03RC1

Point of care monitoring of blood: invasive and non-invasive monitoring

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Introduction

The term 'Point of Care' with respect to point-of-care testing (POCT) or point-of-care monitoring (POCM) covers a broad range of medical devices. POCT is defined as clinical laboratory testing conducted close to the site of patient care, typically used by clinical personnel whose primary training is not in the laboratory sciences or by patients self-testing [1]. Because of the rapidly increasing ability to acquire information with reduced effort and the financial benefits it brings for the manufacturer, the proportion of POCT and POCM tools used in clinical practice is continually increasing [2]. Furthermore, we can observe a shift from POCT to POCM. While POCT tends to consider a number of semi-quantitative tests, POCM also includes the close monitoring of patients with a built-in alarm generation system.

The economically driven needs to shorten length of stay (LOS), reduce hospital costs, and manage care resources without compromising patient outcome have all conspired to prompt health care systems to implement POC testing [3]. However, implementation of POCT without proof of efficacy raises important concerns [4-7]. The issues involved include cost, quality control, personnel limitations, the strengths and weaknesses of the existing laboratory, regulatory matters, and the specific patient population served by the facility.

With POCT diagnostic information can be made available either directly at the patient or in his/her immediate vicinity (Table 1) [8]. Such a facility can have direct therapeutic or live-preserving implications (Table 2). The clinical value of POCT and POCM can be analyzed from a number of perspectives and is based on the analysis of the benefits and disadvantages (Table 3), as regards necessity, urgency, organisation and the underlying goals. This analysis is then only effective if standardised definitions of the procedure and its implementation are lodged, which are then oriented towards the spatial requirements and adapted towards specific modalities. Because of the marked increase in complexity, the operator should define therapeutic rules with predefined goals, incorporate quality management systems, ensure a reliable data and therapy documentation, and monitor the effect (related to the predefined therapeutic goal, see Figure 1). A connection within a network represents the most important way of achieving this (Table 4) [9].

Table 1

Sites with increasing use of POCT and POCM

Hospital			
	Intervention suites	Endoscopy	Angiography
	Critical care suites	OR, ICU, IMCU, RR, ED	
	Functional testing	i.e. Pulmonary diagnostic	
	Bedsite		
	Satellite suites		

Outpatient			
	Care centers		
	Physician offices		
	Home care		
	Wellness		

Rescue			
	Patient transportation		
	Disaster and emergency rescue		
	Military field operations		
	Geographic considerations		
	Space shuttle and station		

The course of action with decentralized POC testing in a patient care management program. The loop described by the arrows can be repeated several times to achieve the target. A clear definition of the target and the effect control documentation are essential. The clinical state of the patient should be incorporated in the decisions. QC – quality control, SOP – standard operating procedure

OR – Operation Room, ICU – Intensive Care Unit, IMCU – Intermediate Care Unit, RR – Recovery Room, ED – Emergency Department

Table 2

Methods and systems at POCT

Vital parameter		
Module 1	Blood gases partial pressures	PO_2, PCO_2
	Acid base balance	pH, HCO_3-, base excess
Module 2	Co-oximetry	SO_2, MetHb, COHb haemoglobin, haematocrit
Module 3	Electrolytes	potassium, sodium, (calcium, magnesium)
Module 4	Metabolites	glucose, lactate
Assessment of organ function		
	Cardiac markers (ischaemia, insufficiency)	
	Kidney function panel (urine analysis, creatinine, urea nitrogen)	
	Liver function panel	
	Coagulation (PT, aPTT, ACT, platelet function, D-dimer, blood count)	
Information about special (disease) states		
	Pregnancy	
	Microbiology (HIV, malaria, group A Strep, legionellae, pneumococci, influenza A, B, H1N1)	
	Immunology	
	Toxicology	

Table 3

Pros and Cons of POCT

PROS		CONS	
Decreased	therapeutic TAT	Lack	of quality management
	pre-analytic error		of proficiency testing
	blood loss at sample volume		of analytic performance
	redundant blood tests		of training and education
	patient cost per therapy		of data recording
	LOS		of adequate documentation
Increased	patient`s satisfaction		in regulatory control
	decision making		of IT connection
	clinical convenience	Increased	pre-analytic failure
	clinician-patient interface		postanalytic failure
Rapid	data availability		costs per sample/test
	response to critical results		
Reproducability		No critical values notification system	
Integration in algorithm and pathway		Duplication of instruments and methods	
Convenience when laboratory is inaccessible			
Customized instrumentation			
Customized care			

