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.

Air Medical Journal 39 (2020) 231–234

Contents lists available at ScienceDirect

Air Medical Journal

journal homepage: http://www.airmedicaljournal.com/

Critical Care Update

The Virus

David J. Dries, MSE, MD

In The Beginning. . .

Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020;382:727-733.

Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med*. 2020;382:1199-1207.

Perlman S. Another decade, another coronavirus. *N Engl J Med*. 2020;382:760-762.

Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:m1091.

Emerging and re-emerging pathogens are global challenges for public health. One such pathogen, a coronavirus, is an enveloped RNA virus distributed broadly among humans, other mammals, and birds that causes respiratory, enteric, hepatic, and neurologic disease. Six coronavirus species are known to cause human disease. Four of these viruses are prevalent and typically cause common cold symptoms in immunocompetent individuals. Two other strains, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome–related coronavirus, are zoonotic in origin and have been linked to fatal illness. SARS-CoV was the causal agent of severe acute respiratory syndrome outbreaks in 2002 and 2003 in China. Middle East respiratory syndrome–related coronavirus was the pathogen responsible for severe respiratory disease outbreaks in 2012 in the Middle East. Given the high prevalence and wide distribution of coronaviruses, the large genetic diversity and frequent recombination of genomes, and increasing human/animal interface activities, coronaviruses are likely to emerge periodically in humans because of frequent cross-species infection and occasional spillover.

It is likely that such an event occurred in late 2019 when local health facilities reported clusters of patients with pneumonia of unknown origin linked to a seafood and wet animal wholesale market in Wuhan Providence, China. At the end of the year, the Chinese Center for Disease Control and Prevention dispatched a rapid response team to investigate these reports. This initial work described a novel coronavirus in patients with pneumonia whose specimens were tested by the Chinese Center for Disease Control and Prevention early in the outbreak.

The virus was isolated using bronchoalveolar lavage fluid samples collected in sterile cups to which virus transport medium was added. These specimens were ultimately tested using a variety of molecular techniques to identify viral pathogens. Three representative adult patients presenting with severe pneumonia were admitted to the hospital in Wuhan in late December 2019. Patients included a 49-year-old woman, a 61-year-old man, and a 32-year-old man. A fever, cough, and chest discomfort were the presenting complaints. Two of these patients survived. One patient ultimately died after aggressive respiratory care. From an epidemiologic standpoint, these individuals had contact with the seafood market in Wuhan. Ultimately, investigators identified a novel coronavirus in hospitalized patients from Wuhan in December 2019 and January 2020. Genetic analysis of the virus identified in early patients revealed coronavirus pathogens similar to SARS-CoV, which had been discovered in humans, bats, and other wild animals.

The initial working case definitions for suspected novel coronavirus-infected pneumonia were based on the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) case definitions as recommended by the World Health Organization in 2003 and 2012. A suspected novel coronavirus pneumonia case was defined as pneumonia that fulfilled the following criteria: fever with or without a recorded temperature, radiographic evidence of pneumonia, low or normal white cell or low lymphocyte count, and no reduction in symptoms after antimicrobial therapy for 3 days following standard clinical guidelines. Epidemiologic data were updated to include a travel history from Wuhan or direct contact with patients from Wuhan who had a fever or respiratory symptoms within 14 days before the onset of illness. Confirmed cases were identified by isolation of the novel coronavirus or at least two positive results by teal-time reverse transcription polymerase chain reaction assay for 2019 novel coronavirus or a genetic sequence matching this pathogen.

The rate of spread for infection was obtained by analyzing data on cases with illness onset between December 10, 2019, and January 4, 2020. Mathematical modeling was then used to characterize the outbreak of illness. The earliest cases included reported exposure to the Wuhan seafood market. There was an exponential increase in the number of other cases beginning in late December 2019. The median age of patients identified was 59 years with a range of 15 to 89 years, and 240 of the initial 425 patients studied were male. There were no initial cases of children below the age of 15 years.

In the epidemic growth curve up to January 4, 2020, the doubling time of patients with virus exposure was 7.4 days. With further evaluation of the epidemiologic data, it became clear that human-to-human transmission had been occurring for weeks without identification. Initial mathematical modeling suggested that on average each

1067-991X/$36.00

https://doi.org/10.1016/j.amj.2020.04.013

patient with coronavirus spread the infection to 2.1 other people. In general, an epidemic will persist as long as a pathogen spreads to more than 1 individual per infected patient. Control measures aim to reduce the reproductive number to less than 1. During the SARS outbreak, initial patients affected spread infection to three individuals. Successful control was achieved by isolation of patients and careful infection management. A challenge with the new coronavirus is the apparent presence of many mild infections with limited resources for the isolation of cases and quarantine of close contacts. As we become more sophisticated in identifying cases, the pattern of spread of disease will be better identified. The initial estimate of the incubation period for this new viral pathogen was 14 days for observation or quarantine to determine the presence or absence of symptoms. As additional demographic data are gathered from affected patients, better detail regarding isolation practices may become available. The current limitations of business and travel activity reflect the attempts to reduce the transmission of infection within the community. Working case definitions may be refined as more is learned about the epidemiologic characteristics and outbreak dynamics of this new coronavirus.

