IMMY

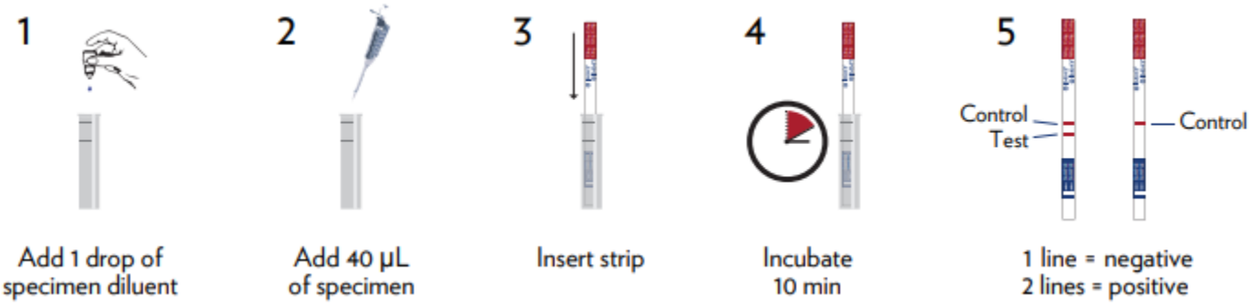
CrAg LFA

REF #: CR2025

For the detection of Cryptococcal Antigen

℞ ONLY

IVD



INTENDED USE

The Cryptococcal Antigen Lateral Flow Assay (CrAg LFA) is a non-automated, immunochromatographic test system for the qualitative or semi-quantitative detection of the capsular polysaccharide antigens of *Cryptococcus* species complex (*Cryptococcus neoformans* and *Cryptococcus gattii*) in serum, plasma, whole blood (venous and finger stick), and cerebral spinal fluid (CSF).

The CrAg LFA is a prescription-use, laboratory assay which can be used as an aid in the diagnosis of cryptococcosis.

SUMMARY AND EXPLANATION OF THE TEST

Cryptococcosis is caused by both species of the *Cryptococcus* species complex (*Cryptococcus neoformans* and *Cryptococcus gattii*).[1] Individuals with impaired cell-mediated immunity are at greatest risk of infection.[2] Cryptococcosis is one of the most common opportunistic infections in AIDS patients.[3] Cryptococcosis is responsible for 15% of HIV deaths worldwide.[4] Detection of cryptococcal antigen (CrAg) in serum and CSF has been extensively utilized with very high sensitivity and specificity.[5-6] The CrAg LFA utilizes highly sensitive and specific anti-cryptococcal mouse monoclonal antibodies. These antibodies are highly sensitive to glucuronoxylomannan, (GXM) the primary antigen shed by the organism. The CrAg LFA shows increased sensitivity across all serotypes of the organism, especially serotype C (*C. gattii*).[7-9] Detection of CrAg with the CrAg LFA has been widely employed when cryptococcal disease is suspected.[10-13] Preliminary reports suggest that trained lay healthcare workers and laboratory personnel can use the assay as a point-of-care assay outside the laboratory.[14]

BIOLOGICAL PRINCIPLES

The CrAg LFA is a non-automated, dipstick sandwich immunochromatographic assay which detect Cryptococcal antigen in serum, plasma, whole blood, and cerebral spinal fluid (CSF). Specimens are pipetted into a clean, flat-bottom receptacle and LF Specimen Diluent (REF #: GLF010) is followed by a CrAg Lateral Flow Test Strip (REF #: LFCR25). The test is run for 10 minutes, and results should be read between 10 minutes and 2 hours.

The CrAg LFA is constructed by having anti-CrAg monoclonal antibodies conjugated to colloidal gold that bind to capsular polysaccharide antigens of *Cryptococcus* species complex (*Cryptococcus neoformans* and *Cryptococcus gattii*) that may be present in the specimen as it wicks up the test strip. If CrAg is present in the specimen, then it binds to the anti-CrAg monoclonal antibodies. The antibody-antigen complex continues to migrate up the membrane by capillary flow where it will interact with the test line, which has immobilized anti-CrAg monoclonal antibodies. The antibody-antigen complex forms a sandwich at the test line causing a visible line to form. With proper flow and reagent reactivity the wicking of any specimen, positive or negative, will cause the control antibody to move to the control line. Immobilized antibodies at the control line will bind to the control antibody and form a visible control line.
NOTE: The control line is a migration control and not a specimen addition control. Positive test results create two lines (test and control). Negative test results form only one line (control). If a control line fails to develop then the test is not valid.