TAT – turnaround time, LOS – length of stay

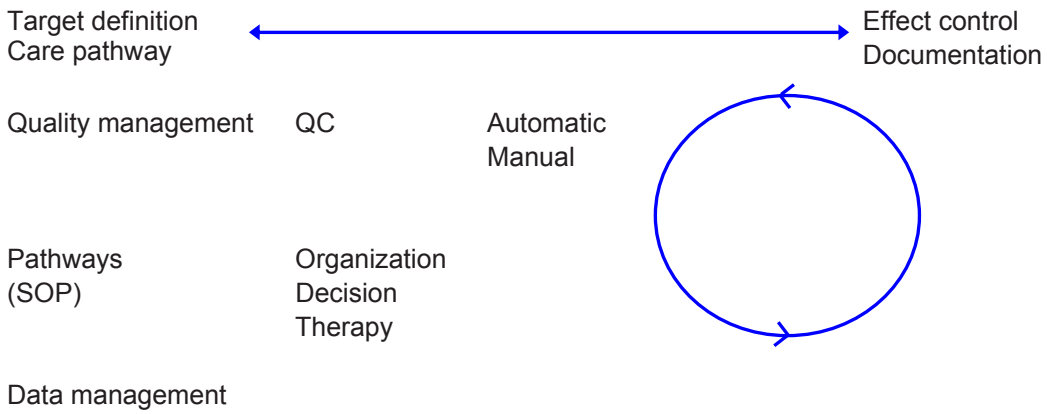
Table 4

POCT system related issues		
Reliable systems		
Quality management		
IT connection	WLAN	bidirectional
Support	Central laboratory	
	Standardized network	

Institutional related issues	
Motivation	Operator
	Staff
	Patients
Education & Training	
Definition of responsibilities	
Documentation	
Communication	

The success of POCT implementation near the patient depends on several issues with respect to the system and to the institution.

Figure 1



The course of action with decentralized POC testing in a patient care management program. The loop described by the arrows can be repeated several times to achieve the target. A clear definition of the target and the effect control documentation are essential. The clinical state of the patient should be incorporated in the decisions. QC – quality control, SOP – standard operating procedure

Blood gas analysis – from invasive to non-invasive measurement

Blood gas analyzers (BGA) are the most advanced POCT devices available. In the comprehensive configuration BGA systems consist of four modules that provide information to help the physician make life-saving decisions. In contrast to qualitative or semi-quantitative POCT, BGA include a number of additional functions: the measurement principles of the modules themselves serve as references, and reduce the costs and the time involved in staying in the ICU or other sites, thereby improving patient outcome.

Each year in Europe, nearly 240 million arterial blood gas tests are performed, and of these, approximately half are performed on patients in critically ill or unstable conditions. In 2008, sales of blood gas monitoring products in the European countries of France, Germany, Italy, Spain, and the United Kingdom (UK) totaled ~ $660 million. Market segments covered in this area include arterial blood gas sampling products, capnography or end-tidal carbon dioxide monitors, laboratory-based blood gas analyzers, point of care blood gas analyzers, and pulse oximeters [10].

Quality controls and data processing

Documentation of data in patient records, a continuously available connection with the central laboratory, and the display of the results on monitors at the point of care require a safeguarded data management and software system corresponding to the required standards. For these reasons the industry has adopted data management systems and automatically or manually activated quality controls (QC) for all their BGA devices and the systems fulfill most of the current national and international regulatory requirements (Table 5).

The uncomplicated and inexpensive use of non-invasive and continuous monitoring directly competes with procedures involving the sampling of arterial, venous or capillary blood at specific time-points. If the measurements correlate with blood gas analysis measurements, as is the case for oxygen saturation and end-tidal CO_2 partial pressure, the user is faced with a 'win-win' situation. Even in critical situations the user need not control with the blood gas analyzer and can treat patients using the monitoring measurements alone as a reference. This is certainly understandable wherever a threatening hypoxaemia or the ventilation setting have to be corrected immediately.