It is instructive to recall that the current coronavirus pandemic is caused by a pathogen from the same family that caused SARS and MERS. Microbiologists suggest that the 2019 coronavirus will behave more like the SARS coronavirus and adapt to the human host using similar receptors. As more specimens are obtained, it may be possible to assess the degree to which the virus is mutating and determine whether mutations suggest adaptation to the human host increasing virulence of the infection. Further study describes the zoonotic origin of the virus. Given its close similarity to bat coronaviruses, it seems possible that bats are the primary reservoir for the current coronavirus pathogen. SARS was transmitted to humans from exotic animals in wet markets. MERS was transmitted from camels to humans. In each case, the ancestral hosts were probably bats.

Transmission of the 2019 coronavirus probably occurs by means of large droplets and contact and less so by means of aerosols and fomites. Public health measures including quarantine in the community along with timely diagnosis and strict adherence to universal precautions in health care settings were essential in managing SARS and MERS. Similar measures will be important and, hopefully as successful, in reducing transmission of the current coronavirus outbreak. A recent Chinese report details the multisystem impact of coronavirus disease 2019 (COVID-19) infection. Much of the data discussed here comes from the analysis of deceased patients. Among the deceased patients, respiratory and cardiac complications were numerous including acute respiratory distress syndrome (ARDS), acute cardiac injury, heart failure, shock, alkalosis, hyperkalemia, acute kidney injury, and hypoxic encephalopathy. All of these problems were prominent with COVID-19 in the deceased relative and recovered patients, suggesting a multisystem insult in patients with this problem.

From a demographic standpoint, the median age of the deceased patients was significantly greater than that of the recovered patients. Male sex was more common in patients who died than in those who recovered. Chronic hypertension and other cardiovascular disease were more frequent among deceased patients than recovered patients. Deceased patients more often developed systemic inflammation and multiorgan dysfunction than recovered patients. Indicators of cardiac injury showed more frequent or prominent abnormalities in deceased patients than in those who recovered. Remarkably, the overall mortality of COVID-19 is much lower than for SARS (10%) and MERS (30%). However, COVID-19 has proven more deadly because it has spread to more people globally than the other two viral pathogens because of rapid person-to-person transmission and atypical symptoms at an early stage for many patients.

The differences in abnormalities of laboratory findings between deceased patients and survivors were also significant. Deceased patients and only a few of the recovered patients developed leukocytosis, and one third of the deceased patients and only a few of those who recovered had elevated procalcitonin levels, indicating that a large portion of deceased patients might have had secondary bacterial infection, which could be strongly associated with death. Deceased patients had persistent and more severe lymphopenia compared with recovered patients, suggesting that cellular immunity was compromised in patients with a poor prognosis.

Therapy

Alhazzani W, Moller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Crit Care Med*. 2020; [Epub ahead of print].

A combination of critical care societies including the Society of Critical Care Medicine and the European Society of Intensive Care Medicine have released an initial set of guidelines on the management of critically ill patients with COVID-19. I will briefly summarize these. I fully expect the evolution of recommendations as we better understand the relevant pathophysiology.

Infection Control

Airborne and contact spread is common in this virus as we now understand it. Thus, health care workers performing aerosol-generating procedures on patients with COVID-19 in the intensive care unit should wear fitted respirator masks (N95, FFP2, or equivalent) as opposed to standard surgical or medical masks, in addition to other personal protective equipment such as gowns, gloves, and eye protection. If possible, aerosol-generating procedures should be performed in a negative-pressure room. If a patient is not ventilated, medical/surgical masks, in addition to other personal protective equipment, should be worn. Similarly, if non–aerosol-generating procedures are performed, medical/surgical masks as opposed to respirator masks are recommended. Endotracheal intubation should be performed with video-guided laryngoscopy as opposed to direct laryngoscopy if this video technology is available. This group makes a weak recommendation with regard to sampling the lower respiratory tract favoring the collection of endotracheal aspirates as opposed to bronchial wash or bronchoalveolar lavage specimens.

