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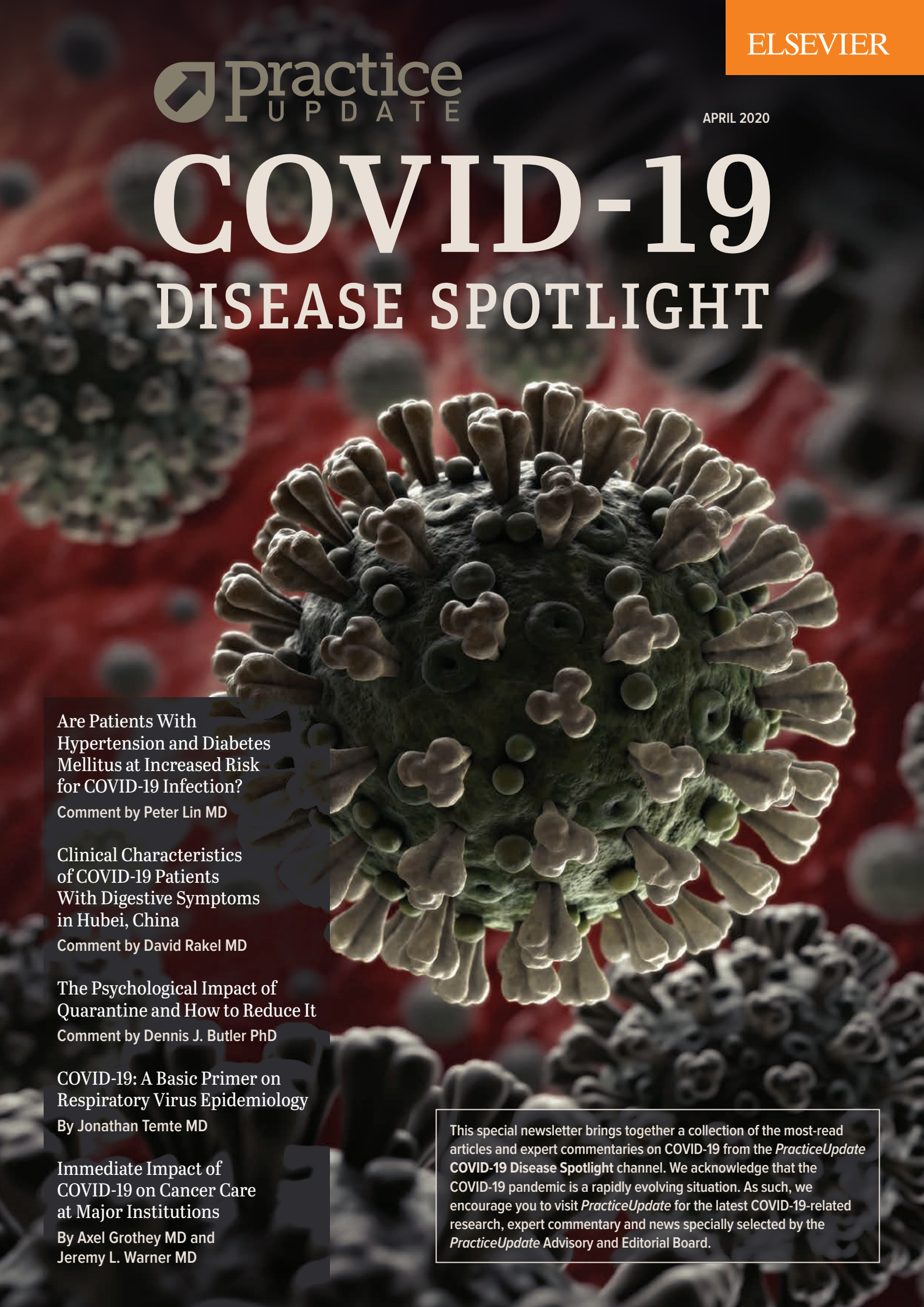
Practice UPDATE

APRIL 2020

COVID-19
DISEASE SPOTLIGHT



This special newsletter brings together a collection of the most-read articles and expert commentaries on COVID-19 from the *PracticeUpdate* **COVID-19 Disease Spotlight** channel. We acknowledge that the COVID-19 pandemic is a rapidly evolving situation. As such, we encourage you to visit *PracticeUpdate* for the latest COVID-19-related research, expert commentary and news specially selected by the *PracticeUpdate* Advisory and Editorial Board.

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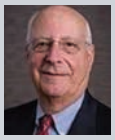

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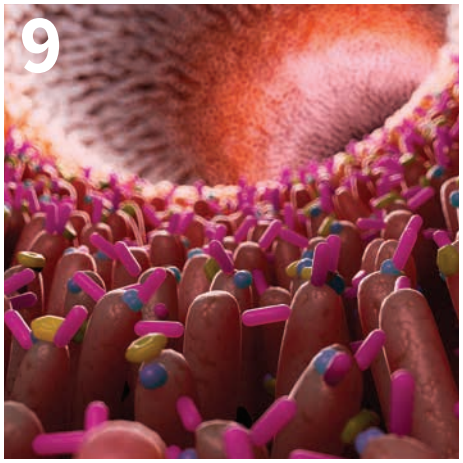

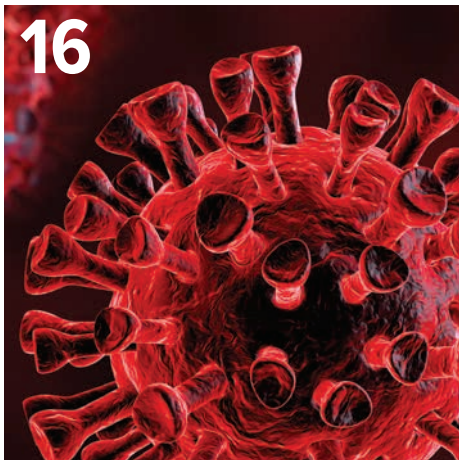

EDITOR'S PICKS

EXPERT OPINION

Clinical Course and Risk Factors for Mortality of Adult Inpatients With COVID-19 in Wuhan, China

The Lancet

Take-home message

- A study of 191 patients hospitalized with confirmed COVID-19 in Wuhan, China, demonstrated an increased mortality risk associated with older age, higher Sequential Organ Failure Assessment score, and elevated D-dimer. Researchers also found a median viral shedding period of 20 days.
- Figure 1 in the article is a very good display of symptom onset in the disease course based on survivors and non-survivors. Of note, both groups had a period of 6 days with only cough and fever preceding any shortness of breath.

Andrea Dotson MD, MSPH

COMMENT

By Jonathan Temte MD, PhD

Risk Factors for COVID-19 Death

First a quick word about nomenclature so that we are all on the same page: the novel coronavirus causing coronavirus disease-19 (COVID-19) has now been named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2).

The pandemic of SARS-CoV-2 is accelerating with rapidly increasing numbers. In the United States alone, we now have recorded over 10,000 cases and 150 deaths. It is sobering. We are now able to look into the recent past for some guidance in care management and assessment. Using a retrospective cases series of patients from two hospitals in Wuhan, China, Zhou and colleagues evaluated risk factors for death from COVID-19.[1] They included 191 hospitalized patients in this analysis who had either recovered and were discharged (72%) or had died (28%). Of these, 62% were male and about half had comorbidities (30% with hypertension, 19% with diabetes, and 8% with coronary heart disease). Only 6% were current smokers.

In a multivariate assessment, three factors emerged as predictors of death: higher age (aOR: 1.10 per year [95% CI: 1.07–1.17] P = .0043), higher SOFA (Sequential Organ Failure Assessment) score (aOR: 5.65 [2.61–12.23] P < .0001), and D-dimer level >1 µg/L (aOR: 18.42 [2.64–128.55] P = .0033) on admission. Other significant findings included an average time from illness onset to hospital discharge of 22 days and 18.5 days for death. Of concern was the long average period of virus shedding of 20 days (range = 8 to 37 days) found in these patients.

Some thoughts for primary care physicians:

- The average age of the admitted COVID-19 patients was 56 years.
- D-dimer is a commonly available lab test.
  - Remember to obtain this on admission if COVID-19 is suspected.
- The SOFA score can be readily calculated using multiple on-line tools.[2]
- Virus shedding in hospitalized patients continues for a prolonged period. ■

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2. ClinCalc.com. Critical Care, Sequential Organ Failure Assessment (SOFA) Calculator. Accessed 3/19/2020 at: https://clincalc.com/IcuMortality/SOFA.aspx

Abstract

BACKGROUND Since December, 2019, Wuhan, China, has experienced an outbreak of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Epidemiological and clinical characteristics of patients with COVID-19 have been reported but risk factors for mortality and a detailed clinical course of illness, including viral shedding, have not been well described.

METHODS In this retrospective, multicentre cohort study, we included all adult inpatients (≥18 years old) with laboratory-confirmed COVID-19 from Jinyintan Hospital and Wuhan Pulmonary Hospital (Wuhan, China) who had been discharged or had died by Jan 31, 2020. Demographic, clinical, treatment, and laboratory data, including serial samples for viral RNA detection, were extracted from electronic medical records and compared between survivors and non-survivors. We used univariable and multivariable logistic regression methods to explore the risk factors associated with in-hospital death.

FINDINGS 191 patients (135 from Jinyintan Hospital and 56 from Wuhan Pulmonary Hospital) were included in this study, of whom 137 were discharged and 54 died in hospital. 91 (48%) patients had a comorbidity, with hypertension being the most common (58 [30%] patients), followed by diabetes (36 [19%] patients) and coronary heart disease (15 [8%] patients). Multivariable regression showed increasing odds of in-hospital death associated with older age (odds ratio 1·10, 95% CI 1·03-1·17, per year increase; p=0·0043), higher Sequential Organ Failure Assessment (SOFA) score (5·65, 2·61-12·23; p<0·0001), and d-dimer greater than 1 µg/L (18·42, 2·64-128·55; p=0·0033) on admission. Median duration of viral shedding was 20·0 days (IQR 17·0-24·0) in survivors, but SARS-CoV-2 was detectable until death in non-survivors. The longest observed duration of viral shedding in survivors was 37 days.

INTERPRETATION The potential risk factors of older age, high SOFA score, and d-dimer greater than 1 µg/L could help clinicians to identify patients with poor prognosis at an early stage. Prolonged viral shedding provides the rationale for a strategy of isolation of infected patients and optimal antiviral interventions in the future.

Clinical Course and Risk Factors for Mortality of Adult Inpatients With COVID-19 in Wuhan, China: A Retrospective Cohort Study. *Lancet* 2020 Mar 11;[EPub Ahead of Print], F Zhou, T Yu, R Du, et al. ■

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Are Patients With Hypertension and Diabetes Mellitus at Increased Risk for COVID-19 Infection?

The Lancet Respiratory Medicine

Take-home message

- In this commentary, the authors take up the topic of comorbidities of patients with confirmed COVID-19, basing their discussion on three recently published studies.
- Although the most frequent comorbidities reported in these studies, including diabetes and hypertension, are frequently treated with ACE inhibitors, none of the three studies assessed the treatment related to the comorbidities.