REAGENTS PROVIDED

Each kit contains sufficient reagents for 25 tests.

1	GLF010	**LF Specimen Diluent** Glycine buffered saline solution; contains 0.095% Sodium Azide, 0.5 mg/mL Blocking Agent	1 mL
2	LFCR25	**CrAg Lateral Flow Test Strips** 25 LFA dipsticks packaged into a desiccant vial with an attached cap; strips are 0.4 cm wide by 7.6 cm tall	25 Ea
+	CB1020	**CrAg Positive Control** 500 ng/mL Cryptococcal Antigen (Strain 184A – Clinical Isolate from Tulane University)[15] in a glycine buffered saline solution; contains 0.095% Sodium Azide	1 mL

Refer to the Safety Data Sheets for more information on hazards and warnings.

MATERIALS REQUIRED BUT NOT PROVIDED

- Disposable gloves
- Protective glasses
- Pipette(s) capable of measuring and delivering 40 µL and 80 µL and associated disposable tips or disposable fixed-volume (40 µL) transfer pipettes
- Disposable flat-bottom micro-centrifuge tubes, flat-bottom test tubes, or a flat-bottom micro-titer plate that can hold the test strip
- Permanent pen to label tubes or strips
- Timer
- Biohazard waste receptacle
- LF Titration Diluent (REF #: EI0010) – Required only for Semi-Quantitative Procedure

REAGENT STABILITY AND STORAGE

The entire CrAg LFA test kit should be stored at the stated temperature (2-30°C) until the expiration dates listed on the reagent labels. The quality of the product cannot be guaranteed after the expiration date.

Unused test strips should be returned immediately to the desiccant vial with the attached cap firmly closed. All reagents should be tightly capped immediately after use.

REAGENT PRECAUTIONS

1. Specific standardization is necessary to produce our high-quality reagents and materials. The user assumes full responsibility for any modification to the procedures published herein.
2. Do not use kit or any kit reagents after the stated expiration date.
3. At the time of each use, kit components should be visually inspected for obvious signs of microbial contamination, leakage, or significant physical damage to the test strip. Discard if these conditions are found.
4. IMMY cannot guarantee the performance of its products when used with materials purchased from other manufacturers. The use of other products with this test has not been evaluated and may result in erroneous results.
5. Always wear gloves when handling reagents in this kit as some reagents are preserved with less than 0.1 % (w/w) sodium azide. Sodium azide should never be flushed down the drain as this chemical may react with lead or copper plumbing to form potentially explosive metal azides. Excess reagents should be discarded in an appropriate waste receptacle.
6. The following components are not test system lot dependent: LF Specimen Diluent (REF #: GLF010) and therefore can be used with any lot of CrAg Lateral Flow Test Strips (REF #: LFCR25), provided they have not expired.
7. The control line is a migration control and not intended as a specimen addition control.

WARNINGS AND PRECAUTIONS FOR USERS

1. For In Vitro Diagnostic use only.
2. Use of this kit with samples other than human serum, plasma, whole blood, and cerebral spinal fluid (CSF) is not recommended.
3. Wear protective clothing, including lab coat, eye/face protection, and disposable gloves, and handle the kit reagents and patient samples with the requisite Good Laboratory Practices. Wash hands thoroughly after performing the test.
4. Avoid splashing samples or solutions.
5. Biological spills should be wiped thoroughly with an effective disinfectant. Disinfectants that can be used include (but are not limited to) a solution of 10% bleach, 70% ethanol, or 0.5% Wescodyne Plus™. Materials used to wipe up spills may require biohazardous waste disposal.
6. Dispose of all specimens and materials used to perform the test as though they contain an infectious agent. Laboratory chemical and biohazardous

wastes must be handled and discarded in accordance with all local, regional, and national regulations.
7. The CrAg Lateral Flow Test Strips (REF #: LFCR25) may be biohazardous after running specimens. Handle and dispose of accordingly.
8. Safety Data Sheets are available upon request.

