**CHAPTER:**

**POINT OF CARE TESTS- PRESENT AND FUTURE IN CLINICAL MICROBIOLOGY.**

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**The Point-of-Care Laboratory in Clinical Microbiology**

**Summary:**

Point-of-Care Testing (POCT) has been highlighted in the health care system in recent decades. Point-of-care testing (POCT) is defined as a laboratory test performed outside a central laboratory, usually at or near a clinical treatment site or by a patient. Point-of-care testing is usually performed when quick decision-making is required, such as in an emergency room or when urgent treatment is to be determined. The advantages of POCT compared with central laboratory testing include shorter wait times for results and earlier discharge home.

 On the other hand, due to its low demand, POCT has a disadvantage compared to conventional equipment, as its cost is inversely proportional to the volume of use. The awareness of health professionals of the importance of each step is the critical success factor. The trend of advancement of the use of POCT and the great potential of its contributions reinforce the need to implement quality management tools, including performance indicators, to ensure their results.

POC laboratories operate 24h a day and 7 days a week and provide diagnoses within few hours, mainly based on immunochromatography and real-time PCR tests, mostly combined in syndrome-based kits that facilitate sampling, including self-sampling and test operations. POC laboratories are a way of easily providing clinical microbiology testing for populations distant from laboratories in developing as well as developed countries. Now a days Internet connections enable support from core laboratories. Recently, POCT devices using molecular genetic method techniques have been developed and there is need to further improve them. As POCT technology improves ,the list of tests that could be done also expands and areas where POCT can be applied will also increase.. POCT can help clinicians make quick medical decisions in medical resource limited countries. However there is need to understand the limitations of POCT so that it can be optimally used to improve patient management.

**INTRODUCTION:**

The increase in the number of biomarkers has led to the need for more well equipped laboratories to perform as many diagnostic tests as possible. Moreover, there is a need to obtain rapid biological test results during treatment to identify contagious disease so as to implement timely isolation of patient , precise diagnosis and to select the treatment best suited to the situation. It is also important to detect infections that can be easily cured through ambulatory care and those which may require hospitalization. The field of microbiology has evolved during recent years to take these issues into consideration. Core laboratories that reduce costs, operate 24 h a day and 7 days a week have emerged , but the remoteness of care points and transport time is the major drawback.

In recent years, many definitions of POCTs have been proposed in the literature[2-4]. The most widely used one is: POC tests are performed at the site of patient care. Three key features distinguish them from traditional laboratory tests: they do not need significant laboratory infrastructures or specialized staff in order to be performed, they are designed to be easy to use and interpret, and they are often able to deliver a rapid diagnosis[5]. Moreover they could be more cost-effective than conventional tests. In low-income countries, which face a strong shortage of human resources and lack laboratory infrastructures, the availability of laboratory tests, including diagnostic tests, is very limited. Moreover often too costly to be widely accessible to the patients and health care professionals who need them[6] . In such setting, the introduction of POCTs, may improve access to diagnostic tests and potentially generate significant health benefits by providing key information to guide therapeutic decisions[7]. Conversely, in high-income countries, laboratory tests are widely available, and health care professionals have the choice between different laboratory techniques. In such setting, the main added significance of POCT compared with traditional ones is decrease of time between sample collection and diagnosis, thus optimizing medical decisions made regarding isolation, hospitalization, and treatment of patients diagnosed with infectious diseases [8].

**POC TESTS:**

**HISTORY**

One of the first POCT to be introduced was the detection of *Streptococcus pyogenes,* the sample tested is throat swab, helping in the prescription of antibiotic treatment when the test is positive and tests to detect bacterial vaginosis using direct microscopic observation to detect the presence of *Trichomonas vaginalis*, Gram-negative bacteria, or gonococci [9].

