REVIEW ARTICLE

In search of a home-based HbA1c point-of-care testing device that is fit-for-purpose: a non-systematic review

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ABSTRACT

Aims: Lockdown conditions and the potential for misreporting of self-monitored blood glucose levels posed challenges for monitoring outpatient diabetic children. The primary objective was to investigate clinical, analytical and technical performance of handheld point-of-care testing devices for glycated haemoglobin. A secondary objective was to report on a proof-of-concept comparison of HbA1c results for the A1CNow+ (PTS Diagnostics, Indianapolis, USA) and the DCA Vantage bench-top point-of-care testing analyzer (Siemens Healthcare Diagnostics, Germany) used in paediatric outpatient clinics.

Methods: Four databases were interrogated in a non-systematic review of English language literature, and 14 pairs of finger-prick HbA1c results were compared in-house.

Results: Sixteen evaluation studies were reviewed. Most studies omitted important elements of a comprehensive evaluation. Findings were heterogeneous and conflicting. HbA1c results from the A1CNow+ were approximately 80% lower than those from the DCA Vantage in the in-house comparison.

Conclusions: Evidence on the performance of A1CNow+ did not support its use in our paediatric population. Evidence on the performance of a second device, the A1c EZ 2.0 (BioHermes, Wuxi, China), was limited. No studies on other devices were found. Paediatricians need to be aware of the limitations of home-based point of care HbA1c testing for monitoring and decision making. Standardization of reporting of evaluation studies for point-of-care testing and improvement in statistical analyses is needed.

Key Words: *Point-of-care testing (POCT), HbA1c, glycated haemoglobin, handheld, home-based, A1CNow+, A1c EZ, telemedicine.*

NZ J Med Lab Sci 2023; 77(2) 59-64

INTRODUCTION

Glycated haemoglobin (HbA1c) may be used to diagnose children with type 2 diabetes mellitus (T2DM) and to guide the management of children with T2DM and type 1 diabetes mellitus (T1DM). Maintaining good glycaemic control is the mainstay for preventing and controlling diabetic complications (1). The incidence of both T2DM (2) and T1DM in children is increasing in New Zealand and internationally. The psychosocial burden of diabetes is large, particularly for children (3-5).

HbA1c is measured every three months in children with diabetes and complements frequent home monitoring of blood glucose (finger-prick blood glucose testing or continuous blood glucose monitoring). In most paediatric clinics in the Auckland Region, HbA1c is measured using point-of-care (POC) benchtop analysers, for example DCA Vantage (Siemens Healthcare Diagnostics, Germany), as part of the outpatient clinic visit. Inpatients or children in the community who are unable to attend outpatient clinics have their testing done in a laboratory (4).

Point-of-care testing (POCT) can be conducted on smaller handheld devices that can be used by patients at home (home-based testing). POCT HbA1c devices use various technologies to measure HbA1c but in miniaturized form.

Evidence regarding the efficacy and cost-effectiveness of POCT HbA1c supports its utility particularly in hard-to-reach and under-served populations, marginalized groups, remote people, and when quick decision-making is of the essence (6-11). Misreporting of self-monitored blood glucose levels is surprisingly common, particularly in the adolescent population, (12) and recent lockdown restrictions in response to the global COVID-19 pandemic highlighted difficulties in obtaining reliable blood glucose data.

The International Society for Pediatric and Adolescent Diabetes (ISPAD) highlights the potential that telemedicine has on improving diabetes outcomes (13). Increased availability of POC HbA1c testing is seen as a vital component of comprehensive telemedicine packages. Paediatric endocrinologists approached our POCT department requesting implementation and support of home-based HbA1c testing. The A1cNow+ (PTS Diagnostics, Indianapolis, USA) device was specifically considered given it is well established in the market.

This review is a practical non-systematic review aiming to identify reliable home-based HbA1c POCT devices that would be fit-for-purpose to use in our paediatric population. We also present results of a limited comparison study conducted in our department. A discussion on important aspects of POCT evaluation studies in general, POCT HbA1c testing for improving access and outcomes for diabetic children in lockdown and social distancing environments and as part of telemedicine.

METHODS

A non-systematic review of literature was conducted investigating the availability and analytical, clinical, and technical performance, of home-based HbA1c devices. We also conducted a limited study comparing A1CNow+ results to the DCA Vantage analyser.