Table 5

POCT definition and international, European, and national regulatories

POCT definition and international, European, and national regulatories
Point of care testing is defined as: “Diagnostic testing that is performed near to or at the site of the patient care with the result leading to possible change in the care of the patient” in EN ISO 22870 “Point-of-care testing (POCT) - Requirements for quality and competence”.
This Standard is intended to use in conjunction with EN ISO 15189:2007 “Medical laboratories - Particular requirements for quality and competence”.
The requirements of EN ISO 22870:2006 should be applied when POCT is carried out in hospital, clinic and by a healthcare organization providing ambulatory care.
Patient self-testing in a home or community setting is excluded, but elements of ISO 22870:2006 can be applicable.
National regulatories are based on EN ISO 22870:2006 and EN ISO 15189:2007 and were amended by local medical associations, i. e.:
‘Guidelines for safe and effective management and use of point-of-care testing’ at the Royal College of Physicians of Ireland, 2008
‘Guidelines for quality assurance for laboratorial-medical investigations’ of the German Medical Association, 2008

How is this seen against the currently available procedures for non-invasive measurement of haemoglobin concentration before transfusion, the assessment of volume depletion with following volume substitution therapy or the use of near infrared spectroscopy for assessing cerebral oxygenation? The therapeutic consequences from this form of monitoring can be invasive and burdensome for the patient.

These following points should be considered as critical: a. the guidelines for POCT are now much stricter, and in being so are designed to assure therapeutic quality (Table 5); b. these guidelines apply to POCT devices, but do they also apply to POCM systems? A gray area currently exists because different standards committees and their parent medical associations are involved in setting the norms and guidelines. The complexity of such a development can be presented using the example of glucose measurement.

POCT and POCM of glucose

Glucose monitoring for patient self-control [12] or close supervision of glycaemia in an ICU setting [13, 14] have both been demonstrated to improve patient outcome. However, just as with glucose monitoring, there is an ongoing discussion about the accuracy and precision of POCT and POCM. Moreover, blood sampling procedures and the principles of measurement are contradictory [15, 16]. Blood and plasma samples measured in a laboratory setting or with POC tests have a reference function when collected from arterial or venous blood, but invasive samples taken from capillary blood or tissue cannot be used for close supervision [16]. Non-invasive glycaemia monitoring devices are currently being tested but have not yet been approved for sale [17].

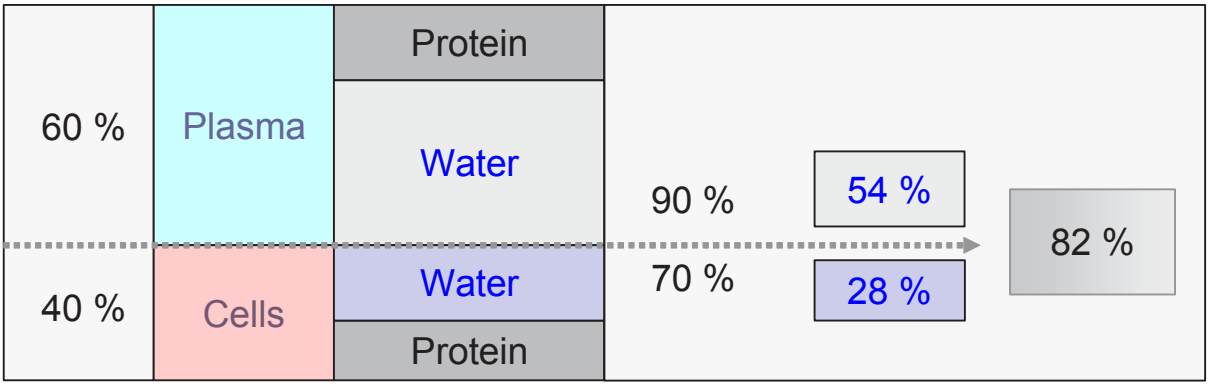
Whole blood glucose: what are we actually measuring?

