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COVID-19: a primer for healthcare providers

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Summary According to the World Health Organization (WHO) the China office was first notified of cases of atypical pneumonia in Wuhan City on 31 December 2019. A viral genome sequence of a novel coronavirus, currently termed SARS-CoV-2, with a disease process called COVID-19 was released 1 week later via online resources to obtain public health support in control of spread. Since then, the virus rapidly evolved into a global pandemic. Therefore, healthcare providers need to be familiar with the clinical presentation of infected patients and measures to quickly isolate them. The prevention of nosocomial spread is paramount to proper control of COVID-19 and is reviewed. Currently, treatment is supportive. Researchers are working to develop vaccines and identify effective antiviral interventions. Those recently discussed in the literature are briefly reviewed.

Keywords Pandemic · SARS-CoV-2 · Hospitalist · Coronavirus · Nosocomial

The virus

Coronaviruses include a large number of viruses found in animals. Human coronaviruses were first identified in the 1960s, isolated from patients with mild upper respiratory infections [1]. Since then, additional human coronaviruses have been discovered, including the causative agents of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). The first human coronaviruses identified cause approximately one third of mild upper respiratory infections in humans. In immunocompromised hosts and children, however, they can result in severe pneumonia and bronchiolitis [1].

The SARS represented the first pandemic of a coronavirus. It started in Guangdong Province in China in 2002 [2]. Severe atypical cases of pneumonia emerged and quickly spread worldwide. Investigation by epidemiologists suggested that animal to human transmission occurred at live game markets in Guangdong. Small mammals such as racoon dogs and palm civets likely transmitted the disease to humans. The natural hosts are bats [2].

The epidemiology

Eventually, public health systems and governments were able to contain the outbreak and bring it to a close. The World Health Organization (WHO) reported 8422 cases of SARS worldwide, spread out among 32 countries. They reported 916 deaths from the virus, with a fatality rate of 10–15% [1]. A recent report in JAMA also suggested a 10% fatality rate and estimated that 20–30% of infected patients required mechanical ventilation [2]. As expected, the fatality rate was higher among the aged and those with comorbidities. Perhaps most importantly, the SARS outbreak showed that animal coronaviruses could spread to humans.

The coronavirus has also demonstrated the ability to emerge into new hosts and then cause novel severe disease. In 2012, the MERS coronavirus was discovered in Saudi Arabia, isolated from the sputum of a man who died from a severe respiratory syndrome. The illness was subsequently termed MERS and since then 2494 cases have been reported, resulting in 858 deaths. This yields a higher case fatality rate than SARS, at 36%, with mechanical ventilation needed in 50–89% of patients [2]. The MERS is en-

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demic in camels, and in the Middle East and East Africa it continues to cause human infections [3]. To date, MERS has spread to 20 countries by air travel [4]. In 2018, a single patient caused an outbreak of 186 cases in South Korea, while a more recent case identified in an emergency department patient, was contained due to rapid implementation of public health interventions [4, 5].

Public containment measures

At outbreak onset, the Chinese government rapidly initiated broad isolation measures in an attempt to contain the virus. First the city of Wuhan was quarantined, then the entire Hubei province, stranding 35 million residents [6]. Currently, however, the disease continues to spread. A retrospective study suggested travelling by train in China yielded the highest proportion of imported cases to new provinces (69%), followed by flying (19%) and car (12%) [7].

Several factors contribute to continued spread. Qun et al. reported that delays between onset of illness and seeking medical attention are usually short, with 27% seeking attention within 2 days of onset; however, delays to hospitalization were longer, with 89% of patients not hospitalized until at least 5 days of illness, during which time multiple other persons are exposed to the virus [8]. They suggest "committing considerable resources to testing in outpatient clinics and emergency departments for proactive case finding, both as part of the containment strategy" [8].

Qun et al.'s preliminary estimate of the incubation period supported a 14-day quarantine for exposed persons, but was based on only 10 cases [8]. Subsequent reports on quarantined patients have demonstrated the disease can occasionally manifest past the observed 14-day isolation period.

Furthermore, it has been demonstrated that the virus can spread during the incubation period, when patients are asymptomatic [9]. It has also been detected in patients during the convalescent period. Additionally, the first person in the USA with coronavirus infection shed the virus in loose stool specimens, yielding concerns for fecal-oral transmission [10].

To clean public surface areas after potential contamination, one group of researchers in China reported that previous research on SARS and MERS suggested that liquid solvents, such 75% ethanol, disinfectants containing chlorine , peroxyacetic acid and chloroform have the potential to inactivate SARS-CoV-2. They also reported ultraviolet radiation and heating to 56 °C for 30 min may inactivate the virus. Chlorhexidine is not recommended as a disinfectant [11].

