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HemoCue® Urine Albumin Microcuvettes and the HemoCue® Albumin 201 Analyzer.

The HemoCue® Albumin 201
System consists of the HemoCue Albumin 201 Analyzer and the HemoCue Urine Albumin Microcuvettes. The system is calibrated against a turbidimetric method with traceability to CRM 470 (Certified Reference Material). The HemoCue Urine Albumin Microcuvettes are designed for use with the HemoCue Albumin 201 Analyzer. Only use microcuvettes recommended by HemoCue. HemoCue Urine Albumin Microcuvettes are available in individual packages. Please read the Operating Manual for HemoCue Albumin 201 System for proper use of the system.
The HemoCue Albumin 201 System is classified as Waived under the CLIA Guidelines and can be used by all laboratories holding a CLIA certificate of waiver. If the laboratory modifies the HemoCue Albumin 201 test procedure, the test no longer meets the requirements for waived categorization. A modified test is considered to be highly complex and is subject to all applicable CLIA requirements. For information on how to obtain a CLIA Waiver certificate, please refer to CMS CLIA program.

Intended use

The quantitative, rapid, turbidimetric immunoassay of albumin in human urine using a specially designed system, the HemoCue Albumin 201 System. The system is designed to be used for the quantitative determination of low levels of albumin in urine at the point-of-care for the purpose of screening for, diagnosing, monitoring and to supplement the clinical evidence in the treatment of microalbuminuria. The system is designed for testing using spot samples or timed collections. A quantitative result is obtained within 90 seconds. HemoCue Urine Albumin Microcuvettes are for *In Vitro* Diagnostic use only. The HemoCue Albumin 201 Analyzer is only to be used with HemoCue Urine Albumin Microcuvettes.

Summary and explanation of the test

Microalbuminuria is defined as a urinary albumin excretion rate of between 20–200 mg/L in the first morning sample, 20–200 µg/min in a timed overnight or 24 hour sample on at least 2 of 3 occasions within a period of 6 months[1]. An albumin excretion rate of 20–200 µg/min is approximately equivalent to 30–300 mg/24 hours. The test can be performed with spot urine, preferably the first morning urine as well as urine collected over night or during 24 hours. Nephropathy is a leading cause of morbidity and mortality in diabetes. Microalbuminuria is a powerful predictor for the future development of diabetic nephropathy, retinopathy and cardiovascular complications to type 1 diabetes[2,3]. For type 2 diabetes and patients with hypertension[4], there is an increased risk of cardiovascular disease if microalbuminuria is present[5,6,7]. According to the American Diabetes Association guidelines, annual screening in individuals with type 1 diabetes should begin after 5 years' disease duration or at the age of 12, and from the time of diagnosis of type 2 diabetes[8]. Microalbuminuria is also suggested as a risk marker for cardiovascular complications and increased cardiovascular risk in hypertension[9,10]. Microalbuminuria is also an independent risk factor for cardiovascular disease among patients without diabetes or hypertension[11]. Several studies have shown that early detection of microalbuminuria will delay or prevent further deterioration through early treatment[12]. Microalbuminuria before pregnancy is the strongest predictor of pre-eclampsia in Type I diabetes[13].

Principles of the procedure

The technique

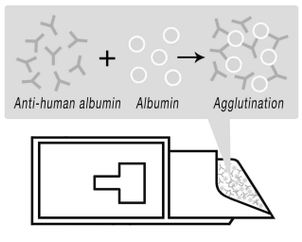
The HemoCue Albumin technique is based on an optical measuring cuvette with a small and exact volume and a short light path. The cuvette cavity contains reagents deposited on its inner walls. The urine sample is drawn into the cavity by capillary action. The filled cuvette is inserted into the HemoCue Albumin 201 Analyzer where the contents of the cuvette are mixed through vibration. Within 90 seconds, the immunochemical reaction is completed and the turbidity is measured photometrically at 610 nm. The albumin concentration is proportional to the turbidity. When the end point is reached, the result is displayed in mg/L. Thus the technique makes it possible to obtain a measured amount of specimen, mix it with reagents, follow the chemical reaction to endpoint and determine the result, all within the microcuvette.

The Microcuvette

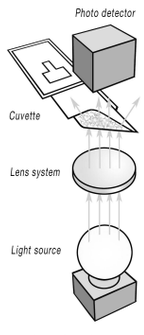
The cuvette is made of polystyrene and contains a cavity that holds approximately 18 µL of specimen. The narrow distance between the walls of the optical eye permits a photometric determination of albumin in urine.

