

Mini-Review

Point-of-Care Testing and Creatinine Measurement

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Abstract

This paper reviews the current status of point-of-care testing (PoCT) devices that are available for measuring whole blood or serum/plasma creatinine globally and within Australasia. Information on non-analytical specifications and analytical performance is provided using data sourced from recently published literature, external quality assurance programs and evaluative work by the author's unit. The limitations of current devices are summarised.

Introduction

Chronic kidney disease (CKD) has become a significant global health problem. For example, prevalence rates of CKD in Australia and the United States are approximately 16% and 13% respectively, while the number of patients requiring dialysis in Australia has more than doubled in the past decade.¹⁻³ Creatinine is a well established biochemical marker for renal function and it is now widely used to estimate the glomerular filtration rate (eGFR).⁴⁻⁶ The measurement of creatinine has also been the subject of considerable recent international attention to align all current methods (including point-of-care) to isotope dilution mass spectrometry (IDMS) equivalent standards.⁷ There are now a number of options for measuring creatinine by PoCT devices, which can be applied in different clinical settings including the hospital emergency department, risk assessment prior to the administration of contrast media, and community-based screening.^{8,9}

PoCT Devices for Creatinine

The range of PoCT devices for measuring creatinine that are marketed globally is summarised in Tables 1 and 2. In addition, a creatinine module for the GEM Premier 4000 (Abacus ALS) device is known to be under development.^{10,11}

PoCT creatinine devices can be conveniently divided into two types: those that are primarily blood gas analysers that offer creatinine as one of the metabolites that they measure; and those that are 'non blood gas' analysers. The i-STAT and ABL devices are examples of the former category that are available in Australasia, while the Reflotron, Dri-Chem, StatSensor and Piccolo are Australasian examples of the latter category.

Table 3 summarises the non-analytical specifications of those devices currently in Australasia. Method principles are based on a cascade of enzymatic reactions, followed by either photometric or electrochemical detection. In terms of calibration, the ABL is IDMS-aligned while others are traceable to IDMS through Standard Reference Material (SRM) products. Measurement consumables range from strips to cassettes and cartridges to a rotor system. Preferred sample types vary from whole blood to serum/plasma or both. Sample volumes range from 1 to 30 μ L generally, but the i-STAT requires 65 μ L of venous whole blood and the ABL systems even more, depending on sample type. All devices have rapid turnaround times for results varying from 30 seconds to 5 minutes, except the Piccolo which takes 8.5 minutes for the first result and 40 seconds thereafter for each subsequent result. Measuring ranges are generally very wide. Some devices such as the ABL, Reflotron and StatSensor can provide an automatic calculation of eGFR, using aligned and non-aligned Modification of Diet in Renal Disease (MDRD) formulae. The i-STAT and StatSensor are hand-held devices while the remainder are benchtop, weighing 5 kg or more. The ABL and Dri-Chem systems are heavier again (more than 20 kg) and more suited to the hospital or satellite laboratory environment than the community-based screening setting for example. The i-STAT and NovaStat devices both work off battery as well as mains power. All have good connectivity to laboratory or clinical information systems. Apart from the StatSensor which is a discrete whole blood creatinine measuring device, all other instruments can test for a range of other analytes.

Table 1. PoCT creatinine analysers available globally.

Type	Device	Manufacturer	In Australia and New Zealand
Blood Gas	i-STAT	Abbott POC	Yes
	ABL 700/800	Radiometer	Yes
	IRMA TRUpoint	ITC	No
	Stat Profile CCX	Nova Biomedical	No
Non Blood Gas	Stat Sensor	Nova Biomedical	Yes
	Piccolo xpress	Abaxis	Yes
	Reflotron Plus	Roche	Yes
	Dri-Chem 4000	FujiFilm, Japan	Yes*
	Pentra C200	Horiba, France	No

*Not confirmed for New Zealand.

The GEM Premier 4000 (Abacus ALS) is likely to be available in Australasia in late 2011.

