases with identifiable exposure and symptom onset, the median incubation period was 5.1 days, but it was not until 11.5 days that 97.5% of patients had symptoms (6). In experimental studies, SARS-CoV-2 can remain viable in aerosols for hours and on surfaces for days, making aerosol and environmental spread possible (7). These findings have implications not only for community dissemination of illness by apparently healthy and asymptomatic patients but also for the safety of PCCM providers and their staff as they evaluate and treat these patients early and later in the course of the illness.

To contain the illness, it is essential to make an accurate and early diagnosis. In China, in the absence of an early test, it was difficult to prevent person-to-person spread in the community because of an initial lack of surveillance. Earlier hands-on input from respiratory specialists may also have been valuable. To address these issues, Bai and colleagues are developing a handheld, web-based tool to identify and manage suspected COVID-19 patients (8). This approach, called nCAPP, uses a handheld device that performs eight functions: patient identification, consultation with simple questions, diagnostic suggestions, treatment recommendations, identification of local experts, mapping of disease locations, advice about self-protection, and dissemination of resources to control the disease. Diagnostic testing involves nucleic acid detection in a variety of samples, including nasopharyngeal and oropharyngeal swabs, lower respiratory tract (BAL and sputum) samples, blood, feces, and urine. In Singapore, disease control occurred with a combination of widespread testing, contact tracing, use of negative pressure isolation rooms for infected patients, and social distancing to minimize disease spread.

All of the authors of this editorial have had experience with COVID-19 patients in different healthcare settings, including China, Singapore, Italy, and the United States, and we have put together some observations and practical suggestions for PCCM practitioners. Mortality is the highest for those with respiratory failure, and many deaths are related to refractory ARDS, but death can also result from later complications such as cardiac arrhythmias and renal dysfunction (which tend to occur in the second week of critical illness), although multisystem organ failure is less common. The risk of dying is highest in those with older age, hypertension,

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diabetes, and lower temperature. In addition, IL-6 levels were slightly higher in those who died, leading to a trial in China of methylprednisolone, which was associated with a lower mortality, in an uncontrolled intervention (3). In over 2,000 patients with COVID-19 who died mainly in northern Italy (www.epicentro.iss.it [accessed 2020 Mar 22]), the mean age was 79.5 years, with an interquartile range between 74.3 and 85.9 years and with females older than male patients (mean age, 83.7 vs. 79.5 yr). This group was about 15 years older than those who survived (80.5 vs. 63.0 yr). Patients with COVID-19 who died had a mean of 2.7 comorbidities, with cardiovascular disease being the most common, but many had chronic lung disease: <1% of deceased patients had no concomitant disease. These findings are similar to those of a retrospective Chinese series on 54 patients who died in hospital (out of 191 admitted) (4). In a Chinese study of patients with ARDS, hypertension was present in 19.4%, diabetes in 10.9%, and cardiovascular disease in 3.5% (3).

One major concern for all of us has been whether our respiratory wards and ICUs will have the capacity of both beds and mechanical ventilators to provide for a surge of patients with COVID-19 if community spread is not contained. This has led to efforts to "flatten the curve" of incidence over time, so that even if a large segment of the population is infected, this will occur over many months, rather than weeks. If a surge of illness overwhelms our existing resources, it may lead to the moral distress of having to ration limited lifesaving resources (9). From the experience in Italy, it is clear that all respiratory and ICU physicians will need to work together to form a network of care that accommodates the needs of as many patients as possible (9). Physicians also understandably worry about their own health and well-being. Demands are great, and burnout from overwork and emotional stress are a real concern, as is worry about becoming infected owing to high-risk exposures (urgent intubation or aerosol-generating procedures), and lack of adequate PPE. In Italy, over 2,000 cases of COVID-19 among healthcare workers (with a mean age of 49.0 yr) have been documented, representing about 14% of all cases (www.epicentro.iss.it [accessed 2020 Mar 22]); these numbers represent a major concern at the moment in many Italian hospital settings. In China, 3.8% of cases were in healthcare workers, and 14.8% were classified as severe or critical (3). The recommendations for PPE in the United States (surgical masks being acceptable, and not N95 masks for everyone) differ from other countries (10). Currently, this has led to recommendations to avoid noninvasive ventilation, high-flow oxygen, and bag valve mask ventilation if possible, and if not, that these procedures be done in negative pressure rooms, if available. When a patient is in respiratory distress, it seems wise to perform an early and controlled intubation to manage the patient, in an effort to reduce the risk of contaminating the healthcare team (11). Ideally patients with COVID-19 should be grouped together and critically ill patients kept in negative pressure rooms, and in Italy, this has been applied, with entire hospital centers devoted to these patients, and those with other illnesses taken care of at other facilities.

