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Rapid Diagnostic Testing in the ED for Mononucleosis, Strep Pharyngitis, Influenza, Respiratory Syncytial Virus, and Procalcitonin

Introduction

Emergency physicians (EPs) must accurately interpret common test results, and it is vital to understand the statistical methods associated with the development and integration of these laboratory tests in a clinical context. Clinicians strive to use the most accurate tests available while also considering other factors, such as cost, ease of use, and turnaround time for results. It is important to understand the limitations of a test while interpreting the results. This issue will deal with a few of the most common rapid or point-of-care tests used in the emergency department (ED).

Sensitivity and Specificity

When reviewing rapid or point-of-care (POC) diagnostic laboratory tests, there are two major results possible from a test, negative and positive. However, tests are never perfect, and they may be inaccurate. A person with a positive test may or may not actually have the condition being tested. Therefore, there are four actual results from a test: true positive, false positive, true negative, and false negative. A true positive is a positive test result where the individual truly has the identified health problem, whereas a false positive is a positive test result in a person who does not have the health problem investigated. If a test is negative and the individual does have the disease, then it is considered a false negative. If the test is negative and the individual does not have the disease, then it is considered a true negative. The accuracy, or validity, of a test can be described further in terms of sensitivity and specificity in addition to positive and negative predictive values. These are extrapolated by analysis from the true and false and the positive and negative results. Formulas and the common method of analysis are shown in Table 1.

Sensitivity and specificity are two complementary statistical concepts that help characterize the degree to which tests are able to determine the presence of disease. According to the Centers for Disease Control and Prevention (CDC), sensitivity is defined as the ability to correctly identify the health problem that a test is intended to detect. Specificity is the ability of a test to exclude the presence of the health problem of interest.[1] High sensitivity gives confidence that a negative test is truly negative (as the test approaches 100%, the rate of false negatives must approach 0%), and a high specificity gives confidence that a positive test is truly positive (as the test approaches 100%, the

EXECUTIVE SUMMARY

- The sensitivity and specificity of the monospot are related to the age of the patient (low in children younger than 4 years of age) and to the time since the onset of symptoms (highest at six weeks). The test may remain positive for up to one year.
- The rapid test for strep has a low sensitivity (70%). Patients with a negative test may benefit from a throat culture.
- Rapid influenza tests have a low sensitivity (50% to 70%) but high specificity (few false positives). The accuracy of the test is related to the prevalence in the community.
- There are several rapid tests for respiratory syncytial virus and their sensitivity and specificity vary, but, in general, sensitivity is low.
- Rapid tests for procalcitonin can be difficult to interpret, although the level provides some guide to the use of antibiotics.

rate of false positives must approach 0%). (*See Table 1.*) The sensitivity and specificity of a test are determined by factors related to the test itself (e.g., the lower threshold limit of detection of the test, how well a sample was collected and prepared prior to analysis, how the sample was stored and how much time passed from collection to analysis, as well as how much time has passed from disease onset to sample collection). These are not affected by the prevalence of the disease in question within the sample population.

A highly sensitive test can be used to rule out a disease state, while a highly specific test can be used to rule in a disease. However, sensitivity and specificity are inversely proportional, meaning that as one increases, the other decreases. As EPs focus primarily on not missing a case and secondarily on accurate diagnosis, EPs generally rely on tests that are highly sensitive to accurately rule out life-threatening conditions. It should be noted that highly sensitive tests often are low in specificity because of the inverse relationship. A positive result in a highly sensitive but lowly specific test does not imply the presence of a disease state in the same way that a negative result in a highly specific test but lowly sensitive test does not verify the absence of the health problem.[2]

Sensitivity and specificity are not related to the prevalence of the disease within a population. A high sensitivity makes one feel confident that a negative value is truly negative, and a high specificity allows for confidence in a positive value. However, these values do not allow one to determine how likely it is that the positive value is truly predictive of a disease state in a given individual or, vice versa, how likely a negative result will predict a given individual does not actually have a disease. To determine the likelihood of a true result, the EP also must consider predictive values when interpreting a test result.

"Gold Standard"

An important concept to understand that is related to the determination of a test's sensitivity and specificity is how the disease state is defined. In other words, the test in question is being compared to a "gold standard," a test that is accepted to be able to determine the presence or absence of the disease. In theory, the "gold standard" should have a 100% sensitivity and specificity. It can always determine if the disease is present, and always exclude the diagnosis when the disease is absent. In practice, this is not always possible. Sometimes the "gold standard" is a very good test that is unable to be used clinically because of resources, cost, time, or other logistical constraints. However, sometimes the "gold standard" may be flawed, with only modest sensitivity and specificity. In fact, as newer technology evolves, the new test may even be superior to the "gold standard." While this concept is less important in a clinical scenario, it is an important point to consider when reading scientific literature to fully understand the implications of the study's findings.

Positive and Negative Predictive Values

The positive predictive value (PPV) is the percentage of patients with a positive test that truly have the disease. A high PPV implies a low false-positive rate. The negative predictive value (NPV) is the ratio of negative test results to the total number of patients without the disease. A low NPV implies a high false-negative rate. PPV and NPV are dependent on the overall prevalence of disease in the population being tested. As the prevalence of disease increases, the PPV increases and the NPV decreases. Conversely, as the prevalence decreases, the PPV decreases and the NPV increases.