Table 2. PoCT creatinine devices not available in Australia and New Zealand.

Device	IRMA TRU point	Stat Profile CCX	Pentra C200
Manufacturer	ITC	Nova Biomedical	Horiba
Method Principle	Enzymatic with amperometric biosensor	Enzymatic with amperometric biosensor	Jaffe
Calibration Traceable To	NIST	NIST 914a	NIST SRM 967
Measurement Consumable	Cartridge	Sensor and cap	Cuvette
Sample Type	Whole blood (A,V,C)	Whole blood, serum or plasma	Serum or plasma
Sample Volume	200 µL	120 µL	9 µL
Time for Result	2.6 min	2.5 min	8.5 min (first result)

NIST = National Institute of Standards and Technology, SRM = Standard Reference Material; A = arterial, V = venous, C = capillary.

Analytical Performance Standards

To the author's knowledge, there are no analytical performance standards that relate specifically to PoCT creatinine methods and devices. However, as PoCT methods should strive to be of equivalent analytical standard to those of the laboratory, it is appropriate to apply currently accepted specifications for laboratory measurement of creatinine to PoCT.¹² Analytical goals derived from biological variation allow for a minimum total error goal of 11.4% (comprising a goal for imprecision of 3.2% and a goal for bias of 5.1%), desirable total error of 7.6% (2.2% for imprecision and 3.4% for bias) and optimal total error of 3.8% (1.1% for imprecision and 1.7% for bias).^{7,13} Westgard has recently updated the desirable analytical goals for serum creatinine to 8.2% for total error, 3.8% for imprecision and 2.7% for bias.¹⁴

The Laboratory Working Group of the National Kidney Disease Education Program (NKDEP) stated that the combination of systematic bias and random error should not give rise to an error in eGFR calculation of >10%.⁷ In real terms this goal is a trade-off between imprecision and bias, with the lower

the method bias, the wider the allowable imprecision. The NKDEP further stated that, after recalibration to IDMS, imprecision should be <8% and bias with respect to IDMS should be <5% at a serum creatinine concentration of 88.4 µmol/L (1.00 mg/dL).⁷ (The <8% imprecision goal includes inter-laboratory variation.)

For many years, the allowable limit of performance for blood creatinine in the RCPA Quality Assurance Program's (QAP) General Chemistry Program in Australasia has been ±10 up to 100 µmol/L and 10% for concentrations ≥100 µmol/L.¹⁵ In August 2010, this limit was tightened to ±8 up to 100 µmol/L and 8% for concentrations ≥100 µmol/L.

State-of-the-Art Performance for PoCT Creatinine Devices

Large-scale Multi-device Evaluations

In 2010, the National Health Service (NHS) in the United Kingdom published an excellent evaluation report on seven PoCT creatinine devices (all the above mentioned devices except the two Nova analysers).¹⁶ In terms of accuracy, most

Table 3. Non-analytical specifications of PoCT creatinine devices available in Australia and New Zealand (as noted in Table 1).