Abstract

The most distinctive comorbidities of 32 non-survivors from a group of 52 intensive care unit patients with novel coronavirus disease 2019 (COVID-19) in the study by Xiaobo Yang and colleagues were cerebrovascular diseases (22%) and diabetes (22%). Another study included 1099 patients with confirmed COVID-19, of whom 173 had severe disease with comorbidities of hypertension (23·7%), diabetes mellitus (16·2%), coronary heart diseases (5·8%), and cerebrovascular disease (2·3%). In a third study, of 140 patients who were admitted to hospital with COVID-19, 30% had hypertension and 12% had diabetes. Notably, the most frequent comorbidities reported in these three studies of patients with COVID-19 are often treated with angiotensinconverting enzyme (ACE) inhibitors; however, treatment was not assessed in either study.

Are Patients With Hypertension and Diabetes Mellitus at Increased Risk for COVID-19 Infection? *Lancet Respir Med* 2020 Mar 11;[EPub Ahead of Print], L Fang, G Karakiulakis, M Roth.

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COMMENT

By Peter Lin MD, CCFP

COVID-19 and ACE Inhibitors and ARBs

On March 11, 2020, *The Lancet Respiratory Medicine* published a commentary entitled "Are Patients With Hypertension and Diabetes at Increased Risk for COVID-19 Infection?"

The authors pointed out that the patients with severe COVID-19 were likely to have hypertension and diabetes. They then explained that the virus uses its spike proteins to attach to angiotensin-converting enzyme 2 (ACE2), which is expressed by lung epithelial cells, which is how the virus gets into the lungs, where it replicates.

ACE inhibitors and angiotensin receptor blockers (ARBs) cause upregulation of ACE2, and the commentators state, "consequently, the increased expression of ACE2 would facilitate infection with COVID-19. We therefore hypothesise that diabetes and hypertension treatment with ACE2-stimulating drugs increases the risk of developing severe and fatal COVID-19."

This statement is a hypothesis and completely unsubstantiated; but, of course, some people read it as factual. Then they go on to say, "Based on a PubMed search on Feb 28, 2020, we did not find any evidence to suggest that antihypertensive calcium channel blockers increased ACE2 expression or activity, therefore these could be a suitable alternative treatment in these patients."

The commentators went from an hypothesis all the way to a recommendation of stopping ACE inhibitors and ARBs within a one-page document. They did not present any data that COVID-19 patients taking ACE inhibitors or ARBs had worse outcomes. They also did not discuss the consequences of stopping the drugs, which could lead to increased cardiovascular events, worsening of heart failure, and renal complications.

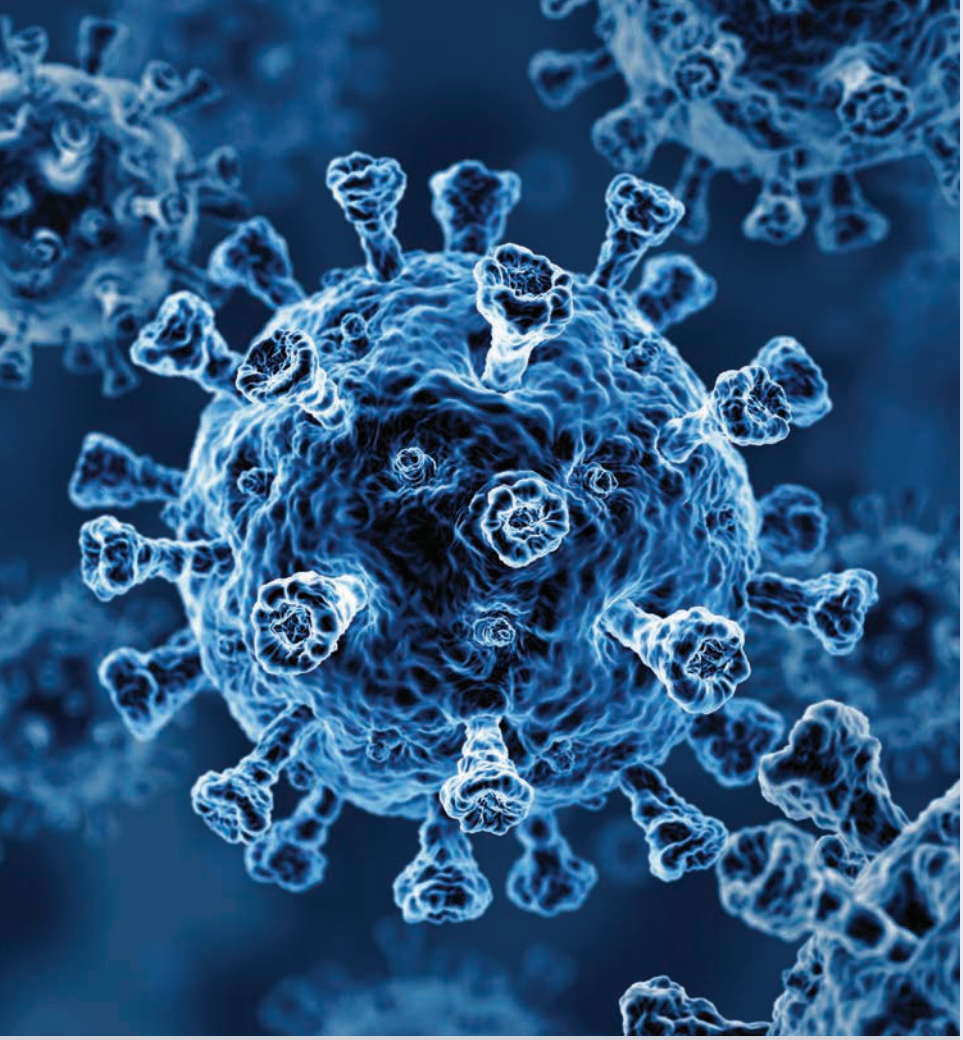
Interestingly, other researchers have pointed out that there is a soluble version of ACE2, which is not on the cell membrane and which could act as a decoy for the virus to bind to and so the lung cells would be spared.[1] This would mean that an increase in soluble ACE2 might be protective, and, if ACE inhibitors and ARBs increase soluble ACE2, then they may actually be beneficial. Now, we don't know if the soluble ACE2 can even get to the virus considering that the virus is coming in from the airway side; however, if there is soluble ACE2 in the fluid layer just on top of the lung cells, the drugs might have a protective effect.

Other research has shown that angiotensin II is needed for lung fibrosis to occur.[2] COVID-19 and SARS patients who recovered had excessive scaring of their lungs. In animal models, when there is no angiotensin II, the scarring does not happen. ACE2 breaks down angiotensin II, and less angiotensin II might mean less fibrosis. So, if ACE inhibitors and ARBs increase ACE2, the effect could be protective against lung fibrosis and further damage.

The SARS virus used ACE2 as its entry point as well,[3] and we never saw detrimental effects of being on ACE inhibitors or ARBs during the SARS epidemic.

I cite all these different studies and facts to point out that there are many aspects that we need to consider and that that oversimplification is not always wise.

That is why the American Heart Association, the Heart Failure Society of America, and the American College of Cardiology put out a statement on March 17, 2020. The three organizations recommend, "continuation of angiotensin converting enzyme inhibitors (ACE-i) or angiotensin receptor blocker (ARB) medications for all patients already prescribed for indications such as heart failure, hypertension or ischemic heart disease."



> "...we should keep our patients on their ACE inhibitors or ARBs. One caveat is that, if they are dehydrated, vomiting, or have diarrhea..."

They go on to say, "we have reviewed the latest research – the evidence does not confirm the need to discontinue ACE-i or ARBs, and we strongly recommend all physicians to consider the individual needs of each patient before making any changes to ACE-i or ARB treatment regimens...." They concluded by saying, "these recommendations will be adjusted as needed to correspond with the latest research."

Think of a patient who has COVID-19. The virus has already gained entry into the cell, so stopping the ACE inhibitor or ARB would not reduce the COVID-19 risk but it would increase the cardiovascular and renal risk. Keeping the patient on therapy makes sense. Now, think of your patients who are not infected with COVID-19. Stopping their drugs would put them at high risk of cardiovascular and renal complications, and, if they never get COVID-19, their risk would have been heightened for no reason.

This all means, basically, that we should keep our patients on their ACE inhibitors or ARBs. One caveat is that, if they are dehydrated, vomiting, or have diarrhea, then we should be thinking about holding the drugs; otherwise...

We can protect our patients from COVID-19 by encouraging them to protect their personal borders through social distancing; however, we should let the ACE inhibitors and ARBs do their job at protecting their cardiovascular and renal systems.

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Care for Critically Ill Patients With COVID-19

The Journal of the American Medical Association

Take-home message

- This article addresses critical care concerns and logistics in the midst of the COVID-19 epidemic. Data from initial sites of disease suggest that approximately 5% of patients will require intensive care-level services, mainly for respiratory failure consistent with ARDS. There are no data about the safety of using high-flow nasal cannula and similar support when clinically appropriate, versus mechanical ventilation, which is a closed system and thus theoretically less likely to spread disease via droplets to close contacts. Available epidemiologic data suggest that the ability to provide effective critical care to patients in need is associated with a significant reduction in case fatality rate.
- This article addresses the importance of sufficient critical care resources for managing patients with COVID-19 and discusses logistics and clinical aspects of appropriate management.

Amy S. Korwin MD

Abstract

Initial reports suggest that COVID-19 is associated with severe disease that requires intensive care in approximately 5% of proven infections. Given how common the disease is becoming, as in prior major severe acute respiratory infection outbreaks – SARS (severe acute respiratory syndrome), MERS (Middle East respiratory syndrome), avian influenza A(H7N9), and influenza A(H1N1)pdm09 – critical care will be an integral component of the global response to this emerging infection.

The rapid increase in the number of cases of COVID-19 in Wuhan, China, in late 2019 highlighted how quickly health systems can be challenged to provide adequate care. Case-fatality proportions were 7-fold higher for patients in Hubei Province compared with those outside of the region, 2.9% vs 0.4%, emphasizing the importance of health system capacity in the care of patients who are critically ill with COVID-19.

Care for Critically Ill Patients With COVID-19. JAMA 2020 Mar 11;[EPub Ahead of Print], S Murthy, CD Gomersall, RA Fowler.

www.practiceupdate.com/c/97645

COVID-19 and Cancer

The Lancet Oncology

Take-home message

- Individuals who have cancer are immunosuppressed, a state caused by both the cancer and its treatment; as such, they are more susceptible to infections than those without cancer. COVID-19 is a case in point. In this Chinese study, among 1590 patients with COVID-19, 18 had a history of cancer. These patients had a higher risk of ICU admission requiring invasive ventilation and a higher risk of death compared with COVID-19 patients without cancer (7/18 [39%] vs 124/1572 [8%]; Fisher's exact P = .0003). The patients who underwent chemotherapy or surgery in the previous month had a higher risk of clinically severe events than those who did not (OR, 5·34; P = .0026).
- The authors of the study suggest an intentional postponing of adjuvant chemotherapy or elective surgery for patients with stable cancer, improving personal protection for cancer patients or cancer survivors, and more aggressive monitoring and treatment when patients with cancer become infected with SARS-CoV-2.