When disease prevalence is high, a true positive test is relatively more likely than a false-positive test, and a false negative becomes more likely than a true negative, as many individuals actually do have the disease. However, when the prevalence is low, a false-positive test is more likely than a true-positive test, and a true-negative test is more likely than a false-negative test. Therefore, when the prevalence of a disease is low, it may not be useful to use that test. Of course, these values and changes are not absolute and are relative to each other given a particular prevalence. This concept is most important in seasonal illnesses, when the PPV and NPV actually change depending on what time of year it is and whether the disease is prevalent.

This change in predictive values based on prevalence implies that there is a high required specificity to achieve higher PPV when there is low disease prevalence in the population. When disease is common and prevalence is high, a test must be very sensitive to generate a higher NPV.[3] See Tables 2A and 2B for calculated examples including the effect of disease prevalence on predictive values. In a population of 1,000 with test sensitivity and specificity of 90%, when the disease prevalence is 1%, the PPV is only 8.33%. However, when the

Table 1. Common Statistical Analysis and Derivation of Specificity, Sensitivity, Positive Predictive Value, and Negative Predictive Value

	Disease Present	Disease Absent
Test Positive	A (true positive)	B (false positive)
Test Negative	C (false negative)	D (true negative)

Sensitivity = (true positive) / (true positive + false negative)
A / A + C
Specificity = (true negative) / (true negative + false positive)
D / D + B
Positive predictive value = True positive / (true positive + false negative) x 100
A / A + B
Negative predictive value = True negative / (true negative + false negative) x 100
D / D + C

same test sensitivity and specificity is applied to a population with a disease prevalence of 10%, the PPV increases to 50.5%.

When applying the reported statistics of a test during a patient encounter, the patient population and test characteristics should be similar to the studied population to accurately extrapolate results.[4] Changes to disease prevalence will affect predictive values, and changes to the test itself will affect sensitivity and specificity. It is critical that these variances be taken into account by the EP when clinically evaluating test results in daily practice. Understanding this statistical framework provides a foundation to explore commonly ordered tests in the emergency department and their interpretation. It should be noted that this exemplified analysis is strictly applied to binary tests with results reported as either positive or negative, and it cannot be directly applied to other results with numerical values or radiology reports.

Monospot

Introduction

Infectious mononucleosis (IM), although generally a benign illness caused by Epstein-Barr virus (EBV), is an important emergency department diagnosis. With an accurate diagnosis, the emergency clinician can provide symptomatic care, avoid unnecessary antibiotics, and discuss appropriate anticipatory guidance, including prognosis and physical limitations to prevent the rare complication of splenic rupture. EBV infection is common, with more than 90% of adults becoming seropositive by age 35.[5] However, in adults, IM accounts for only 2% of all pharyngeal disease.[6]

Transmitted through saliva, EBV is noted to have a high attack rate in adolescents, corresponding to normal sexual maturation.[7] IM has a wide range of clinical presentations, including asymptomatic and nonspecific symptoms in children, sore throat in young adults, and jaundice in older adults.[5] Table 3 lists the typical signs and symptoms associated with IM. In patients presenting with pharyngitis, some clinical signs may lead the emergency clinician to suspect infectious mononucleosis, including lymphadenopathy, palatal petechiae, splenomegaly, and atypical leukocytosis.[8] It can be difficult to distinguish infectious mononucleosis from other causes of pharyngitis with nonspecific symptoms such as fatigue, fever, and malaise. There are a multitude of diagnostic tests available to aid in the diagnosis of IM, with the monospot the most widely used because of its rapidly available results and low cost.[9]

Type of Test

The monospot test is a heterophile antibody test that uses a red cell or latex agglutination assay. The test is designed to detect anti-red cell antibodies produced in the polyclonal antibody response during EBV infection. Using equine erythrocytes as the primary substrate, specific heterophile antibodies are detected when the patient's blood is added to the mixture and causes clumping of the specimen. Blood samples may be obtained intravenously or via fingerstick. If there is no clumping when the substrate is added, the test is considered negative. The degree of agglutination (clumping) does not correlate to an antibody titer.[10] Commercial kits are available for POC testing, producing results in as few as five to 10 minutes.[9] Other diagnostic tests for EBV include virus-specific serology and polymerase chain reaction (PCR) testing, which are more expensive, may not be available to the EP prior to patient discharge, and are used less commonly.

Pitfalls

To achieve the best sensitivity and specificity of the monospot test, the patient must be selected appropriately with optimized test timing. Age greatly affects the sensitivity and specificity, most notably with children younger than 4 years of age having a significant false-negative testing rate. In this age group, sensitivity reported in the literature varies from 27% to 76%.[9] For this reason, heterophile antibody testing for EBV in children younger than age 4 is not recommended.

