VERSÉA™ OPHTHALMICS T-POC LACTOFERRIN IMMUNOASSAY KIT INSTRUCTION FOR USE

The T-POC LACTOFERRIN IMMUNOASSAY SYSTEM is an in vitro diagnostic device for the quantitative measurement of lactoferrin in human tears to assess lacrimal gland function as an aid in the diagnosis of aqueous deficient dry eye disease or keratoconjunctivitis sicca (KCS).

SUMMARY AND EXPLANATION OF THE TEST

Approximately 1/3 of the global population is affected by ocular surface disease (OSD) which most commonly results from either or a combination of ocular allergies (OA) and Dry Eye Disease (DED). DED complaints are most frequently caused by a malfunction of the lacrimal gland but can also result from an instable tear film formed during blinking. KCS, inflammation of the cornea and conjunctiva associated with dry eye may occur because of deficiencies in tear chemistry, tear volume or biomechanical failure of the eye to maintain a proper tear film. KCS patients, who wear soft contact lenses, may also run a greater risk of bacterial conjunctivitis, blepharitis, and sterile corneal infiltrates.[1]

DED most often affects adults over 50 years old. Risk factors include age, female gender, poor health, use of contact lenses, smoking, systemic drug effects (e.g. diuretics, antihistamines, antihypertensives), autoimmune diseases, low humidity, environmental factors, thyroid disease, and previous refractive surgeries.[1]

Dry eye complaints, due to a malfunction of the lacrimal gland, can be neurogenic, iatrogenic or, most frequently, degenerative in nature. Degeneration of the lacrimal gland is usually an isolated, involutional process (most of the patients are women over 50 years of age). This degeneration can be part of a general disease, the "sicca syndrome", i.e., KCS in combination with xerostomia. It can also be part of a systemic disease, Sjogren's Syndrome, i.e., KCS or xerostomia in combination with rheumatoid arthritis or other connective tissue diseases.

Normal tear film dynamics include distribution, turnover (and drainage), evaporation, and absorption of the tears. DED is a multifactorial disorder of the tear film caused by decreased tear production and/or increased evaporation that leads to loss of homeostasis and tear film instability, inflammation, hyperosmolarity, and neurosensory dysfunction.[1] OA has been shown to be associated with changes in tear film composition that leads to tear film dysfunction.[2] Despite the fact that DED and OA are different ocular conditions, there is significant clinical overlap between the two diseases and OA and DED can be considered as predisposing or, at least, facilitating conditions to each other, or co-existing conditions.[3] It is essential to consider the implications of both DED and OA together in the effective management of ocular surface disease.

Changes in the quality and quantity of tears will lead to the development of OSD and these parameters are important for making a correct diagnosis. DED is separated into two primary underlying mechanisms, 1) aqueous production deficient dry eye disease (ADDE); 2) evaporative dry eye disease (EDE). The aqueous layer accounts for most of the thickness of the tear film and is produced primarily by the main and accessory lacrimal glands. The lipid layer is produced by the meibomian glands and serves to stabilize the tear film and protect it from evaporation.[4] ADDE reflects a reduction of lacrimal secretion and EDE is due to excessive fluid loss from the exposed ocular surface in the presence of normal lacrimal secretory function which both lead to tear film instability, increased tear film osmolarity, and inflammation.

Lactoferrin is a glycoprotein secreted by acinar cells of the main and accessory lacrimal glands and binds iron, providing both an antibacterial and anti-inflammatory effect on the ocular surface.[5] The secretions of the lacrimal gland that form the majority of the aqueous component of the tear film contain proteins including lactoferrin and lysozyme, enzymes, immunoglobulins, and electrolytes that are involved in maintaining the health of the ocular surface.[6] Lactoferrin is one of the important predictors of the stability and volume of the tear film. The concentration of lactoferrin is reduced in the setting of ADDE and is shown to be significantly reduced in the tears of both non-Sjogren's and Sjogren's Syndrome patients with DED as well as patients with chronic medication-induced DED.[5] A tear film sample used to measure protein components of lacrimal secretions, such as lactoferrin, have found altered levels in the tear film of patients with ocular surface disease. This allows lactoferrin to serve as a novel biomarker for DED.[7] A prospective study examined 103 dry eye patients into three groups: Sjogren's syndrome (n: 23); dry eye not associated with Sjogren's (n: 71); and Stevens-Johnson syndrome (n: 9). Sixteen normal patients also had their tears tested. The investigators found that the concentration of lactoferrin was significantly decreased in tears of non-Sjogren's (p=0.0001), Sjogren's (p=0.00005) and Stevens-Johnson syndrome compared to control patients. The study's researchers confirm that the tear components in dry eye patients differ from those in normal patients both quantitatively and qualitatively.[7]