**POC IN MICROBIOLOGY DESERTS**

**Reorganization of Clinical Microbiology**

Microbiological POCT is suitable wherever a population of 500 to 1,000 people is located at a distance more than an hour from the core laboratory. This situation is very common in developed countries, where core laboratories are centralized around technical platforms, thus creating medical deserts. In countries with low and intermediate levels of development, the laboratory network can be underdeveloped[10]. Off-shore platforms require access to tests for rapid diagnosis of infectious diseases. As diagnostic uncertainty can lead to inappropriate medical decisions, putting ship personnel and passengers at risk of contagion and delayed treatment[5].

**POC DEVELOPMENT**

**Cohorts**

The syndrome-based approach in POC laboratories contributes to measuring the epidemiology of infectious diseases, abnormal events in real time, and the cost of diagnostic tests[11].

**Epidemiology and Infection Control**

The data from computerized POC help to ensure real-time, local epidemiology, which in turn can assist medical decision-making. Hence, help public health microbiologist in the rapid detection of pathogens, to identify the threat of bioterrorism if any, and providing an appropriate and prompt medical response to the situation [12]. The impact of some POC tests on the appropriate use of antimicrobials in cases of different systemic infections and hence to help in infection control has also been favorably evaluated [13,14] One of important impacts of POC testing is to prevent the hospitalization of patients presenting at the emergency room with some contagious infection[15]. A second impact is placing patients with the same epidemic and contagious infection into the same cohort in addition to isolation of such kind of patient at the earliest[14].

**TYPES**

**Direct Detection of Pathogens by Antigen Detection Assays**

Specific microorganism antigens can be rapidly detected from a clinical specimen through an immunochromatographic test (ICT). Lateral flow tests rely on the binding of a microbial antigen present in the clinical sample and test reading is taken within 15 min. Currently, ICTs are available for diagnosis of infections by several bacteria, viruses, parasites, and fungi, and multiplexed strip tests are available to detect 3 to 14 pathogens, using the syndromic approach presented below.(Table 1). The benefits of the ICT are its speed, lack of instrumentation, no need for a power source, maintenance, or training making the test low cost. Moreover the test is easy to transport and store due to its small size and, in particular, its resistance to variations in temperature. The two main drawbacks of the ICT are its low sensitivity,( 60% to 95%,) and the fact that visual interpretation of results is operator dependent, being based on a subjective interpretation of test positivity in weakly positive cases. This can lead to false-positive and false-negative results [16].However development of strip readers overcomes this drawback.



**Direct Diagnosis by Nucleic Acid Amplification Tests**

Nucleic acid amplification tests (NAATs) have revolutionized the diagnosis of infectious diseases. They aim to detect one or more nuclicacid sequences specific to a single pathogen. Two techniques are available for POC testing: PCR-based techniques and isothermal nucleic acid amplification techniques. Briefly, PCR incorporates 30 to 40 cycles of heating to 72°C, which requires specific equipment and electrical power, limiting the widespread use of PCR in resource-limited settings. Real-time PCR (rt-PCR) is the variant used in POC testing, Loop mediated isothermal amplification (LAMP) is a newer, alternative technique for amplifying DNA by means of a DNA polymerase, operating at a constant temperature of 60 to 65°C. Advantage of LAMP over rt-PCR is due to the reason that thermocycler is not needed, hence making NAATs cheap, energy-saving, and easy to perform in the POC laboratory. One more added advantages of NAATs over ICT is their greater sensitivity. Now a days the rapid diagnosis of malaria, tuberculosis, and Buruli ulcer is possible is because of NAATs. However they require a higher degree of technicality and training. Moreover power shortages and the need to store some reagents at 4°C may limit the implementation of NAATs in POC laboratories in some resource-limited tropical countries.

**Direct Diagnosis by Miscellaneous Tests**

A few pathogens can be detected at the POC by hybridizing a specific fluorescent antibody. A test which can perform 25-min multiplex detection of respiratory tract pathogens, including influenza virus, respiratory syncytial virus (RSV), adenovirus, coronavirus, and parainfluenza virus is commercially available though has not yet been approved by the FDA and the European Community [17]. Many pathogens causing tropical disease can be detected by using a technique for hybridizing DNA or RNA extracted from a clinical specimen, after amplification using the principle of hybridization, with good sensitivity and specificity however their field test is awaited[18].