In older children and adults, the sensitivity of the monospot test is reported to be 70% to 90%. However, results vary depending on the time from symptom onset that the sample is collected. Peak antibody concentrations exist at two to six weeks from inoculation. The sensitivity of the test is highest at six weeks of disease. Early tests may have a false-negative result because of a low serum titer load. It is important to identify the risks of false-negative results as patient's may need repeat testing later in the disease course.[9] Specific antibody testing may be indicated when a false-negative result is suspected.[5]

The specificity of the monospot test is reported at 95% to 100%. However, there are noteworthy causes of false-positive results, including other viral

Table 2A. Effect of Prevalence on Predictive Values in a Population of 1,000 with Disease Prevalence of 1% with Test Sensitivity and Specificity of 90%

	Disease Present	Disease Absent
Test Positive	9	99
Test Negative	1	891
PPV = 9 / (9 + 99) x 100 = 8.33% NPV = 891 / (891 + 1) x 100 = 99.8%		

Table 2B. Effect of Prevalence on Predictive Values in a Population of 1,000 with Disease Prevalence of 10% with Test Sensitivity and Specificity of 90%

	Disease Present	Disease Absent
Test Positive	90	90
Test Negative	10	810
PPV = 90 / (90 + 90) x 100 = 50.5% NPV = 810 / (810 + 10) x 100 = 98.8%		

infections, such as cytomegalovirus, rubella, herpes simplex virus, and human immunodeficiency virus. Malignancy and autoimmune diseases, such as lymphoma or lupus, also may cause false-positive results. Additionally, the test may be positive long after resolution of the illness, since heterophile antibodies typically persist at low levels for many months and may be present up to one year after the resolution of symptoms. Although some studies have reported a PPV of nearly 100%, it is important to consider these confounders when interpreting monospot test results.[10]

Conclusion

Infectious mononucleosis caused by EBV should be considered as a diagnosis in patients presenting to the emergency department with concerning symptoms. Monospot testing may be considered; however, it should be noted that patient age and length of disease may affect the accuracy of the result. Due to its significant limitations, the CDC does not currently recommend monospot testing for general use.[11]

Rapid Strep

Introduction

Sore throat is a common reason for presentation to the emergency department. It is estimated that 70% to 90% of pharyngitis presentations are viral in etiology.[12] Bacterial pharyngitis is caused most commonly by Group A *Streptococcus pyogenes* (GAS); however, it only accounts for 30% of pharyngitis in children and 5% to 15% in adults. Despite this low prevalence, it has been shown that nearly 60% of patients presenting with sore throat will receive antibiotic therapy. With accurate diagnosis and appropriate management of pharyngitis, there is opportunity for antibiotic stewardship in the emergency department.[13] Diagnosis is key to avoid complications of GAS, such as rheumatic fever, rheumatic heart disease, peritonsillar abscess, sinusitis, Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS), and bacteremia.[14]

The diagnosis of GAS pharyngitis can be difficult. The history and physical examination have proven to be insufficient for accurate diagnosis since the history and physical examination of patients with bacterial and viral pharyngitis overlap so significantly. Clinical decision tools such as the Centor criteria and McIssac score have been developed to help guide clinicians to determine if further testing is indicated, but they have poor reported sensitivity and specificity, which is also highly variable depending on the scoring thresholds used.[13,15] The use of rapid GAS testing and/or throat culture has become widely available and is recommended by the CDC and the Infectious Diseases Society of America.[14,16]

Type of Test

There are a number of commercially available rapid GAS tests. A majority use rapid antigen detection test (RADT) via latex agglutination, enzyme immunoassay, or optical chromatographic immunoassay techniques.[17] Nucleic acid amplification test assays also are approved by the FDA to rapidly detect GAS. These assays amplify targeted regions of *S. pyogenes* DNA.[18] Samples are obtained from patients via pharyngeal swab. Either directly from the swab or via extraction, the sample is exposed to a strip with the GAS antibody present. Conjugation of the sample antigen with the antibody produces a colored line indicative of a positive result. If no colored line appears, the test is presumed to be negative.[17] Test results can be interpreted either manually by visual reading or electronically via optical reader and usually are available in five to 10 minutes.

Pitfalls

Given the wide variety of testing kits available, it is imperative that clinicians are familiar with the brand and type of rapid GAS test available at their facility. There is a paucity of literature comparing the sensitivity and specificity of these individual tests. In a recent systematic review, a summary sensitivity of 85.6% and specificity of 95.4% were reported among RADTs.[19] However, the sensitivity of RADTs has been noted as low as nearly 70%.[12,16-18] Because of the poor sensitivity, it is recommended that a negative RADT be followed by the gold standard for GAS

Table 3. Clinical Presentation Suggestive of Infectious Mononucleosis[8]

Signs and Symptoms

- Sore throat with tonsillar exudate
- Extreme fatigue
- Adenopathy
- Splenomegaly
- Palatal petechiae
- Atypical lymphocytosis

pharyngitis diagnosis, throat culture.[16] The reported diagnostic accuracy of these tests is determined by comparison of RADT to throat culture.