Hemodynamic Management

Fluid support recommendations include conservative strategies and using crystalloids that are buffered over unbalanced crystalloids. “Conservative” fluid administration targets little or no net fluid accumulation on a daily basis. Gelatins and starches are not recommended as part of resuscitation protocols. Similarly, albumin should not be used for initial resuscitation, and dextrans should be avoided. Norepinephrine is considered the first-line vasoactive drug. Vasopressin and epinephrine may be used in patients with shock if norepinephrine is not available. This group recommends against the use of dopamine and supports using vasopressin as a second-line agent in combination with norepinephrine if a second drug is necessary. The mean arterial pressure goal recommended is 60 to 65 mm Hg. Dobutamine should be considered in patients with evidence of cardiac dysfunction and persistent hypoperfusion. In patients with COVID-19 and refractory shock, low-dose corticosteroid therapy should be considered typically at a dose of intravenous hydrocortisone 200 mg/d given as an infusion or intermittent doses.

Respiratory Support

The group made a number of recommendations with respect to pulmonary and oxygenation support. Supplemental oxygen was recommended if finger oximetry (peripheral

capillary oxygen saturation) results are less than 90%. In patients with hypoxemic respiratory insufficiency on oxygen, peripheral capillary oxygen saturation should be maintained no higher than 96%. A high-flow nasal cannula is the next step up in treatment over conventional oxygen therapy. A high-flow nasal cannula is also recommended over other forms of noninvasive positive-pressure ventilation. If high-flow nasal cannula technology is not available, other forms of noninvasive ventilation may be tried. When patients fail noninvasive ventilation, intubation with low tidal volume ventilation (4-8 mL/kg/predicted body weight) is recommended with plateau pressures on the ventilator less than 30 cm/H_2O. A higher positive end-expiratory pressure (PEEP) strategy is recommended over a lower PEEP strategy in patients with refractory hypoxemia on mechanical ventilation. "Higher PEEP" consists of PEEP greater than 10 cm/H_2O. As in hemodynamic recommendations, conservative fluid administration is recommended over a liberal fluid administration strategy. Prone ventilation may be considered in patients with moderate to severe ARDS with intermittent doses of neuromuscular blockade to facilitate lung-protective ventilation. If ventilator dyssynchrony is a significant concern, continuous neuromuscular blockade for up to 48 hours is recommended. Inhaled nitric oxide is not recommended. Inhaled pulmonary vasodilators may be considered in patients with severe hypoxemia with recruitment maneuvers to reopen gas exchange units. Extracorporeal membrane oxygenation is a final therapy that should be considered in carefully selected patients with COVID-19 associated with severe ARDS.

Finally, the group makes a number of general therapeutic recommendations including avoidance of routine use of systemic corticosteroids, except possibly in the severely ill patient with COVID-19 and ARDS. Empiric antimicrobials should be considered over avoidance of antimicrobials. De-escalation of antimicrobial therapy should be considered daily, and the spectrum of coverage changed based on microbiology results and the clinical state of the patient.

Medications

Tylenol (Johnson & Johnson [McNeil Laboratories, Fort Washington, PA], New Brunswick, NJ) is recommended for a fever. Immunoglobulin administration is not recommended at this time. There is no clear evidence to support the use of specific antiviral agents in COVID-19 patients at this time. Similarly, recombinant interferons are not recommended. The group offered no recommendation regarding the use of chloroquine or hydroxychloroquine in critically ill patients with COVID-19.

Osterholm M. What's "Normal" Now? What's Next? Opinion Exchange. *Minneapolis Star Tribune*. March 22, 2020.

Morens DM, Daszak P, Taubenberger JK. Escaping Pandora's box—another novel coronavirus. *N Engl J Med*. 2020;382:1293-1295.

Professor Michael Osterholm, based in the Twin Cities, has been one of the nation's leading epidemiologists and has recently joined the faculty at the University of Minnesota. In previous publications, Osterholm, now a public health professor and director for the Center of Infectious Disease Research and Policy, reviewed older infections (MERS and SARS) caused by a coronavirus, the same viral family now driving the COVID-19 pandemic.

Osterholm makes two initial observations. First is that we, as a nation, had a sense of invincibility that we had a border that would not allow infectious disease agents to penetrate. We are now seeing that this is foolish. A microbe anywhere in the world today can be anywhere in the world tomorrow. A second fallacy was the lack of creative imagination "unless related to a video game or movie." None of the COVID-19 presentation was exotic. People who knew health care and epidemiology knew that our health care system had been carved down to the bone for which there was no resiliency of any substantial nature, no excess capacity, and no money to stockpile large volumes of protective equipment. There has been no real understanding of the vulnerability of this country caused by outsourcing all of its drug manufacturing to places like China. COVID-19 showed that events in one country make many countries vulnerable. Even when COVID-19 was sitting on our doorstep, people did not take it seriously.