Management of COVID-19 is not different from management of most viral pneumonias causing respiratory failure. Treatment of those with ARDS should include conservative fluid strategies, empirical early antibiotics for suspected bacterial coinfection until a specific diagnosis is made, lung-protective ventilation, prone positioning, and consideration of extracorporeal membrane oxygenation for refractory hypoxemia (12). In the Singapore experience, early invasive mechanical ventilation appears beneficial, with an average of 1 week between symptom onset and the need for ICU admission. ICU admissions consisted of predominantly males, with single-organ (respiratory) failure necessitating average ICU stays of 1–2 weeks. Some individuals required high positive end-expiratory pressure, but plateau and driving pressures were not excessive. Hypoxia tended to be positional and not correlated with radiological appearance in individual patients, and therefore prone positioning has been useful (13). Desaturations may be sudden with hypoxemia that requires time to improve, so patience is justified. Deterioration may occur suddenly and happen even >1 week after ventilation when nosocomial infection, ARDS, further organ involvement, cardiac arrhythmias, and/or shock can complicate the clinical picture. In some circumstances, extracorporeal membrane oxygenation may be necessary.

No antiviral or other drug is currently recommended, but therapeutic options that have been proposed include steroids, intravenous immunoglobulin, selective cytokine blockade (e.g., anakinra or tocilizumab), and JAK (Janus kinase) inhibition. Clinical trials with agents such as lopinavir/ritonavir, remdesivir, and tocilizumab are ongoing. One randomized evaluation of lopinavir/ritonavir in 199 patients in China showed no benefit compared with placebo (14). The evidence for the potential effectiveness of chloroquine is based on *in vitro* data and unpublished single arm studies in China, but many centers are now using hydroxychloroquine. In one single arm study on 20 patientws with confirmed COVID-19, treatment with hydroxychloroquine was associated with viral load reduction, and this effect seemed to be reinforced by the combination with azithromycin (15). Empiric therapy has potential safety risks, and our priority should be recruitment of patients into well-designed, multinational clinical trials to ensure the assessment of safety and effectiveness of treatment options.

The outpatient management of lung disease patients has been complicated by concerns about COVID-19. In the United States and elsewhere, many patients are receiving care via telemedicine, which has inherent benefits and some limitations, as we work to improve this approach (16). Many outpatients are being encouraged to delay routine visits, but for those with complex lung disease (advanced chronic obstructive pulmonary disease, asthma, or pulmonary fibrosis), periodic face-to-face evaluation may be needed, and the potential for harm with long delays needs to be determined. For patients with exacerbations of chronic lung disease, office evaluation needs to be done in a way to minimize infection risk for both the patient and the healthcare team; this may necessitate availability of private rooms, a segregated waiting room for those with suspected infection, PPE, and diagnostic testing. Routine radiography is even more complex as X-ray facilities need to slow down workflow to allow for room cleaning between patients.

We now need to think about ways to move forward with a robust research agenda. This can be done with clinical and epidemiologic observations, use of new diagnostic testing tools, and

Table 1. Key Priorities for COVID-19 Research by Pulmonary and Critical Care Investigators