Elshad Hasanov MD

Abstract

China and the rest of the world are experiencing an outbreak of a novel betacoronavirus known as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). By Feb 12, 2020, the rapid spread of the virus had caused 42 747 cases and 1017 deaths in China and cases have been reported in 25 countries, including the USA, Japan, and Spain. WHO has declared 2019 novel coronavirus disease (COVID-19), caused by SARS-CoV-2, a public health emergency of international concern. In contrast to severe acute respiratory system coronavirus and Middle East respiratory syndrome coronavirus, more deaths from COVID-19 have been caused by multiple organ dysfunction syndrome rather than respiratory failure, which might be attributable to the widespread distribution of angiotensin converting enzyme 2 – the functional receptor for SARS-CoV-2 – in multiple organs. Patients with cancer are more susceptible to infection than individuals without cancer because of their systemic immunosuppressive state caused by the malignancy and anticancer treatments, such as chemotherapy or surgery. Therefore, these patients might be at increased risk of COVID-19 and have a poorer prognosis.

Cancer Patients in SARS-CoV-2 Infection: A Nationwide Analysis in China. *Lancet Oncol* 2020 Mar 01;21(3)335-337, W Liang, W Guan, R Chen, et al.

www.practiceupdate.com/c/97719

COMMENT

By Ari VanderWalde MD, MPH, FACP

This first report on the increased likelihood of COVID-19 infection in cancer patients is timely and important for all oncologists to read. Recognizing that our patients are all at increased risk should spur all of us to re-examine the way in which we deliver care for patients during this health crisis. To prevent infection in our vulnerable patients, we need to strongly consider important mitigation measures within our clinics. Limiting large gatherings, keeping waiting rooms clean and relatively empty, allowing nonessential personnel to work from home, discouraging the MD/RN culture of working while sick, and ensuring the safety of healthcare workers should be on the top of the mind for all cancer providers. This article clearly shows the risk to cancer patients, which increases the risk to those who care for them as well.

Dr. VanderWalde is Director of Clinical Research at West Cancer Center and Research Institute, Associate Vice Chancellor of Research and Associate Professor of Hematology/Oncology at the University of Tennessee Health Science Center, Memphis, Tennessee.

By Sumanta Kumar Pal MD

The coronavirus has taken a toll on the healthcare system in ways unimaginable. In particular, patients and individuals who are more vulnerable may be at higher risk. This includes cancer patients. Data reported by Liang and colleagues shed some light on the potential increased risk that cancer patients face. In particular, a history of cancer appeared to put patients in China at the highest risk for severe events related to COVID-19. Among 18 cases noted with infection with COVID-19 and concomitant cancer, a large proportion had lung cancer. Again, with a limited number of events, severe events appeared to occur at a much higher proportion in patients with active disease versus cancer survivors.

These data are important to consider as hospitals begin to make recommendations regarding triage of cancer-related care. Certainly, elective procedures for low-risk disease that can be deferred could be pushed back. What comes to mind in this setting, for instance, are patients with low-risk prostate cancer on active surveillance requiring biopsies. However, the dilemma comes for patients who have more aggressive cancer. Physicians should be cautioned against suggesting any regimens being rendered (eg, immunotherapy) offer any sort of protective benefit. Rather, all patients with advanced cancer should be considered to be at higher risk. Patients who are simply in surveillance may consider deferring their visits for a short period of time. For patients with active cancer, the decision to treat can be on a case-by-case basis.

Dr. Pal is Clinical Professor in the Department of Medical Oncology & Therapeutics Research and Co-director of the Kidney Cancer Program at City of Hope, Duarte, California.

Clinical Characteristics of COVID-19 Patients With Digestive Symptoms in Hubei, China

The American Journal of Gastroenterology

Take-home message

- Among 204 patients with confirmed COVID-19 in China, 48.5% had digestive symptoms at presentation to the hospital. They presented with myriad symptoms, such as anorexia, diarrhea, vomiting, and abdominal pain. There were 7 patients recorded who presented with only digestive symptoms and no respiratory symptoms. Patients with digestive symptoms had a significantly longer time from disease onset to admission than patients who did not have digestive symptoms and were less likely to be cured of the disease.
- Patients with COVID-19 who have digestive symptoms were shown to have a worse prognosis than those without. Atypical symptoms, such as diarrhea, may be the presenting features of COVID-19, and physicians should consider these symptoms in screening. Checking the stool of patients for viral nucleic acid should be considered, as previous reports have shown it to be present in 53.4% of infected patients.

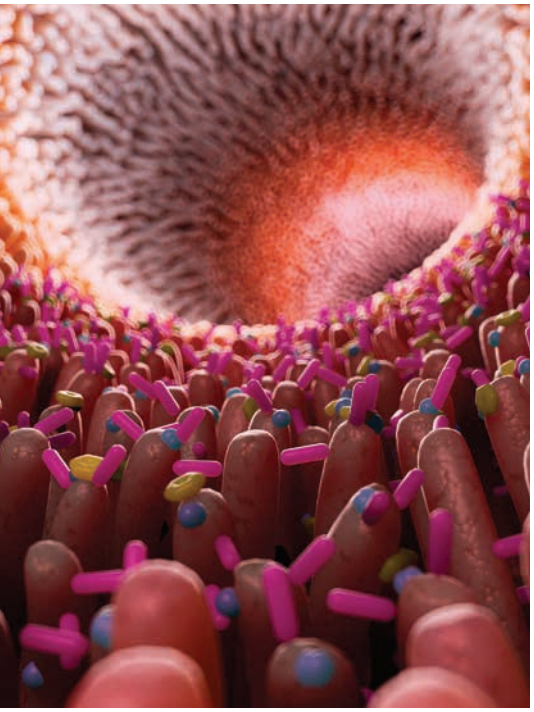
Abstract

BACKGROUND Since the outbreak of Corona Virus Disease 2019 (COVID-19) in December 2019, various digestive symptoms have been frequently reported in patients infected with the virus. In this study, we aimed to further investigate the prevalence and outcomes of COVID-19 patients with digestive symptoms.

METHODS In this descriptive, cross-sectional, multicenter study, we enrolled confirmed patients with COVID-19 who presented to three hospitals from January 18th to February 28th, All patients were confirmed by real-time RT-PCR and were analyzed for clinical characteristics, laboratory data, and treatment. Data were followed up until March 5th, 2020.

RESULTS In the present study, 204 patients with COVID-19 and full laboratory, imaging, and historical data were analyzed. The average age was 54.9 years (SD +15.4), including 107 men and 97 women. We found that 99 patients (48.5%) presented to the hospital with digestive symptoms as their chief complaint. Patients with digestive symptoms had a significantly longer time from onset to admission than patients without digestive symptoms (9.0 days vs.7.3 days). Patients with digestive symptoms had a variety of anifestations, such as anorexia (83 [83.8%] cases), diarrhea (29 [29.3%] cases), vomiting (8 [0.8%] cases), and abdominal pain (4 [0.4%] cases). In 7 cases there were digestive symptoms but no respiratory symptoms. As the severity of the disease increased, digestive symptoms became more pronounced. Patients without digestive symptoms were more likely to be cured and discharged than patients with digestive symptoms (60% vs. 34.3%). Laboratory data revealed no significant liver injury in this case series.

CONCLUSION We found that digestive symptoms are common in patients with COVID-19. Moreover, these patients have a longer time from onset to admission and their prognosis is worse than patients without digestive symptoms. Clinicians should recognize that digestive symptoms, such as diarrhea, may be a presenting feature of COVID-19, and that the index of suspicion may need to be raised earlier in at-risk patients presenting with digestive symptoms rather than waiting for respiratory symptoms to emerge. However, further large sample studies are needed to confirm these findings.



> "In hospitalized patients, consider testing stool for viral nucleic acid."

Clinical Characteristics of COVID-19 Patients With Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. *Am J Gastroenterol* 2020 Mar 19;[EPub Ahead of Print], L Pan, M Mu, HG Ren, et al.

www.practiceupdate.com/c/98000

COMMENT

By David Rakel MD, FAAFP

COVID-19 and GI Symptoms: More Prevalent Than Initially Thought

Most of us are screening for upper respiratory symptoms for COVID-19, but this study of 206 COVID-19–positive patients in Hubei, China, revealed that we should also be looking for GI symptoms. Specifically, 46% (99/206) of patients had digestive symptoms: anorexia (83.8%), diarrhea (29.3%), vomiting (8.1%), and abdominal pain (4%). The diarrhea was described as "loose" and up to three times a day.

Those with GI symptoms had a longer time from disease onset to admission, and the cases were more severe than those without GI symptoms. This may have been related to the fact that diagnosis and treatment were delayed because GI symptoms were not being assessed. It may also be related to the gut–lung axis, suggesting that intestinal infection can promote a more severe respiratory response by activating ACE2 in the liver, creating dysbiosis of the microbiome, and promoting a more robust systemic inflammatory response.

Here are the take-home messages:

- GI symptoms are more common than initially thought and should be included in the screening process.
- Diarrhea is the most specific GI symptom, but it is not severe until the disease progresses.
- Those COVID-19 cases that include GI symptoms are more severe, involve a longer hospital stay, and have a higher mortality rate.
- A small percentage of patients (3%) presented only with digestive symptoms.
- In hospitalized patients, consider testing stool for viral nucleic acid. Prior studies reveal it to be present in 53.4% of infected patients.

Epidemiology of Pediatric Patients With COVID-19 in China

Pediatrics

Take-home message

- Among 731 laboratory-confirmed cases of children with COVID-19 and 1412 suspected cases, over 90% of all patients had asymptomatic, mild, or moderate disease. The median time from onset of illness to a diagnosis of the disease was 2 days. At the early onset of COVID-19, it spread rapidly from the Hubei province to other provinces in China, then gradually decreased over time. More children in the Hubei province were infected than in any other province.
- There was no significant age or gender difference among children infected with COVID-19. The clinical manifestations of disease among children were noticeably less severe than in adults. However, younger patients, in particular, infants, were susceptible to more severe infection.

Abstract

OBJECTIVES To identify the epidemiological characteristics and transmission patterns of pediatric patients with COVID-19 in China.

METHODS Nationwide case series of 2143 pediatric patients with COVID-19 reported to the Chinese Center for Disease Control and Prevention from January 16 to February 8, 2020 were included. The epidemic curves were constructed by key dates of disease onset and case diagnosis. Onset-to-diagnosis curves were constructed by fitting a log-normal distribution to data on both onset and diagnosis dates.