SPECIMEN COLLECTION

Collect specimens aseptically using established techniques by qualified personnel. When handling patient specimens, adequate measures should be taken to prevent exposure to potentially present etiologic agents. For optimal results, sterile non-hemolyzed specimens should be used.

If a delay is encountered in specimen processing, storage at 2-8°C for up to 72 hours is permissible. Serum, plasma, and CSF may be stored for longer periods at <-20°C, provided they are not repeatedly thawed and refrozen. Sodium EDTA, Potassium EDTA, Sodium Citrate, and Sodium Heparin anticoagulants have been validated for plasma collection. Whole Blood CANNOT be stored at <0°C. Serum, plasma, and CSF in transit should be maintained at 2-8°C or <-20°C. Whole blood in transit should be maintained at 2-8°C, not <-20°C.

Specimens should be brought to room temperature prior to testing.

PROCEDURE

QUALITATIVE PROCEDURE

1. Add 1 drop or pipette 40 µL of LF Specimen Diluent (REF #: GLF010) to an appropriate, labeled, flat-bottom reservoir (disposable flat-bottom micro-centrifuge tube, flat-bottom test tube, or flat-bottom micro-titer plate, etc.). It is also good practice to label the lateral flow test strip prior to inserting it into the specimen.
2. Add 40 µL of the specimen into the reservoir from Step 1 and mix.
3. Place one CrAg Lateral Flow Test Strip (REF #: LFCR25) into the reservoir.
   NOTE: Return all unused test strips to the desiccant vial and firmly close the attached cap. Firmly cap all reagent bottles when not in use.
4. Allow the test to run for 10 minutes at room temperature.
   NOTE: You can read the results between 10 minutes and 2 hours after inserting the test strips.
5. Read and record the results (see "READING THE TEST PROCEDURE" below).

SEMI-QUANTITATIVE PROCEDURE

NOTE: For a Semi-Quantitative Procedure, additional products (including Titration Diluent, REF #: EI0010) are available for purchase.

1. Prepare dilutions starting with an initial dilution of 1:5, followed by 1:2 serial dilutions to 1:2560:
2. Place 10 flat-bottom micro-centrifuge tubes or flat-bottom test tubes in an appropriate rack and label them 1-10 (1:5 through 1:2560). 10 microwells from a flat-bottom micro-titer plate may be used for this step.
   NOTE: Additional dilutions may be necessary if the specimen is positive at 1:2560. For methods to conserve strips, contact IMMY to request our Titration Algorithm Procedure.
3. Add 4 drops or pipette 160 µL of LF Specimen Diluent (REF #: GLF010) to tube #1.
4. Add 2 drops or pipette 80 µL of LF Titration Diluent (REF #: EI0010) to each of the tubes labeled 2-10.
5. Add 40 µL of specimen to tube #1 and mix well. This is a 1:5 dilution of the specimen.
6. Transfer 80 µL of the 1:5 specimen from tube #1 to tube #2 and mix well. Continue this dilution procedure through tube #10. Discard 80 µL from tube #10 and 40 µL from tube #1 so that each of the 10 tubes contain a volume of 80 µL.
7. Place one CrAg Lateral Flow Test Strip (REF #: LFCR25) into each of the 10 tubes.
8. Allow the test to run for 10 minutes at room temperature.
   NOTE: You can read the results between 10 minutes and 2 hours after inserting the test strips.
9. Read and record the results (see "READING THE TEST PROCEDURE" below).

QUALITY CONTROL PROCEDURE

Positive and negative controls verify the kit is working as intended and ensure no product failure or no contamination has occurred. A positive control (CrAg Positive Control) can be evaluated by combining 1 drop or 40 µL of LF Specimen Diluent (REF #: GLF010) followed by 1 drop or 40 µL of CrAg Positive Control (REF #: CB1020) to a flat-bottom micro-centrifuge tube, flat-bottom test tube, or flat-bottom micro-titer plate. A negative control (LF Specimen Diluent) can be evaluated by adding 2 drops or 80 µL of LF Specimen Diluent (REF #: GLF010) to a separate flat-bottom micro-centrifuge tube, flat-bottom test tube, or flat-bottom micro-titer plate. Insert a CrAg Lateral Flow Test Strip (REF #: LFCR25) into each tube containing a control and allow the test to run for 10 minutes.
NOTE: You can read the results between 10 minutes and 2 hours after inserting the strips.