Tear volumes from the lacrimal gland are observed to have a positive correlation with the concentration of lactoferrin. Lactoferrin levels have an inverse correlation with corneal staining scores and a negative correlation to OSDI scores. The fluorescein staining score and lactoferrin concentration are inversely correlated. TBUT and Schirmer test values tended to have a positive correlation with lactoferrin.[8] Patients with lower tear production tend to have lower lactoferrin concentration.[9] Further, a direct correlation between lactoferrin concentration and TBUT time[6] as well as a significant negative correlation was found between Rose Bengal staining score and level of tear lactoferrin in dry eye patients with either primary or secondary Sjogren's Syndrome as well as DED without a diagnosis of Sjogren's Syndrome.[10] In comparison with traditional diagnostics such as the STT, the vital dyes and the tear film break-up-time, the lactoferrin test is reported to be the most reliable, single marker in the diagnosis of KCS.[11] Lactoferrin levels are normal, and not reduced, in the setting of meibomitis related rosacea[12] and OA.[13] A fall in lactoferrin has been often reported as a good indicator of contact lens intolerance.[14] Tears obtained from 38 normal human subjects contained a mean lactoferrin content of 2.2 mg/ml (g/l). No differences in the mean level of lactoferrin were found when tears were collected by either Schirmer tear strips or by glass capillaries after short tear gas stimulation. Tear lactoferrin levels were not influenced by age or sex of the subjects investigated in this study. It was found that lactoferrin represents approximately 25% by weight of the total tear protein[7] Since Lactoferrin is produced by the accessory and lacrimal gland it has been shown to be in similar concentrations in both basal tears and in reflex tears.[15] A cutoff for lactoferrin below 0.9-1.1 mg/ml provides optimal accuracy for the diagnosis of DED[16] and confirms the presence of ADDE while patients less than 1.5 mg/ml are borderline and may benefit from closer management. Lactoferrin has been advocated for the diagnosis of primary Sjogren's Syndrome, where the test had a sensitivity of 72% and specificity of 95% while Schirmers had a sensitivity of 64% and specificity of 85%[17] while in patients with non-Sjogren's Syndrome DED, lactoferrin showed a sensitivity 79.4% and specificity of 78.3%.[18] A recent meta-analysis confirms a significant decrease in lactoferrin concentrations in the tears of subjects affected by DED.[19] The severity of the DED correlates with lower levels of the biomarker[6] and a decrease of lactoferrin accompanies the course of DED progression.[20] With age, there is a slight decrease in the tear fluid concentrations of the proteins originating from the lacrimal gland.[21] The decrease of tear lactoferrin levels in patients suffering from an abnormal degeneration of the lacrimal gland can be very dramatic. In severe cases of KCS, lactoferrin may be undetectable.[22, 23] Lactoferrin concentrations respond to treatment and allow for therapeutic monitoring. Treatment of DED with punctal occlusion[24] and cyclosporine[25] was associated with increased tear lactoferrin levels.

The difficulty in diagnosis and evaluation of the severity of DED is potentially attributed to an inconsistent correlation between reported symptoms and observed signs.[26] Symptoms alone are inadequate for the differential diagnosis of OSD, because the same symptoms can be experienced from a wide variety of ocular surface and tear film disorders[27] such as DED, OA, blepharitis, meibomian gland dysfunction (MGD) and bacterial or viral infections.[28] Symptoms alone are inadequate for the differential diagnosis of OSD, because the same symptoms can be experienced from a wide variety of ocular surface and tear film disorders[27] such as DED, OA, blepharitis, meibomian gland dysfunction (MGD) and bacterial or viral infections.[28] Only about 2/3 of patients with dry eye symptoms test positive for DED with traditional confirmatory tests.[30] Some patients complain of severe ocular irritation and have minimal objective signs such as punctate corneal fluorescein staining, whereas others present with severe staining and have minimal irritation.[30]

Typical ocular surface related symptoms include eye irritation, a gritty or foreign body sensation, burning, tearing, photophobia, stinging, intermittent sharp pain and blurry vision that improves with blinking or instillation of non-viscous artificial tears. Adverse environments that generate desiccating stress including low humidity, high temperature, air conditioning, and activities that lead to reduced blinking such as computer use, driving, watching television, and reading can trigger and/or exacerbate dry eye symptoms.[31]

The T-POC LACTOFERRIN IMMUNOASSAY SYSTEM is a sensitive immunological device which may enable early detection of malfunctioning lacrimal glands. It does this by measuring lactoferrin, a protein in tears which is derived exclusively from the lacrimal and accessory lacrimal glands. Symptoms alone are inadequate for the differential diagnosis of OSD, because the same symptoms can be experienced from a wide variety of ocular surface and tear film disorders[27] such as DED, OA, blepharitis, meibomian gland dysfunction (MGD) and bacterial or viral infections.[28] Early detection can permit knowledgeable management of the disease.