Performance of testing is affected by several variables, including duration of symptoms, severity of disease, and sample quality.[20] The GAS rapid tests are obtained via pharyngeal swab. There have been reports of operator effect on the accuracy of the sample collection.[21] Swabs should be collected appropriately following the manufacturer's recommendations. There also are inherent operator-produced variations when the test is interpreted by visual reading. Computerized or digital interpretation of test results has been shown to be more accurate.[20]

Positive results may be noted in patients who are considered carriers of group A strep. In asymptomatic children with a history of recurrent tonsillitis or tonsillar hypertrophy, 20% are considered to be GAS carriers.[22] In this population, clinical correlation of test results is necessary for accurate interpretation.

Conclusion

Several variables affect the reliability of rapid strep testing. Numerous commercial testing kits are available; therefore, the provider should be familiar with which test they are using because sample collection recommendations, as well as sensitivity and specificity, vary with each type of test.

Influenza

Introduction

Despite the vast availability of vaccination, seasonal influenza continues to cause significant morbidity and mortality worldwide. Influenza is a negative-sense RNA virus known to cause a classic constellation of symptoms consisting of fever, chills, headache, cough, myalgias, and malaise. In humans, three common forms of the virus cause infection: A, B, and C. Influenza A is most notorious in pandemics because of its tendency for antigenic drift, shift, and transmission from animal species.[23] The virus is transmitted by respiratory droplets and contact with contaminated surfaces. Influenza has been reported to cause an estimated 61,000 yearly deaths in the United States[24] and up to 500,000 deaths worldwide.[25] According to the CDC, when the disease is circulating, influenza testing should be considered for patients who present with symptoms consistent with acute infection, for those in whom complications from influenza may be severe, or for patients who are being admitted to the hospital or for whom a positive test result would change management.[26] When the disease is clinically suspected, treatment with antiviral medications should be initiated if deemed appropriate regardless of laboratory testing.

The use of rapid tests can guide appropriate patient management and infection control. POC influenza testing in the emergency department has been associated with more antiviral prescriptions in patients who test positive in addition to decreased antibiotic prescriptions in patients who test negative.[25] Among admitted patients, identification of communicable infections is vital for proper isolation procedures and infection control to prevent nosocomial transmission.

Type of Test

The mainstay of POC influenza testing is the rapid influenza diagnostic test (RIDT), as compared to the gold standard of diagnosis obtained by reverse transcriptase PCR (RT-PCR) or viral culture. RIDTs are immunoassays that detect viral antigens. When the specified influenza antigen is detected in the sample, a color change reaction is indicated. RIDTs have the advantages of low cost and rapid turn-around of test results in 10-20 minutes. These tests have been Clinical Laboratory Improvement Amendments (CLIA) waived, meaning they are generally simple to perform and do not require advanced laboratory techniques.[27] Molecular identification of influenza RNA via RT-PCR detection or nucleic acid amplification testing is generally not favored for rapid POC testing because of longer time to test results, increased cost, and requirement for specialized technicians. It has been noted that this may be a future development for rapid influenza diagnostic testing and may be ideal given its superior specificity and sensitivity.

Samples for testing generally are collected by the clinician via nasopharyngeal swab; however, saliva testing has been shown to have similar sensitivity.[28] Some assays require a nasal wash or aspirate. The CDC has recommended that sample collection, transportation, and storage occur according to the test manufacturer's recommendations.[29]

Pitfalls

Rapid influenza tests have been reported to have sensitivity of 50% to 70%, with specificity of 90% to 95%.[30] False-negative tests are common, while false positives generally are rare. RT-PCR identification tests have sensitivities noted around 95%.[31] There are several factors that affect the accuracy of influenza testing, including viral virulence changes and sample collection variation, in addition to storage, transport, and interpretation errors.

The influenza virus is made of RNA. It presents seasonally with antigenic shift and drift resulting from mutations in the antigens. Viral surface proteins detected in the RIDT sample may vary from year to year, limiting the accuracy of the test. Seasonal and yearly variability in the virulence of the pathogen also may preferentially affect the lower respiratory tract and make nasopharyngeal sampling inaccurate. It should also be recognized that rapid identification of the influenza virus does not include specific subtypes. General distinction between influenza A and B is noted, but the tests lack further subtype classification (H1 vs. H3), which may limit epidemiologic studies and surveillance.[27] In the emergency department, detailed classification of the influenza subtype does not alter clinical management.

Sample collection affects testing results in that inappropriate or poor sample quantity may lead to false-negative results. The timing of symptom onset to test collection is important to consider since viral shedding affects results. Optimal testing occurs within 72 hours of symptom onset. A significant viral load of 10^4 to 10^6 influenza particles are required for a positive detection. Samples from children generally are more concentrated than those from adults and, therefore, results are more accurate in the pediatric population.[27]

Appropriate storage and transportation of rapid influenza testing samples is vital to resultant accuracy. Samples should be transferred to the laboratory immediately since delays affect quality. If necessary, storage of collected samples should occur according to manufacturer recommendations.[27]

The large seasonal variability of influenza infection affects pooled accuracy of test results. In times of high community presence of the disease, RIDTs with their general poor sensitivity have a large portion of false-negative results. When activity is low, the low sensitivity of the test precludes an acceptable negative predictive value, however the positive predictive value is low. During times of low community prevalence of influenza, rapid testing in the ED most often affects clinical decision making. However, given the poor sensitivity and positive predictive value, it gives largely inaccurate results.[27] It is recommended antiviral therapy be considered even if the test is negative in an appropriate patient who clinically appears to have influenza, particularly if the patient is in a high-risk group that would benefit from antiviral therapy or is being admitted.[26]

Conclusion

Rapid detection of influenza in the emergency department has a number of benefits, including epidemiologic data, antibiotic stewardship, and infection control. RIDTs are noted to have very poor sensitivity, and their accuracy is affected by both viral and sample collection factors. In cases with high clinical suspicion, results of RIDTs should not change the use of appropriate antiviral therapy.

