CHAPTER 30

The Role of Point-of-Care Testing in Travel Medicine

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Health threats to travelers from infectious disease are common, with estimates of up to 75% of travelers becoming ill at some time during their travel. The World Health Organization (WHO) cites an extensive list (http://www.who.int/ith/diseases/en) of potential infectious agents, dependent on the countries visited. Because international travel can expose individuals to serious health risks, it is important that travelers have a medical consultation before traveling to consider appropriate medications for common symptoms such as upper respiratory illnesses and gastrointestinal disturbances, as well as to assure an awareness of health threats in the countries being visited.

For the returning traveler with illness, an accurate travel history is critical for development of a differential diagnosis. The process of developing a diagnosis often requires a number of laboratory tests. The availability and use of point of care (POC) tests for many suspected infectious agents may assist clinicians in more rapid diagnosis and treatment than conventional laboratory-based tests, but there are currently few such tests available that would benefit a healthcare provider attending to a returning traveler. An international survey of the use of POC tests in primary care turns up a long list of tests currently in use globally. However, not all of these POC tests are approved for use in the United States. **Table 30.1** lists some of the tests currently approved by the Food and Drug Administration (FDA) for use by healthcare providers in the United States.

In addition to being a diagnostic aid for acute infections, POC tests are also used for the purpose of monitoring, such as blood glucose control or anticoagulant therapy. For those anticipating international travel, there are a number of issues that must be considered to assure testing accuracy.

It is widely accepted that POC testing has the potential to improve access for the diagnosis and treatment of disease. POC testing is often mentioned as among the solutions in environments where "traditional" laboratory testing is not available. However, there are a number of factors that influence the true impact of POC testing, such as capital costs (equipment), maintaining an inventory in an environment of infrequent use, ease of use, associated instructions, training, and quality assurance of testing. In addition, accredited laboratories and laboratory professionals have the responsibility of documenting training, assuring appropriate quality control, and reporting test results. For nonlaboratory healthcare workers, there may be a lack of awareness of the importance of these elements in providing overall quality of testing. When these key quality issues are addressed, POC tests that have been rigorously evaluated can be important tools in rapid diagnosis of some infectious diseases.

DEFINITION AND USE OF POINT OF CARE TESTS

POC tests are generally defined as diagnostic tests used near the patient that provide results in a time frame that allows diagnostic results to inform clinical decision making while the

TABLE 30.1 Partial List and FDA Classification of Point of Care Tests Currently Available in the United States (i.e., FDA-Approved)

Analyte	TEST COMPLEXITY	
	Waived	Moderate
Bacteria		
Group A Strep	X	
Helicobacter pylori (urease and antibody)	X	
Lyme disease (antibody)		X
Salmonella (culture and detection of toxin in broth)		X
Chlamydia (nucleic acid)		X
Neisseria *gonorrhoeae*		X
Viruses		
Influenza A and B (virus)	X	
Respiratory syncytial virus (virus)	X	
Adenovirus (virus)	X	
HIV (antibody)	X	
Hepatitis C (antibody)	X	
Infectious mononucleosis (antibody)	X	
Hematology		
Hemoglobin	X	
Hematocrit	X	
Erythrocyte sedimentation rate	X	
Prothrombin time	X	
White cell count		X
Chemistry		
Glucose	X	
Glycosylated hemoglobin	X	
Cholesterol, HDL cholesterol, and triglyceride	X	
Troponin		X
Blood gases		X
C-reactive protein		X
Fecal occult blood	X	
Urine test strips	X	
Parasitology		
Trichomonas	X	

FDA, US Food and Drug Administration; *HDL,* high-density lipoprotein; *HIV,* human immunodeficiency virus.

patient is present. In the United States, regulations also play a role in determining which tests can be performed in that environment.