The clinical presentation

Human to human transmission was realized early in the SARS pandemic. Primary symptoms included fever, cough and dyspnea [2]. Outbreaks were reported in hotel and housing complexes. Healthcare facilities served as a reservoir for the virus, with many healthcare workers sustaining infections. It is theorized that nosocomial spread occurred because the human receptor for the SARS spike glycoprotein occurs in the lower respiratory tract. Hence, most patients present with pneumonia rather than upper respiratory tract symptoms. Viral shedding occurs about 10 days after initial infection, when most patients were already hospitalized. Then, interventions such as nebulizer treatments, oxygen, intubation and mechanical ventilation contributed to aerosolization of the virus, with increased risk of iatrogenic infection [2].

The MERS also causes a severe atypical pneumonia, but patients frequently have accompanying gastrointestinal symptoms and acute renal failure. Like SARS, the human receptors for the MERS virus are located in the lower respiratory tract, but additional receptors are found in the gastrointestinal tract and kidneys [2].

It is most important, however, to glean data from patients infected with SARS-CoV-2. Several papers have reported on clinical presentation and characteristics of early cases in China and 1 of the latest publications studied the first 425 confirmed cases in Wuhan. Their median age was 59 years and 56% were male. None of the cases reported were in children below the age of 15 years [8]; however, an increasing number of pediatric cases are now being reported from China [11].

The adult patients in the Wuhan study had a mean incubation period of 5.2 days, with the 95th percentile of the distribution at 12.5 days. At onset, the epidemic grew exponentially, doubling in size every 7.4 days. The basic reproductive number was estimated to be 2.2, meaning "that on average, each patient has been spreading infection to 2.2 other people" [8]. The authors report that as long as the basic reproductive number is greater than 1, the epidemic will continue to spread. Control measures are designed to decrease the reproductive number to less than 1.

Perhaps the most detailed study to date, shedding light on how patients may present and progress, is an analysis of the first 99 cases of confirmed novel corona pneumonia in Wuhan [12]. Infections were confirmed by obtaining throat swab specimens from all patients on admission and testing for the virus using real-time polymerase chain reaction protocols previously described [13].

Of the cases studied, 68% were men and 32% were women, with a mean age of 55.5 years. Only a slight majority of patients (51%) had chronic diseases, the majority being cardiovascular or cerebrovascular diseases [12].

Presenting symptoms were fever in 83% of patients and cough in 82%. Shortness of breath on admission was present in 31%. Other presenting symptoms in 4% or more of admitted patients included: myalgia, headache, confusion, sore throat and rhinorrhea. Only 1–2% of patients reported nausea and vomiting, or chest pain or diarrhea and 90% of patients had more than one sign or symptom present on admittance [12].

An analysis of laboratory values of infected patients showed the erythrocyte sedimentation rate was elevated in 85% of patients on admittance and the C-reactive protein was elevated in 86%. Surprisingly, the procalcitonin level was only increased in 6% of patients with confirmed COVID-19 pneumonia. A low albumin was identified in 98% of patients admitted, an elevated lactate dehydrogenase in 76% of patients and 51% had a decreased hemoglobin [12]. Based on chest X-ray and computed tomography (CT) results, 75% of patients had bilateral pneumonia at presentation, and 25% had unilateral pneumonia.

During hospitalization, 76% of patients required oxygen therapy, 13% required noninvasive mechanical ventilation and 4% required invasive mechanical ventilation. At the time the study was released, 31% of patients had been discharged, and 11% had died. All other patients were still hospitalized [12].

Discharge criteria suggested by pediatricians in China include children with a normal body temperature for at least 3 days, significant improvement in respiratory symptoms and completion of two consecutive negative tests of respiratory respiratory pathogenic ribonucleic acid. They suggested sampling intervals of at least 1 day. If patients meet these criteria, they are considered safe for discharge. If needed, home isolation for 14 days can be advised [11].

A retrospective study from China analyzed chest CT scans from 21 symptomatic patients with confirmed COVID-19 [14]. Consistent with clinical findings among infected a patients, radiographic finding demonstrated most patients (76%) had bilateral involvement on CT and in 71% more than 2 lung lobes were involved. The most frequent CT findings included bilateral pulmonary parenchymal ground-glass and consolidative pulmonary opacities (57%). Lung consolidation was observed in 29%. Lung cavitation, discrete pulmonary nodules, pleural effusions and lymphadenopathy were absent in all of the scans. Follow-up imaging in eight patients during the study period demonstrated mild or moderate progression of disease [14].