Respiratory Syncytial Virus

Introduction

Respiratory syncytial virus (RSV) is a negative-sense RNA virus commonly known to cause serious lower respiratory infection in children, infecting 90% of children by age 2 years.[32] A majority of infections in children consist of mild upper respiratory symptoms; however, infants and younger children commonly develop serious lower respiratory infection known as bronchiolitis. RSV also causes significant infection in adults, with similar morbidity and mortality to influenza in older adults.[33]

Adults with RSV may present with mild cold symptoms, such as headache, nasal congestion, cough, wheezing, and hoarseness. In children, the presentation often varies based on location and severity of illness. Upper respiratory infection may present with rhinorrhea, congestion, cough, sneezing, and, less frequently, fevers or myalgia. Signs of lower respiratory infection with bronchiolitis include tachypnea, wheezing with prolonged expiratory phase, diffusely coarse breath sounds with rhonchi, and accessory muscle use. Critically ill patients may have lethargy, hypoxic respiratory failure, and apnea.

Most commonly, RSV is seen in the winter to spring months, with noted seasonal variance in temperate climates. In tropical settings, there is more uniform prevalence throughout the year. Infection with RSV does not provide the host life-long immunity. Adults commonly are re-infected every five to seven years.[33] Infection occurs via spread of respiratory droplets with inoculation of the nasal or conjunctival mucosa. The mean incubation period is four to six days.[32]

Accurate detection of RSV infection is important for infection control practices and avoidance of unnecessary antibiotics. For admitted patients and those in care facilities, diagnosis of RSV and other acute respiratory viruses allows for appropriate isolation precautions to avoid further transmission. Although supportive care is the mainstay of treatment for non-influenza viral respiratory pathogens, determination between viral and bacterial causes of pneumonia is a diagnostic dilemma. Use of testing for respiratory pathogens has been associated with decreased use of antibiotics without an increase in morbidity; however, it is important to consider concomitant bacterial superinfection. Accurate diagnosis of viral respiratory infection has been associated with a decreased length of stay among admitted patients. RSV bronchiolitis has been associated with more severe illness than non-RSV bronchiolitis.[34] With the exception of influenza, there is a lack of specific recommended antiviral treatment for common viral upper respiratory infections. The use of rapid diagnostic testing for acute respiratory pathogens can guide antibiotic stewardship and promote infection control.[33]

Type of Test

Several tests are available to detect RSV. Often, testing occurs as a part of a multiplex panel for several respiratory viruses, which is useful in the clinical setting since upper respiratory viruses often present with a similar constellation of symptoms. In addition to RSV, other viruses commonly included in these panels are human metapneumovirus, human rhinovirus/enterovirus, coronavirus, parainfluenza, adenovirus, and influenza. Newer panels also may include bacterial respiratory pathogens, such as *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*.[35]

Samples are collected via nasopharyngeal swab and added to viral transport medium. Viral detection occurs via antigen identification or PCR amplification. Depending on the assay and institutional practices, turnaround times vary significantly from two to 24 hours.[36]

Pitfalls

The sensitivity of rapid RSV testing is variable at 41.2% to 88.6%, with pooled reported sensitivity of 75.3%. Pooled specificity is about 98.7%. As with many POC tests, false-negative results are common. However, the accuracy of RSV detection tests was noted to be superior to influenza detection rates. Age generally is inversely proportional to viral load, and, therefore, viral respiratory pathogens are detected more accurately in children. However, it has been shown that viral load does not correlate directly with

Table 4. Pooled Sensitivities of Commonly Ordered Point-of-Care Tests

Test	Reported Sensitivity
Monospot	70% to 90%
Rapid group A Streptococcus	70% to 85%
Rapid influenza	50% to 70%
Respiratory syncytial virus	75%

disease severity in children.[37] A majority of the literature regarding RSV testing is performed in children because of the high rate of hospitalization, morbidity, and mortality from the illness.[38]

Even though a portion of RSV testing has the capability to be obtained rapidly as a POC test, the majority of these tests are not used in this fashion. Turnaround times for results may not be applicable to patients evaluated in the ED with planned disposition to home. It should be noted that rapid identification tests with faster turnaround times are being developed; however, further research regarding their accuracy still is underway. Use of viral respiratory panel testing is largely reported for antibiotic stewardship and infection control.