Use and Regulation of Point-of-Care Tests in the United States

The regulation of laboratory testing in the United States is administered by the FDA and is based on complexity of performance, including specimen preparation. The complexity model assigns a category of moderate or high complexity category based on the guidelines in the Clinical Laboratory Improvement Amendments of 1988 (CLIA 88). These moderate and highly complex tests are most often performed in a traditional laboratory setting. Some

rapid tests (e.g., Remel XPECT Giardia/Cryptosporidium lateral flow assay) fall into the category of moderate complexity, meaning that they are subject to inspection and that technicians must perform proficiency testing and quality control and meet personnel requirements. POC tests in the moderate complexity category (e.g., blood gases, electrolytes) are often performed in a healthcare environment in which the laboratory supports these requirements. A third category, and the category most often associated with POC testing, is known as "waived tests." Waived tests are defined as "simple laboratory examinations and procedures that have an insignificant risk of an erroneous result." Clearly, this definition is problematic if applied to tests such as human immunodeficiency virus (HIV), hepatitis C virus (HCV), and others that can have significant consequences if results are erroneous. In addition, a single positive result for those tests that require confirmation (e.g., HIV) should never be provided to the patient without confirmation; therefore, personnel performing such POC tests much be trained and have appropriate oversight to prevent such occurrences. In 1988 when the CLIA regulations were written, there were only eight analytes; as of February 2016 there were currently more than 125 analytes and hundreds of test systems available.

Importantly, waived tests, even though they may be regarded as "simple," require knowledge, competence, and an understanding of basic testing procedures. If reagents have expired or are used in either insufficient or excessive volume or the testing times are either prolonged or abbreviated, the results of testing may be difficult to interpret. For example, the interpretation of many tests is based on the accumulation of a specific color reaction after 1-2 minutes of reaction. If reaction times are not monitored closely and tests are allowed to sit for an extra 2-3 minutes or more, the extra time can greatly enhance the accumulation of color, resulting in false positive results.

In the United States it is important to distinguish which POC tests are in the moderate complexity or "waived" category, because that categorization determines the personnel, training, and quality assurance requirements for performing the test. A list of waived analytes is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfClia/analyteswaived.cfm and a list of waived test systems is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfClia/testswaived.cfm.

For travel clinics in the United States in which there is no laboratory oversight (e.g., no requirements for training, quality assurance, or proficiency testing), there are a limited number of tests in the waived category for infectious diseases. Tests cleared by the FDA as "waived tests" include those for HIV, HCV, influenza, respiratory syncytial virus, Epstein-Barr virus, Group A *Streptococcus*, adenovirus, *Helicobacter pylori*, trichomonas, and presence of Gram-negative bacteria in vaginal specimens (bacterial vaginitis).

An example of a rapid diagnostic test (RDT) that is considered a POC in international settings is the malaria antigen detection assay. While their use in malaria-endemic areas has proven a major step forward in providing rapid treatment, in the United States only one test system (BinaxNOW® Malaria) for malaria has been approved by the FDA. It is categorized as moderately complex and must meet the requirements listed above for performance of moderately complex testing.

Use and Regulation for Point-of-Care Tests in Resource-Limited Settings

Many of the countries that present the highest risk to international travelers lack regulatory standards regarding production or importation of test kits. A WHO report addressing regulation of in vitro diagnostics established that many POC tests sold in limited-resource countries perform poorly due to the lack of regulatory oversight or enforcement. Because many of these low-quality POC tests are inexpensive, countries where there are no quality standards often use cost as the single factor in the decision to purchase and use a test kit.

POC tests in resource-limited settings have been valuable in addressing the HIV epidemic, in providing rapid diagnosis of malaria infections, and, more recently, in transfusion medicine (rapid syphilis test). However, studies describing the value of these tests emphasize that the effectiveness of POC tests is dependent on test quality and conditions of use.

In international settings where there is no oversight of performance or of manufacturing of tests, there are insufficient data to determine common parameters such as sensitivity and specificity, and no studies in populations of intended use to provide data on predictive value. Therefore, test results from these settings should be viewed with caution and repeated if necessary.

Good Laboratory Practices for Point-of-Care Testing

Commonly used tests at POC in the United States include those for glucose, blood gas analysis/electrolytes, activated clotting time, urine dipsticks, occult blood, hemoglobin, and rapid tests for Group A *Streptococcus*. As noted above, the requirement for performing these tests is dependent on the FDA categorization. For the purposes of most travel clinics, these tests will be of limited use for the returning traveler in the United States.