Device	i-STAT	ABL 800 Flex	Reflotron	Dri-Chem 4000	StatSensor	Piccolo
Manufacturer	Abbott POC	Radiometer	Roche	Fuji Film	Nova Biomedical	Abaxis
Method Principle	Enzymatic with amp biosensor SRM 967	Enzymatic with amp biosensor IDMS via HPLC	Enzymatic with dye reflectance Not available	Enzymatic with dye absorbance SRM 914	Enzymatic with amp biosensor Not available	Enzymatic with indicator absorbance SRM 967
Calibration						
Traceable To						
Consumable	Cartridge	Sensor Cassette	Dry strip	Dry slide	Dry strip	Rotor
Sample Type	Whole blood (A, V, C)	Whole blood (A, V, C) or serum, plasma	Whole blood (V, C) or serum, plasma	Serum or plasma	Whole blood (A, V, C)	Whole blood, serum or plasma
Sample Volume	65 µL	125 (c)/250 (syr) µL	30 µL	10 µL	1 µL	9 µL
Time for Result	2 min	1 min	2 min	5 min	0.5 min	8.5 min, then 0.6 min
Measuring Range	18–1768 µM	10–2000 µM	45–884 µM	18–2122 µM	27–1056 µM	18–1768 µM
eGFR Calculation	No	Yes	Yes	No	Yes	No
Size, Weight	Hand held, 0.7 kg	Benchtop, 33 kg	Benchtop, 5 kg	Benchtop, 20 kg	Hand held, 0.4 kg	Benchtop, 5 kg
Power	AC or battery	AC	AC	AC	AC or battery	AC
Connectivity	Yes	Yes	Yes	Yes	Yes	Yes
Other Analytes	Elu, Bgas, metab, Hb, coag, cardiac	Elu, Bgas, metab	Elu, Hb, metab, lipids, enzymes	Elu, Hb, metab, lipids, enzymes	Nil	Elu, metab, lipids, enzymes

SRM = Standard Reference Material; IDMS = Isotope Dilution Mass Spectrometry; amp, amperometric; A = arterial, V = venous, C = capillary; syr = syringe; AC = mains power; Elu = electrolytes, Bgas = blood gases, coag = coagulation, metab = metabolites, Hb = haemoglobin.

devices showed a positive bias of 10–15% relative to the IDMS method. For those devices which used whole blood as the preferred sample type, the Piccolo and i-STAT displayed best agreement (that is, the smallest bias for patient and/or spiked patient samples) with the IDMS method. For those using serum or plasma, the Piccolo and Dri-Chem devices showed closest agreement with patient and/or spiked patient samples.

Using the 5-day CLSI EP15-A protocol¹⁷ to assess imprecision, none of the devices tested met the minimum goal derived from biological variation at the lowest creatinine concentration tested (70 $\mu\text{mol/L}$). The best imprecision at this concentration was observed with the Pentra (3.6%), followed by the i-STAT (4.1%). The i-STAT met the minimum and desirable biological variation goals at 150 and 550 $\mu\text{mol/L}$, the Piccolo met the desirable goal at 150 $\mu\text{mol/L}$ and the optimal goal at 550 $\mu\text{mol/L}$, while the Dri-Chem met the minimum goal at 550 $\mu\text{mol/L}$ only.

Imprecision was also assessed using patient duplicates ($n=25$). For whole blood, the best imprecision (paired SD <15 $\mu\text{mol/L}$) was achieved by the ABL 800 and Piccolo devices. For serum/plasma, the best imprecision was observed with the Pentra C200.

The NHS study also looked at the effect of the accuracy of each PoCT device (relative to the IDMS method) on eGFR results for a 60-year-old white male at six different creatinine concentrations. At IDMS creatinine concentrations of 30, 60 and 300 $\mu\text{mol/L}$, differing accuracy bases between the PoCT devices did not change CKD staging. At IDMS creatinine concentrations of 90, 120 and 150 $\mu\text{mol/L}$ there were some changes in CKD staging for some devices. Specifically looking at the devices available in Australia, the i-STAT, ABL (both sample types) and Piccolo (whole blood) recorded the same CKD staging as IDMS results at all concentrations, whereas the Dri-Chem and Reflotron Plus underestimated the stage of CKD at creatinine concentrations between 90 and 150 $\mu\text{mol/L}$.