Two (2) lines (test and control) indicate a positive result, and one line (control) indicates a negative result. Additional controls may be tested according to guidelines or requirements of local, state, and/or federal regulations or accrediting organizations.

READING THE TEST PROCEDURE

Read the reaction on each test strip. The presence of two lines (test and control), regardless of the intensity of the test line, including faint lines, indicates a positive result.

For the semi-quantitative titration procedure, the patient's titer should be reported as the highest dilution that yields a positive result.

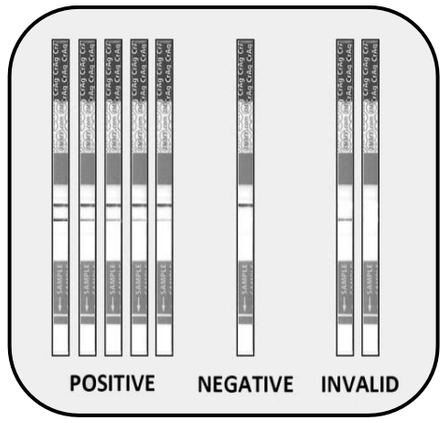
NOTE: Titers obtained by IMMY's CrAg LFA are not equivocal to titers obtained from other cryptococcal antigen assays.

Faint line intensity could be indicative of a high titer specimen. The semi-quantitative procedure should be run to rule out high titer inhibition of the test line.

A single control line indicates a negative result. If clinical signs and symptoms indicate cryptococcosis infection, the semi-quantitative procedure should be run to rule out false negative results caused by high concentrations of antigen in the sample, which can inhibit the test line from forming.

If the control line does not appear, the results are invalid, and the test should be repeated. Partial test lines that only develop on one half of the test strip should be interpreted as invalid and repeat testing should be performed to confirm positive or negative results. The control line is a migration control and not intended as a specimen addition control.

The stability of the control and test lines beyond the reading time (10 minutes – 2 hours) has not been validated.



RESULTS

The control line must be present for a valid test. If a control line is not present, the test should be considered invalid and repeat testing should occur. Partial test lines that only develop on one half of the test strip should be interpreted as invalid and repeat testing should be performed to confirm positive or negative results. The control line is a migration control and not intended as a specimen addition control.

The presence of two lines (a control line and a line in the test zone) regardless of the intensity of the test line, including faint lines, indicates a positive result. Faint line intensity could be indicative of a high titer specimen. The semi-quantitative procedure should be run to rule out high titer inhibition of test line.

A single control line indicates a negative result. If clinical signs and symptoms indicate cryptococcosis infection, the semi-quantitative procedure should be run to rule out false negative results caused by high concentrations of antigen in the sample, which can inhibit the test line from forming.

Interpretations based upon the semi-quantitative methodology can be indicative of prognosis and response to treatment. Cryptococcal antigen titers greater than 1:160 are associated with meningitis development.[16-17]

Negative results do not rule out the diagnosis of disease. The specimen may be drawn before detectable antigen is present.

The stability of the control and test lines beyond the reading time (10 minutes to 2 hours) has not been validated.

LIMITATIONS OF THE PROCEDURE

1. The assay performance characteristics have not been established for matrices other than serum, plasma, whole blood, and CSF.
2. Finger stick whole blood should be measured with a pipette for proper accuracy.[17]
3. Titers obtained by the CrAg LFA are not equivalent to titers obtained by other cryptococcal antigen tests.[18]
4. Depending on the disease and organism prevalence, testing should not be performed as a screening procedure for the general population. The predictive value of a positive or negative serologic result depends on the pretest likelihood of cryptococcal disease being present.
5. Testing hemolyzed serum samples could lead to false negatives and false positives due to the high background color on the strip.
6. Weakly encapsulated strains can lead to false negative results.[19]
7. According to published reports, *T. beigelii* can cause false positives.[20]
8. Patients with high levels (> 40 µg/mL) of heterophilic antibodies such as human anti-mouse antibodies (HAMA) may cause false positives.
9. At high concentrations (> 0.1 mg/mL), antigens from Paracoccidioides brasiliensis may exhibit some cross-reactivity.
10. Some cross-reactivity was observed with human sera containing *Aspergillus* GM.
11. The CrAg LFA has not been evaluated in neonatal patients.
12. Flat-bottom reservoirs should be used during testing to maintain sufficient contact between the specimen and the CrAg LFA Test Strip.