RESULTS There were 731 (34.1%) laboratory-confirmed cases and 1412 (65.9%) suspected cases. The median age of all patients was 7 years (interquartile range: 2-13), and 1213 cases (56.6%) were boys. Over 90% of all patients were asymptomatic, mild, or moderate cases. The median time from illness onset to diagnoses was 2 days (range: 0 to 42 days). There was a rapid increase of disease at the early stage of the epidemic and then there was a gradual and steady decrease. Disease rapidly spread from Hubei Province to surrounding provinces over time. More children were infected in Hubei province than any other province.

CONCLUSIONS Children at all ages appeared susceptible to COVID-19, and there was no significant

COMMENT

By Dipesh Navsaria MPH, MSLIS, MD

As I noted in another commentary (see right), children's infection with COVID-19 may be less about a high risk of harm to the children themselves, but rather their possible roles as vectors of disease transmission to others. So, what do we know about the epidemiology of COVID-19 in children?

This study examined 2143 pediatric patients with COVID-19, of whom about a third were laboratory-confirmed cases; the rest were suspected cases. The researchers found that over 90% of the patients had asymptomatic, mild, or moderate disease. The spread of disease was found to be very rapid early on, but the decline was rather gradual, albeit steady. Notably, these data also made the case for human-to-human transmission since children were not likely to visit the seafood market where the first human cases were thought to have originated.

Transmission seemed to radiate from where the illness began in Hubei province, although it's unclear to me whether this reflects a relative lack of longer-distance travel among children in China. However, even then, social factors can alter that – the one province in which there was higher spread was the rather distant Heilongjiang province, perhaps attractive because of a well-known ice sculpture festival in Harbin, the capital of the province.

Notably, there is some brief exploration of why children seem less affected: the researchers speculate that, since angiotensin-converting enzyme II (ACE2) is the cell receptor for SARS-CoV, that COVID-19 may also target ACE2...which is less mature and functional in children versus adults. They also speculate that the much higher rate of respiratory infections in children versus adults may yield higher levels of antibody which may offer some crossover protection. However, this is a summary of available hypotheses provided by the authors, and certainly not a study testing any of these concepts. ■

By Deborah R. Liptzin MD, MS

The COVID-19 pandemic is a global health crisis. How it affects children is poorly understood. Dong et al provide a review of 2143 pediatric patients with COVID-19 reported to the Chinese Center for Disease Control and Prevention. The authors include suspected (1412, or 66%) and laboratory-confirmed (731, or 34%) cases. Median age was 7 years (range, 1 day to 18 years). They rated the severity of infection from asymptomatic to mild (URI symptoms) to moderate (pneumonia) to severe (oxygen saturations <92%), to critical (ARDS). Most children had mild (51%) or moderate (39%) disease, with only 5% described as severe and <1% described as critical. Only 1 child died (mortality rate <1%). Children under 5 years of age were more likely to have severe or critical disease. Patients with severe and critical disease were more likely to be suspected cases than confirmed cases.

The authors have done an impressive job describing COVID-19 in children in a remarkably short timeframe. The main take-home message from their study is that children have less severe disease than adults (mortality estimates in adults or all comers range from 2.5% to 33%).[1,2] It is unclear why children have less severe disease than adults, but the authors describe previous studies demonstrating that children have less ACE2 than adults, and previous authors describe that COVID-19 binds avidly to ACE2.[3,4]

There are a number of limitations to the current study. There were likely far more

gender difference. Although clinical manifestations of children's COVID-19 cases were generally less severe than those of adults' patients, young children, particularly infants, were vulnerable to infection. The distribution of children's COVID-19 cases varied with time and space, and most of the cases concentrated in Hubei province and surrounding areas. Furthermore, this study provides strong evidence for human-to-human transmission.

Epidemiological Characteristics of 2143 Pediatric Patients With 2019 Coronavirus Disease in China. *Pediatrics* 2020 Mar 16;[EPub Ahead of Print], Y Dong, X Mo, Y Hu, et al.

www.practiceupdate.com/c/97991

asymptomatic children than were reported. Including suspected disease as well as confirmed disease is more comprehensive, but also challenging to interpret in the midst of respiratory season. It is still not well-understood how chronic lung diseases such as asthma, neuromuscular disease, cystic fibrosis, primary ciliary dyskinesia, children's interstitial and diffuse lung disease, pulmonary hypertension, and chronic lung disease of prematurity contribute to the risk of more severe disease in children.

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Dr. Liptzin is a pediatric pulmonologist at the Children's Hospital Colorado and Assistant Professor of Medicine at the University of Colorado School of Medicine in Aurora, Colorado.

SARS-CoV-2 Infection in Children

The New England Journal of Medicine

Take-home message

- A commentary discussing data from Wuhan described 171 children infected with SARS-CoV-2. The median age for infection was 6.7 years. Fewer than half (41%) had a fever during the illness, and 16% of patients had neither fever nor symptoms during illness. There was 1 reported death in a 10-month old, and 3 children required mechanical ventilation; all had coexisting conditions.
- As more information is published regarding COVID-19, we learn more about the effects on children. Many reports describe a high incidence among children, but they seem to be mostly asymptomatic. This fact is particularly worrisome in the US, where our testing criteria are restricted to symptoms at this time. It seems that children are often silent carriers, making it more dangerous in terms of continued spread of COVID-19, particularly to susceptible grandparents.

Andrea Dotson MD, MSPH

COMMENT

By Dipesh Navsaria MPH, MSLIS, MD

The SARS-CoV-2 (also known as COVID-19, or more colloquially, "the coronavirus") epidemic has become a global pandemic. One relatively early feature of the outbreak in China were reports that children seemed to be largely unaffected, with only mild symptoms. Over 72,000 cases reviewed showed fewer than 1% of cases were in children <10 years. But what does the disease look like?

This correspondence looks at 171 children with confirmed COVID-19 infection, out of almost 1400 followed for a month. The most common symptom is thoroughly unhelpful "cough" — unhelpful because that is true for so many viral respiratory illnesses — in about 48% of the cases. Pharyngeal erythema was present in 46%, and fever in 41%.

Lab findings were not particularly specific, but nearly a third of patients had bilateral, ground-glass opacities on chest radiograph. Only 3 patients required intensive care support and intubation/ventilation. Interestingly, 27 of the patients had no symptoms of infection, or radiologic evidence of pneumonia — and, oddly 12 patients had radiologic evidence of pneumonia, but no infection symptoms!

Main takeaway? Virtually nothing aside from COVID-19-specific testing is all that helpful. The good news is that if you're in an ambulatory setting, children are highly unlikely to come to harm themselves and — if not requiring hospitalization — may primarily be a concern for whether they may transmit COVID-19 to other, more vulnerable individuals. So think public health!

Abstract

As of March 10, 2020, the 2019 novel coronavirus (SARS-CoV-2) has been responsible for more than 110,000 infections and 4000 deaths worldwide, but data regarding the epidemiologic characteristics and clinical features of infected children are limited.[1-3] A recent review of 72,314 cases by the Chinese Center for Disease Control and Prevention showed that less than 1% of the cases were in children younger than 10 years of age.[2] In order to determine the spectrum of disease in children, we evaluated children infected with SARS-CoV-2 and treated at the Wuhan Children's Hospital, the only center assigned by the central government for treating infected children under 16 years of age in Wuhan. Both symptomatic and asymptomatic children with known contact with persons having confirmed or suspected SARS-CoV-2 infection were evaluated. Nasopharyngeal or throat swabs were obtained for detection of SARS-CoV-2 RNA by established methods.4 The clinical outcomes were monitored up to March 8, 2020.

SARS-CoV-2 Infection in Children. *N Engl J Med* 2020 Mar 18;[EPub Ahead of Print], X Lu, L Zhang, H Du.

www.practiceupdate.com/c/97984

SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients

The New England Journal of Medicine

Take-home message

- Researchers monitored the SARS-Cov-2 viral loads in 9 women and 9 men from China. They collected a total of 72 throat swabs and 72 nasal swabs from each patient. Of 14 patients who recently returned from Wuhan in January, 13 had evidence of pneumonia on CT. None of these patients visited the Huanan Seafood Market within 14 days before developing symptoms. Some patients required ICU care, and some had secondary infections.
- Researchers found that soon after symptom onset, higher viral loads were detected in the nose rather than the throat of patients. They concluded that the viral shedding pattern resembles that of influenza rather than SARS-Cov. Also, viral load was detected in asymptomatic patients, suggesting that patients without symptoms or minimal symptoms have the potential to transmit the virus.

"Everyone is talking about the possibility of a second wave of infection, so let us not create that scenario by letting our recovered patients be the vector again."

Abstract

The 2019 novel coronavirus (SARS-CoV-2) epidemic, which was first reported in December 2019 in Wuhan, China, and has been declared a public health emergency of international concern by the World Health Organization, may progress to a pandemic associated with substantial morbidity and mortality. SARS-CoV-2 is genetically related to SARS-CoV, which caused a global epidemic with 8096 confirmed cases in more than 25 countries in 2002–2003. The

COMMENT

By Peter Lin MD, CCFP

After You Have COVID-19, When Are You COVID-19 Free?

This is an important question because it will govern when you can stop all the isolation measures and also when you can go back to work. This is especially important for the front line health care providers (HCP) because we don't want them to pass the virus to their patients when they return to work. Yet we are low on health care personnel so getting those people back safely is critical.

This letter to the editor helps to highlight this issue. It is only 17 COVID-19 patients but it nicely illustrates the variability in the duration of viral shedding. First of all severe patients had higher viral loads overall and still had detectable levels out to day 12 after the onset of symptoms. Some of the secondary cases, which got it from a close contact had very high viral titres right from day 1 of their symptoms. What this means is that the COVID-19 virus could have high viral titres in the first few days but the virus can still be present well into the 12th day after symptoms have started. That means patients are infectious over a very long period of time.

This may explain why this virus can transmit so easily because even before patients have a lot of symptoms, the viral load is already high. This means that physical distancing is really important because people will not look ill and if you are close to them then you could breathe the same airspace as them and therefore pick up the virus. Now at the other end, when the patient has "recovered," he can still be transmitting the virus as well.

The WHO report from China stated that the Guangzhou CDC as of 20 February said that the "virus can initially be detected in upper respiratory samples 1–2 days prior to symptom onset and persist for 7–12 days in moderate cases and up to 2 weeks in severe cases." This becomes important as we decide when to clear people to return to work and when to remove self-isolation protocols.

Currently, for health care providers, CDC needs two negative swabs that are 24 hours apart in order to clear that person. However, we do not have enough swabs so for non-test based patients, CDC says that 3 days without fever, without using fever-reducing medications, and improved respiratory symptoms and at least 7 days have passed since the start of symptoms then they are clear to go back to work. But for HCP, they must wear masks until 14 days have passed from the start of the illness and they must stay away from all immunocompromised patients.

However, the data from China says that the severe cases could shed virus for 2 weeks so perhaps we should be erring on the side of caution. So even if the patient feels well on day 8, we should still follow strict isolation protocols for the full 2 weeks to make sure that the recovered patient does not accidentally spread the virus.