**Non-Pathogen-Specific Diagnosis**

In addition to hematology and biochemistry tests, there are some tests that can be incorporated into POC testing for the nonspecific diagnosis of infectious diseases. Urinary tract infection is caused by various bacteria, mainly *Escherichia coli*. POC tests, like the standard urine test strip features the nitrite test, detects nitrate-reducing bacteria enteric Gram-negative bacteria, and an esterase test, which detects leukocytes. Moreover monospot test which detects heterophile antibodies in the course of mononucleosis syndrome due to Epstein-Barr virus and performing cell counts for the laboratory diagnosis of meningitis are another examples of commonly used POCT. However the limitation is most commercial readers have a limit of sensitivity that is higher than the limit of 10 cells/ml used for the biological definition of meningitis and a test sample of several hundred microliters, which is incompatible with the very low volume of cerebrospinal fluid (CSF) received at the POC. New instruments using innovative optical technologies are currently being evaluated. Procalcitonin levels can also be measured at the POC laboratory in order to assist medical decision-making regarding the prescription of antibiotics for systemic infections. Whole-blood lactate test has also been used as a predictor of prognosis in patients diagnosed with severe sepsis.

**POC LABORATORIES AND SYNDROMIC APPROACHES**

POC microbiology laboratories adopt a syndromic approach in order to organize them and to speed up and optimize diagnosis. Most patients present with clinical signs and symptoms that are not pathognomonic of any particular infectious disease. However, clinical signs and symptoms are indicative of one particular diseased organ,

potentially infected. It is therefore of medical interest to simultaneously test the multiple pathogens that may cause signs and symptoms in the patient at the POC. This is “syndromic POC,” approach which has been facilitated by the emergence of moderately complex multiplexed tests. Moreover, there are tremendous number of emerging pathogenswhich makes it difficult for physicians to memorize the actual list of pathogens and the corresponding list of appropriate clinical samples. The advantages of sampling kits over the usual disease-based sampling include the limited and nonrepetitive number of specimens collected from the patient, a simplified laboratory test prescription for the physician, a plannable workflow for the nurse and the doctor, and easily traceable samples for the laboratory. Syndromic kits are used to test most of the pathogens known to be responsible for one particular syndrome, such as endocarditis, pericarditis, diarrhea, osteitis, meningitis, encephalitis, uveitis, keratitis, or infections in one particular epidemiological group of individuals, such as febrile patients presenting to the emergency room, with a worsening of chronic respiratory tract infection in cystic fibrosis patients, fever in travelers, fever in pilgrims to Mecca, and fever in homeless patients and neonates, for whom a specific menu of pathogens has to be drawn up (Table 1). Syndromic kits allow laboratories to constitute large clinical series and to preserve large collections of specimens in dedicated biological resource centers for retrospective testing using emerging pathogens. POC laboratory procedures have to specify supplementary tests to be performed in the core laboratory. These may include, for example, additional core laboratory NAATs to confirm negative results yielded by a lower-sensitivity POC ICT. Genotyping

may also be conducted as a second-line test, the result of which will be incorporated into the laboratory epidemiology database. In any case, POC laboratory menus and procedures have to be conducted in agreement with the medical director of the core laboratory.