Osterholm offers no pretenses about what will ultimately happen. He says directly that we may never go back to normal. We will have a new normal just as the airlines did after 9/11. We want to do what we can to help people psychologically work through the implications of COVID-19. The bottom line is people need direct answers, straight talk, and the truth including what we know and what we don't know.

Ironically, companies that could be making protective equipment and ventilators had been working nonstop for weeks before the government showed interest. However, even if everyone recognized the need to increase manufacturing capability, this is impossible to do overnight. For example, after Pearl Harbor, it took over 3 years to restore the Pacific Fleet.

Osterholm had an interesting closing observation regarding keeping children out of school. He noted that Singapore and Hong Kong each broached the question of keeping children out of school. The bottom line was that Singapore did not close schools, whereas Hong Kong did. There was no difference in outcome. It appears that behavioral goals are more complex than simple school attendance. A more important factor in saving lives in a hospital is when you consider that 20% of nurses, doctors, and respiratory therapists are unable to work because they must stay home to watch their kids.

Another view comes from the Greek myth of Pandora's box; the gods gave Pandora a locked jar that she was never to open. Driven by human weakness, she nevertheless opened it and released the world's misfortunes and plagues.

In our crowded world of 7.8 billion people, a combination of altered human behaviors, environmental changes, and inadequate global public health mechanisms can easily turn obscure animal viruses into existential human threats. We have created a global human-dominated ecosystem that serves as a playground for the emergence and host switching of animal viruses, particularly the genetically error-prone RNA viruses whose high mutation rates provide opportunity for changing hosts in new ecosystems. For example, it took the genome of man millions of years to evolve by 1%. Many animal RNA viruses can evolve by more than 1% in a matter of days. It is not surprising that we see the emergence of more viral pathogens.

Preventing and controlling future pandemic episodes is a global priority. The present COVID-19 epidemic can be compared with the flu epidemic of 1918, which took millions of lives. Wherever the 1918 pandemic began, it spread silently around the world causing only mild cases but also mortality of 0.5% to 1% or higher, a rate that was initially too low to be detected against a high background of death from unrelated respiratory illnesses. Then, suddenly, the flu epidemic exploded in urban centers almost everywhere at once, making a dramatic entrance after a long stealthy approach. We now see the early stages of COVID-19 emergence in the form of growing and geographically expanding case totals, and there are concerning similarities between the two respiratory disease pathogens. Like the pandemic influenza of 1918, COVID-19 is associated with respiratory spread and an undetermined percentage of infected people with presymptomatic or asymptomatic cases transmitting infection to others with a high ultimate fatality rate.

The problem is that most influenza cases are either asymptomatic or subsymptomatic, undiagnosed, or transmitted to others before the onset of symptoms. Can we do better with the present viral pandemic, facing a pathogen with longer incubation and serial generation time but with an as-yet-

undetermined ratio of silent cases to apparent cases and an unknown rate of asymptomatic spread? The answer to this question is vital. In the end, the only comfort for Pandora was hope.

Summary Points

- Although the current coronavirus has lower virulence than the SARS virus or the MERS virus, because of atypical presentation and delay in the development of symptoms, it can spread widely before identification as a health problem in a particular patient.
- The manifestations of the new COVID-19 are more than a simple respiratory infection. I think of this as a vasculitis with multiorgan involvement. Included prominently are the neurologic system, the kidneys, and the heart in the form of a myocarditis.
- We need to decrease the exposure ratio to less than 1 for a patient who carries this pathogen. Thus, at this point, social distancing is still the most effective strategy.
- Clinical recommendations at this point are simple, including conservative fluid administration and standard ARDS ventilator settings. I expect additional work in this area and anticipate summarizing it in future columns.
- Given the ease in replication and mutation of the viral family causing COVID-19, our society must learn from this experience to be better prepared for the inevitable reappearance of viruses from the coronavirus family.

Acknowledgments

The author gratefully acknowledges the assistance of Ms. Sherry Willett in preparation of this series for *Air Medical Journal*.

David J. Dries, MSE, MD, is a member of the Department of Surgery at HealthPartners Medical Group and a professor of surgery and an adjunct clinical professor of emergency medicine at the University of Minnesota in St Paul, MN, and can be reached at david.j.dries@healthpartners.com.