Although the measurement of glucose is one of the oldest established tests in clinical chemistry, it is complex and sometimes only approximate due to the different fractions of the blood sample used. Glucose measurement can be performed on whole blood, plasma or serum, and these may be native or deproteinized, or even haemolyzed in the case of whole capillary blood.

Do all samples provide the same result?

The simple answer is no, and moreover, the difference may depend on nutritional state, perfusion, haematocrit or albumin blood concentrations. Glucose is dissolved only in the aqueous part of the drawn sample and not in its entire volume (which contains other dissolved solids such as proteins, see Figure 2). This is the major reason why glucose concentrations differ in plasma and whole blood samples [15].

Figure 2



Glucose is dissolved in the aqueous part of the blood sample and not in its entire volume. Due to the different protein and water contents between cells and plasma the measured values in whole blood sample or in plasma differ. Even with the glucose concentration being the same in plasma water and red blood cell water, the concentration of glucose per unit volume of red blood cells is lower than that per unit volume of plasma [with modification from 15].

Measurements of glucose levels should be considered according to the prevalent clinical state:

- In patients with type 1 diabetes, continuous glucose monitoring is helpful when coupled with insulin pump technology in a 'closed-loop' system [18]. All these devices are less accurate than home glucometers, but they do provide information on glucose trends and can warn of noctural glycaemic excursions.
- Closely-knit glucose management in critically ill patients requires a very accurate and reproducible test if personnel are to have confidence in their use. Samples of arterial blood measured by a blood gas analyzer exhibit a bias close to that of the laboratory reference. In contrast, handheld glucometers (particularly when using capillary blood samples) are subject to a higher variability due to several reasons, such as low haematocrit and low perfusion [19].

POCT and POCM sample acquisition and preparation

A key factor in determining the accuracy and precision of the measured values is the tissue from which the samples or readings are taken, and this applies both for invasive and noninvasive procedures (Table 6). Wherever samples are taken from blood, metabolic processes continue and the coagulation cascade is activated. Under certain circumstances the use of reagents, either in liquid or solid form (or anchored on surfaces), is necessary. Sample acquisition as well as storage and transport can lead to substantial changes in measurements (Table 7). Such pre-analytical artifacts can arise during the interval between sample preparation and measurement in the sensor. In contrast, post-analytic error may increase when measurements of individual variables are not considered in a clinical context and often also in association with other measurements [8].

Table 6

Characteristics of probe sampling and preparation with respect to invasive and noninvasive POCM sensors, and with POCT probes.

POCT			
Patient probe			
Easy probe sampling			
Measurement direct	Blood, urine, saliva,		
	cerebrospinal fluid		
Use of reagents	Heparin		
With untrained staff			

POCM			
Invasive		**Noninvasive**	
Invasive sensor	Intravascular, tissue	Sensor positioning	
Complex system		Probe sampling	Gas, fluids
Regional conditions	Perfusion		transcutaneous
Delay time		Interaction with skin	Contact,
Calibration			pressure, heating
Drift		Regional conditions	Perfusion
			Ventilation/Perfusion
		Delay time	
		Calibration	
		Drift	

Systems		**Systems**	
Interstitial	Glucose	Transcutaneous	$PtcCO_2$
	Microdialysis		$PtcO_2$
			pH *
Intravascular	Blood gas analysis	Breath gas	$PetCO_2$
		Pulsatile signal	SO_2
			MetHb
			COHb
			ctHb
			Perfusion
		Transcutaneous	Glucose *
			Lactate *

* under laboratory test

P – partial pressure, tc – transcutaneous, et – endtidal, Hb – haemoglobin, S -saturation

Table 7

Pre-analytic errors for systems using blood samples

Use of arterial, venous or capillary blood
Temperature, protein and haematocrit
Measurements on whole blood, plasma, serum or after haemolysis
Anticoagulation of the syringe with heparin – dry vs. liquid
No continuously mixing of the sample
Incorporated bubbles
Advanced time to measurement

Any sample measured in flowing blood should represent an ideal basis for producing reliable measurements. In order to reduce invasiveness, capillary samples are often resorted to. Alternatively, catheters are also available for intravascular or interstitial (subcutaneous) measurements if continuous monitoring procedures are preferred. The final step towards non-invasiveness requires the development of sensors which are able to obtain signals from the tissue through the skin. Pulse oximetry records a clear signal from the pulsatile component of the pulse, either at the capillaries of the fingers in transmission mode, at the forehead in reflection mode, or at the earlobe. The signal also contains a non-pulsatile component which, in the absence of any pulsation, reveals information about the tissues. It makes sense to evaluate this component to obtain information about tissue oxygen saturation using near infrared spectroscopy (NIRS).