Non-systematic review

Four databases were interrogated: PubMed, Embase, CINAHL Plus, and Medline. Overall three searches were conducted; the first a general search using the following search terms: HbA1c, A1c, glycated haemoglobin, glycosylated haemoglobin, haemoglobin A1c, point of care, POCT. Two additional focused searches were conducted; for the A1CNow+ and A1c EZ 2.0 (BioHermes, Wuxi, China) respectively, the latter being the only other device for which literature was found. The following terms were used: A1CNow+ and A1c EZ 2.0.

Inclusion criteria were: English language, studies conducted between 2003 - July 2020. The year 2003 was chosen for the start of the search because it was at around 2003-2004 that the A1CNow+ device was certified by the National Glycohemoglobin Standardization Program (NGSP) (15). Furthermore, a search within a timeframe of approximately 17 years was considered sufficient for POCT technology since it is a rapidly developing field. Populations of all age groups were included.

Conference proceedings and abstracts, and studies that did not include an evaluation or comparison of the HbA1c POCT device to another HbA1c method were excluded.

In-house proof-of-concept study

The paediatric endocrine department purchased a small number of A1CNow+ test kits in order to conduct a proof-of-concept comparison with the DCA Vantage, the benchtop POCT analyzer routinely used in outpatient clinics. Fifteen children aged 2-16 years, with T1DM, were tested using the DCA Vantage as part of routine practice. A second blood drop was tested using the A1CNow+ handheld analyzer. Verbal consent for the second test performed at the time of the finger-prick blood collection was obtained from all parents and children invited to participate. This was a quality assurance exercise to investigate the comparability of two testing techniques therefore ethical approval was not needed according to the New Zealand National Ethics Advisory Committee(16) and verbal consent was considered sufficient.

All testing was performed by nurses or children, sequentially as they arrived in clinic. None of the children tested were known to have a haemoglobinopathy or recent blood transfusions.

MEDCAL statistical software, MedCal software Ltd. version 19, was used to compare HbA1c results from the A1CNow+ and DCA Vantage with Passing-Bablok correlation.

RESULTS

Devices and tests

The A1CNow+ device is a small, 100 x 191 x 121mm, handheld battery powered meter, sold with its consumables. The test is immunoassay-based and is certified by the NGSP, with a reportable range of 20-119 mmol/mol (4-13%). It requires a drop of capillary or venous whole blood (5 µL) and provides a result in five minutes (14,17). If stored at room temperature (18-28°C) the meter and consumables should be used up within four months but if stored refrigerated, they can be used until expiration date. Results can be retrieved within an hour of testing or until a new test cartridge is inserted. Monthly quality controls are recommended even when the meter is not in use (14). The manufacturer claims overall CVs of 3% and 4% at approximately 42 mmol/mol (6%) HbA1c and 63 mmol/mol (9%) HbA1c respectively (14).

The authors acknowledge that the A1CNow+ is marketed for use by health care professionals not patients but due to the clinical need we opted to investigate it in context of patient self-testing, nonetheless. Its use by patients was also investigated by Klonoff et al (2006), (18). and it was found to be user-friendly. The product information for the kit also states that its accuracy in the hands of untrained users is the same as that in trained users (14).

The A1c EZ 2.0 device is an approximately 100 x 50 x 25mm battery operated device that uses boronate affinity chromatography technology and measures HbA1c in the range of 20-130 mmol/mol (4-14%). The manufacturer claims an overall CV of less than 4%. It needs 5µL of capillary or venous whole blood and takes around 6 minutes to provide a result (19). It needs to be stored at room temperature. The manufacturer claims no interference with fetal haemoglobin (HbF), haemoglobin variants (otherwise unspecified) and unstable HbA1c (19).

Review of literature

Out of a total of 379 studies (including repeated studies) retrieved from the four databases, 20 studies (17 studies and three citations) fulfilled the inclusion criteria. Four were subsequently excluded (15, 20-22) due to the following reasons: study was conducted before NGSP certification (15), type of samples used (EDTA plasma) was against manufacturer instructions (20-21), and study was conducted by the manufacturer of the device (22). The remaining 16 studies were included and appraised for analytical, clinical and technical performance characteristics (18,23-37). One study was a systematic review (23), one a literature search (24), and the remaining were evaluation studies. No randomized controlled trials were found. Of note, no studies on A1CNow Self Check were found. Below is a summary of findings for the systematic review (23) and literature review (24) followed by a summary of findings from the remaining studies.