Conclusion

POC testing for RSV, largely included in a panel with other respiratory viruses, may improve hospital length of stay, decrease the use of inappropriate antibiotic therapy, and reduce nosocomial transmission of respiratory pathogens. Clinicians should be familiar with their institution's diagnostic testing. The turnaround time of results may affect their utility in the ED among discharged patients. RSV testing results are more accurate in pediatric patients given their often higher viral loads and shedding.

Procalcitonin

Introduction

Procalcitonin (PCT) is the prohormone of calcitonin.[39] Generally, in healthy individuals, it is produced by the neuroendocrine C cells of the thyroid gland[40] where it is subsequently cleaved to functional calcitonin.[41] Since production is limited to these cells in healthy individuals and it is rapidly cleaved to an active hormone, serum levels generally are low, less than 0.05 ng/mL to undetectable, in the absence of disease.[42,43] In 1993, it was found that PCT concentrations increase in pediatric patients with bacterial sepsis, but not in those with severe viral illnesses, with levels reaching 53 ng/mL in patients with invasive bacterial illnesses.[41]

While the systemic inflammatory response syndrome (SIRS), C-reactive protein (CRP), and other biomarkers of inflammation are nonspecific and may increase in response to any inflammatory condition (e.g., viral illnesses, inflammatory autoimmune disorders, noninfectious inflammatory conditions such as burns, acute biliary pancreatitis, and cardiogenic shock), PCT is raised almost exclusively in response to bacterial infection.[44] Since this discovery, there have been numerous studies attempting to validate procalcitonin as a biomarker of severe bacterial infection.

Severe bacterial infection triggers a ubiquitous release of PCT induced directly by bacterial endotoxins and lipopolysaccharides.[45,46] It also can be induced indirectly by humoral factors (e.g., interleukin 1, tumor necrosis factor α, and interleukin 6). However, bacterial endotoxins seem to be the most potent stimulators of procalcitonin.[47] Parenchymal cells lack the ability to cleave the prohormone into mature calcitonin, and so serum calcitonin levels remain low while PCT levels increase.[43]

The role PCT plays in the severe bacterial illness is unknown but may contribute to the local and systemic immune response by modulating both immune and vascular function.[48] It does not appear to have any hormonal activity itself,[42] and it is unknown if it is a cytokine or acute phase reactant.[49] PCT may not be beneficial and may even be detrimental in the presence of bacterial infection. Nylen et al injected PCT into healthy hamsters without any deleterious effect; however, when PCT was injected into hamsters with bacterial infections that already had elevated PCT levels, mortality increased to nearly 100%.[50] Moreover, immunoneutralization of PCT in severely infected hamsters and pigs actually decreased mortality and improved survival.[50-52]

The kinetic profile of PCT lends itself to rapid identification and exclusion of severe bacterial infections. After a bacterial stimulus in healthy volunteers, PCT was found to increase within four hours, with peak levels by six hours. This peak is maintained anywhere from eight hours through 24 hours in these noninfected individuals, but it persists in individuals with severe bacterial infections.[47] Because of the persistent elevation of PCT in the presence of continued infection, but fairly rapid decline as the infection resolves, it has been recommended that the PCT level help guide the length of antibiotic treatment.[53] This strategy has been shown to be effective in minimizing antibiotic usage without an increase in treatment failure or mortality.[54-59] The elimination half-life is about 24 hours and is not affected by impaired renal function.[60]

The degree of increase in PCT correlates with the severity of disease,[49] reaching levels as high as 700 ng/mL in invasive bacterial infections, but rarely exceeding 2 ng/mL in viral illnesses,[61] as well as other noninfectious inflammatory conditions.[49,62,63] In general, the conditions that may cause a PCT elevation are several bacterial infections and sepsis, nonbacterial infections (parasitic [parasite dependent], fungal, and viral [both of which produce only mild elevations]), noninfectious systemic inflammation (pulmonary aspiration, inhalational injury, pancreatitis, heat stroke, mesenteric infarction), mechanical trauma and extensive surgery, and neuroendocrine tumors.[63]

By contrast, CRP, which has been used routinely as a marker in

inflammation for more than 30 years, is a nonspecific, acute phase reactant[64] and, therefore, is not specific enough to help differentiate serious bacterial illness from more benign infectious and noninfectious causes of inflammation.[65] However, when a bacterial infection does exist, the degree of elevation is correlated with the severity of the illness.[44] CRP has good sensitivity for the presence of inflammation;[66] however, it is not elevated for at least six hours, and may be as late as 12 hours after the onset of infection. It does not reach peak until 20-72 hours,[49,67] allowing for false negatives. The combination of false negatives and a high risk of false positives make CRP a less than ideal candidate in the acute evaluation of patients with suspected severe bacterial infection. In fact, CRP provides the lion's share of points in the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score, which has a sensitivity of 68.2% at a score greater than or equal to 6.[68] This highlights the fact that a patient may have a severe bacterial infection with a relatively benign CRP early in their course, falsely reassuring the provider.