**Syndromic Kit Menus**

**Tropical Fever**

Fever is a nonspecific yet frequent sign in natives, expatriates, and travelers exposed to tropical regions , indicating an infection due to a ubiquitous pathogen or a pathogen specifically found in tropical countries. Fever can be the initial sign of, among other specific pathogens, deadly malaria and deadly Ebola virus infection and may signal other disabling infections that can be cured by specific anti-infectious treatments. Therefore, it is medically important to conduct rapid POCT for some pathogens in patients exposed to tropical countries. Malaria continues to be a leading cause of fever in countries where the disease is endemic .The WHO now recommends that parasite-based diagnosis should be used in all cases of suspected malaria before treatment of patients . Rapid diagnostic POCT include the BinaxNOW malaria test ,which is able to detect the four *Plasmodium* species infecting patients and is the only such FDA approved test; the Parascreen Pan/Pf test and the OptiMAL test which identify both *Plasmodium falciparum* and *Plasmodium* *vivax*; and the Paracheck Pf test which identifies only *P. falciparum* [19]. Dengue virus can be tested by using a rapid diagnostic test (RDT), which detects either IgM and IgG antibodies or IgM antibodies and the NS1 protein .Detection of the NS1 protein is more suitable for POC testing because of its higher sensitivity during the acute phase of infection[20]. Recurrent fevers due to various cross-reacting *Borrelia* species, typhus group and spotted fever group rickettsiae ( *Rickettsia felis* and *Rickettsia africae*), and *Bartonella* spp are frequent causes of tropical fever. They can be detected by appropriate reported but noncommercialized RT-PCR assays[21]. A nanogold particle lateral flow assay was recently reported for POC diagnosis of dengue virus, yellow fever virus, and Ebola virus infections . Moreover these infections can also be diagnosed at the POC by using a commercially available RT-PCR assay and a recently evaluated immunoassay detecting the Ebola virus VP40 antigenic protein [22,23].

**Community-Acquired Respiratory Tract Infection**

Community-acquired respiratory tract infections hold a major place in infectious pathology especially in the case of pneumonia and were responsible for 2.7 million deaths in 2013. They are caused mainly by bacteria, viruses, and coinfections by influenza virus. These elements illustrate the importance of rapid diagnosis of *S. pneumoniae* pneumonia, *Legionella pneumophila* infection, influenza virus and RSV infections. [24,25] With incidence of 9 million cases and 1.5 million deaths in 2013, tuberculosis (TB) currently remains one of the deadliest threats to public health and its diagnosis in POC laboratories relies on real-time PCR, including the commercialized Xpert MTB/RIF assay which provides accurate results within 2 h for detection of pulmonary TB disease and can also identify resistance to rifampin. Rifampin is a critical first line drug for treatment of TB and a reliable surrogate marker of multidrug-resistant TB (MDR-TB) strains. Since 2010, the WHO has recommended the use of Xpert rather than smear microscopy for diagnosis of patients suspected of having TB. Diagnosis of community-acquired pneumonia at the POC involves multiplex RT-PCR tests integrating nucleic acid extraction and amplification in a single cassette. The Respiratory Film Array Panel system is FDA and EC approved and can detect 17 viruses and 3 types of bacteria within 1 h. Several other multiplex RT-PCR assays are commercially available. [26,27]

**Pharyngitis**

*Streptococcus pyogenes* is one of the pathogens to be detected in the case of clinical pharyngitis . Specimens used is pharyngeal swab and detection is most commonly achieved by using lateral flow assays (POCT).

**Digestive Tract Infection**

Diarrhea is a leading cause of death worldwide and a frequent reason for hospital visit. Prognosis varies between a self-limited infection and fatal infection. Many ICT techniques have been developed for the POC diagnosis of diarrhea, including the rapid agglutination-based detection of rotavirus and adenovirus as well as the detection of *C.* *difficile* toxins. The rapid detection of *C. difficile* toxins A and B or *C. difficile*, its toxin B, and an additional binary toxin can be detected within 90 min by using commercially available RT-PCR assays such as GeneXpert, with 98% agreement with reference testing in the core laboratory and higher sensitivity than ICTs. A commercially available *Campylobacter* antigen detection kit has also been evaluated and will be introduced for testing shortly. A dipstick test for the rapid detection of *Shigella* is under evaluation. Currently, several RT-PCR tests allow multiplexed detection of bacteria, including *C. difficile* and *E. coli* pathovars; parasites; and viruses, like norovirus 5, within 1 h.[28-33] (Table 1).