Non-invasive procedures

The measurement principle for the co-oximeter module in the blood gas analyser is based on optical technology. Individual components of haemoglobin are able to absorb light at specific wavelengths. As such, any form of haemoglobin can be measured and the sum of all the components represents the total amount of haemoglobin. Given the physiological definition of functional oxygen saturation as the ratio of the oxygenated proportion of haemoglobin to the amount of oxygenated and reduced haemoglobin, and marked by the pulsatile component in the arterial vascular bed of the capillaries, measurement of arterial oxygen saturation is carried out by pulse oximetry (Table 8). The latest developments show that this principle can also be applied to measure the total amount of haemoglobin as well as the so-called dyshaemoglobins, that is, carboxyhaemoglobin and methaemoglobin [20]. The pulsatile signal from the pulse oximeter is then further analysed to derive information about the filling of the vessels, and to control a volume substitution therapy [21]. The non-pulsatile component of the signal can be evaluated if the path of the light is guided through and absorbed by the desired tissue (such as the brain). A prerequisite for this is adequate calibration and a constant tissue thickness [22].

Table 8

Optical monitoring based on laser or LED or laser light (in pulse oximeter or cerebral oximetry using near infrared spectroscopy)

Optical monitoring
Based on two or more wavelengths
Ratio oxygenated / deoxygenated haemoglobin
Reflects pulsatile (arterial) blood (AC signal)
Reflects non pulsatile tissue (DC signal)
One time calibration
Easy sensor positioning

Content of information
Oxygen transport from air to peripheral tissue
Pulsatile peripheral perfusion
Heart rate
Haemoglobin oxygenation
Reflects MetHb, COHb, and total Hb (multi wavelengths)

Capnometry can measure indirectly the CO_2 partial pressure in arterial blood by measuring it in the alveolar part of the expired respiratory gas, or transcutaneously via the skin (Tables 9 and 10) [23]. The correlation of these procedures with the CO_2 partial pressure measured in the blood gas analysis varies depending on the ventilation-perfusion ratio in the lungs (end-tidal) and the perfusion within the tissue in the sensor area (transcutaneous). Under critical pathophysiological conditions the correlation is markedly reduced by this indirect measurement [24].

Table 9

In- and expiratory gas measurements with special respect to capnometry and capnography

In- and expiratory gas measurement
Reflects central compartment
Depends on ventilation and perfusion ratio
Identifying alveolar ventilation
Identifying endotracheal gas flow
Differentiation of inspiration and expiration
Alveolar gas extraction
Zero point calibration with ambient air

Content of information – capnometry
CO_2 production
Transport of CO_2 from cells to air
Status of ventilation
Reflecting arterial CO_2 partial pressure
Delta Pa-et CO_2 reflects low cardiac output and low volume status

Table 10

Pros and Cons of POCM

Pros	System
Continuously measured values	All
Trend display	All
Alarm settings	All

Cons	
Depends on regional physiology at the sensor place	PO, TC
Depends on ventilation and perfusion	ET
Periodically needed calibration	ET, TC
Sensor signal drift	ET, TC
Low sensor dynamic	TC
Temperature dependency	TC

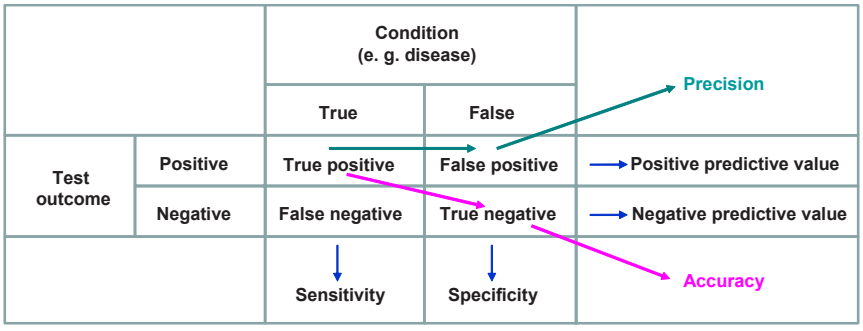
What are the consequences when migrating from POCT to POCM?