13. Partial test lines that only develop on one half of the test strip should be interpreted as invalid and repeat testing should be performed to confirm positive or negative results.
14. Patients with extremely high concentrations (≥ 0.140 mg/mL) of cryptococcal antigen can result in weak test lines and, in some instances, yield false negatives.

EXPECTED VALUES

The frequency of cryptococcosis is dependent on several factors including patient population, type of institution, and epidemiology. In this study, 100% of true positives as determined by culture and/or India Ink were detected.

SPECIFIC PERFORMANCE CHARACTERISTICS

CLINICAL SENSITIVITY AND SPECIFICITY

The CrAg LFA was compared to the gold standard diagnoses of cryptococcosis (culture and/or India Ink) to evaluate the sensitivity and specificity of the assay. These studies contained a mix of both prospective and retrospective specimens. Summary tables of the data collected are included below.

Serum		Culture/India Ink	
		Positive	Negative
CrAg LFA	Positive	138	6
	Negative	0	152

Serum	Calculated	95% CI
Sensitivity	100%	97.4% - 100%
Specificity	96.2%	91.9% - 98.6%

Plasma		Culture/India Ink	
		Positive	Negative
CrAg LFA	Positive	81	0
	Negative	1	54

Plasma	Calculated	95% CI
Sensitivity	98.8%	93.4% - 99.8%
Specificity	100%	93.4% - 100%

Whole Blood		Culture/India Ink	
		Positive	Negative
CrAg LFA	Positive	148	11
	Negative	2	186

Whole Blood	Calculated	95% CI
Sensitivity	98.7%	95.3% - 99.8%
Specificity	94.4%	90.2% - 97.2%

CSF		Culture/India Ink	
		Positive	Negative
CrAg LFA	Positive	65	1
	Negative	0	99

CSF	Calculated	95% CI
Sensitivity	100%	94.5% - 100%
Specificity	99%	94.6% - 100%

EIA METHOD COMPARISON

The CrAg LFA was evaluated using 197 serum specimens that were submitted to a US reference laboratory for cryptococcal antigen testing. These specimens were tested using the CrAg LFA and a commercially available cryptococcal antigen EIA. The results of these comparisons are shown in the tables below.

Serum		CrAg EIA	
		Positive	Negative
CrAg LFA	Positive	96	7
	Negative	0	94

Serum	Calculated	95% CI
% Positive Agreement	100% (96/96)	96% - 100%
% Negative Agreement	93% (94/101)	86% - 97%

IMMY LATEX AGGLUTINATION METHOD COMPARISON

The CrAg LFA was evaluated using 197 serum specimens that were submitted to a US reference laboratory for cryptococcal antigen testing. These specimens were tested using the CrAg LFA and the IMMY Cryptococcal Antigen Latex Agglutination Assay. This comparison yielded an overall percent agreement of 99%.

SEMI-QUANTITATIVE METHOD COMPARISON

In addition, 62 of these specimens were tested using the semi-quantitative titration procedure in both the CrAg LFA and the IMMY Cryptococcal Antigen Latex Agglutination Assay. Linear regression analysis of the data yielded an R^2 value of 0.905.

ANALYTICAL SENSITIVITY

In order to establish the limit of detection, a C_5- C_{95} experiment was conducted on the CrAg LFA by diluting purified cryptococcal antigen in LF Specimen Diluent (REF #: GLF010) and testing 24 replicates per concentration using the CrAg Lateral Flow Test Strips (REF #: LFCR25). The results of this testing are shown in the following table:

Concentration	# Positive	% Positive
0.50 ng/mL	0	0% (0/24)
0.75 ng/mL	0	0% (0/24)
1.00 ng/mL	4	17% (4/24)
1.25 ng/mL	12	50% (12/24)
1.50 ng/mL	21	88% (21/24)
1.75 ng/mL	24	100% (24/24)
2.00 ng/mL	24	100% (24/24)
2.50 ng/mL	24	100% (24/24)
3.00 ng/mL	24	100% (24/24)

C_5 – C_{95} Interval	1.00 – 1.50 ng/mL

CROSS-REACTIVITY

The CrAg LFA was evaluated for cross-reactivity against a panel of patients' serum specimens across a variety of different pathologies. The results of this testing are shown in the table below.

