Point of care testing in clinical chemistry: a review

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Abstract
Point of care testing (POCT) is fast becoming a widely used and available technique not only in the field of chemical pathology and laboratory medicine but in the practice of medicine as a whole. Its use in aiding diagnosis has contributed a lot in reducing laboratory turnaround time (TAT), has improved the quality and outcome of emergency care patients and has generally improved both physician and patient satisfaction. It however, like other areas of medical diagnostics, has its own peculiar problems. Available literature on point of care testing in clinical chemistry was sourced for using both manual and online library search. Point of care testing is a rapidly evolving and ever growing area of laboratory diagnostics. With the application of technologies ranging from simple dipsticks to hand held devices to complex auto analyzers, the innovation of POCT is ever gaining popularity even in developing countries like Nigeria. Though POCT used in clinical chemistry has started evolving in some secondary and tertiary health care centres in Nigeria, especially in their emergency and critical care rooms, it is important that pathologists and clinicians embrace its use, considering its great benefit to patient care.

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Introduction

Point of care testing is that clinical laboratory testing that is performed close to the site of patient care. It is typically performed by clinical personnel whose primary training is not in clinical laboratory sciences, or by patients themselves, thus it is any test performed outside traditional care or control laboratory[1,2] POCT can also be more appropriately defined as when a test is performed at the time at which the test result enables a decision to be made and an action taken that leads to an improved health outcome [3]. Other names by which POCT is referred include bedside, near patient, physician's office, extra-Laboratory, decentralized, off-site, ancillary, kiosk, and alternative site testing [3-6].

POCT is a rapidly growing component of health care and has found great use in both primary secondary and tertiary health care setting[3] it has been variously described asone of the key innovations needed to radically change the standard of healthcare delivery [7] It'ssuccess is as a result of advances in nanotechnology, thin film severs, semi conductor and micro fabrication engineering and microfiuiditics[8]

POCT is found useful in primary healthcare settings such as the home, community pharmacy health centres, physicians' offices and paramedical support vehicles etc. Its usefulness in secondary and tertiary health care settings includes its use in emergency units such as, the accident and emergency rooms, adult and peadiatric intensive care rooms, recovery units etc. Whilen on emergency settings include the peadiatric, medical, and surgical wards

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Most importantly, self testing is increasingly becoming useful function of POCT , as an increasing repertoire of tests that can be performed by patients are being developed[3].

Uses / Advantages of POCT

Studies by Forman RW[9] in 1996 and Becich MJ[10]in 2006, estimate that more than 70% of patient care decisions are based on laboratory testing. This coupled with an increasing pressure and desire of health care service providers, to provide better patient care at lower cost in the face reducing available resources, has driven the stimulus, need and reliance on POCT[5]

POCT provides many of the acutely needed diagnostic results to help the physician make a diagnosis in good time and generally improves the quality of health care. Potential benefits can be divided into four broad groups, for the physician, the patient, the laboratory and the health care administrator.

For the physician, the benefits includes improved turn around time (TAT) for laboratory results, better and more immediate patient care with a good opportunity to counsel patients, since, results are often available while patient is still being examined, and less labour for the physician and his assistants with the elimination of the need for staff to look up or pursue result.

For the patients, POCT investigations are less traumatic, for example most tests require only a finger prick for sample collection, less blood is required which is of greater benefit in the pediatric age group,Investigations are more patient focused and convenient since they are done on-site.

For the laboratory, there is decreased pre-analytical errors, improved visibility, improved collaboration with clinicians and improved contact with patients, while for the healthcare services administration there is the potential benefit of shorted ICU and emergency room stays with the consequent financial savings.[3,5]

POCT has been formed more useful in the management of critically ill patients with unstable conditions. Analysis such as blood gases, electrolytes e.g Na K,$^{+}$Ca^{2+}and mg^{2+}Glucose, Heamoglobin and coagulation profile,which demonstrate rapidly changing levels of fluctuations faster than the turnaround time for results from a central laboratory are important tests commonly adapted into the POCT, thus making results available when the patient's test results are still most physiologically valid, unlike the result from the routine laboratory which because of the turn around time, may not be reflective of the patient's status at the time it is made available.

Other important POCT investigations with immense advantage include lactate, which is a marker of perfusion, important in the diagnosis of sepsis and hypoxia, coagulations studiesin patient undergoing catheterization or on close monitoring heparin therapy, cardiac biomarkersuseful in the evaluation of chest pain in the emergency room, glucose level useful in diabetic emergencies and the unconscious patient and creatinine to monitor renal function and reduce patient wait time for chemotherapy. None of these investigations has a turn around time greater that 5-60minutes, these fast results often translate to reduced morbidity and mortality[4]

Also POCT carried out in the physician's office has been demonstrated to enhance patient counseling, improve patient participation in his own management and on the long run improve patient and physician satisfaction[11,12,13].