When using a non-invasive indirect measurement procedure, increased discrepancies between the monitoring measurements and the true values can occur. This may be due to physiological processes (for example, perfusion/ventilation), or a faulty association between the sensor measurements at the sensor site and the information which should be recorded at the predestined tissue site. The underlying correlation and the measurement time-course, that is the trend, however, tends to form the basis for a therapeutic decision if no POCT-based control is available. One can assume that errors in POCM can occur much more frequently and with an greater discrepancy than they do in POCT, although improvements in safety by implementing a quality management system and other measures are now mandatory.

Assessment of the results for POCT and POCM

The information behind the results of POCT measurements are usually presented as sensitivity and specificity (Figure 3) due to discontinuously measured data and with respect to the clinical diagnosis. Continuously recorded data of non-invasive monitoring are usually compared with reference methods – in principle the point to point measures in corresponding blood – and expressed as accuracy and precision (Table 11). One further principle for assessment of accuracy is the Bland & Altman method comparing the bias with the mean of the two techniques. The term precision is sometimes used with different definitions. Mostly, it is a determined by assessing the standard deviation of the data with respect to scattering.

Figure 3



$$\text{Sensitivity} = \frac{n\,(++)}{n\,(++) + n\,(--)} \qquad \text{Accuracy} = \frac{n\,(++) + n\,(+-)}{n\,(\text{all})}$$

$$\text{Specificity} = \frac{n\,(--)}{n\,(+-) + n\,(-+)} \qquad \text{Precision} = \frac{n\,(++)}{n\,(++) + n\,(-+)}$$

Composition of measures for assessment the results of POCT and POCM. First sign in parenthesis marked 'true = +' and 'false = -', second sign means 'positive' or 'negative'.

Table 11

Definitions of statistical terminology for assessing the results of POCT and POCM

Sensitivity	High true positive, low false negative values. Depends mostly on true positive values. Getting the right information.
Specificity	Show, how accurate is the test. Depends mostly on false positive values.
Accuracy	Is the closeness of agreement between a test result and an accepted reference value. It describes a combination of random and systematic error.
Bias	Is the difference between the test result and a reference value. It describes the systematic error.
Precision	Describes the closeness of agreement between independent test results. It is in main the random error and it is usually expressed in terms of imprecision and computed as a standard deviation of the test results. Less precision is reflected by a larger standard deviation.

Are POCT and POCM economical?

This question cannot be answered definitively. There are several items to be considered: the cost of the test per patient/probe compared with standard laboratory procedures and the impact on patient healthcare and total healthcare costs [2]. Increased costs per patient, probe or monitor may be offset by reducing the overall costs of patient care through improved therapeutic decision making and interventions. Furthermore, effective and rapid post-intervention action must also be considered to avoid adverse effects. POCT involves additional risks which should be reduced by a strategy. Medical errors in POCT, which lead to preventable adverse events most often arise in three processes - patient identification, specimen integrity, and result reporting. Several authors recommend ongoing monitoring of these critical steps [4, 5].

Policies and regulations

POCT and POCM involve additional and new risks, especially regarding issues of quality, security, and confidentiality. The Institute of Medicine has focused on medical errors and methods to prevent them [25]. Quality management, evidence-based medicine analysis, and outcome research are essential tools for ensuring POC safety and efficacy. International, European, and national standardization committees have introduced guidelines for the use of POCT (Table 5).

CE certification may lead many to assume that an external validation of the test has already been carried out. This, however, is not the case. CE certification with the cited criteria contained therein is initiated by the manufacturer itself and only confirms that the product corresponds to the basic requirements of European guidelines.

