Annals of Internal Medicine

SPECIAL ARTICLE

Clinical Decision Making During the COVID-19 Pandemic

Among the many extraordinary aspects of the coronavirus disease 2019 (COVID-19) pandemic, the rapidity with which new scientific information has been shared and incorporated into clinical decision making is almost unprecedented. Undoubtedly, rapid incorporation of new scientific information into preventive and therapeutic strategies has been critical in minimizing the morbidity and mortality of this illness. At the same time, the rapid spread of new data has created the potential for premature implementation of new evidence to have widespread negative effects on decisions at the individual patient and health system levels. At the core of this dilemma is an understanding of how much certainty we require for new information to be adopted and change practice.

Uncertainty in medicine is a fact of life. *Annals* has recently published a series of articles that provides a road map for translating imprecision in diagnostic and therapeutic information into clinical decisions (1). Here, we apply some of those principles to address the following 3 ongoing areas of uncertainty in COVID-19 management: the broad categories of diagnosis, treatment, and prevention. In each case, we briefly review the current state of knowledge, highlight the level of uncertainty, and then suggest a pathway forward for clinical decision making during the pandemic.

Diagnosis

Your patient presents with fever, anosmia, cough, and dyspnea to a local emergency department. The patient is 67 years old and has stable coronary artery disease. Oxygen saturation is normal on room air. A viral polymerase chain reaction (PCR) test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has negative results. Is the diagnosis of COVID-19 ruled out?

The key to using diagnostic tests is the ability to integrate information about a patient's pretest probability and test characteristics into the selection of the appropriate test and interpretation of test results. Several tests are available for detecting SARS-CoV-2 infection. Viral PCR tests are the standard for diagnosing COVID-19 because they have the highest sensitivity, leading to a lower rate of false-negative results. Antigen tests have lower sensitivity but may be useful for rapid identification of infectivity in community settings (2). Antibody tests do not return positive results early in the disease course so are not helpful for acute diagnosis. Fortunately, the correct test was done for this patient, which is the first step in the diagnosis.

To estimate pretest probability of COVID-19, you are able to access current national and state epidemiologic data online that indicate that 30% of all patients having COVID-19 testing receive positive results and that this percentage is even higher among symptomatic adults seen in emergency departments. Moreover, certain clinical and epidemiologic factors, including the presence of anosmia (3), increase the probability of infection further, resulting in a pretest estimate of at least 50% in this case. As Woloshin and colleagues (4) recently calculated using a sensitivity of 70% and specificity of 95% for the test characteristics and an online tool or 2-by-2 table, such a patient still has a 24% probability of having COVID-19 despite a negative test result.

How then can we decide whether the patient truly has COVID-19? One strategy is to understand more about why the test result might be a false negative in this patient. Reviewing the published evidence, it is clear that results of a PCR test can be negative early in the disease course because the viral load is still below the limit of detection (5). Thus, repeating the test after 24 to 48 hours can be useful in improving sensitivity. Repeated testing can also rectify false negatives resulting from inadequate sampling of the nasopharynx. In addition, viral load in the nasopharynx may decrease as the immune response grows during the infection—an issue that cannot be addressed by repeated nasopharyngeal testing. In that setting, other tests can provide additional information about the probability that the patient has COVID-19. For example, patients with significant immune response are likely to have abnormal findings on chest imaging, so chest imaging can improve the sensitivity of a COVID-19 diagnostic strategy (6).

For this patient, the clinician decided to order a chest radiograph, which showed bilateral infiltrates. A follow-up computed tomography scan showed bilateral ground-glass opacities, a pattern consistent with COVID-19. Given a sufficiently high probability of COVID-19 and additional risk factors for clinical deterioration (advanced age and cardiovascular disease), the patient was hospitalized. However, the posttest probability was not judged to be high enough to begin potential empirical treatments or consider enrollment in a clinical trial because the threshold is much higher for treatment decisions than for admission decisions. The next day, results of a repeated viral PCR test were positive, the patient started receiving remdesivir because of risk for disease progression, and the question of whether to start dexamethasone treatment was raised.

The key principles of clinical decision making to consider include the following. First, diagnostic tests are neither perfectly sensitive nor perfectly specific. Interpretation of test results requires an understanding of pretest probability (7). Second, testing and treatment decisions involve thresholds that do not require certainty that a diagnosis has been ruled in or ruled out (7, 8).

Treatment

The patient is hospitalized and now has confirmed COVID-19. Oxygen saturation on room air remains normal. Should the patient be treated with corticosteroids?

This article was published at Annals.org on 2 February 2021.

Clinical trials of therapeutic agents for COVID-19 have occurred at a remarkable pace. Given the significant role of inflammation and lung injury in causing morbidity and mortality, considerable attention has focused on immunomodulatory therapies. Corticosteroids have long been evaluated as potential adjunct therapies for patients with a range of inflammatory conditions due to pulmonary infections, with evidence for and against their use depending on the pathogens and conditions (9). The RECOVERY (Randomized Evaluation of Covid-19 Therapy) trial (10) was a multigroup pragmatic trial that published results in July 2020 showing a mortality benefit for dexamethasone among hospitalized patients with COVID-19. Of note, the demonstration of significant benefit was restricted to preplanned subgroups of patients who received mechanical ventilation or supplemental oxygen. Hospitalized patients without an oxygen requirement did not show a mortality benefit.