Reviews

In 2016 Hirst et al (23) conducted a systematic review and meta-analysis to compare the accuracy and precision of POC HbA1c devices. Mean bias and variability between the POC and laboratory test were combined in a meta-analysis of 13 devices in 60 studies including 15 that studied the A1cNow+. Because of pooling and estimation of data for precision and accuracy, findings were taken as a rough estimate of performance.

The majority of POC devices had an average negative bias when compared to laboratory-based methods. A1cNow+ in particular had a total mean bias compared to various laboratory methods of -0.05% HbA1c (95% CI: -0.35 to +0.05). Its mean bias compared to the Vitros 51 FS, the only immunoassay comparator method, was + 0.67% HbA1c (95% CI: -0.52 to +0.81). Its mean bias compared to the Primus CLC 330, a boronate affinity chromatography method was + 0.01% HbA1c (95% CI: -0.01to +1.03).

Bias for capillary samples was higher than that for venous samples. Coefficient of variation (CV% = [(standard deviation/mean) x100]), a measure of precision or repeatability at a pre-specified level, was 2.9% at >64 mmol/mol (8%), based on limited data.

A literature search was conducted by Health Quality Ontario (24) with the goal to review the correlation between POC HbA1c testing and laboratory HbA1c measurement in patients with diabetes in clinical settings. No randomized controlled trials were found. Five observational studies were included, two of which were for the A1CNow+ device.

The overall evidence for the correlation of POC HbA1c testing and laboratory HbA1c measurement in patients with diabetes in clinical settings was deemed moderate i.e. “the true effect is likely to be close to the estimate of the effect, but may be substantially different”. Reasons for this outcome included the lack of identification of the laboratory comparator methods and the lack of statistical estimation of agreement between POCT and laboratory method by Bland-Altman difference plots in some studies. Furthermore, there was a high risk of selection bias in the Arrendale et al study (27), and a high risk in the Flow and Timing category of QUADAS-2 in the Leal et al study (30).

Arrendale et al (27) and Leal et al (30) studies had been retrieved independently in our literature search and were included in the review of individual studies summarized in Appendix A.*

Studies

Appendix A* summarises findings from the 12 evaluation studies for A1CNow+. Appendix B* summarises findings from the A1c EZ 2.0 device evaluation studies. Only two studies were retrieved (36,37).

Populations studied varied in number, age, ethnicities, and proportions of individuals with T1DM and T2DM. Settings varied; community locale, hospitals and clinics. For testing on A1CNow+, some studies used capillary whole blood, the sample that would be used in real life home-based testing, and others used venous blood. Samples for comparator methods also varied, some were venous blood and others capillary samples collected at the POC and forwarded to the laboratory (26). Users varied in number and most were healthcare professionals, not the type of users that would be testing in a home environment. There was also a variation in performance characteristics studied; some studies did not examine precision and some provided correlation data but no Bland-Altman (difference plots) data.

In-house proof-of-concept comparison

Results ranged between 34 mmol/mol and >130 mmol/mol (DCA Vantage). The minimum and maximum differences between the DCA Vantage and A1CNow+ were +4.0 and -27.0 mmol/mol respectively. (Table 1) The median difference was 5.5 mmol/mol (average difference 7.14 mmol/mol), with the DCA Vantage giving overall higher results compared to the A1cNOW+.

Several A1CNow+ cartridges showed error messages in which case testing had to be repeated or abandoned. It is important to note that testing was conducted or overseen by specialist diabetes nurses who are accustomed to POCT. These findings would be the best-case-scenario because they did not factor-in unsupervised patient self-testing nor inter-assay (between day) variation.

DISCUSSION

Findings

Studies reviewed (23-37) exhibited variable findings which makes it difficult to formulate an incontestable opinion. In only two studies was self-testing included (23,24). This was an important aspect for our purposes because A1CNow+ was aimed for home use in our population. It also meant that analytical findings in most studies were best-case-scenario since they were based on testing by professionals.