One step to overcome inadequate quality control is the integration of POC devices into an IT network with bidirectional connections to a patient data management system and a central laboratory. Daily automatic or manually performed quality controls under the direction of the central laboratory may be able to reduce systematic deviations of POC variables. The distance between a decentralized use of POC systems at the patient site and a central structure for control, co-ordination, and documentation can be bridged by wireless connectivity.

Outcome and evidence-based practice

The principles of POCT and POCM (as well as the equipment and procedures developed for them) are now widely available and continue to grow. The use of POCT and POCM has already had a significant impact on patient management and clinical outcome with respect to certain parameters. [1, 3, 26]. One can see the effects that POCT and POCM can have on patient management. Using evidence-based practice it seems clear that long waiting times can be reduced, and that patient satisfaction will increase. One can also assume that the rapid turnaround time provided by the POCT is the main factor responsible for an improvement in outcome [27]. The National Academy of Clinical Biochemistry has developed evidence-based Laboratory Medicine Practice Guidelines for POCT [1]. These systematically review the background to clinical outcomes and offer recommendations for improving the clinical utility of POCT (Table 12).

Table 12

Extract from the “Executive summary. NACB-LMPG: Evidence-based practice for point-of-care testing” [1]

Management	
Question: Does the application of quality assurance to POCT reduce medical errors and does management improve the quality of POCT?	
B, III	A formal process of quality assurance of POCT be developed
	in support of risk management and a reduction in medical errors
A, II-III	Use of an interdisciplinary committee to manage POCT
A, II-III	Training programs to improve quality of POCT
B. II-III	Data management as a mechanism to improve quality of POCT
A, II	Continuous quality improvement with quality
	indicators

Critical Care	
1. Question: More rapid TTAT of a lab test result leads to outcome improvement?	
2. Question: Does POCT of a lab test improve outcome, when compared to core laboratory testing?	
B, II	POCT of ABG leads to improved clinical outcome in ICU and ED
A, I	POCT of glucose leads to improved clinical outcome
B, II	POCT of lactate leads to improved clinical outcome
I, III	Insufficient evidence that POCT of magnesium leads to improved clinical outcome
C, II	SO2 from COox is not recommended; PO is recommend as preferred method for POCT of oxygen saturation
B, II	POCT of potassium leads to improved clinical outcome
B, III	Fair evidence that POCT of ionized calcium may lead to improved clinical outcome

pH	
C, II - III	Lack of evidence that pH monitoring to adjust antacid therapy improves either morbidity or mortality in these patients

Levels of evidence	
I	Evidences includes consistent results from studies in representative populations
II	Evidence is sufficient to determine effects
III	Evidence is insufficient to assess the effects on health outcomes

according to U.S. Preventive Services Task Force recommendations

Guideline language	
A	NACB strongly recommends adoption
B	NACB recommends adoption
C	NACB recommends against adoption
I	NACB concludes that the evidence is insufficient to make recommendations

structured according to Agency for Healthcare Research and Quality classification

NACB and LMPG see [1], ABG – arterial blood gas, TTAT – therapeutic TAT

Conclusion

POCT and POCM have entered clinical practice and brought with them a need to restructure overall patient management. The motivation of both staff and patients forms the basis for their effectiveness, combined with a decision strategy and a goal-directed therapy [25]. Evidence based analyses and outcomes, with trials already confirming the medical necessity of POCT and PCOM have also highlighted some limitations (Table 12). Quality management and controllable strategies regarding decisions and therapy based on evidence-based guidelines are necessary for success. POCT and POCM are growing in importance for the management of both rapidly spreading infectious diseases [28] and disaster medicine [29, 30].

Key learning points

- Point of care testing (POCT) and monitoring (POCM) overlap in many aspects.
- The management of patients has become more and more adjusted towards the principles of POCT and POCM.
- Although they certainly have benefits, including the rapid availability of results to assist in therapeutic decision making, the increased frequency of errors does represent one disadvantage. Regulations for laboratory medicine, which also cover POCT systems, demand that quality assurance measures be implemented. These have not yet been elaborated for POCM.
- POCM is becoming less and less invasive in its application.
- For POCT and POCM pre-analytical error is often underestimated.

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