**Genital Tract Infection**

Genital tract infections are caused by microorganisms transmitted mainly during sexual intercourse. Genital tract infections are one of main causes of infertility. High contagiousness of these organisms, demand rapid diagnosis to initiate both treatment and prevention at the earliest. *Chlamydia trachomatis*, herpes simplex virus and *Neisseria gonorrhoeae* can all be detected by lateral flow assays and by RT-PCR assays in POC laboratory. POC prenatal syphilis screening was developed to address the limitations of conventional rapid plasma reagin (RPR) tests, followed by a confirmatory *Treponema pallidum* hemagglutination assay (TPHA). These new POCTs are based on principle of immunochromatography and detect both treponemal and nontreponemal antibodies. POC tests for the diagnosis of most of sexually transmitted infections has been evaluated and the results are favourable [34,35] .However the impact of POC tests for the diagnosis of syphilis has not yet been evaluated [36]. *C. trachomatis* infection is the most frequent sexually transmitted infection in the world. *C. trachomatis* alone can be detected by using the ICT and NAAT in multiplex RT-PCR assays. Vaginosis due to *Atopobium vaginae* and *Gardnerella vaginalis* can be diagnosed at the POC by using ionmotility spectrometry and the more commonly by ICT andNAAT assays.[37]

**Meningitis**

Meningitis involves a wide spectrum of causative agents. The prognoses and medical management, highlights the value of rapid POC diagnosis . CSF cytology can have errors, as microscopic observation and cell counting are operator-dependent techniques. Lens-free devices are under evaluation . POC meningitis menu systematically aim at testing for enterovirus , *Streptococcus pneumoniae*, *Neisseria* *meningitidis* , and herpesviruses, including herpes simplex and varicella-zoster viruses , in cerebrospinal fluid collected from symptomatic patients clinically suspected of having meningitis . A few commercially available multiplexed NAATs currently under development would detect six bacteria, eight viruses, and two *Cryptococcus* species within 1 h. A LFA detecting *Cryptococcus neoformans* polysaccharide capsule glucuronoxylomannan antigen performed on CSF , plasma, serum, and urine samples , but tests on saliva were disappointing and should not be recommended.

**COST-EFFECTIVENESS**

According to WHO guidelines an intervention is considered to be very cost-effective if its ICER is below the annual gross domestic product (GDP) per capita of the study country and if its ICER was less than three times the country’s annual GDP per capita . The cost effectiveness analysis for four most common infective diseases has been summarized as:

1. **Tuberculosis**

A cost-effectiveness analysis in 2011, using a decision analytic model simulating costs and health gains for a cohort of 10,000 individuals suspected of having TB in India, South Africa, and Uganda comparing three different diagnostic techniques: (i) smear microscopy alone, defined as two sputum microscopy examinations followed by clinical diagnosis for smear-negative individuals with suspected TB (base case); (ii) use of the Xpert system after two smear-negative examinations (“in addition to”); and (iii) use of Xpert instead of smear microscopy with one single sputum specimen tested (“as replacement for”) was conducted.[38] ICERs computed for the use of Xpert in addition to smear microscopy compared with the base case , results suggest that both strategies incorporating Xpert were cost effective in the study countries, except for the replacement of smear microscopy with Xpert in Uganda. Sensitivity analyses based on Monte Carlo simulations confirmed the results. Another study compared Xpert and smear microscopy in Botswana, Lesotho, Namibia, South Africa, and Swaziland, where TB and HIV prevalences are high [39]. In most cases, ICERs were found to be below the standard benchmarks set by the WHO, suggesting that Xpert is a cost-effective strategy for these southern African countries. Conclusions were robust in sensitivity analyses many more studies from different parts of world prove the same[40,41,42,43]

1. **Malaria**

The results of the studies show the cost-effectiveness for RDTs were consistent across most of studies world over, suggesting that approval should be given to consider the use of RDTs, especially when malaria prevalence is high. However further more studies are needed to assess the long-term benefits of RDTs in terms of the development of antimalarial resistance.