The Chemistry Principles

A specific rabbit anti-human albumin antibody (polyclonal) forms an agglutinate with human albumin in the sample. The agglutination is enhanced by polymers. The turbidity created by the formation of antigen-antibody agglutinates, is measured photometrically at 610 nm.



The anti-human albumin antibodies in the reagent forms agglutination complexes with the albumin present in the sample.



Within 90 seconds, the immunochemical reaction is completed and the turbidity is measured photometrically at 610 nm.

Reagents

11 % w/w rabbit anti-human albumin antibody (polyclonal), 35% w/w PEG, 18% w/wTris/HCl-buffer, 2 % w/w polymer and 33 % w/w non-reactive ingredients.

Warnings and precautions

HemoCue Urine Albumin Microcuvettes are for *In Vitro* Diagnostic use only. The chemicals deposited in the cavity of the microcuvette are harmful if swallowed. Although the reagents are present in the cuvette in extremely low quantities, consult local environmental authorities for appropriate disposal. Always handle body fluids with care, including urine samples, as they might be infectious.

Storage and handling of HemoCue Urine Albumin Microcuvettes

Store HemoCue Urine Albumin Microcuvettes in their package in a refrigerator, at 35–46 °F (2–8 °C). The individually packaged cuvettes can be stored at room temperature for up to 3 days. The cuvettes may NOT be stored in a freezer. Use HemoCue Urine Albumin Microcuvettes prior to their expiration date. The expiration date is printed on each container as well as on each individual package. The reagents within HemoCue Urine Albumin Microcuvettes are moisture and temperature sensitive. As this test method relies on photometric measurement, care should be taken not to hold the microcuvette by the filling end. Take care to wipe away all contaminating substances from the outer surface of the filled cuvette. Unused HemoCue Urine Albumin Microcuvettes should be kept in the original package. Once a package is opened, the cuvette must be used immediately or discarded.

Analyzer

The analyzer is factory calibrated and needs no further calibration. The analyzer performs a selftest every time it is turned on. For further information, please see the instructions under Quality control. The cuvette holder should be cleaned after each day of testing. The analyzer needs no electronic or mechanical maintenance.The Troubleshooting Guide in the Operating Manual contains information on possible errors, explanations of errors and recommendations for actions to be taken.

Specimen collection and preparation

The test can be performed using a spot sample, preferably the first morning specimen. The system is designed for testing at the point-of care using fresh urine preferably within 1-2 hours after collection.
The turbidity scale in the operating manual can be used to detect the grade of turbidity. Cloudy samples should not be analyzed.

Procedure

Read the Operating Manual for the HemoCue Albumin 201 System to ensure correct use of the instrument.

Materials Provided

HemoCue Urine Albumin Microcuvettes

Materials required but not provided

HemoCue Albumin 201 Analyzer.
Gauze or lint free wipe.
Quality Control Material.

Proper temperatures

The HemoCue Albumin 201 System is designed for use at room temperature 59–86 °F (15–30 °C).

Directions for use

1. Make sure that the analyzer lid is closed. Press and hold the left button until the display is activated. The display shows the version number of the program and an automatic self test is performed. When the HemoCue symbol and three flashing dashes are displayed, the analyzer is ready for use. Also see the Operating Manual for the HemoCue Albumin 201 System.
2. Use of HemoCue Urine Albumin Microcuvettes

a) Take out only as many cuvettes from the package as you need for the im mediate use. Follow the instructions, given under "Handling of HemoCue Urine Albumin Micro-cuvettes".

b) The shape of the cuvette and the names of the different parts of the cuvette can be seen in figure 1.

c) Pipette a drop of urine onto a plastic film, such as Parafilm.

d) Hold the cuvette by the rectangular end as shown in Figures 2 and 3. Bring the filling end of the cuvette into contact with the urine sample, see figure 2. Always avoid contamination of the optical eye. It is also possible to fill the cuvette directly from the sample, if it is not to be used for any other analysis. Allow the cavity of the cuvette to fill completely in one step. **Do not refill the cuvette!** The cuvette can not be overfilled. If too little specimen is added, discard and repeat with a new cuvette.