So the key take-away from all this data, is that this virus spreads before the patients look sick and it continues to spread well past the time when the patient is feeling better. There are other studies that say that they can find the virus RNA for 20 days after symptoms start and there is even viral

epidemic of SARS-CoV was successfully contained through public health interventions, including case detection and isolation. Transmission of SARS-CoV occurred mainly after days of illness and was associated with modest viral loads in the respiratory tract early in the illness, with viral loads peaking approximately 10 days after symptom onset. We monitored SARS-CoV-2 viral loads in upper respiratory specimens obtained from 18 patients (9 men and 9 women; median age, 59 years; range, 26 to 76) in Zhuhai, Guangdong, China, including 4 patients with secondary infections (1 of whom never had symptoms) within two family clusters (Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). The patient who never had symptoms was a close contact of a patient with a known case and was therefore monitored. A total of 72 nasal swabs (sampled from the mid-turbinate and nasopharynx) (Figure 1A) and 72 throat swabs (Figure 1B) were analyzed, with 1 to 9 sequential samples obtained from each patient. Polyester flock swabs were used for all the patients.

SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *N Engl J Med* 2020 Mar 19;382(12)1177-1179, L Zou, F Ruan, M Huang, et al.

www.practiceupdate.com/c/97954

RNA detected in stool samples as well. Now we have to be smart and ask the question are we just detecting remnant RNA after the virus is destroyed? Or are we really detecting viable viral particles that could go onto infect others? These are important questions that need to be answered with further studies.

For now let us simply practice physical distancing, masking and good hand hygiene, and hopefully we will not infect others as we return patients back to the workplace. Everyone is talking about the possibility of a second wave of infection, so let us not create that scenario by letting our recovered patients be the vector again. So let's keep our guard up even when the patients say that they feel better.

World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID19). Geneva: WHO; 2020. www.who.int/docs/default-source/coronaviruse/whochina-joint-mission-on-covid-19-final-report.pdf.

www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html

Care of Hematology Patients in a COVID-19 Epidemic

British Journal of Haematology

Take-home message

- This commentary reviews the unique challenges facing patients with hematological disorders and the physicians who care for them during the ongoing COVID-19 pandemic. The review highlights the anticipated increased risk especially in the hematological malignancy population, and the measures that can be taken to reduce this risk. Such measures include remote visits via telemedicine clinic visits, change in structures to outpatient clinic flow, consideration of importance of timing and administration of maintenance and curative chemotherapy, and stem cell transplant; and changes to both visitor and workforce populations during a pandemic.
- This commentary provides key areas of focus unique to hematologists caring for patients during the COVID-19 pandemic, providing guidance in preparation for changes to the healthcare system as a result of the ongoing pandemic.

Curtis Lachowiez MD

Abstract

The threat to health of the COVID-19 infection (caused by the novel zoonotic SARS-CoV-2 coronavirus) is now established.[1,2] As widespread community transmission becomes likely, it is necessary to urgently consider the unique impact this may have on haematology patients and the practical steps that can be taken to reduce their risk during ongoing care. The importance of personal hygiene, the use of protective equipment and the investigation, isolation and treatment of infected patients are well documented elsewhere (*https://www.england.nhs.uk/ourwork/eprr/coronavirus/*), and are not discussed here.

Care of Haematology Patients in a COVID-19 Epidemic. *Br J Haematol* 2020 Mar 15;[EPub Ahead of Print], J Willan, AJ King, S Hayes, et al.

www.practiceupdate.com/c/97896

CV Considerations for Patients, Healthcare Workers, and Health Systems During the COVID-19 Pandemic

Journal of the American College of Cardiology

Take-home message

- The authors review the available literature regarding the cardiovascular considerations of the current COVID-19 pandemic. Patients with preexisting cardiovascular disease (CVD) plus COVID-19 have an increased risk of severe illness and death compared with patients without CVD. In addition, COVID-19 appears to have multiple cardiovascular complications, such as acute myocardial injury, myocarditis, arrhythmias, and venous thromboembolism. Current therapies under review may impact the cardiovascular system. Healthcare workers are especially vulnerable to infection or to becoming host or vectors of virus transmission.
- The cardiovascular community has a key role to play in the management of patients affected by COVID-19 as well as in the continued management of patients with established CVD who are at high-risk for severe infection.

Abstract

The coronavirus disease-2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 that has significant implications for the cardiovascular care of patients. First, those with COVID-19 and preexisting cardiovascular disease (CVD) have an increased risk of severe disease and death. Second, infection has been associated with multiple direct and indirect cardiovascular complications including acute myocardial injury, myocarditis, arrhythmias and venous thromboembolism. Third, therapies under investigation for COVID-19 may have cardiovascular side effects. Fourth, the response to COVID-19 can compromise the rapid triage of non-COVID-19 patients with cardiovascular conditions. Finally, the provision of cardiovascular care may place health care workers in a position of vulnerability as they become host or vectors of virus transmission. We hereby review the peer-reviewed and preprint literature pertaining to cardiovascular considerations related to COVID-19 and highlight gaps in knowledge that require further study pertinent to patients, health care workers, and health systems.

Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the Coronavirus Disease 2019 (COVID-19) Pandemic. *J Am Coll Cardiol* 2020 Mar 19;[EPub Ahead of Print], E Driggin, MV Madhavan, B Bikdeli, et al.

www.practiceupdate.com/c/98139

COMMENT

By Jonathan Temte MD, PhD

COVID-19: Considerations for Cardiac Care

In a daily situation report I just received, I note that across 13 hospitals there are 986 patients under investigation for coronavirus disease 19 (COVID-19) and 77 confirmed with sudden acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Of these, 43 are inpatients and 14 are ventilated. Wow… 4 months ago no one saw this coming, and now we are in the midst of a global pandemic. COVID-19 has changed everything and catapulted cardiologists into the forefront of hospital-based response. Two recent articles are of acute interest to all cardiologists and any other clinicians caring for patients with cardiac conditions.

A quick review, provided by Xiong and colleagues,[1] outlines the very basics of epidemiology, underlying cardiovascular disease (CVD) risk factors for worsened COVID-19 outcomes, the cardiovascular complications of infection, and long-term sequelae. For a much deeper and well-referenced dive (but one that I would suggest as essential), invest a few minutes in the comprehensive review by Driggen et al.[2] The epidemiology, pathogenesis, and clinical features of SARS-CoV-2 are succinctly presented. The presence of risk factors for CVD and existing CVD are associated with increased COVID-19 morbidity and mortality. Moreover, significant cardiovascular sequelae are commonly reported with SARS-CoV-2 infection and include myocardial ischemia and myocarditis, risk for plaque rupture, arrhythmia, cardiac arrest, cardiomyopathy, heart failure, cardiogenic and mixed shock, venous thromboembolic disease, and confusing symptomology (e.g., chest pain and electrocardiographic changes with normal coronary arteries on catheterization).

The cardiac considerations and complications of the pharmaceutical interventions currently under evaluation or in compassionate use are summarized and their potential interactions with common cardiovascular agents are discussed. For additional and up-to-date information on medications that may be in use for COVID-19 patients, however, I suggest an excellent resource, "Assessment of Evidence for COVID-19-Related Treatments," provided by the American Society of Health-System Pharmacists at: *www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/ASHP-COVID-19-Evidence-Table.ashx*.

Finally, the authors provide an extensive overview regarding self-protection during aerosol producing interventions, such as cardiopulmonary resuscitation, and approaches to lowering risk of transmission to healthcare workers and patients. It's a new world out there and COVID-19 is likely to be with us for at least several months. As CVD risk factors contribute to COVID-19 hospitalizations and COVID-19 results in cardiovascular complications, cardiologists will increasingly feel the press of this pandemic. Accordingly, thoughtful preparation is a key component of navigating this threat.

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The Psychological Impact of Quarantine and How to Reduce It

The Lancet

Take-home message

- The authors present a review of quarantine with strategies for the management of associated distress.
- This topic is relevant during the current coronavirus outbreak and associated increased need for quarantine.

Morgan Soffler MD

Abstract

The December, 2019 coronavirus disease outbreak has seen many countries ask people who have potentially come into contact with the infection to isolate themselves at home or in a dedicated quarantine facility. Decisions on how to apply quarantine should be based on the best available evidence. We did a Review of the psychological impact of quarantine using three electronic databases. Of 3166 papers found, 24 are included in this Review. Most reviewed studies reported negative psychological effects including post-traumatic stress symptoms, confusion, and anger. Stressors included longer quarantine duration, infection fears, frustration, boredom, inadequate supplies, inadequate information, financial loss, and stigma. Some researchers have suggested long-lasting effects. In situations where quarantine is deemed necessary, officials should quarantine individuals for no longer than required, provide clear rationale for quarantine and information about protocols, and ensure sufficient supplies are provided. Appeals to altruism by reminding the public about the benefits of quarantine to wider society can be favourable.

The Psychological Impact of Quarantine and How to Reduce It: Rapid Review of the Evidence. *Lancet* 2020 Feb 26;[EPub Ahead of Print], SK Brooks, RK Webster, LE Smith, et al.

www.practiceupdate.com/c/97231

COMMENT

By Dennis J. Butler PhD

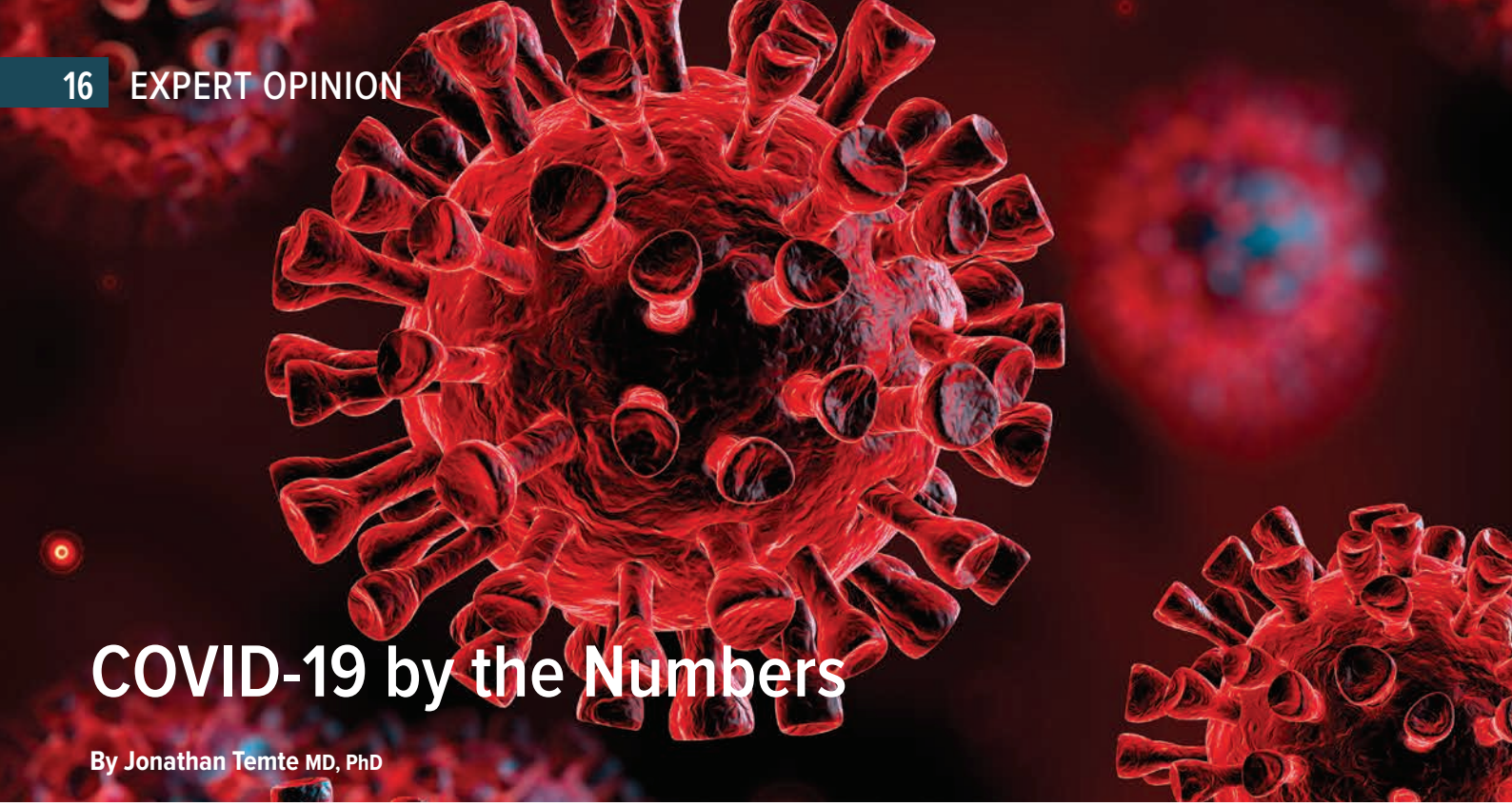
This *Lancet* "Rapid Review" finds that the limited research on the psychological effects of quarantine pretty much confirms what most would suspect.