1. **Syphilis**

In sub-Saharan Africa where prevalence of syphilis is very high as compared to rest of world the cost-effectiveness of different diagnostic strategies was estimated by different studies. The results strongly support the use of POCTs in sub-Saharan Africa[44,45] .The main limitations of the studies, are that transmission to partners was not studied, which would probably improve the cost-effectiveness of screening and only one study assessed the long term benefits of incidence reduction [46].

1. ***Chlamydia trachomatis***

The cost-effectiveness of a vaginal swab POC test using the Chlamydia Rapid Test (CRT) versus a standard vaginal swab NAAT was measured by using a decision tree model Those authors concluded that replacing standard

laboratory tests for chlamydia and gonorrhea with a POC NAAT could reduce costs, and patients would benefit from more accurate diagnosis and less unnecessary treatment. However all studies were conducted in European countries [47]. Another study concluded that if future POCT improvements were able to reduce waiting time

while maintaining sensitivity, the use of POC testing would prevent more PIDs and become more cost-effective[48]. Studies based on antigen screening tests [45, 49] appeared to be less accurate than the PCR method, implying that POCTs were not a cost-effective strategy [44].

**CONCLUSION**

Point-of-care testing is likely to play an increasing role in health care delivery in the future. It will improve access to health care and increase the efficacy of service provided to patients. Although POCT provides laboratory results faster than the traditional central laboratory, process improvement is needed to optimize the accuracy of laboratory results. Molecular POCT for common pathogens in select populations, such as in intensive care or other common illness presentations, needs to be evaluated to further improve patient care and effectively manage health care resources. Despite different issues, POCTs appear to be cost-effective for the diagnosis of tuberculosis, malaria, and syphilis in comparison with current diagnostic strategies in both southern and northern countries, leading to cost savings in some situations. It is worth noting that very few cost-effectiveness studies were conducted in northern countries, and these studies mainly concerned infectious disease caused by *Chlamydia*. POCTs increased the number of correct diagnoses especially in resource-limited settings, provided rapid test results, and enabled physicians to make decisions regarding patient treatment, notably at the time of care. Their rapidity and ease of use increased their use worldwide. Moreover, the use of POCTs allows exploration by syndrome. Cost-effectiveness depends on the sensitivity of diagnostic tests and their prices. Improvements of these parameters would make these tests even more cost-effective and would enable health interventions to promote the use of POCTs for improving patient care. Despite several advantages of POCT, limitations include cost, imprecision and inaccuracy, requirement for an interdisciplinary approach, and human error. Although the use of POCT is expanding in many areas, the limitations must be understood and improvements in analytical performance achieved to properly interpret POCT results.

**FUTURE DIRECTIONS**

It is clear that a radical change has been made in diagnostic microbiology during the 21st century. Indeed, it is now possible to reach a diagnosis at the time of care using the latest molecular techniques with lower production costs. Validation will soon be performed remotely over the Internet or via direct data transmission. In terms

of a more speculative future, three-dimensional (3D) printer technology and remote fault diagnosis will repair some failures using a small stock of materials, including versatile components . The development of microfluidic PCR will allow many of microorganisms to be rapidly tested at low cost. Smartphoneoperated enzyme-linked immunosorbent assays (ELISAs) have already been reported. The connection of all real-time data will enable epidemiological surveillance, the significance of which is difficult to imagine at this time. The key elements of the global development strategy of outsourced points of care will be based on a first-stage repertoire. The rapid detection of antimicro- bial resistance, currently limited to a few antibiotics, will be expanded to assist doctors in reaching treatment decisions . Test organization will likely be a syndromic approach, validation will be performed remotely, and it is easy to imagine that this could be connected to the therapeutic management system.

The combination of a repertoire of geographic infections, the syndromic approach, and the versatility of microorganism testing and remote validation are the steps in this clinical microbiological revolution.

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