Type of Test

All PCT assays are serum tests based on the immunoassay technique, where antibodies directed at PCT are able to detect the presence and amount of PCT. Automated PCT assays are generally sandwich immunoassays, where after the PCT binds to a fixed antibody, a secondary labeled antibody is added that binds to the PCT a second time.[54] The amount of this secondary labeled antibody that binds determines the amount of PCT. There is also a POC test for PCT, allowing for rapid results within one hour, but this test is only able to provide semiquantitative results (< 0.5, 0.5-2.0, 2.0-10 and > 10 ng/mL).[54] Immunoassays are generally highly specific tests; however, false positives can result when non-PCT antigens bind PCT-antibodies sufficiently enough to cause the machine to falsely detect the presence of PCT. False negatives are rarer and unlikely to be caused by the immunoassay laboratory process.

Pitfalls

No simple answer can provide the sensitivity and specificity of PCT. This is partly because the sensitivity and specificity partially depend on which disease entity is studied (e.g,. severe bacterial illness, meningitis, pneumonia, severe lower respiratory tract infection, urinary tract infections), which population is observed (e.g., pediatric patients, neonates, general ED patients, and geriatric patients), as well as what cutoffs are set. The cutoff is the most important variable, and most studies have been performed using a cutoff anywhere from 0.2 ng/mL to 0.5 ng/mL, but, at times, they are as high a 5 ng/mL. Using an area under the curve (AUC) to determine the optimal cutoff, maximizing both sensitivity and specificity, usually provides a result of approximately 0.4 ng/mL. However, which cutoff is used depends on what the goal is. The higher the cutoff, the more specific the test becomes (there is a decreased chance the result is a false positive), but the less sensitive the test becomes (the likelihood of a false negative increases). A lower cutoff provides a more sensitive test (less likely the result is a false negative) but decreases the specificity (increases the risk of a false positive).

Most of the literature investigating the use of PCT has focused on its ability to positively identify severe bacterial illnesses, prognosticate the severity of illness, and guide antibiotic use; therefore, most of the studies have attempted to optimize specificity.

At a cutoff of 0.2 ng/mL, the PCT assay has a sensitivity of 62% to 96% (mean 82%) and a specificity of 38% to 100% (mean 68%) for all causes of severe bacterial illnesses in ED patients.[40,69-73] These studies also found a range of PPV and NPV of 12% to 100% (mean 48%) and 54% to 99% (mean 87%), respectively. Of note is one study that used a cutoff of 0.383 ng/mL and another that used 0.1475 ng/mL. In these studies, PCT outperformed comparators, which included CRP, white blood cell count (WBC), EP judgment, and SIRS.

When a cutoff of 0.5 ng/mL (ranges in these studies were from 0.4-0.55 ng/mL) was used, the sensitivity and specificity were 23% to 100% (mean 75%) and 63% to 99% (mean 81%), respectively, with a PPV and NPV range of 22% to 96% (mean 57%) and 37% to 100% (mean 83%), respectively.[42,44,69-72,74-79] As with the prior cutoff, PCT generally outperformed, or was comparable to, all comparators (CRP, mortality in emergency department sepsis [MEDS] score, WBC, absolute neutrophil count, and EP judgment).

Beyond using PCT as a diagnostic tool for bacterial infection, an elevated PCT, particularly above 5 ng/mL, is strongly predictive of 30-day mortality.[75,80] Additionally, patients in whom the PCT testing was performed were found to have a decreased total length of hospital stay, ICU length of stay, and overall hospital cost.[81] The degree of cost savings that a PCT test may effect is debated.[82]

Overall, the use of PCT is complicated. Schuetz and colleagues put forth a tiered protocol for the use of PCT that considers the initial presenting respiratory illness severity as well as the PCT level.[83] Overall, they recommend that if a patient in the ED presents with a respiratory illness and has a PCT of < 0.1 ng/mL, they would strongly discourage antibiotics. For a PCT level of < 0.25 ng/mL, they would discourage antibiotics; for a level ≥ 0.25 ng/mL, they would encourage antibiotics; and, finally, for a PCT > 0.5 ng/mL, they would strongly encourage antibiotic use. Although the protocol was developed for respiratory illnesses, it may be useful in all patients with infection.[54]

Conclusion

Overall, PCT appears to be a reasonably effective test that is at least comparable to or, in many cases, superior to all other biomarkers of infection, clinical gestalt, and decision scores in predicting severe bacterial infection. Additionally, as a prognostic tool when PCT levels are excessively high, it appears to be an effective tool for guiding the use and duration of antibiotics for patients. However, PCT is not a straightforward test and requires a nuanced approach for use.

Summary

To appropriately interpret common POC laboratory tests, the EP must

understand the definitions of statistical methods that are used frequently to determine the accuracy or validity of a test result. The EP should consider all possibilities of results, including false-positive and false-negative values. To avoid inaccurate results, it is imperative that the provider understand the limitations and pitfalls associated with the test. It is important to select the test with consideration to the clinical scenario, patient population, and particular clinical question. It has been shown that more accurate results are available when the test sample is obtained at the optimal time in the disease course and handled according to standard procedures. When appropriate, the EP should consider local disease prevalence since it affects the application of test results, especially for diseases with seasonal variance. Overall, the POC tests discussed have been noted to have poor sensitivity and specificity, and the EP should proceed with caution when interpreting these rapid test results.