Disadvantages/Limitations to the use of POCT

However despite all the potential and real benefits of POCT, it has Its own limitations, chief among which is cost. As a result of the complex technology involved in the design of POCT and the purpose for which it was designed, they come with a higher rate of disposable requirements and reagents compared to the traditional laboratory system and this comes with a cost which is transferred to the patient.

Also therequirement for training, quality control, method validation,maintenance, documentation of results, and performance of external quality control/ proficiency training, make POCT systems more

expensive to run than automated chemistry analyzers especially considering that the bulk of the people who use POCT are not trained laboratory staff. Because POCT uses whole blood and very little samples, results from POCT instruments are usually much different from that of the central laboratory which in most cases use either serum or plasma because of the difference in matrix effects, and this may cause confusion with clinicians, who may not be able to adjust or accommodate for the differences.

Also POCT devices measuring the same analyteproduced by different manufacturers employ different methodologies and technology and thus often give different results of the same analyte in the same patient[4]. This is better highlighted by Chen and associates[14] in a 2003 study, were they dida performance comparisonof glucose meters from different manufacturers and found a great bias at virtually all levels of the reportable ranges for glucose. Because of the rapidity of the test in POCT, there is very little room for quality control checks which may cause errors, also most POCTdevices because of their unique design and intended use rely on inbuilt internal quality control mechanisms designed by the manufacturers which occasionally is not adequately monitored by the governmental and none governmental bodies put in place for such. Worse still most underdeveloped countries do not even have the mechanism in place to monitor or ensure the standard of these equipment.

The Medicine and Health care Regulatory Agency (MHRA) in the UK, Norwegian Quality improvement of Primary Care Laboratory in Norway [15]and The joint Commission[16]and the College of American Pathologists[17] in theUnited States of America, are bodies mandated by their respective governments government tomonitor the production and use of these POCT devices, with a view to ensuring conformitywith laid down quality guidelines and reducing errors. POCT is often performed by patients orstaffs, who have little or no laboratory training, thus their knowledge of the pre-, intra- and post analytical variables, that would affect results are rather limited, and errors arising from these variables are innocently, transferred to the results generated which in turn could mislead the physician in the management of his patients. In a 2001 survey of physicians' offices in the United States of America, the US department of health and human services office of the Inspector General[18]found that though staff wanted the best for their patients, mostof themwere untrained, lacked knowledge of quality control, could not identify poor results, had little knowledge of the equipments they were using and did not follow manufacturers instruction.They however improved dramatically with education.

Technologies used in POCT

Technologies used in POCT devises, are broadly grouped into two: those formatted for non instrumental platform and those formatted for instrumental platforms.

Non-Instrumental Platform:

Those formatted for non-instrumental platform include the qualitative assays which use the principle of reflectance chemical reactions, and immunoassay on impregnated paper strips and dry reagent cartridges to assay for analytes such as human chorionic gonadothropin (hCG), urine analytes (urinalysis)fecal occult blood, drugs of abuse in serum and urine, and cardiac enzymes. The impregnated paper strips(dipsticks) for urinalysis, pregnancy test using urine beta hCG, bilirubin, heamoglobin and glucose, were the first POCT methods introduced in the 1940s/1950s by companies such as Ames and Roche[3]. They are relatively simple to construct and are composed of a pad of porous material such as cellulose that is impregnated with reagent and then dried[19]. They relied on colour changes produced from chemical and enzymatic reactions resulting from analytes of interest in the sample, results are usually qualitative andoften require accurate timing in addition togood visual acuity and colour vision by the performer. With time simple meters were introduced to improve the performance of these investigationsThis technology is widely available in Nigeria and other developing countries and still serves as the first line of routine investigations carried

out in clinics, hospital wards and emergency rooms, they are very cheap, involve minimal distress to the patients and require very little training for performance, moreover the results produced from these tests, while not confirmatory are usually adequate pointers to need for further investigations[20].

Another type of dipstick is that which employs immunoassay technique, here the pads are more complex and composed ofseveral layers, the uppermost of which is a semipermeable membrane that prevents red cells from entering the matrix where the antibodies or antigens are impregnated, it is often colour based as well and do not require any instrumentation for resolution, an example of a common one in use, is the test strips for HIV antibodies, Hepatitis B and C, pregnancy test etc. these are also commonly available in Nigeria.

While yet another design of dipsticks use multiple pads arranged in sequence to measure different concentrations of the analytes such as cholesterol, creatinine, lactate, uric acid, glucose etc. in whole blood and bilirubin, ketones, pH, nitrite specific gravity etc. in urine.

The semi quantitative and quantitative assays using non instrument technology also rely on the above assay principles, but are better formatted to produce quantitative values from the same specimens. An example of technology applied in this instance is the use of reflectance meter to quantitate the color change produced in the urinalysis dipstick[21]. All non- instrument technology methods for POCTare formatted for single use on hand held devices.

Instrument Platforms

The various technologies used on instrument platforms for POCT have been formatted for use on instruments ranging from simple hand held devices to complex desk top equipment. The commonest handheld devices in use both in this environment and worldwide will be reviewed.

