Rising to the Challenge of the Novel SARS-coronavirus-2 (SARS-CoV-2): Advice for Pulmonary and Critical Care and an Agenda for Research

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AJRCCM Articles in Press. Published March 23, 2020 as 10.1164/rccm.202003-0741ED

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AJRCCM Articles in Press. Published March 23, 2020 as 10.1164/rccm.202003-0741ED

The explosion of coronavirus disease 2019 (COVID-19), the illness related to the novel SARS coronavirus-2 (SARS-CoV-2), has had worldwide health implications, but 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 needed ICU care, and for those in the ICU, mortality was 49%, while 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, due to 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, 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 the assessment of Benjamin Franklin, 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

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organ dysfunction (4). However, the calculated mortality rate is also a reflection of the degree of widespread diagnostic testing, since many infected individuals have minimal symptoms and may not be routinely evaluated. In South Korea, efforts have been made to do broad population testing, and when a more accurate number of infected individuals is included, the overall mortality rate may be less than 1%. However, this makes COVID-19 more deadly than seasonal influenza, which has a 0.1% mortality rate, which may reflect not only the natural history of influenza, but also the favorable impact of vaccination and anti-viral medication. Other coronaviruses such as MERS 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 days) during which community spread may occur, and the prolonged shedding of virus after symptom resolution (an additional 7-14 days) (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 well 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 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

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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 8 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 (bronchoalveolar lavage 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 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 multi-system organ failure is less common. The risk of dying is highest in those with older age, hypertension, 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 2000 COVID-19 patients who died mainly in northern Italy (www.epicentro.iss.it), 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 (83.7 vs 79.5 years).

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This group was about 15 years older than those who survived (80.5 vs 63.0 years). COVID-19 patients who died had an average of 2.7 co-morbidities, with cardiovascular disease being the most common, but many having chronic lung disease: less than 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 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 COVID-19 patients, 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 for 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 due to high risk exposures (urgent intubation, aerosol generating procedures), and lack of adequate personal protective equipment (PPE). In Italy, over 2000 cases of COVID-19 among healthcare workers (with a mean age of 49.0 years) have been documented, representing about 14% of all cases (www.epicentro.iss.it): 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

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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 non-invasive 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 COVID-19 patients should be cohorted and critically ill patients kept in negative pressure rooms, and in Italy, this has been applied, with entire hospital centers being devoted to these patients, and those with other illnesses being 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 co-infection 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 one week between symptom onset and the need for ICU admission. ICU admissions were predominantly males, with single organ (respiratory) failure necessitating average ICU stays of 1-2 weeks. Some individuals required high PEEP 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 hypoxaemia 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 inhibition. Clinical trials with the combination lopinavir/ritonavir, remdesivir and tocilizumab are ongoing. One randomized evaluation of lopinavir/ritonavir in 199 patients in China showed no benefit compared to 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 confirmed COVID-19 patients, 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 COPD, asthma, 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

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be done in a way to minimize infection risk for both the patient and the healthcare team, which 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 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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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 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; aspirin and non-steroidal anti-inflammatory agents, hydroxychloroquine anginotensin converting enzyme inhibitors and receptor blockers: 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 anti-viral drugs (remdesivir), pooled serum or immunoglobulin, hydroxychloroquine, IL-6 inhibitors, and other agents

-- Define the role of antibiotics to treat initial bacterial co-infection and subsequent nosocomial pneumonia

-- Conduct randomized controlled trials of anti-inflammatory 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

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---- 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 non-invasive ventilation without risking harm to healthcare workers

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