Understanding disease spread and management of asymptomatic patients who are shedding the virus
Defining host and viral virulence factors that can predict and explain which patients are likely to have mild or severe disease and by what mechanism
Define viral incubation period and the optimal duration of quarantine
Determine if group quarantine of suspected or at-risk patients is an effective control measure or a means of spreading disease
Identify common medications that might alter disease susceptibility and outcome, such as aspirin and nonsteroidal antiinflammatory agents, hydroxychloroquine, anginotensin-converting enzyme inhibitors and receptor blockers, or agents that could alter cellular binding sites for the virus
Develop optimal methods to slow disease spread
Define how much herd immunity will be needed to slow pandemic spread
Develop biomarkers or clinical tools to predict disease course and severity
Conduct randomized clinical trials with promising agents such as antiviral drugs (remdesivir), pooled serum or immunoglobulin, hydroxychloroquine, IL-6 inhibitors, JAK inhibitors, and other agents
Define the role of antibiotics to treat initial bacterial coinfection and subsequent nosocomial pneumonia
Conduct randomized controlled trials of antiinflammatory agents such as corticosteroids to see if they are helpful or harmful, or if specific subsets and timing of administration can be identified to define those most likely to benefit
Study ways to measure and minimize the psychological stress to healthcare workers and the public of pandemic COVID-19
Study tools to improve patient management, allowing effective isolation and disease monitoring (e.g., telemonitoring in home or in residential facilities)
Define methods to allow for noninvasive ventilation without risking harm to healthcare workers

Definition of abbreviation: COVID-19 = coronavirus disease.

clinical trials with new and repurposed therapies. Some of the key priorities for research are summarized in Table 1. The challenges to the pulmonary and critical care community are immense, but the opportunity for us to improve the lives of our patients and expand knowledge of an important illness will be extremely gratifying. ■

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Guidance for the Better Care of Patients with Chronic Obstructive Pulmonary Disease

Writing guidelines is hard work. At first sight, it seems simple to summarize what you believe to be optimal care, but beliefs should be based on evidence, and that can be hard to identify in an unbiased way. To reduce the risk of bias when preparing guidelines, a range of complex methodologies have been developed. Documents such as the standards of care for chronic obstructive pulmonary disease (COPD) developed jointly by the American Thoracic Society (ATS) and European Respiratory Society in 2004 (1) would not be methodologically acceptable today. The newer approach has narrowed the scope of the guidance offered, improving the certainty of the conclusions drawn at the cost of restricting the number of questions addressed. Although there have been moves in the guidelines community to open up the types of evidence considered, most published guidelines try to identify randomized controlled trials (RCTs) that offer evidence directly or indirectly with which the guideline writers can address the clinical question they are trying to understand. Limiting acceptable answers to questions for which RCT evidence is present can lead to some strange anomalies, as we found when writing the European Respiratory Society/ATS guidance about the management of acute exacerbations of COPD (2). Although observational studies suggested that stopping smoking had a beneficial on exacerbation numbers, we could not make a recommendation about this, because no RCT to test this idea was ethically possible! However, there are still questions to consider for which RCT data can provide answers, even in a well-worked area such as COPD care, and this was the challenge taken up by a group of North American and British physicians (pp. e56–e69) who developed the clinical practice guideline on the pharmacologic management of COPD published in this issue of the *Journal* (3).

The expert group considered six questions in relation to the effectiveness of drug treatment in COPD and assigned a priority to a range of outcomes that differed between the interventions. Thus, the risk of pneumonia was prioritized above efficacy outcomes for questions that related to corticosteroids, but it is not discussed in connection with long-acting bronchodilator therapy or opiate use to manage breathlessness. This suggests that prior knowledge of the field does influence the weighting given to particular outcomes. Clinical practice guidance needs to address people other than practicing clinicians with both patients and payers. The authors explain clearly the interests of these different stakeholders and use carefully nuanced language to support their conclusions and what these conclusions might mean to these interest groups. Whether people reading the summary of the document will take in these subtleties is unclear, and this would be a fertile area for further research. Understanding why guideline writers reached their conclusions is always interesting, and this is set out in the section on committee discussion, which, together with a series of research needs, accompanies each question.

So, what conclusions do the authors draw? First, there is strong evidence that initial therapy for symptomatic patients with COPD should be administered with both a long-acting β-agonist (LABA) bronchodilator and a long-acting muscarinic antagonist (LAMA) bronchodilator rather than either drug singly. This analysis is in line with recommendations from the UK National Institute for Health and Care Excellence, which used the same methodology to ask a similar question of much the same data (4). Reproducibility is always a welcome finding in any area of medicine, although the cost-effectiveness of this treatment policy is likely to vary from region to region, reflecting local cost issues and healthcare access. The next two questions looked at the need for additional inhaled

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