

Out With the Old, In With the Flu

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ANNALS CASE

It's another winter overnight shift and the waiting room track board looks like a cough syrup commercial: sore throat, flulike illness, cough, fever, viral illness, body aches, and, yep, another flulike illness. Your first patient is a pregnant 35-year-old with 2 days of fever, vomiting, and body aches. In the next room is a 75-year-old man who complains of fever and cough for the past day. Do these 2 have influenza (flu)? Should we treat them for the flu? What about the tachypneic, febrile nursing home patient you just saw whose infectious evaluation is negative for a source? Should that patient get a flu test?

Emergency clinicians may not view flu testing to be especially useful for clinical management, as demonstrated by the fraction of emergency department (ED) patients (5% to 21%) who receive rapid flu testing when presenting with an acute respiratory illness during influenza season.¹ The antigen-based point-of-care testing traditionally used in clinics and EDs has such poor sensitivity that a negative test result is of little clinical utility. Hence, patients with a high clinical suspicion of flu or who are at high risk should be presumed to have the flu even after a negative rapid flu test result! Definitive testing by batched polymerase chain reaction has seemingly been reserved for identifying the start of the flu season. This may be a helpful step to mentally prepare for the onslaught of incoming patients in the following weeks, but it takes multiple days to provide a result, too long to be clinically useful. However, after reading the article by Frazee et al² in this month's *Annals of*

Emergency Medicine, we think it's time to take another look at our previously less-than-helpful friend, the flu test.

CAN'T WE DIAGNOSE FLU BY GESTALT?

Studies have shown that clinically diagnosing influenza is challenging and, well, we aren't good at it, to say the least.³ Fortunately, it's not our fault; influenza can manifest with a wide variety of presentations and can often present with vague complaints. Additionally, there is a seasonal pattern to influenza and to our diagnostic bias! The patients whom we clinically diagnose with a viral infection in the summer just seem to become flu victims in the winter. To add to the confusion, influenza incidence peaks alongside a multitude of other seasonal viruses that present similarly. Anyone out there think they can clinically differentiate between influenza and respiratory syncytial virus?

Despite what drug manufacturers may suggest, the nighttime, sniffing, sneezing, aching, coughing, stuffy-head, feverish-appearing patient might not actually have the flu. It turns out that none of these findings are able to differentiate influenza from other viral diseases, and a specific clinical presentation for the flu has been found only in the elderly population (>60 years). In these older patients, the abrupt onset of fevers and cough is highly suggestive of influenza. Unfortunately, no other constellation of symptoms has been found to be predictive of the disease in this population, and even worse, this clinical presentation loses its diagnostic power when applied to the general public and other subpopulations.

Subjective fevers, headache, myalgias, malaise, sore throat, and sneezing have little diagnostic value in either ruling in or ruling out influenza.⁴ Even when a textbook flu patient walks into the ED, we correctly identify influenza less than half the time.^{1,3,5} Is flu the actual great masquerader (eat *that*, syphilis!)? Probably not, but it's shifty nonetheless (and we aren't talking antigenic shift).

WELL, THANK GOODNESS WE HAVE A TEST!

Much of the dissatisfaction with the traditional antigen-based rapid influenza detection tests (RIDTs) stems

from their poor sensitivity (50% to 70%).⁶ Although a 15-minute turnaround time is exemplary, these RIDTs result in a considerable amount of false-negative results. A negative RIDT result, in the end, contributes little to the clinical picture, except of course for increased cost.⁷ So, yes, we are saying that flu is difficult to diagnose clinically and that the test isn't good either.

This dilemma in diagnosis is a particular challenge for our high-risk patients during influenza season, such as our pregnant patient with a flulike illness and our sick elderly patient with fever of unknown origin. The Centers for Disease Control and Prevention recommends they should receive a diagnosis of influenza and be treated empirically with antivirals regardless of RIDT result.⁶ This approach has been incorporated into hospital-based diagnostic pathways such as North Memorial Care's.⁸ In this pathway, high-risk patients with possible flu within the treatment window do not receive an RIDT for the flu, but are presumed to be flu positive and are empirically treated. The antigen-based RIDT has no place in this algorithm.

The definitive confirmatory tests for influenza, including reverse transcription–polymerase chain reaction (2- to 4-hour turnaround time, but typically batched), viral culture (>2 days), and serology (>2 weeks),⁹ are impractical for patient care by the practicing emergency physician. So we are left without a good confirmatory test and largely rely on our uncertain clinical gestalt. When the patient looks miserable enough and presents within the window for treatment or is at high risk, we sit down and have the “antiviral talk” with him or her. Certainly this thinking lacks the precision we seek in emergency medicine, but the antigen-based RIDT does not contribute much to improve this process. Similar to the Focused Assessment with Sonography in Trauma (FAST) examination, it can be helpful when the result is positive, but when negative, it leaves us scratching our heads. It is a common dilemma we see in diagnostic tests that have high specificity but low sensitivity. And thus, for the past decade or so, point-of-care flu testing has been written off as an unhelpful tool, subsequently falling out of the wheelhouse of most emergency physicians.