- Quarantine is often associated with negative psychological effects, some of which may endure for 3 years or more. The inventory of complications includes PTSD/acute stress disorder, depression, anxiety, fear of infections, persistent anger, irritability and decreased frustration tolerance, and detachment. Extended quarantine is associated with poorer mental health outcomes.
- Unfortunately, the research is too imprecise to estimate prevalence and too inadequate for identifying demographic variables associated with increased risk. Based on the reaction of mental health patients to previous outbreaks, there is good reason to anticipate that this population is at risk for worsening symptoms and functional deterioration during quarantine. Routine medical and psychotherapeutic care for these patients is disrupted during quarantine. Telephone contact to offer support and to address worsening symptoms can help; the review authors also encourage the use of mental health hotlines.
- Quarantined healthcare workers are more extensively studied and experience difficulties in multiple areas during and following quarantine. Personal difficulties include exhaustion, detachment, irritability, insomnia, and poor concentration. Professional difficulties include guilt over abandoning coworkers and patients, anxiety with febrile patients, indecisiveness, and reluctance to return to work. Social difficulties include feeling stigmatized and loss of social engagement, especially with their healthcare team. In some studies, health workers reported clinical symptoms 3 years post quarantine. At least one study identified increased alcohol use. I have worked with international healthcare professionals and Peace Corp volunteers extracted and quarantined after exposure to life-threatening diseases who experienced intense feelings of vulnerability and terror about exposure with concurrent guilt and regret about "abandoning" their humanitarian work.

Although this review sensitizes clinicians to the psychological consequences of (typically brief) quarantine, the current international recommendations and mandates for prolonged social isolation and distancing exceed anything previously investigated. But, based on this Rapid Report, we can anticipate the psychological complications will be greater given the global disruption of social life, uncertainty about disease transmission, and the absence of specific treatment. Isolation and anxiety are never good companions. The encouraging finding is that voluntary quarantine appears associated with less distress and fewer long-term consequences.

The authors believe altruism may buffer distressing effects. Messages that we are all in this together and that quarantining oneself will help your fellow man may balance some negative effects for some people. Much, much progress is needed (and soon) to advance other elements known to alleviate patient anxiety, communicating accurate, up-to-date information and providing adequate healthcare resources (eg, testing).

Finally, a few lessons previously learned from patient care regarding quarantine: Patients need to keep their (cell) phones handy and charged, and use them to maintain their social network. They should limit the amount of time listening to and watching media reports, and start keeping a record of daily events and their reactions. And, because of confusion about terminology, they need to be instructed on the difference between quarantine (exposed) versus isolation (infected) and the critical importance in maintaining quarantine guidelines.



COVID-19 by the Numbers

By Jonathan Temte MD, PhD

Dr. Temte is Professor in the Department of Family Medicine and Community Health at the University of Wisconsin School of Medicine and Public Health in Madison, Wisconsin.

Numerators are necessary, and nimble; denominators are difficult. In any epidemiological assessment, the devil is in the details; and, more commonly, the devil is in the denominator. The phase, derived from a German proverb – "Der liebe Gott steckt im detail (God is in the detail)" – is especially relevant to COVID-19. Let me explain.

With the emergence of a new and worrisome pathogen, the medical and public health community responds initially to the notable cases, and rightly so. Our attention is focused on severe and unexpected events, which present as something out of the ordinary. With COVID-19, these were the cases in Wuhan with severe respiratory consequences. These initial cases, some resulting in death, immediately became the numerator. The denominator, from which we could describe relevant epidemiological characteristics such as case-fatality rates (CFR), was the total number of confirmed cases based on positive COVID-19 tests. To this day, we continue to intently follow these numbers. My phone app this morning reports 107,442 confirmed cases and 3648 deaths, for a CFR of 3.2%. Herein lies the genesis of epidemiological misinterpretation with global consequences.

> "I suspect that containment of COVID-19 is out of the question. Response and mitigation efforts are our now most imminent responsibility."

Because COVID-19 tests are a limited resource, the most appropriate deployment was to those individuals who were most likely to have COVID-19. In the US, our initial testing required significant symptomology and reasonable exposure (travel) history. Again, this was sound; however, it opened the door to ignoring those individuals with subclinical and minimally clinical symptoms. What we are learning is that there can be a significant COVID-19 burden across a very wide spectrum of clinical presentations. As a consequence, we can have wide-ranging estimates of CFR and rates of severe disease. As more and more testing becomes available, we will become smarter; our estimates of the impact will become more accurate. Unfortunately, we now have widespread seeding of this virus across the globe.

COVID-19 is unfolding in a relatively predictable manner. Initial severe cases attract attention and very comprehensive mitigation efforts. As a respiratory virus with an incubation period that is longer than transoceanic flights and symptomology that is manifold, complete detection at checkpoints is impossible, allowing for widespread dispersion. Arrival in new populations is unchecked by existing immunity and, with a respectable basic reproduction number (the number of secondary cases generated by each case), easily seeds and spreads through communities. As this is occurring during the typical "respiratory virus season" in the Northern Hemisphere, COVID-19 cases can easily hide among the plethora of other viral acute respiratory infections. Amidst this outbreak, we spend too much time on recrimination, as opposed to supporting those medical and public health professions who are frontline to our response efforts.

I suspect that containment of COVID-19 is out of the question. Response and mitigation efforts are our now most imminent responsibility. Clinicians need to keep abreast of reliable information, participate with their health communities for adequate planning and resourcing. Finally, messaging everywhere – on hand hygiene, respiratory hygiene, social distancing, appropriate use of PPE in medical settings, and self-isolation when ill – is our best defense. ■

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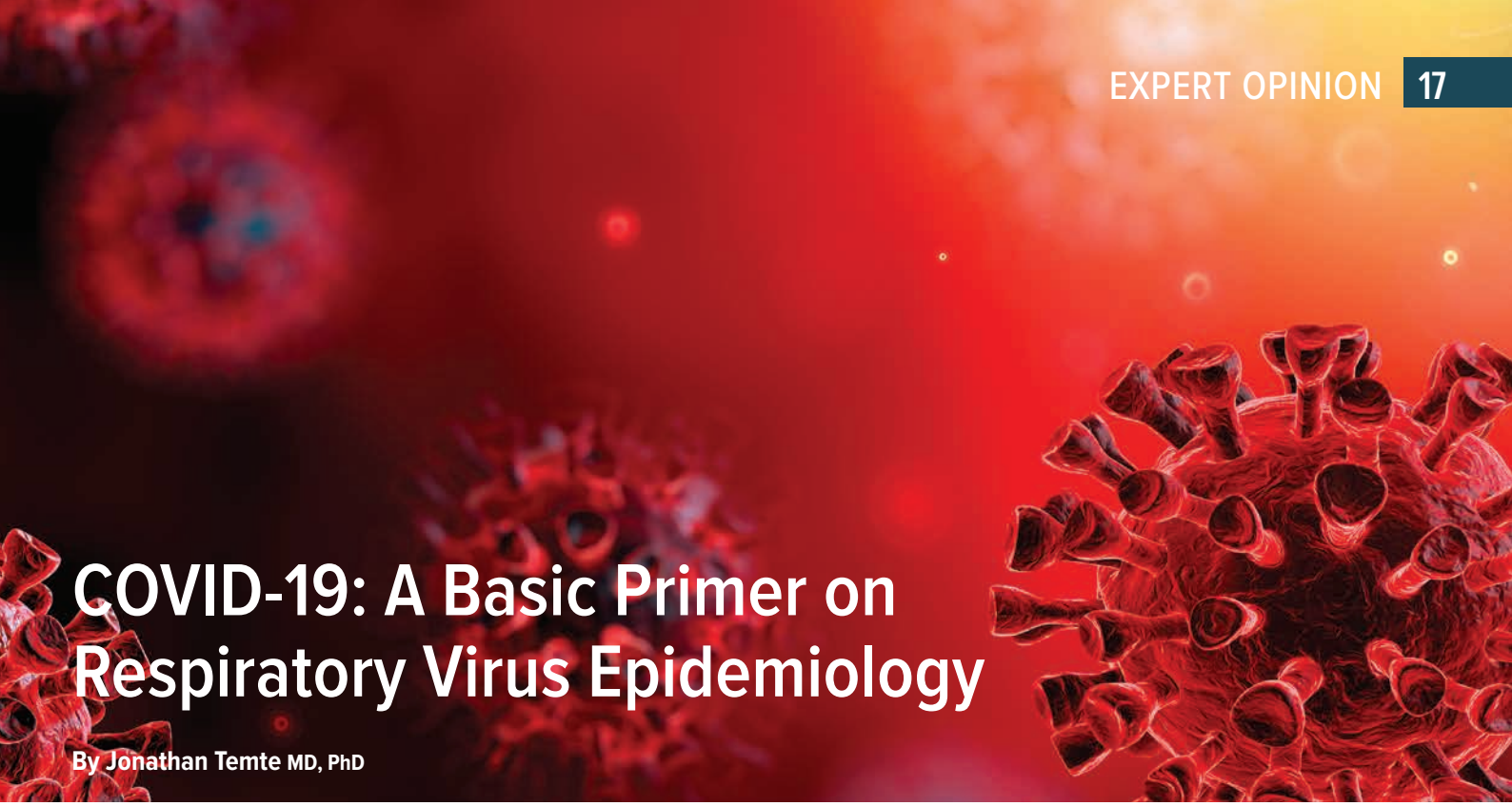
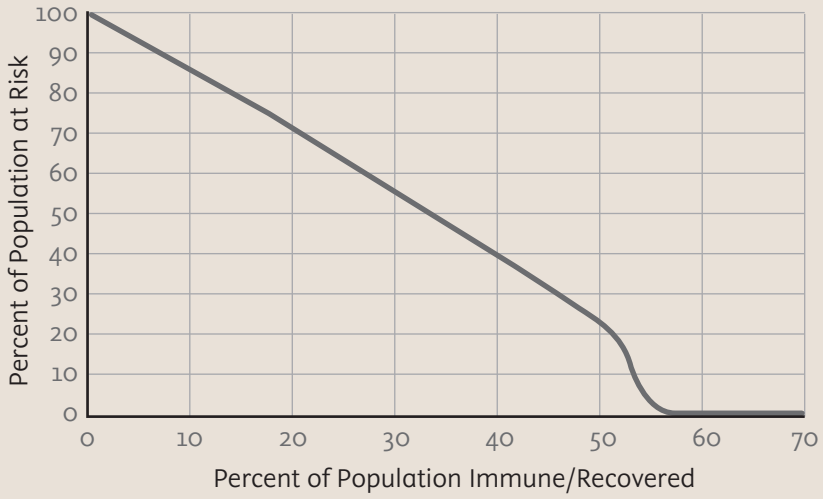