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CME/CE Questions

1. Which of the following test characteristics can be used to rule out a disease?
   a. High sensitivity
   b. High specificity
   c. High positive predictive value
   d. Low sensitivity
2. Which of the following values will increase when the prevalence of a disease increases within the population?
   a. False positive
   b. Negative predictive value
   c. Positive predictive value
   d. Sensitivity

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3. You are seeing a patient for whom you are concerned about a particular disease. You know the prevalence in this population is 5%, and the laboratory test has a sensitivity and specificity of 98% and 80%, respectively. What is the positive predictive value of a positive test result?
   a. 2%
   b. 13%
   c. 21%
   d. 80%
4. Which patient would be most appropriate for monospot testing?
   a. A 3-year-old male with two days of sore throat and rash
   b. A 17-year-old female with one month of fatigue, intermittent sore throat, and lymphadenopathy
   c. An 8-year-old female with four days of conjunctivitis, fever, rash, and lymphadenopathy
   d. A 67-year-old male with dental pain, facial swelling, and fever
5. What microbe is detected in the rapid strep test?
   a. *Staphylococcus aureus*
   b. *Streptococcus epidermidis*
   c. Epstein-Barr virus
   d. *Streptococcus pyogenes*
6. Which of the following affects the accuracy of influenza testing?
   a. Antigenic shift causing variation in detected viral surface protein
   b. Interaction of influenza vaccination
   c. Cross reactivity with other common viral pathogens
   d. Handling samples according to manufacturer's recommendations
7. Which is *not* a benefit associated with respiratory syncytial virus testing?
   a. Infection control
   b. Antibiotic stewardship
   c. Improved length of stay
   d. Patient satisfaction
8. An 8-year-old patient presents with fever, cough, and sore throat for three days. He was seen at urgent care yesterday and had a normal chest X-ray and lab work. Vital signs are normal, and he appears well hydrated. A procalcitonin level is measured at < 0.1 ng/mL. What is the best course of action?
   a. Admit the patient and start sepsis care, including fluids and broad-spectrum antibiotics.
   b. Admit the patient and intiate antibiotics.
   c. Discharge home with a prescription for an oral antibiotic.
   d. Discharge home without antibiotics.
9. Which of the following is most likely to cause a false-negative procalcitonin test?
   a. A sample mislabeled with the identification of a patient with meningococcal meningitis
   b. Collecting the sample early in the disease process
   c. Collecting the sample late in the disease process
   d. A poorly collected sample
10. Which of the following is most likely to cause a significant increase in procalcitonin?
    a. A small localized bacterial infection
    b. Bacterial endotoxin
    c. Influenza
    d. Rheumatoid factor

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EMERGENCY MEDICINE **REPORTS**

Rapid Diagnostic Testing in the ED for Mononucleosis, Strep Pharyngitis, Influenza, Respiratory Syncytial Virus, and Procalcitonin

Common Statistical Analysis and Derivation of Specificity, Sensitivity, Positive Predictive Value, and Negative Predictive Value

	Disease Present	Disease Absent
Test Positive	A (true positive)	B (false positive)
Test Negative	C (false negative)	D (true negative)

Sensitivity = (true positive) / (true positive + false negative)
A / A + C
Specificity = (true negative) / (true negative + false positive)
D / D + B
Positive predictive value = True positive / (true positive + false negative) x 100
A / A + B
Negative predictive value = True negative / (true negative + false negative) x 100
D / D + C

Effect of Prevalence on Predictive Values in a Population of 1,000 with Disease Prevalence of 1% with Test Sensitivity and Specificity of 90%

	Disease Present	Disease Absent
Test Positive	9	99
Test Negative	1	891

PPV = 9 / (9 + 99) x 100 = 8.33%
NPV = 891 / (891 + 1) x 100 = 99.8%

Effect of Prevalence on Predictive Values in a Population of 1,000 with Disease Prevalence of 10% with Test Sensitivity and Specificity of 90%

	Disease Present	Disease Absent
Test Positive	90	90
Test Negative	10	810

PPV = 90 / (90 + 90) x 100 = 50.5%
NPV = 810 / (810 + 10) x 100 = 98.8%

Pooled Sensitivities of Commonly Ordered Point-of-Care Tests

Test	Reported Sensitivity
Monospot	70% to 90%
Rapid group A Streptococcus	70% to 85%
Rapid influenza	50% to 70%
Respiratory syncytial virus	75%

Clinical Presentation Suggestive of Infectious Mononucleosis[8]

Signs and Symptoms
- Sore throat with tonsillar exudate
- Extreme fatigue
- Adenopathy
- Splenomegaly
- Palatal petechiae
- Atypical lymphocytosis

Supplement to *Emergency Medicine Reports*, December 1, 2020: "Rapid Diagnostic Testing in the ED for Mononucleosis, Strep Pharyngitis, Influenza, Respiratory Syncytial Virus, and Procalcitonin." Authors: Brian Patrick Murray, DO, Assistant Professor, Emergency Medicine, Wright State University, Kettering, OH; Kelli Thomas, MD, Emergency Medicine, Wright State University, Kettering, OH; Shivam Patel, Wright State University Boonshoft School of Medicine, Kettering, OH.