SO WHAT SHOULD WE DO?

Fortunately, influenza is generally a self-limited disease whose victims are mostly ambulatory; miserable...but ambulatory. Because of this, our diagnostic uncertainty has been tolerated and we have grown comfortable with not needing to know definitively whether a patient has the flu. However, the potential benefits of confirmed influenza are important: decreased number of laboratory and diagnostic tests ordered, decreased prescribing of antibiotics, and shorter ED length of stay.^{10,11} It can be useful diagnostic

information, but we had no means to obtain it practically...until now. Recognized by the Food and Drug Administration early in 2017,¹² the new generation of RIDTs show great promise. Even through a mere midturbinate tickle, the new-generation flu test shows a startling improvement in sensitivity, as demonstrated by Frazee et al.² These new molecular flu tests carry high diagnostic accuracy (both sensitive and specific) because they detect viral ribonucleic acid (similar to reverse transcription–polymerase chain reaction) but provide a result in well under an hour, comparable to the turnaround time of the previous antigen-based influenza tests. The new generation of RIDTs seem to accurately identify both when a patient does and does not have the flu, which has many potential downstream benefits.

BENEFIT TO FLU DIAGNOSIS

Definitively diagnosing influenza remains an important medical decision point even if there is controversy in regard to its treatment. Influenza is a significant cause of morbidity and mortality, particularly among our most vulnerable patients, the elderly, pregnant, those with immunocompromised states, and very young children.¹³ There is a serious need for identifying these patients in the ED to minimize transmission within the hospital. Flu identification may also be helpful outside the hospital in providing appropriate discharge instructions for patients to prevent its spread, especially for those in close contact with vulnerable populations. Additionally, identification of this disease may prevent lengthy evaluation in patients who may be having an inflammatory response of unclear cause. For some patients, accurate flu diagnosis may help decrease cost of testing, prevent invasive procedures, and avoid unnecessary admissions.

CONCLUSION

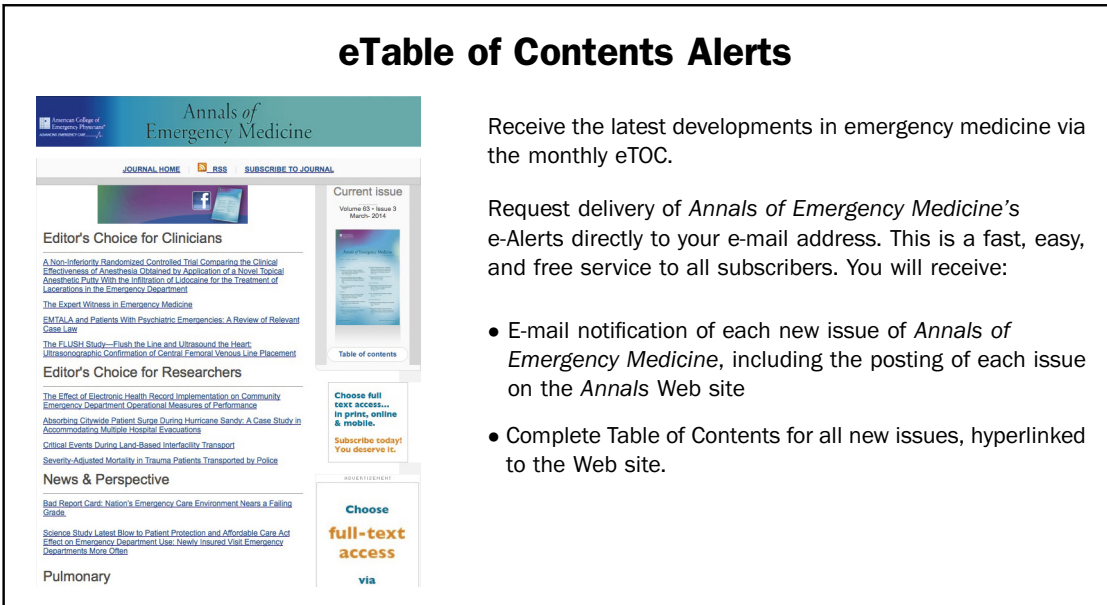
Until recently, the combination of an inability to make an accurate clinical diagnosis and a rapid antigen-based test with poor sensitivity left us in a catch-20-flu (sorry! bad pun). As this new generation of influenza testing becomes more available, it is up to you as the clinician to decide, “Does immediately knowing whether this patient has the flu change what I will do?” If so, we now have a way to do that.

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