The i-STAT and the ABL were interference-free with the compounds tested (bilirubin, glucose, haemoglobin and lipids). The Reflotron showed very slight interference with bilirubin, the Piccolo showed interference with bilirubin and lipids, while very slight interference was observed with glucose on the Dri-Chem. The effects of other interferents are covered elsewhere in the literature.^{4,7,9}

Performance Data from RCPA Quality Assurance Programs

At the time of writing, the Nova StatSensor and Piccolo devices are not currently enrolled in any quality assurance

program offered by the RCPA Chemical Pathology QAP. The i-STAT and ABL 700/800 devices are well-represented in the Blood Gases and Co-oximetry Program (with approximately 50 and 30 participants respectively), while there is a small number (approximately 5) of Reflotron and Dri-Chem devices in the Near Patient Testing program. Over the past year, the median imprecision achieved by the i-STAT and ABL 700/800 devices has averaged 3.9% and 3.3% respectively. The median imprecision recorded by laboratories in the General Chemistry Program over the same time period was 3.3%. As mentioned earlier, the minimum goal for imprecision from biological variation is 3.2%. Thus the i-STAT and ABL devices can achieve imprecision close to the current median laboratory performance and the analytical goal from biological variation. There was insufficient data available to comment on other devices.

Single-device Evaluations

There are some excellent papers in the recent literature which have evaluated PoCT devices for creatinine either individually or in small comparative studies.^{9,18-20} In the author's Community Point-of-Care Services (CPS) unit at Flinders University, we have evaluated the i-STAT device in field and laboratory studies and the Nova StatSensor device in laboratory studies.

The Abbott i-STAT is used in 35 remote health centres in the Northern Territory POCT Program, which is a partnership between our Flinders CPS unit and the Northern Territory Department of Health and Families. The i-STAT has also been used in the Kidney Evaluation for You (KEY) Study, a partnership between Kidney Health Australia and our CPS unit.^{8,21} The KEY study was a targeted community-based screening program for CKD risk that involved 402 patients from three community locations across urban, rural and remote Australia. As part of the study, the i-STAT was used to measure whole blood creatinine, from which the eGFR and CKD staging were calculated 'on the spot' and fed back to patients. Prior to field use, the i-STAT underwent a full internal evaluation and IDMS alignment (against the Roche Creatinine Plus enzymatic laboratory method on the Hitachi Modular P unit). Post-alignment, the bias on the i-STAT was eliminated (average 0.2% across all concentrations). The imprecision (from duplicate patient samples) observed in the evaluation was 5.5% across all concentrations. In the KEY field study, imprecision on the i-STAT (assessed by between-day bi-level quality control testing, $n=16$) averaged 4.5%.²¹

The Nova StatSensor was evaluated with a view to using this device in large-scale screening situations, due to its ability to use a finger-prick sample and provide a result with calculated eGFR in just 30 seconds.²² However, in our hands, the device

exhibited poorer between-day imprecision than the i-STAT (7.8% at all concentrations), poor between-device agreement, and a significant negative bias of 47 $\mu\text{mol/L}$ across all concentrations. IDMS alignment failed to improve the ability of the device to accurately identify patients with an eGFR of $<60 \text{ mL/min/1.73m}^2$, with many falsely low eGFR results that required laboratory confirmation.

Summary and Limitations

Globally there are currently at least nine devices that are available to measure whole blood or serum/plasma creatinine by PoCT. In Australasia, the number of PoCT devices used widely in laboratory or community health settings is limited primarily to the i-STAT and ABL instruments. Many challenges remain for PoCT creatinine device manufacturers. Only one device has undergone full IDMS alignment, with the remainder still exhibiting varying degrees of positive bias. Most devices exhibit poor precision at low creatinine concentrations ($<120 \mu\text{mol/L}$), concentrations which may (depending on age and sex) often correspond closely to an eGFR cut-off of $60 \text{ mL/min/1.73m}^2$ and Stage 3 CKD. Creatinine measurement in whole blood is challenging due to the complexity of its matrix (including variations in haematocrit) and influences arising from different disease states (e.g. hyperglycaemia, uraemia and treatment medications).⁹

With the prevalence of CKD increasing across the world, the need for good screening methods for identifying CKD risk is becoming more important. A PoCT device fit-for-purpose in this setting requires not only capillary sampling, fast turnaround of result and automatic eGFR calculation, but also good analytical performance specifications to correctly categorise CKD risk. Currently no device fulfils these requirements.

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