The heterogeneity in study characteristics contributed to the different and often inconsistent findings. Importantly, the lack of alignment of study parameters with characteristics important for real world use of a home-based HbA1c device weakens the relevance of findings to our paediatric population.

Table 1. HbA1c results for the A1cNOW+ and the DCA Vantage

A1CNow+ mmol/mol (%)	DCA mmol/mol (%)	Absolute Difference: A1CNow+ - DCA mmol/mol (%)
38 (5.6)	34 (5.3)	+4 (0.3)
57 (7.4)	61 (7.7)	-4 (0.3)
115 (12.7)	>130 (14)	…….
68 (8.4)	70 (8.6)	-2 (0.2)
61 (7.7)	64 (8)	-3 (0.3)
66 (8.2)	93 (10.7)	-27 (2.5)
56 (7.3)	65 (8.1)	-9 (0.8)
53 (7)	53 (7)	0 (0)
54 (7.1)	68 (8.4)	-14 (1.3)
64 (8)	71 (8.6)	-7 (0.6)
43 6.1)	58 (7.5)	-5 (1.4)
51 (6.8)	64 (8)	-13 (1.2)
64 (8)	66 (8.2)	-2 (0.2)
74 (8.9)	82 (9.7)	-8 (0.8)
64 (8)	64 (8)	0 (0)

The relationship between the two methods was illustrated by the regression equation: DCA Vantage HbA1c mmol/mol = 1.22 A1c-NOW+.

The limited in-house proof-of-concept comparison demonstrated an overall negative bias of the A1CNow+ compared to the DCA Vantage analyzer, more pronounced at higher levels.

Ultimately all tests and devices have limitations but accurate knowledge of these limitations is important to ensure informed decision making. The test can then be implemented in the suitable clinical context, within a tailored clinical pathway and results would be interpreted within the test's limitations. Analytical findings for the A1CNow+ device were inconsistent. Results for the local proof-of-concept comparison were not encouraging. Evidence for the A1c EZ 2.0 device was promising albeit limited. No literature was found on other home-based HbA1c POCT devices.

Evaluating a POC device and test peculiarities

Evaluation of a POC test has requirements that set it apart from its laboratory counterpart. These distinctions arise from the different nature of the two types of testing: POCT is used in a relatively uncontrolled environment and by a variety of users while the laboratory test is performed in a well-controlled and quality-assured environment by laboratory trained professionals. The distinctions include but are not limited to: the need to evaluate the exact same sample type used in POCT which is usually capillary blood; testing by actual users who are not limited to healthcare professionals but include patients, and in this case parents and children from various socioeconomic and educational backgrounds; evaluating the accuracy of results under relevant environmental conditions such as a range of local seasonal temperatures; and investigating lock-out and quality control failure modes that prevent the release of inaccurate results.

Haemoglobinopathies

The inclusion of samples with haemoglobinopathies relevantto the community is a component that adds value to any evaluation of HbA1c testing. While such information can be retrieved from the NGSP (38), the latter may not list all relevant hemoglobinopathies that can be encountered. The A1cNow+ test is affected by HbS, HbC and high levels of HbF (>10-15%), and high levels of rheumatoid factor (14,38,39). The prevalence of HbS, HbC and hereditary persistent HbF in New Zealand is not clear but in a limited three-way platform comparison of HbA1c in 145 samples most of which have hemoglobinopathies, one sample of each of hereditary persistent HbF, heterozygous HbS, heterozygous HbC and heterozygous HbS- beta thalassemia were found. No homozygous HbS or HbC were encountered (40).

Nevertheless, New Zealand has a population of increasing diversity (41) with an inevitable increase in prevalence of associated hemoglobinopathies. None of the studies explicitly evaluated samples with haemoglobinopathies.

NGSP

Many of the studies compared their analytical results with those from an NGSP certified laboratory and used that comparison to judge the acceptability of the POC test without conducting precision studies. Such practice falls short of dedicated inter-assay (between day), inter-user, and between reagent lot, precision studies. The NGSP recommends an overall CV that is less than 3% but ideally less than 2% (42). The Australasian Association for Clinical Biochemists, the Royal College and Pathologists of Australasia and Australian Diabetes Association recommend an intra-laboratory CV <2% (43). Comparison studies would not inform an assay's CV.