However, regardless of the test being performed, good laboratory practice dictates that performance of any test includes the use of quality control material and that the test be performed by trained personnel who are periodically evaluated on their ability to perform the testing. For example, a survey of general practitioners in the Netherlands found that there is not always attention to quality control measures such as checking storage conditions, performing calibration and maintenance, or performing acceptable hygienic practices such as hand washing prior to collecting a blood sample. In 2005 the Centers for Disease Control and Prevention (CDC) and the Centers for Medicare and Medicaid Services (CMS) published "Good Laboratory Practices for Waived Settings," a guide that provides a list of important considerations before introducing waived testing.

THE TRAVELER USING POINT-OF-CARE TESTS

Patients involved in their own healthcare and using monitoring devices to determine glucose levels or to monitor coagulation times need to be advised of potential problems with equipment and reagents as well as potential problems in maintaining appropriate storage for medications. There are some obvious issues such as assuring monitoring devices will have sufficient power (extra batteries) or assuring the ability to connect to systems with voltage other than the standard 120 V available in the United States. Depending on the country and location within the country, availability of continuous electrical power is a common problem.

In addition to these more obvious issues, a letter from a physician that lists a traveler's diagnoses and the supplies used, including syringes or infusion pumps, may be useful when traveling through airports. All supplies should be transported in carry-on luggage. Assuring a sufficient supply of materials and reagents (some supplies may not be available in resource-limited settings) and the ability to control temperatures of storage while traveling is critical. For example, excessive heat may influence not only the quality of medications, but also the quality of reagents and control materials, and even the ability of the monitoring device to perform properly. For example, the CoaguChek XS meter can be used at temperatures between 2 and 30°C and humidity to 85%. While suitable for the United States and other temperate climates, acceptable operating temperatures and humidity levels are often exceeded in many tropical travel destinations.

For patients monitoring anticoagulant medicine efficacy and their international normalized ratio, it is important they discuss testing options with their physician. To continue to monitor while traveling and modifying dosages based on test results requires the patient to be evaluated and, if a candidate for self-treatment, trained appropriately on the use of the monitoring device and on administration of medication.

ALTERNATIVE SETTINGS AND EMERGENCY USE OF POINT-OF-CARE TESTS

The use of POC tests in alternative settings such as for immigration purposes, adventure travel, on board ships, or during disaster relief (earthquakes, tsunamis, etc.) will require taking into consideration the same issues as noted earlier—that is, accepted good laboratory practices for performance of testing that includes training and assurance of adequacy of test

instructions, maintaining records and logbooks of results, and quality control; these issues are often overlooked in environments where waived tests are performed.

A survey by the CDC and CMS found that among clinician offices in the United States performing waived testing, even the simple requirement of assuring the availability of test directions was not being met among 12% of those surveyed, and 21% did not routinely check to assure there were no changes in instructions when new test kits were received.

While there are no routine inspections of physician office laboratories in the United States and no requirement for training of personnel on the testing menu, there is an expectation that good laboratory practices are followed. The absence of basic accepted laboratory practices among survey participants should heighten awareness around decisions to implement POC testing in alternative sites.

Use of Point-of-Care Testing to Address New or Emerging Disease Outbreaks

During outbreaks of new or emerging diseases (the HIV epidemic, the Ebola epidemic, widespread malaria epidemics, etc.), there is a clear need to react quickly to respond to public health emergencies and to assure that test methods assure accurate results. When such a need is established, government and international organizations have modified policies to assure rapid approval of test systems or, in the case of malaria RDTs, the evaluation of test systems.

For example, the WHO has developed an Emergency Use Assessment and Listing procedure to evaluate and make available diagnostic test kits during public health emergencies. The FDA also makes allowances for expedited review when the Secretary of Health declares a public health emergency. The following are several examples of how these policies affected the introduction of new test systems.