e) When completely filled, carefully wipe off the excess urine from the outside of the cuvette with a clean lint free wipe, see figure 3. Make sure that no sample is drawn out of the cuvette during this procedure.
The filled cuvette should be visually inspected to check that the cuvette is properly filled, i.e. completely filled up to the edge and without air bubbles in the optical eye.
If air bubbles are seen in the optical eye of a filled cuvette, discard it and fill another cuvette for analysis from a second drop of specimen.

f) Open the lid and place the filled cuvette into the cuvette holder, see figure 4a. It is important that the cuvette "snaps" properly into the cuvette holder, see figure 4b.
Start measurement as soon as possible but no later than 30 seconds after filling the microcuvette by gently closing the lid.

g) The display shows and three fixed dashes.

h) Within 90 seconds, the result is displayed in mg/L. Record the result. The result will remain on the display until the lid is opened. If the display shows:
- LLL, the result is below 7 mg/L
- HHH, the result is above 150 mg/L
- Exx, an error has occured.

See the Troubleshooting Guide and the Maintenance section in the Operating Manual for additional information[14].

i) **Do not remeasure the cuvette!**

j) Open the lid and discard the used cuvette.

k) Close the lid. When the display shows the the HemoCue symbol and three flashing dashes, the analyzer is ready for a new measurement. If the display shows E02, an error has occurred and the optical unit must be cleaned. See the Troubleshooting Guide in the Operator's Manual. After cleaning the optical unit, fill a new cuvette from a second drop of specimen and proceed as above.
For further information, consult the Operating Manual for the system.

l) When the measurements for the day have been completed, switch off the analyzer with the ON/OFF button.

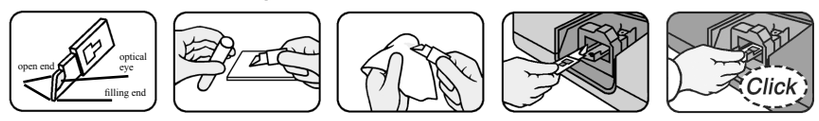


Fig. 1 Fig. 2 Fig. 3 Fig. 4a Fig. 4b

Quality control

- The system should be verified by measuring a commercially available urine albumin control. Note that local, state, or other accreditating agencies may require additional quality control testing. If the control result is out of range, please refer to the Operating Manual for corrective action. Do not run patient samples unless the quality control results are in the expected range.
  For CLIA waived laboratories, HemoCue recommends the control material Eurotrol AlbuTrol to be used on the days of testing, for each new shipment of cuvettes and new lots.
- The HemoCue Albumin 201 Analyzer has an internal electronic self test. Every time the analyzer is turned on it will automatically perform the self test. The self test verifies the performance of the optical unit of the analyzer.

Results

The result is read directly from the HemoCue Albumin 201 Analyzer in mg/L.
The system is linear between 7 - 150 mg/L. The results are displayed as numerical values and results outside the measuring ranges are displayed as "LLL" or "HHH".

Limitations of the procedure

1. Cloudy samples should not be analyzed.
2. The following substances have been tested without interfering with the system. The highest concentration tested is referred to in brackets.
   Acetaminophen (50 mg/dL), acetoacetate (102 mg/dL), acetone (697 mg/dL), acetyl salicylic acid (50 mg/dL), ascorbic acid (50 mg/dL), betanin (0.8 mg/dL), β_2 micro-globulin (0.1 mg/dL), bilirubin (15 mg/dL), calcium (64 mg/dL), creatinine (271 mg/dL), hemoglobin (0.2 g/dL), IgG (1.5 mg/dL), potassium (180 mmol/L), uric acid (6 mg/dL).
   For samples having glucose > 1982 mg/dL, urea > 1541 mg/dL, sodium > 300 mmol/L and pH < 4.5 or > 9.0, the result should be interpreted with caution.
   Interference studies have been performed according to NCCLS EP7.
3. Results obtained from patients undergoing renal dialysis should be interpreted with the utmost caution.
4. The measurement needs to be started no later than 30 seconds after filling the microcuvette.

Expected values

According to the literature [14, 18], the following values are indicators for normal and pathological urine albumin results respectively.

Category	First morning spot sample (mg/L)	24-h collection (mg/24 h)	Timed collection (µg/min)
Normal	< 20	< 30	<20
Microalbuminuria	20-199	30-299	20-199
Clinic albuminuria	> 200	300	200

For screening purposes, a spot sample can be used, preferably the first morning sample.