NGSP certification is awarded annually based on comparison of results from 40 human samples with a secondary reference laboratory (SRL), (44). It is performed under very controlled conditions, based on the lot of reagent and calibrator used at the time. While this reassures users of traceability and reliability of the method in question it does not always translate to adequate clinical performance of a method (42, 44, 45). This challenges the assumption that if a home-based HbA1c device compares well to one NGSP certified method, it will behave similarly towards all certified methods and that the POCT test is fit-for-purpose.

Multiplicity of POCT devices

Analytically, a recommended maximum difference (bias) from a SRL or target value is +/-7.4% IFCC (5% NGSP), (46). Clinically a change of 5 mmol/mol HbA1c warrants a change in management (47). These analytical and clinical parameters are used for both laboratory-based methods and POCT.

POCT involves a large number of users, many devices in different locations, in less controlled environments than laboratories. These factors challenge the ability of a POCT HbA1c service to adhere to the above recommendations and clinical judgment regarding fitness-for-purpose should be exercised.

Statistics

From a statistical perspective, correlation coefficient r is not a reliable measure of agreement. It measures correlation, the relationship between two variables (48). Agreement on the other hand is concordance between two variables and is the parameter that needs to be sought when comparing methods for

a continuous variable. Correlation does not guarantee agreement therefore reliance on an r value close to +/-1.0 is not ideal. The best measures for agreement are intra-class correlation coefficient (ICC) and Bland-Altman plots (48).The latter provide a quantitative measure of agreement and are commonly used in clinical chemistry.

Clinician engagement

HbA1c POCT for the purposes of this review is intended for monitoring of diabetic control not for diagnosis of diabetes, therefore the risk of misclassification in case of inaccuracy, the summation of imprecision and bias, is not relevant. However, inaccuracy can misguide decision making particularly if users are unaware of its extent. Bias is a relative measure; while ideally a POC test's bias should be assessed against a reference measurement system, this is not possible most of the time. Therefore, it is usually assessed against a reliable laboratory method; of particular significance would be the laboratory serving the region or area of domicile of the POCT users. This informs the difference in clinical performance between the two methods which for consistency should be clinically comparable such that clinical decisions based on POCT results are the same as those based on laboratory results. It is important that clinicians are aware of the bias of a particular instrumentation and be notified of any changes which may occur from time to time. This ensures that POCT users are receiving equitable healthcare.

Regulatory environment

A thorough evaluation assumes greater importance when POCT devices are not regulated and when accreditation of the POCT service is not mandatory for running of a service. In New Zealand, both these conditions prevail (49). It remains the sole responsibility of laboratory professionals, scientists and pathologists, to ensure the standard of POCT is clinically safe and fit-for-purpose.

HbA1c targets and challenges of home testing

In New Zealand the target HbA1c range for children is < 53 mmol/mol (7%) (4). This target is stringent with the aim of reducing long term microvascular and macrovascular complications. Higher levels of <58 mmol/mol (7.5%) are accepted under special circumstances (4,50).

Testing HbA1c in diabetic children is recommended every three months (4). In case of home-based testing this means that the device and consumables would not be used for months between testing episodes. This is achievable but it increases emphasis on adherence to correct storage and quality assurance requirements. For A1cNow+ devices this means storage in a refrigerator would be preferred in the long run and to remember to run internal quality controls (IQC) monthly even when not testing. For the A1c EZ 2.0 room temperature is recommended and there is no need for regular quality control when not in use. Environmental temperature is particularly of relevance in certain parts of the country where extremes of +30 to +42^{o}C and – 22^{o}C have been recorded. (51). Children and care givers should be counselled on challenges of storage.

A known risk of POCT is over-testing, something that patients and parents need to be counselled against when they have access to home-based POCT. In New Zealand, like many other countries, there are community medical laboratory services that provide reliable HbA1c results with a turn-around-time of one to three days. Laboratory analysers are quality assured and maintained in a controlled environment. Most children have access to community HbA1c testing. However, in case they do not, due to social or geographical barriers, or at times of lock-down, home-based POCT can be used to support timely management with clinically reliable equipment. If the child needs other blood tests apart from HbA1c, isolated POCT for HbA1C would not be needed.