Pathology	# of Samples	% Positive
Penicilliosis	5	0% (0/5)
Sporotrichosis	6	0% (0/6)
HAMA	5	0% (0/5)
Syphilis	10	0% (0/10)
Rubella	5	0% (0/5)
Mycoplasmosis	10	0% (0/10)
Toxoplasmosis	7	0% (0/7)
CMV	10	0% (0/10)
Blastomycosis	10	0% (0/10)
Coccidioidomycosis	10	0% (0/10)
Histoplasmosis	10	0% (0/10)
Candidiasis	10	0% (0/10)
Aspergillus GM+	10	10% (1/10)
Rheumatoid Factor	10	0% (0/10)

Additionally, cross-reactivity was assessed by testing crude culture filtrate antigens at a range of concentrations using the CrAg LFA. At high concentrations (> 0.1 mg/mL) antigens from *Paracoccidioides brasiliensis* exhibited some cross-reactivity.

Antigens from the following organisms were tested and exhibited no cross-reactivity:

Aspergillus terreus
Aspergillus niger
Aspergillus fumigatus
Aspergillus flavus

This assay was not evaluated for cross-reactivity against the following organisms or pathologies:

Candida dubliniensis
Candida tropicalis
Candida parapsidosis
Candida krusei
Candida glabrata
Cladosporium trichoides
Streptococcus pneumoniae
Salmonella typhi
Pneumocystis carinii
Zygomycetes
Antinuclear antibody +
Hepatitis A Virus
Hepatitis C Virus
Staphylococcus aureus
Neisseria meningitidis
Mycobacterium tuberculosis

INTERFERENCE

The CrAg LFA was evaluated for interference by testing icteric, hemolyzed, and lipemic patients' sera both unspiked and spiked with cryptococcal antigen. The unspiked sera all tested negative while the spiked sera all tested positive; thus, interference was not observed. Hemolyzed patients' sera produced high background reactivity of the lateral flow test strip which could lead to false negative and false positive results.

REPRODUCIBILITY AND PRECISION

The CrAg LFA was evaluated for reproducibility and precision by spiking serum with cryptococcal antigen to produce a panel consisting of a negative sample, a high-negative (C_5) sample, a low-positive sample, and a moderate-positive sample. This panel was tested twice per day at three sites with a total of five operators over a five-day period in order to determine both the inter-lab and the intra-lab reproducibility and precision of the assay. The results of this study are shown in the table below.

PANEL	Site 1 % Pos	Site 2 % Pos	Site 3 % Pos	Overall % Pos
Negative	0% (0/30)	0% (0/30)	0% (0/15)	0% (0/75)
High Negative	7% (2/30)	0% (0/30)	0% (0/15)	3% (2/75)
Low Positive	100% (30/30)	100% (30/30)	100% (15/15)	100% (75/75)

Moderate Positive	100% (30/30)	100% (30/30)	100% (15/15)	100% (75/75)

HIGH DOSE HOOK EFFECT (PROZONING)

Although rare, extremely high concentrations (≥ 0.140 mg/mL) of cryptococcal antigen can result in weak test lines and, in extreme instances, yield negative test results. If prozoning is suspected in weakly positive or negative test results, the semi-quantitative titration procedure should be followed to rule out false negative results.

MEASURING RANGE

The CrAg LFA measuring range of the assay falls between the LoD and the High Dose Hook Effect which is a measuring range of 1.25 ng/mL to 0.140 mg/mL.

REFERENCE PROCEDURES AND MATERIALS

There are no available reference measurement procedures or materials for the user.

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INTERNATIONAL SYMBOL USAGE

	Storage 2-30 °C	LOT	Lot Number
	Manufactured by	REF	Reference Number
	Expiration Date	IVD	In Vitro Diagnostic
	Protect from Humidity		Sufficient for "#" Tests
	Consult Instructions for Use	℞ ONLY	Prescription Use Only
	Single Use Only		

Rev. Date 2025-10-06
Rev. 2
For a list of IFU changes, email info@immy.com
To locate country specific IFUs, visit IMMY.com/resources

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