The Glucose Meter and Strips: This is apparently the commonest POCT device in use worldwide; its popularity is probably tied to the increasing incidence and prevalence of Diabetes mellitus, its cost and its ease of use. It is believed to represent a market worth over 10 billion dollars as at 2008.[3] Glucose strips are biosensors in that they all use enzymes such as glucose oxidase, hexokinase and glucose dehydrogenase as the recognition agents, with photometric reflectance or electrochemical techniques for detection[22], they comprise of different layers with each layer having specific functions. When blood is added, a separating layer often containing glass fibres, glass membrane and or special latex formulations, permits only plasma to get through to the spreading layer where sample homogenization is achieved before getting to the analytic layer which lies directly on the support base which is usually of reflective plastic material,bio signals produced by the enzymatic breakdown of glucose is then detected by the reflectance meter and converted into values.

Glucose strips and meters employing electrochemical sensors, do not have a separation layer and the strips are composed of Ag-AgCl reference electrodes and a carbon based active electrode both manufactured using screen printing technology with ferrocene containing ink. Here enzymatic conversion of glucose is accompanied by the reduction of ferrocene and the release of electrons which are then detected and quantified.[3]

Despite the technology and advancement, the problem of the performance of the glucose meter in comparison to the routine laboratory methods is still a big challenge especially in diabetic patients with poor glycaemic control and in critically ill patients when glucose oxidase based glucose meters are used because ambient oxygen tension affects their performance. Over the years with improved technology and ever stifling competition, a lot of improvements have been made to the glucose meter so as to improve its performance; these include nonwipe strips, use of even smaller sample volumes and reduced testing time.

Lateral flow strips and meters: Lateral flow strips were first developed in the late 70s for immunoassays. They are biological sensors

in which the recognition agent is usually an antibody that binds to the analyte, with the detection of the binding event occurring through reflectance or fluorescencespectrophotometry[3,23]. This is the technology behind several immunosensor based POCT equipments used in measuring analytes like cardiac markers[24,25], and drugs of abuse[26].

The I-Stat: Introduced about two decades ago by Abbot Laboratories, is a hand held device using a single or combination of cartridges to measure blood gases, electrolytes and recently creatinine coagulation parameter and troponin[27], desired investigations decides the combination of cartridges to be used. The cartridges contain electrodes or sensors as wafer structures constructed with thin metal oxide films using microfabrication techniques. They also contain a microfluidic network which directs and controls the movement of calibration liquids and blood samples to each of the sensors[28]. Its ability to perform an electronic self quality control is another innovation that has increased its acceptability and results from the I-stat can be hooked up to the laboratory information system interface where available. The I-Stat though relatively costly, is widely used in the emergency rooms worldwide.

The last category of POCT devices on an Instrument platform to be discussed are the bench top equipment based POCT devices. They use similar technologies to those described previously with the only difference being that their sensors are often more sophisticated and are designed to be reusable[29]. For easy use especially for non-laboratory trained personnel, no precise manual pipetting is required; the reagents come in cartridges which are programmed for quality control and a specific number of uses before disposal. These equipment are portable easy to use and are commonly in critical care rooms where they can be used to measure a wide array of analytes ranging from blood gases and electrolyte to biochemical markers of myocardial infarction[3,5].

Total Quality Management of POCT

Quality control and quality assurance programs provide a formal means of monitoring the quality of a service and POCT not an exception [3]. For within the system quality assurance, a multidisciplinaryteam approach is favored, focus is usually on the entire system rather than individual performance and continual quality improvement is advocated[5]. It is often recommended that aformal policy on POCT delivery should be developed publicized and enforced as a starting point[30].

However these are not adequate, thus the need for external quality assurance programs[19,20]

Various quality control systems have been advocated including the committee method and the core laboratory method, the truth however is that all these methods have essentially the same components, which includes training, retrainingand certification of staff, documentation and records, organization, process control, information management, occurrence management, quality assessment, process improvement and safety[5]

Mandatory government regulation with provision of guidelines and standards by the appropriate regulatory institutions has been advocated and preferred, such includes the Clinical Laboratory Standards Institutes (CLSI)"Risk management techniques to identify and control laboratory errorssources [EP-18 [21] "Presentation of manufactures risk mitigation information for uses of in-vitro diagnostics device" EP -22 [22] and "Laboratory quality control based on risk management EP-23[23] These standards help laboratory directors develop quality control systems.Internal and external monitoring of compliance is also an essential component of total quality assurance of POCT.

Conclusion: Point of care testing (POCT) is an ever growing innovation in medical practice especially in critical care. POCT ranges from the simple, good old dipstick urinalysis to the complex, but user friendly emergency bench top blood gases and electrolyte analyzer. Its numerous benefits to both the clinician and the patients far outweigh its few disadvantages, as such even hospitals and clinics in developing countries like Nigeria are fast appreciating its benefits.

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