Other clinicians in China also studied chest CT scans and confirmed typical multilobar involvement on presentation, but summarized “when one or two lobes are involved, the effect on lung function is not serious, and the symptoms of shortness of breath and dyspnea are not severe” [15]. If the disease progresses, however, the patient will develop a “white lung” with diffuse alveolar damage involving multiple lobes [15].

The clinical characteristics associated with the development of acute respiratory distress syndrome (ARDS) and death after admission for COVID-19 were recently described in a retrospective cohort study [16]. Older age, hypertension and development of fever greater than 39 °C was associated with ARDS, but higher fever was also associated with better outcomes.

Increasingly, it is recognized that other organ systems, besides the pulmonary system, can be adversely affected by infection with SARS-CoV-2. A retrospective, observational analysis of 214 confirmed cases of COVID-19, specifically studied those with severe pneumonia, using criteria established by the American Thoracic Society [17]. Of those patients with severe pneumonia, 36.4% had neurological manifestations of disease, such as acute cerebrovascular disease (5.7%), impaired consciousness (14.8%) and skeletal muscle injury (19.3%). Coagulation disorders and cardiac manifestations of COVID-19 infection have also been reported [18, 19].

Recommendations to prevent nosocomial spread

A recent manuscript out of Canada provided an extensive review of measures designed to prevent the nosocomial spread of the disease [20]. They stressed the importance of identifying and isolating patients infected with SARS-CoV-2 early. Currently, suspicion requires fever and symptoms of respiratory illness. With recent community spread, identifiable links to the virus may be difficult to discern and a high index of suspicion should be maintained. Failure to identify infected patients has led to preventable dissemination in prior pandemics [21].

The primary method of transmission for SARS-CoV-2 is via contact/droplet spread, related to respiratory conditions; however, as with SARS, airborne transmission can occur. There are at least two reports of SARS-CoV-2 being isolated from stool specimens, so fecal-oral transmission is considered possible as well [10, 22].

Currently, the Canadian Public Health Agency advises placing patients with confirmed COVID-19 or patients with suspected infection who are ill, in airborne isolation. Anterooms with space to put on and remove personal protective equipment should be adjacent to these rooms. If an airborne isolation room is not available, the patient should be placed in a single room with closed doors [23].

In the care of critically ill patients, where airborne transmission is possible, recommended personable protective gear includes fluid-resistant gowns, gloves, eye protection, full face shield and fit-tested N-95 respirators. Hair covers or hoods should also be worn. Longer sleeved gloves are preferred to prevent wrist

exposure in the case of glove slippage. If necessary, vertical tape strips can be applied to keep gloves in place. Circumferential taping is not advised as it may make glove and gown removal more difficult. Full face protection with a shield is preferred. If not available, goggles or side shields are needed. Scrubs or full coveralls should be worn under the personal protective gear. Shoes worn should be impermeable to fluids and capable of being decontaminated. Shoe covers can increase the risk of self-contamination during removal. Strict hand hygiene must be performed after removal of protective equipment. Wax and Christian advised that infection control coaches should be used in some circumstances of equipment removal, such as after a "code blue." The coaches go through a checklist as the equipment is removed, to reduce the risk of self-contamination [20].

In fact, during the SARS outbreak the "Protected Code Blue" was developed and published to guide healthcare workers in proper resuscitation techniques for infected patients. Online demonstrations of the procedure have been cited by Candadian researchers [20]. It is advised that team members entering an infected patient's room be restricted to four, with team members bringing the defibrillator, medications and equipment needed in modular packs, rather than an entire cart [20].

Healthcare personnel arriving at the patient's room prior to the specialized response team can assist the patient with resuscitation interventions that have a low risk of viral transmission, such as placing an oral airway, placing an oxygen mask with an exhalation filter, chest compressions, defibrillation and cardioversion, obtaining intravenous or intraosseous access and administering drugs. Higher risk interventions which may generate aerosol and increase risk for infection to staff and nosocomial spread include high flow nasal cannula, bag-mask ventilation, CPAP/BiPAP (continuous positive airway pressure/bilevel positive airway pressure), and endotracheal intubation [20].

The authors also note that during the SARS outbreak, there were "case reports of considerable SARS transmission risk with the use of BiPAP to many patients over extended periods" [20]. They concluded, in general CPAP/BiPAP should be avoided in patients with COVID-19 and should never be used outside of airborne/droplet isolation [20]. They also note that high flow nasal cannula delivery systems may cause an increased risk of viral spread and practitioners should consider avoidance of humidified oxygen in COVID-19 patients as well. Bronchodilators should preferably be administered by metered dose inhalers [20].