COVID-19: A Basic Primer on Respiratory Virus Epidemiology

By Jonathan Temte MD, PhD

Eventually, we will all become infected with SARS-CoV-2. That is not quite true, but may apply to more than half of us. The initial appearances of hotspots across the global map have now been replicated on the US map, and more recently on our state maps. SARS-CoV-2 is spreading exponentially and is everywhere. Let us think about that for a moment and consider some very basic epidemiological modeling.

When unchecked by immunity, illnesses due to respiratory viruses can increase exponentially with the rate governed by what we call the basic reproduction number. This number can best be described as the number of new cases derived – on average – from each existing case. When this number is high – such as with measles – new cases can explode. When this number is close to 1.0, we get a very slow burn. Moreover, should the reproductive number fall below 1.0, an outbreak ends. Primary care clinicians are all familiar with influenza, which is in the low-moderate range of about 1.6. SARS-CoV-2 is higher than influenza with estimates around 2.4.[1]



Epidemiological math then gets more complicated. The realized reproduction number is modifiable. Public health approaches, such as nonpharmaceutical interventions (NPI: social distancing, handwashing, respiratory hygiene, and use of PPE) and community mitigation efforts (quarantining, isolation, school closures, bans on mass gatherings, and travel bans), can effectively lower the transmissibility, thus lowering the realized reproductive number. For example, estimates from Wuhan, China suggest that public health measures lowered the reproductive number to 1.05.[1] In addition, immunity acquired by infection and recovery, or through an effective vaccine, will also lower it. This is the quintessence of "flattening the curve" that we hear bantered around so much these days (see figure 1 in CDC. Community mitigation guidelines to prevent pandemic influenza — United States, 2017).[2]

So, where does that leave us? Assuming very generously that there are 100 additional cases in the U.S. for each confirmed case, less than 1% of us have experienced SARS-CoV-2. Without a vaccine and/or very sustained NPI and community mitigation efforts, another 170,000,000 of us may need to become infected and recover to make SARS-Cov-2 go away... and a case burden of this level is unfathomable in terms of COVID-19 morbidity and mortality. I am hoping that my basic epidemiological musings are wildly incorrect. In the meantime, keep up with NPI, support your public health agencies in their efforts for community mitigation, and hope for a safe and effective vaccine. ■

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Immediate Impact of COVID-19 on Cancer Care at Major Institutions

A conversation between Axel Grothey MD and Jeremy L. Warner MD, MS, FAMIA, FASCO

Dr. Grothey is Director, GI Cancer Research, West Cancer Center, Germantown, Tennessee

Dr. Warner is Associate Professor Medicine in the Division of Hematology and Oncology, and Associate Professor Medicine, Biomedical Informatics at Vanderbilt University Medical Center in Nashville, Tennessee.

Dr. Grothey: In my practice, it's interesting because we always think about delaying elective procedures. You don't need your hip replacement right now, you can get it, let's say 6 months from now, or even dental cleaning, you know. There are certain procedures that we can delay, but cancer doesn't always wait. If you have an aggressive malignancy that a patient has and we need to treat this malignancy, that's more important than the hypothetical risk of infection. So, we are currently treating patients with chemotherapy. It's not as crowded, let's say, as before, and we're trying to shift patients to some telemedicine, routine follow-up patients to limit exposure in the way you said, waiting room is not crowded, etc., but some patients are continuing on therapy, you know, actually a lot of patients, and there is some concern.

I really believe we do not know exactly what's going on. There are some reports from China that the mortality with cancer and COVID infection is higher, but we don't know anything about risk. We think the immunotherapy issue is a very important one, especially since we already know some of the immunotherapy drugs can cause pneumonitis, which seems to be one of the important cytokine storm issues that really is associated with a high lethality in cancer patients once they go through the infection, etc.

So, how is Vanderbilt, your institution, handling this whole epidemic right now? I mean, how are you trying to move patients around, limit exposure, probably telemedicine approaches, etc.

Dr. Warner: Yeah, well I'll say a couple of things, but first I'll say that one of my longer term... so this is like the new full-time job, right, is addressing COVID-19. One of my longer term research interests is formalizing the representation of chemotherapy regimens and their details, which has been actually lacking from medical records and other databases for decades, and we're moving forward on that. Part of my long-term goal is to understand the impacts of treatment delays and dose reductions, and we actually don't know as a community, because we haven't been able to capture that granular data. Does delaying a cycle that's supposed to be every 3 weeks to every 4 weeks, does that have an impact or is

that okay? Does reducing a dose a little bit to try to reduce the neutropenia, you know, is that going to be okay? We're not going to be able to answer those questions right away, but anyway, that's one of my longer term interests.

Dr. Grothey: So, learning from the COVID epidemic to really see beyond just the viral interaction?

Dr. Warner: I think we might [have to] because the impacts on the healthcare system are severe already. And so just speaking about Vanderbilt, first of all, our directives are changing daily, so what I say now might not be true later, but we've addressed some challenges of distance medicine head-on.

You know, we're a state that's long and skinny, right, and you're actually at the edge of the state, but we have a seven-state catchment area where many of our patients come from. Many of our patients are coming from Kentucky for cancer care, and so when the telemedicine started a week or two ago, we couldn't provide care to those patients because of the federal restrictions on licensing, medical licensing. Now, that's changed rapidly. Most of our

clinicians are in the process of getting temporary licenses for our neighboring states so that we can provide telehealth. So the telehealth visits have increased exponentially, but we can't forget that telehealth doesn't really work for people who might not have the internet, you know, might not be savvy about computers. And unfortunately it will worsen certain disparities, but it's clearly what we have to do.

We're delaying elective procedures, as you said, just like most folks, and what's elective and what isn't? That's subject to discussion. Is a curative cancer surgery for something that's not otherwise immediately causing any symptoms, like a localized breast cancer picked up on a mammogram? Is that elective? Technically, I think it is, but it's certainly very distressing, I think, for an individual to have a potentially curative cancer that they need to basically keep in place until things get a little bit stable.

And then you know, the other unfortunate impact of this has been on our clinical trial endeavors. We're not the only institution that has made this decision, but as of yesterday, we have shut down new approvals to clinical trials. We're obviously continuing to treat patients who are already enrolled or who are in the enrollment process, but due to staffing and a host of other factors, we had to make that very tough decision yesterday.

> "...a lot of institutions have really shut down, and wisely shut down new trial approval, and it's going to really have a huge impact on our research system right now beyond everything we're talking about."

Dr. Grothey: Yeah. That's something we discussed actually on a SWOG call too, the Southwest Oncology Group call, earlier this week, that a lot of institutions have really shut down, and wisely shut down new trial approval, and it's going to really have a huge impact on our research system right now beyond everything we're talking about.

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Go to the PracticeUpdate COVID-19 Disease Spotlight at *http://covid19.practiceupdate.com* to watch the rest of this series of conversations between Dr. Grothey and Dr. Warner.

The Impact of COVID-19 on the Business of Urology

By Gautam Jayram MD and Benjamin Lowentritt MD

Dr. Jayram is a urologist and Co-Director of the Advanced Therapeutic Center, Urology Associates, P.C., in Nashville, Tennessee.

Dr. Lowentritt is Director of Prostate Cancer Services at United Urology.

The past month has seen unprecedented change sweep across individuals and businesses throughout the country, including healthcare providers. The COVID-19 pandemic has left physicians and medical practices reeling and trying to balance livelihood with safety and appropriate use of resources. As small business owners, many large-group practices are having to now tackle complicated issues related to labor force, supply chain, and keeping their patients and providers safe during the pandemic. Most of the discussion of physician practices during the first several weeks of the crisis regarded urology under the umbrella of the "critical industry" of healthcare. This would seem to encourage a "business-as-usual" approach in order to keep patients out of the hospital and their primary care physician offices, which conceivably were being inundated with COVID-19 preparation and patients. The CDC and state recommendations were primarily focused on what hospitals should be doing, and centered around restricting elective surgeries. For urologists, that meant very few obligate reasons to perform hospital-based procedures (obstructing stones, high-risk renal/urothelial cancers, acute bleeding, etc).

As the situation has worsened and non-essential happenings around the country are increasingly shutting down, we are all taking a hard look at our practices and critically evaluating the urgency and necessity of our work. Various regulatory bodies have weighed in on all aspects of medical appropriateness and resource preservation. Based on this, large urology groups appear to taking the same approach:

1. **Restricting all office and ASC procedures to those considered emergent or essential.** This means only active pain, bleeding, or cancer progression should be operatively managed. Roughly this comprises about 10% to 15% of typical volume.
2. **Restricting person-to-person office visits;** only patients with urgent issues or receiving active cancer treatments are allowed to be seen.
3. **Identifying and supporting critical services that need to continue for our patients well-being.** For many large groups, this includes in-office dispensing of cancer drugs and continuation of radiation services for patients on therapy. Cancer infusions have been continued but newly started only in selected cases, similar to how medical oncologists are currently operating.

> "The most substantive change in urologic practice has been the emergence of telehealth services."

4. **Practices heavily involved in research have questioned the utility of maintaining research staff and visits during the pandemic.** The FDA has issued guidance on clinical trial proceedings during this time, and many cancer trials are encouraged to continue at the sponsor's discretion.