At the time of this review, August-September 2020, the world is in the grip of the SARS-CoV-2 (COVID-19) pandemic. Cities, towns and rural locations are in lockdown, making access to conventional laboratory testing or attendance at out-patient clinics challenging. Therefore, the use of clinically reliable, POCT devices for monitoring HbA1c and glucose has been and will continue to be, an essential component of telemedicine and clinical decision making for these children.

Point of care testing in context of telemedicine

Telemedicine is a subset of telehealth; while the latter is broad (52), telemedicine is focused on direct clinical management. Both involve communication and exchange of information remotely.

When POCT is used it should form part of an all-rounded package to deliver sustainable and effective tele-medical healthcare. The infrastructure for such a package includes videoconferencing units, software-based videoconferencing programs, adequate bandwidth, and secure connections that ensure patient privacy (53).

In New Zealand telemedicine is regulated and governed by The Health Practitioners Competence Assurance Act, The Code of Health and Disability Services Consumers' Rights, and the Health Information Privacy Code (54).They are aimed at ensuring confidentiality and safety.

Evidence around efficacy of telemedicine in managing diabetes in children, and particularly around reducing HbA1c levels is mixed. A few studies concluded that telemedicine had no impact on HbA1c levels, severe hypoglycaemia or diabetic ketoacidosis in children with T1DM, and hence no evidence to support its role in the management of glycaemic control (55, 56). On the other hand, several studies demonstrated that telemedicine improved access to diabetic care, (57, 58) reduced HbA1c levels (59-61) and reduced hospital admissions and visits to emergency departments and that school telemedicine programs can improve diabetic children's quality of life and reduce the number of urgent diabetes-related calls by school nurses (59).

Advice to local endocrinologists

Evidence for acceptable analytical and clinical performance of the A1cNow+ HbA1c test was deemed weak, and evidence for the A1c EZ 2.0 test was limited. The advice given to local paediatric endocrinologists was that if the need for home-based HbA1c testing was necessary and financially justifiable, it could be used after a thorough local evaluation proved that the test is fit-for-purpose. This evaluation would include regional laboratories of which there are at least three using each of capillary zone electrophoresis, immunoassay, and Boronate affinity chromatography; reference material; and actual users to perform testing i.e., the children and parents that are targeted. The study population size should be adequate to perform interpretable statistical analysis for precision, bias, and user-friendliness.

The New Zealand Point of Care Testing Advisory Group published a set of Best Practice Guidelines (62) which provide guidance on the selection and evaluation of POCT devices. Paediatricians and clinic nurses should be aware of these Guidelines and also the limitations of both POCT and conventional laboratory testing.

Limitations

Conference proceedings and posters were excluded, and while all effort was made to be inclusive, this is a non-systematic review and may therefore have missed relevant studies.

The in-house comparison could not be used to formulate a final decision regarding the performance of the A1cNOW+. Important limitations were the small number of participants and in turn the small number of paired test results, and the lack of precision studies. In addition, some of the A1cNow+ test kits failed to work correctly, which further limited the amount of data acquired.

CONCLUSIONS

The global increase in the prevalence of diabetes combined with mobility constraints as a result of the COVID-19 pandemic highlight an urgent need for thorough, systematic evaluations of POCT HbA1c devices comparing patient sample results against local conventional laboratory analysers.

This is even more important owing to the plethora of POCT devices which can be purchased over the internet for home use. Home-based HbA1c and telemedicine have their place but to deliver their objectives they should be fit-for-purpose and

targeted to populations that need it most to reap maximum benefit. Current evidence on the performance of home-based HbA1c POCT is not consistent with safe and effective clinical management of diabetes.

Manufacturer claims are based on evaluations conducted under controlled conditions and on specific population groups. Validating manufacturer claims on analytical and clinical performance characteristics is good practice and ensures that findings are applicable to the targeted users and environment. Furthermore, evaluating a POCT test has specific requirements beyond evaluating routine laboratory tests, without which strengths and limitations of the test are not fully understood, not least of which is the acceptability of the device to the paediatric population. Not investigating the relevant requirements would impact clinical decision making based on POCT results. This assumes greater importance where regulatory and accreditation requirements are non-existent.

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*Appendix A and B are available as supplementary material at https://mix.nzimls.org.nz/journals-recent.html

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