It is sometimes tempting to dismiss subgroup effects, especially if subgroup size raises concern about power. Mortality is an obviously important end point to evaluate in COVID-19 trials, but death is uncommon among patients who are not initially hospitalized and do not require ventilatory support. However, therapies also carry risk, and as the absolute benefit of a therapy declines, the importance of adverse risks increases—as observed with clinical trials of corticosteroids for pneumonia (11).

Uptake of approved therapies for secondary indications is often much swifter than uptake of new therapeutics because of familiarity with the agent. Corticosteroids are used throughout medical settings and are widely prescribed, raising concern that consideration of benefit could lead to rapid use, even in the absence of clear, demonstrated benefit. In this case, the patient was not prescribed a corticosteroid. Key principles of clinical decision making to emphasize include the following. First, quality of evidence is a critical element to assess when incorporating new data into clinical decision making, and randomized trials with masked assessment of outcomes provide the best nonbiased estimates of benefit (12). Second, subgroup effects are important to consider in deciding whether the results of a trial apply to your patient. Although the average treatment effect for the entire study population is often the best estimate of the effect for all participants, individuals will have heterogeneous responses that can sometimes be predicted on the basis of effect sizes in valid, prespecified subgroups (13, 14).

PREVENTION

You are rounding on the patient at the hospital. Do you need to wear an N95 mask to provide better protection than a regular surgical mask from COVID-19?

Although clear evidence shows that various infection control procedures, including hand hygiene and use of gowns and face masks, are highly effective at reducing nosocomial transmission of a range of pathogens, further details about these procedures are largely not driven by high-grade evidence. For example, a cluster randomized trial from before COVID-19 of N95 respiratory masks versus surgical masks worn during the care of patients with respiratory illnesses during successive respiratory illness seasons did not detect a significant difference in the frequency of laboratory-confirmed influenza among health care workers (15). Yet, an early assumption of the COVID-19 pandemic was that N95 masks provided significantly more protection than surgical masks, with the understanding that absolute risk for transmission likely varied significantly by other factors, including proximity to the patient, whether the patient was also wearing a mask, and whether the patient was having an invasive and/or aerosol-generating procedure. The issue was further complicated by the national shortage of N95 masks, with the immediate consequence that use of N95 masks during all patient interactions would not be sustainable.

In this setting, infection control leaders and hospital administrators needed to make policy decisions to balance the availability of N95 masks with the available evidence regarding effectiveness—a situation in which a different perspective of the decision maker (hospital administrator vs. individual health care worker) would likely lead to a different set of decisions. Indeed, guidance from the Centers for Disease Control and Prevention during this time explicitly noted that N95 mask use could be limited in non–aerosol-generating settings if N95 supply was limited. The mixing of supply issues with clinical decisions, a form of rationing, feels uncomfortable to many.

A systematic review and meta-analysis reported that N95 masks were statistically more likely than surgical masks to reduce risk for COVID-19 among health care workers (16), further highlighting this tension. In fact, the level of evidence supporting that conclusion was weak. No studies directly compared the effectiveness of the 2 types of masks, and only 1 study of N95 masks was of patients with COVID-19. This study compared outcomes across units in a single hospital; the high degree of protection attributed to N95 masks was largely the result of an outbreak on a non-N95 unit attributed to a single patient. Yet, such data continue to fuel concerns that health care worker risk is unacceptably high in the absence of N95 masks for all patient care activities in the era of COVID-19.

As a result of these concerns, your hospital requires N95 mask wearing as part of any direct care activities for patients with confirmed or suspected COVID-19. This decision reflects an additional core principle of clinical decision making: Different perspectives can render different decisions even in the face of the same clinical evidence (17). Hospital administrators may need to preserve N95 masks for the highest-risk procedures, recognizing that a small but real absolute risk may exist for other workers who use alternative personal protective equipment in lower-risk settings. Recognizing the effect of perspective on clinical decisions can help lead to better acceptance of these decisions at all levels and ongoing plans to reassess decisions over time.

The unprecedented health challenges created by the rapid emergence and spread of SARS-CoV-2 have resulted in information being released through faster-tracked channels without time for deliberative review

and consensus building; thus, end users of this information need to have a framework for evaluating the quality of the information and the relevance of the results to everyday clinical decision making. Our goal in this brief article was not to conduct systematic reviews of some of these issues, but rather to illustrate how one could use available strategies to evaluate new information as it emerges and incorporate evidence into clinical decisions at the individual and hospital levels. We recognize that the information that will inform these decisions will evolve over time, potentially rendering the conclusions we have illustrated in this article no longer correct—this highlights the dynamic nature of clinical decision making. We can only make decisions based on the information in front of us, recognizing that these decisions may often come due at a time when the information is incomplete.

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Disclosures: Authors have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M20-8179.

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Ann Intern Med. doi:10.7326/M20-8179

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