Spot samples

The first morning urine specimen after rest is recommended since muscle activity influences the excretion of albumin in urine. Spot samples during the day may be used, but higher results can be expected. Examples of factors that may influence the excretion of albumin in the urine are, physical activity, urinary tract infections and fever. The concentration of albumin in spot urine samples, even if collected as the first-morning urine, are subject to variability from the degree of dilution or concentration of the urine because of variability in hydration.
Users (clinicians, medical professionals, etc.) of the test are encouraged to consult current practice and authorities for interpretation of results [14, 18-19].

The cut off used should be 20 mg/L. Microalbuminuria is defined as 20-200 mg/L and macroalbuminuria as > 200 mg/L Measurements from spot urines during the day may give slightly higher results due to physical activity. In these circumstances, normal values are < 30 mg/L[1].

Specific performance characteristics

Precision

The precision was determined using commercially available controls. Each control was measured in duplicate on five instruments twice a day during twenty consecutive days. The precision studies were performed according to NCCLS EP5-A.

			Within precision		Total Precision	
Level	No of determination (n)	Mean (mg/L)	SD (mg/L)	CV %	SD (mg/L)	CV %
1	400	27.9	2.41	8.6	2.58	9.2
2	400	81.8	3.20	3.9	3.48	4.3

Precision, patient samples

Precision data with patient samples The results given below come from 5 different sites using 3 batches of HemoCue Urine Albumin microcvuettes and 5 different HemoCue Albumin 201 Analyzers. No recalibrations were performed during the analyzing period.

Site	No of operators at each site	5-30 mg/L			31-150 mg/L		
		Mean mg/L	SD mg/L	No of samples	Mean mg/L	SD mg/L	No of samples
A	5	18.3	1.77	41	51.8	4.08	44
B	2	17.9	2.07	47	57.3	4.27	63
C	1	19.1	2.18	43	68.0	4.15	70
D	1	16.8	2.69	80	76.8	3.24	50
E	5	17.7	2.57	55	62.3	3.28	63

Correlation

A correlation study was performed between the HemoCue Albumin 201 and the Beckman Coulter CX5 according to NCCLS EP9A. For results, see figure 5.

Limit of blank

The limit of blank for the HemoCue Albumin 201 system is 7 mg/L. The Limit of Blank is the highest value that is expected in a series of results on a sample that contains no analyte. This study is performed according to NCCLS EP17-A.

Cut Off determination

The % agreement is 99% for microalbuminuria with cut off 20 mg/L for the HemoCue Albumin 201 system using Beckman Coulter CX5 as the ”True” method.

Point of care studies

Point of care studies have been performed at three individual district health centers in primary care with both nursing and physician services. The results are presented in figure 6.

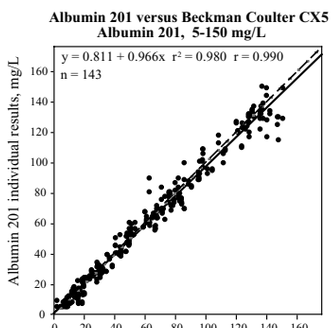


Figure 5. Beckman Coulter CX5, mean values, mg/L

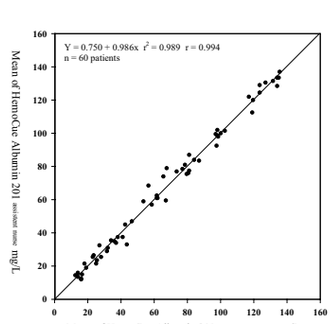


Figure 6. Scatter plot for mean of replicates, HemoCue Albumin 201 (assistant nurse) versus HemoCue Albumin 201 (professional user). Evaluation time: September 27 to September 30 2005

Expected Waiver Performance

A clinical study was conducted at five primary care centers and one site within a hospital over a period of 18 days. There were a total of 18 operators distributed among the sites with each site having 2 or more operators. All operators were described as assistant nurses having an equivalent of a high school education and no formal laboratory training. They were not given any training on the use of the HemoCue Albumin 201 test system. The clinical study was intended to demonstrate that after reading only the test instructions, operators were able to get results on the HemoCue Albumin 201 test system (WM) that were as accurate as those obtained by professionals on the Beckman-Coulter Synchron CX5 PRO comparator method (CM). There were a total of 424 patient specimens each tested in duplicate for a total of 848 results.