HIV

As the HIV epidemic progressed, and as antiretroviral therapy became available, there was a clear need to assure that testing was provided where the patient was being seen to help assure prompt treatment. While the HIV rapid test was initially approved by the FDA as a moderately complex test, that designation presented barriers to the use of the test in alternative settings such as voluntary counseling and testing clinics. In the United States the HIV rapid test was declared a waived test in 2004 with the provision that training and quality assurance was a requirement for use. In the United States, most HIV testing has been implemented through local health departments where there has been provision of training and implementation of quality assurance measures. Algorithms for the determination of HIV infection have been developed and include the use of multiple tests to confirm initial test results.

Malaria

Morbidity and mortality associated with malaria, particularly among children, is greatest in resource-limited countries, and often there is little mechanism for determining the quality of test kits. Recognizing the need to provide information on quality of test system to resource-limited countries, in 2014 the WHO, CDC, and the Foundation for Innovative New Diagnostics published a summary of product testing of RDTs for malaria. The report cites the full evaluation of 206 products from 34 manufacturers for the detection of *Plasmodium falciparum* and *Plasmodium vivax* over a 5-year period. Performance varied widely at low parasite density for all products, but all had a high rate of detection in samples with high parasite density. The report also noted test performance variation among different lots (indicating variation in quality of antibody). In this example of malaria POC tests, it is clearly important that test selection, training, and quality assurance are components of any program anticipating the use of such tests in their clinics.

While not commonly considered as a POC test, microscopy for malaria has many characteristics in common with POC tests. Microscopic analysis can readily be performed in a variety of community and field settings and, if performed by a competent analyst with a functional microscope, can provide diagnostic information in a few minutes. It is important

to note that RDTs do not replace microscopy. The use of RDTs must be carefully evaluated to assure consideration of local algorithms that make clear actions to be taken based on RDT results.

The WHO provides similar information to resource-limited countries addressing the quality of HIV test systems as well. The publication of this work enables a resource-limited country to make an informed decision about what will work best in their settings.

Ebola

As the 2014 Ebola epidemic grew, the need for a rapid and accurate test became clear. The WHO performed an emergency use assessment and made a rapid test kit available to Ebola-affected countries (the ReEBOV™ antigen rapid test kit, Corgenix, Broomfield, CO). While the sensitivity and specificity of the test is only 92% and 85%, respectively, when the population being tested is in an endemic area and patients being tested have signs and symptoms, the predictive value of a positive test is high. A positive test is considered presumptive detection of Ebola Zaire virus disease, and where possible, results should be repeated with a new blood sample using nucleic acid testing. On the other hand, in low-prevalence regions, particularly when testing patients with minimal or few symptoms, the risk of false-positive results may greatly outnumber true-positive results.

While POC testing is often a key component of measures used in addressing disease outbreaks and other public health emergencies, it is important to have appropriate oversight that will assure that rapidly developed test systems provide accurate results. Results of testing are among the factors that help determine where to focus scarce resources when mounting a successful public health response.

THE FUTURE OF POINT-OF-CARE TESTS

As technology enables the development of new and simpler formats for a variety of tests, including molecular and genetic assays more commonly offered in traditional laboratory settings, the sites where testing can be offered will expand. Hospital clinics, physician offices, cruise ships, pharmacies, and health fairs are examples where such testing is now being offered.

US manufacturers are currently working on a number of POC tests including those for infectious disease, markers for stroke and sepsis, and tests such as complete blood count and white blood cell count. While it is desirable for more tests to be available where the patient is being seen, POC tests generally cost more than the same test performed in the laboratory. An important issue will be whether or not use of POC testing improves patient outcomes.

POC tests are most useful where the turnaround time is critical, when the training and quality assurance required is minimal, and when the method has been rigorously investigated for the population for intended use.

These examples of the use of POC tests make clear that a number of issues must be considered before implementation of use. For example, understanding what the test is measuring (e.g., antigens vs. nucleic acids) and assuring awareness of the impact of sensitivity, specificity, and disease prevalence in the population being tested both have a bearing on the predictive values of a test. In addition, training, availability of quality control, and oversight of quality assurance activities are critical elements essential to assure accuracy of testing.

FURTHER READING

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