Pediatricians in China have also provided recommendations for personal protective gear [11]. They stated: 1. all medical personnel are required to wear surgical masks during medical activities. 2. Those in triage areas wear medical overalls, caps and surgical masks. 3. In the emergency department and clinics where exposure is likely: medical overalls, caps, disposable clothing, surgical masks and goggles or face shields for daily rounding. When collecting body fluid samples, latex gloves, impermeable clothing and respiratory hood should be used when needed to prevent contamination by aerosolization or splash. 4. All personal protective equipment should be worn and removed with a strict on-off procedure, and personnel should not leave the ward with contaminated equipment. 5. Patients and their accompanying family members are required to wear surgical masks [11].

Antiviral studies to date

Currently, no effective vaccines or drugs have been approved for clinical use, although inhibitors designed to treat infections in vivo are being developed. In order to increase the speed of development of potential treatments available, two approaches are generally employed. Firstly, testing of current antiviral drugs and medications used to treat other infections or other disease states. The second approach is to develop novel agents based on current information and understanding of the particular coronavirus targeted [1].

Several publications have recently identified associations with decreased in vitro activity against SARS and MERS viruses. Neurotransmitter inhibitors, such as promethazine were among such agents [1]. Pillaiyar et al. list additional compounds with antiviral activity in their extensive review [1].

Nowak and Walkowiak, in a recently released review of five in vitro studies reporting on the effect of lithium in coronavirus infections, concluded that the drug does have antiviral activity and should be explored as a potential treatment or prophylaxis for COVID-19 [24].

Currently, the most widely studied antiviral agents against coronaviruses are remdesivir, ribavirin, lopinavir, ritonavir, and interferon beta. Ribavirin, used alone, has had no demonstrated effect against SARS. When combined with lopinavir, plus rotinavir and a corticosteroid and given to patients infected with SARS, those treated were less likely to develop ARDS, and death rates were lower than those treated with ribavirin and a corticosteroid [1].

Most studies published have not shown a benefit when corticosteroids are used in coronavirus infections. In fact, the use of methylprednisolone as an intervention for SARS patients was associated with a higher 30-day mortality rate [1]. A randomized, placebo-controlled study of SARS patients suggested that those given steroids early in the infection developed prolonged viremia. Finally, patients with MERS who were treated with methylprednisolone, with or without antiviral agents or interferons, showed no improved outcomes [1].

Perhaps remdesivir, a broad-spectrum antiviral drug, shows the most promise for human coronavirus infections. It has superior activity against MERS-CoV in vitro, when tested against existing antivirals. In mouse models, when used for prophylaxis and treatment, it showed improved pulmonary lung function values, reduced lung viral loads and lung pathology findings on post-mortem examination [3]. The authors concluded "our work suggests that remdesivir may improve disease outcomes in coronavirus patients, serve to protect health care workers in area with endemic MERS-CoV and prove valuable in preventing future epidemics " [3].

Another recent report, by a different group of researchers, also supported the use of remdesivir against coronaviruses. This group showed that remdesivir inhibited virus infection efficiently in a human cell line sensitive to SARS-CoV-2 [6]. The same authors tested chloroquine and concluded "remdesivir and chloroquine are highly effective in the control of COVID-19 infection in vitro." They further suggested both should be assessed in human patients with COVID-19 [6].

Finally, neuraminidase inhibitors, such as oral oseltamivir, inhaled zanamivir and intravenous peramivir are approved antiviral treatments for influenza and MERS infections; however, oral oseltamivir has been used in patients with COVID-19 infections in China, but to date, there is no convincing evidence of its' effectiveness [25].

Interferon has been studied in vitro against coronaviruses, but there is no evidence it will be effective against COVID-19. Pediatricians in China have suggested nebulized interferon be considered in infected children [11]; however, they reported there is no data to support its' use and publications from Canada advise against routine nebulizer use, noting the potential for spreading of the virus by aerosolization [20].

Vaccines against COVID-19 are being pursued. Researchers report that the timeline has been compressed to 3.25 months for a phase I trial, using messenger RNA technologies [2]. Other groups are attempting to construct vaccines using viral vectors and vaccines directed at subunits [2]. Despite worldwide efforts to identify methods to prevent and treat COVID-19, a recent comprehensive review concluded "No therapies have been shown effective to date" [26].

Conclusion

Currently, COVID-19 continues to spread. Latest estimates of the replication number remain well above two, so proliferation will continue. Healthcare providers will play a major role in the early identification and isolation of infected patients, important measures to prevent dissemination. Measures to prevent nosocomial spread are also paramount to control. Finally, while treatment is largely supportive, the scientific community is working ceaselessly to develop interventions and vaccines to end this outbreak. Health professionals need to stay abreast of all these developments.

Conflict of interest D.M. Bearden, P.B. Aiken, Y.H. Cheng, E. Mai, and T.M. Peters declare that they have no competing interests.

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