Even for these "essential" services, groups are adjusting down operations to allow for maximal intervals between patients and to minimize the number of visits required. Office and clinic staff have been curtailed. There has been some discussion about completely shutting down ASCs during this time, mainly to preserve personal protective equipment. We feel the ASCs represents an important site of service where patients can get urgent procedures done quickly and with minimal healthcare worker contact. These procedures (catheters, stents, fulgurations, etc) would otherwise need to be done in a hospital setting. Both providers and patients benefit from keeping our patients at the current time out of large medical facilities, which likely represent local epicenters of COVID-19 infections.

The most substantive change in urologic practice has been the emergence of telehealth services. Many groups and institutions have had preliminary experience with telehealth platforms and even participated in pilot programs. However, previous CMS limitations on eligibility and reimbursement for these services kept them out of mainstream practice. With recent urgent passage of the CARES Act, those limitations are now gone and any Medicare-approved provider (including APPs) can now bill and collect on a scale equivalent to in-person visits. Outpatient visits involving both new and established patients can be done easily with a video/audio platform over a phone, computer, or iPad. Early telemedicine experiences in our large groups have been very positive, and patients have been thrilled to be able to communicate to doctors (even about their nonurgent conditions) during this time. There are certainly still some kinks to be worked out, but it appears that telemedicine will be one of the few positives to emerge from this experience and will likely occupy a large role going forward in outpatient practice. It is likely that CMS will reevaluate the "rules" for telemedicine billing once the crisis is over; but, given initial successes, it is unlikely to be changed dramatically. Infrastructure for these visits will likely need to be expanded and supported by all groups looking to stay current in the marketplace. Furthermore, the addition of local/regional facilities for urine drop-offs, blood draw kiosks, and so forth will be necessary to accommodate patients' increasing demand for remote services.

The stark reality is that most urology groups will have approximately 70% to 80% of their typical work postponed or cancelled during this time. Traditional business models and revenue cycles are completely turned upside down for most of us. High capital outlays (large buy-and-bill medications or services, new equipment, new hires) all could be very limited in the months to come. We are seeing many industry sponsors and healthcare companies provide services with discounted and delayed costs. As most of our groups carry 50+ employees, difficult decisions regarding workforce and day-to-day operations have become necessary. Some have chosen to furlough employees; others reduce hours while keeping them on payroll. A few smaller groups have been forced to let go of their employees permanently. We have all had to look into federal unemployment policies and local emergency fund availability for our workers. New government stimulus funds may be helpful in allowing practices to keep a substantial number of employees thus making "the road back" less challenging in a few months. Our groups have consolidated our offices and ASCs as much as possible to provide lean and efficient services for those who need it the most. In many groups, physicians and administrators have agreed to dramatic cuts in salaries, setting a healthy tone for all other financial cuts that need to be made. That being said, there is power and stability in numbers, and many large groups have the resources and leadership to be reliable providers of necessary urologic services during this time. Keeping patients and employees safe and cared for during this time has become our primary goal and something that we can still strive to do well. ■

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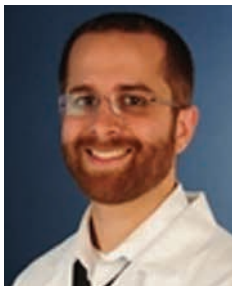
Dermatology in the Time of COVID-19: A Commentary

By Misha A. Rosenbach MD



Dr. Rosenbach is Assistant Professor of Dermatology and Internal Medicine at the Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania.

The novel coronavirus SARS-CoV-2 causes COVID-19, a devastating disease that is changing every aspect of human life on Earth. The breakneck speed at which this virus spreads has led to a firehose of information, which can be hard to keep up with. I have no doubt that, by the time this commentary is posted, there will be new data, recommendations, and guidelines. I would be remiss if I did not start with that warning: please refer to *cdc.gov*, and national, state, and local recommendations for how this virus is specifically impacting your region (in terms of confirmed cases, but also in terms of rules and regulatory changes). The AAD has convened an ad hoc task force focused on evaluating, digesting, and delivering critical updates to members, which is posted on the *aad.org* membership page (conflict of interest disclosure: I am a member of that task force).

Dr. Kwatra and colleagues allude to the issue of rapid spread in the second paragraph of their in-press *JAAD* publication, stating, "the COVID-19 pandemic is set for exponential growth in the United States."[1] This statement however is also outdated – exponential growth is here now. Exponential growth is currently occurring everywhere in the US. As you read this piece, you may be thinking that there is a relatively low number of confirmed cases in your particular region. Please note that the US has had a very slow start to conducting COVID-19 testing. Many locations are doing limited testing of symptomatic patients, or patients in whom the test result would change management – including in New York, where, despite the skyrocketing, nightmarish numbers of confirmed cases, the actual numbers are not captured because of testing limitations. Nowhere in the US is screening being conducted (testing is when we test people we suspect of having the disease; screening is looking at an asymptomatic population). Screening is essential to understand the true prevalence of this disease, as patients may be asymptomatic – and contagious – for up to 5 days. Dr. Kwatra and colleagues explain this nicely in their piece, noting that simply querying patients for fever, cough, known COVID-19 exposures, or travel, is an insufficient mechanism by which to determine if that particular patient poses a risk of transmitting SARS-CoV-2 to other patients in the waiting room or to dermatologists and their staff. Each of those who is infected, then serves as an amplifying vector, transmitting the virus to others before symptoms appear, and contributing to the rapid rate of rise in infections.

Although I think this piece does a nice job in laying out the issues and need for urgent action, in some places the recommendations may go too far. "Prohibiting" specific providers from patient care is challenging – and is not happening in other settings, including the ED and ICU, where the desperate need for skilled clinicians is balanced against the risk that some of those providers take upon themselves when they provide critical care for patients with COVID-19. Additionally, it should be clearly stated that one of the other goals that dermatologists should focus on is keeping dermatology patients out of the ED – the ED providers are overwhelmed with COVID-19 patients, and any patient going to the ED is at risk of contracting COVID-19.

This piece does not mention another critical issue, which should be considered when deciding whether to keep your practice open: the worldwide shortage of personal protective equipment (PPE). There are strict guidelines for what types of PPE are necessary in what clinical settings, and dermatologists who keep their offices open but use PPE risk potentially denying that gear to frontline providers who are facing a desperate shortage. Speaking for myself, I am personally horrified by images on social media of dermatologists in N95 masks advertising that they are open for cosmetic procedures, while our colleagues have resorted to begging for donations of PPE and scrounging masks from libraries, veterinarians, labs, schools, and more.

The AAD has done a nice job of translating recent recommendations from CMS regarding limiting elective, non-urgent office visits for the dual purpose of "flattening the curve" and preserving PPE. Dermatologists would do well to adhere to that advice, and this paper helps highlight those recommendations and the reason, logic, and need to act.

City after city across the globe has watched as first Wuhan, then northern Italy, and now Madrid, New York, and elsewhere have been devastated by the rapid rise of cases, which rapidly overwhelm EDs, hospitals, and ICUs with sheer numbers of patients requiring support. Wherever you are, these cities are windows into your future – should your city fail to act. This piece, and the AAD's guidelines, help provide guidance and a framework to help individual practices and providers to make the right decisions about limiting practice during this period to help reduce spread, while still continuing to provide care for the dermatology patients who need it most. ■

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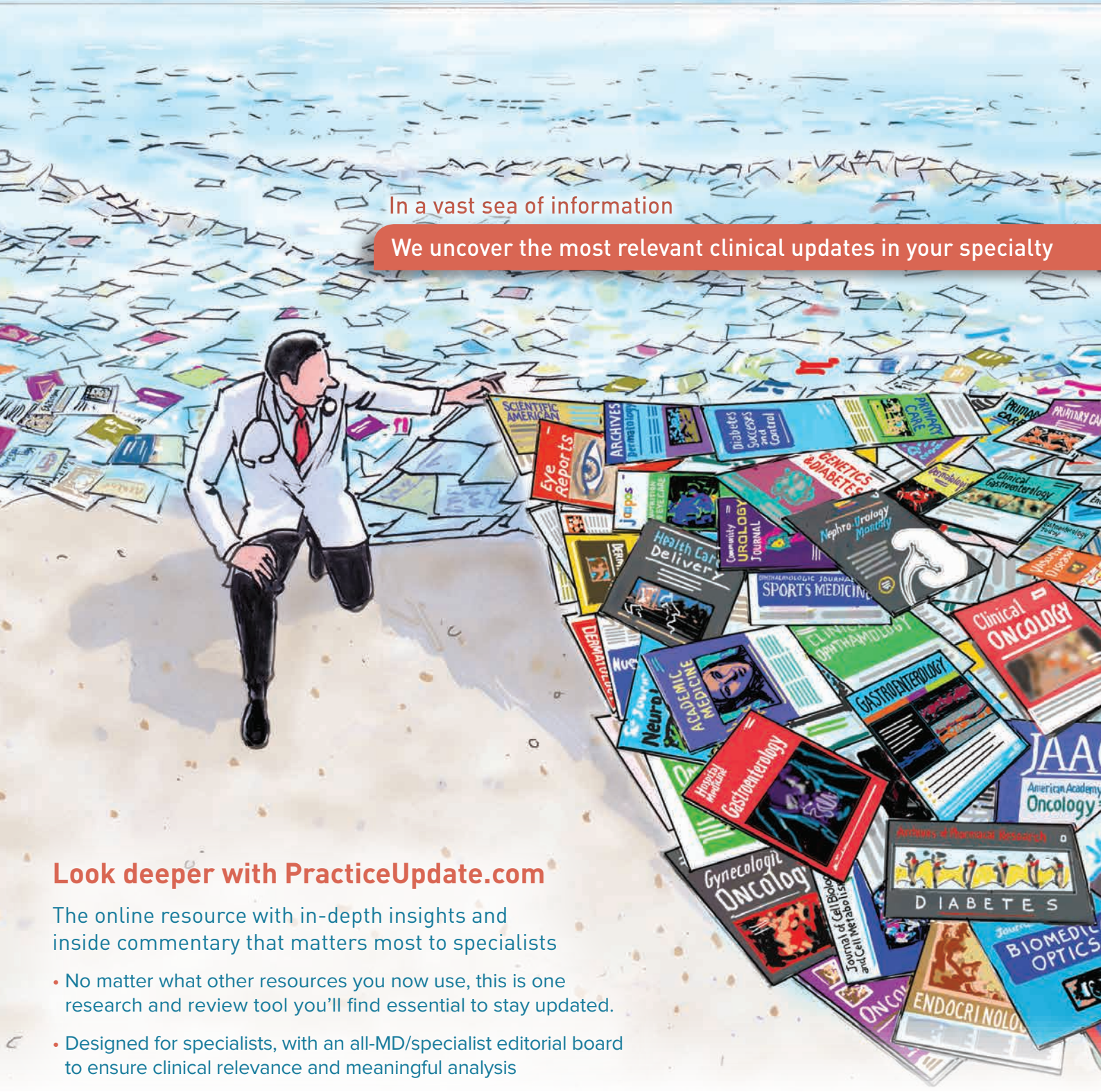

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