Performance criteria were established to define the accuracy of the HemoCue Albumin 201 test system. Values using the HemoCue Albumin 201 test that fall within the Allowable Total Error (ATE) zone are values that can be tolerated without invalidating the medical usefulness of the test. The patient specimens were each tested twice using the HemoCue method (WM) however individual results of the test were assessed for being within the ATE. The lower confidence bound for percent results within the ATE appropriately considered duplicates from a given specimen and were not averaged.

Allowable Total Error (ATE) criteria:

(1) For CM values <33.3 mg/L, the WM is within 10 mg/L of the CM

(2) For CM for values >33.3 mg/L, the WM is within +/-30% of the CM

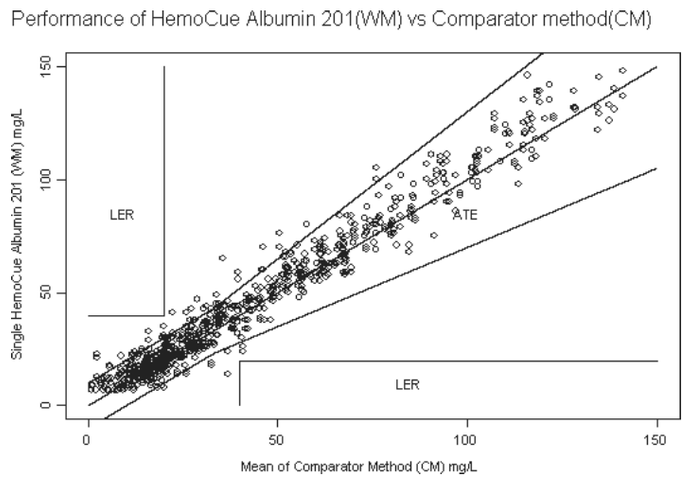
The Limits of Erroneous Results was also defined. When WM values fall inside the LER zones, potential harm can occur to the patients if these results are utilized in medical decision-making.

The (LER) zone is defined as follows:

(1) If CM <20 mg/L and the WM > 40 mg/L or

(2) If CM >40 mg/L and the WM <20 mg/L.

CM=Comparator Method; WM=Waiver Method (HemoCue Albumin 201)



There were 49 observations below the Limit of Blank (i.e. 7 mg/L) of the HemoCue test system, and for these the WM-CM comparison could not be explicitly calculated. All but one fell within the ATE.

The percentage of waiver user values within the defined ATE criteria using low level as CM<10 mg/L, medium level as CM values in the 10-33.3 mg/L range, and high level as CM values above 33.3 mg/L is summarized in the table below.

Percent of results within the ATE

Range of CM Values	Total number results	Number results outside ATE	Percent within ATE	Lower 95%CI
Low(<10 mg/L)	96	6	93.7%	
Mid (10-33 mg/L)	370	27	92.7%	
High (>33.3 mg/L)	382	18	95.3%	
All	848	51	94.0%	92.0%

Based on the above definition of the LER, none of the samples were in the LER zone.

Systematic bias was assessed using a Deming regression comparing mean of HemoCue results (WM) to results using the mean of the comparative method (CM):

Parameter	Estimate	95% confidence interval
Intercept	0.9327	0.0126 to 1.8527
Slope	1.0313	1.0139 to 1.0487

Based on the Deming regression above, the systematic bias at two values of microalbumin is presented in the table below:

CM	Predicted value of WM	Bias
10 mg/L	11.24 mg/L	1.24 mg/L
30 mg/L	31.86 mg/L	1.86 mg/L

Patent

The HemoCue Albumin 201 System is protected by US patent no US 5,674,457, US 6,468,807, US 6,333,007 and US 433,150.

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Problem reporting

Please report technical issues or problems to HemoCue America at: 800-426-7256.

Symbols used

Caution	Temperature limitation
In Vitro Diagnostic medical devic	Catalog number
Do not reuse	Batch code
CE mark	Use by (Year Month Day)
Consult instructions for use	This product is covered by one or more patents
Opened Date of opening	

Manufacturer:

HemoCue AB
Box 1204
SE-262 23 Ängelholm, Sweden
Phone +46 77 570 02 10
Fax +46 77 570 02 12
E-mail: info@hemocue.se
www.hemocue.com

HemoCue Distributor USA
HemoCue America
250 South Kraemer Boulevard
Brea, CA, 92821
Phone (General): 800-881-1611
Orders: 800-323-1674
Technical Support: 800-426-7256
Fax (Cust. Service): 800-333-7034
www.hemocue.com

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