Multiple studies have demonstrated the low value of normal tear lactoferrin levels to be ≥ 1.5 mg/mL. Lesser values indicate lacrimal gland dysfunction (see below under "ASSESSMENT OF RESULTS"). The lower the lactoferrin value, the greater the dysfunction of the lacrimal gland.

PRINCIPLE OF THE TEST

The T-POC LACTOFERRIN IMMUNOASSAY SYSTEM consists of the T-POC LATERAL FLOW READER and a lateral flow immunoassay device. This system is used for the quantitative determination of lactoferrin levels in tears.

The lateral flow immunoassay device uses rabbit antibody to human lactoferrin coupled to gold nanoparticles as the conjugate, with rabbit anti-human lactoferrin antibody on a nitrocellulose membrane. With the addition of a diluted tear sample, immune complexes are formed by the interaction of lactoferrin in the sample with the conjugated gold nanoparticles. These antibody/ lactoferrin complexes flow past the antibody on the nitrocellulose where they are bound and immobilized. The accumulation of gold particles produces a color formation on the membrane, which is measured by the READER. If no lactoferrin is present in the tear sample, the conjugated antibody cannot be bound specifically, so little or no color develops. The T-POC LATERAL FLOW READER (LFR) interprets the intensity of color development which is directly proportional to the concentration of lactoferrin in the tear sample being tested.

KIT COMPONENTS

The T-POC LACTOFERRIN IMMUNOASSAY KIT requires the following:

50 – foil-pouched Test Cassettes

100 – 1.0 µL microcapillary tubes (for sample collection)

2 bulbs for connecting to the microcapillary tubes

100 – Diluent vials filled with 1 mL of assay running buffer

1 Unfoldable vial rack

Lateral Flow Reader (not included)

STORAGE INSTRUCTIONS

1. T-POC LACTOFERRIN IMMUNOASSAY KIT should be stored at room temperature.
2. The expiration dating indicates the limits of stability. The expiration dating is as indicated on the Kit packaging.

ADDITIONAL MATERIALS REQUIRED (available from VERSÉA™ OPHTHALMICS)

The VERSE A™ OPHTHALMICS T-POC LATERAL FLOW READER (LFR)
T-POC LACTOFERRIN Validation Accessory Kit T-POC
LACTOFERRIN Control Set
T-POC LACTOFERRIN Linearity Kit

REAGENT PREPARATION

None.

WARNINGS AND PRECAUTIONS

1. The test cassette should remain in the sealed pouch until ready for use.
2. Do not smoke, eat or drink in the areas where specimens or Kit components are handled.
3. All specimens, reagents, and controls should be potentially hazardous and handled in the same manner as infectious agents.
4. Wear disposable gloves while handling samples and wash hands after the assay is complete.
5. The test cassette and all materials should be discarded in a proper biohazard container after testing.
6. For *in vitro* diagnostic use only.
7. Materials should not be used after the expiration date shown on the package label.

HEALTH AND SAFETY INFORMATION

WARNING: In accordance with the principles of good laboratory practice (GLP) it is recommended that all samples be treated as potentially infectious.

PROCEDURAL NOTES

1. Although the T-POC LACTOFERRIN IMMUNOASSAY SYSTEM is very easy to perform, reliable results will only be obtained when the instructions are followed precisely.
2. TEST CASSETTES may be used only once.
3. A new microcapillary tube must be used to obtain each patient tear sample or standard and used to transfer 1.0 µL of tear sample into the diluent vial.

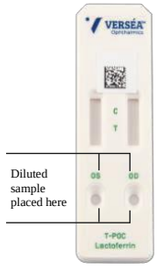
TEST CASSETTE

The TEST CASSETTE has two ports for the diluted tear samples to be delivered (left eye sample on the left (OS) and right eye sample on the right (OD)).

SPECIMEN COLLECTION

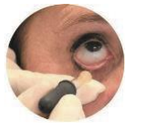
To avoid contamination, please use gloves to collect the sample.

TEST PROCEDURE



Step 1: Assemble the tear collector by inserting supplied glass microcapillary into the associated rubber bulb assembly with about a third of the microcapillary tube visible in the bulb assembly. Stabilize the bulb with glass microcapillary between the thumb and the middle finger, making sure the hole on top of the bulb is not closed with your index finger.

Note: The microcapillary tube container has a protective plastic foam plug under the cap which must be removed before the glass microcapillary tubes may be dispensed from their container. Once the plug is removed, replace the cap, and obtain individual microcapillary tubes by gently shaking container and allowing the tubes to emerge through the hole in the cap.



Step 2: Tear sample is obtained through capillary action by placing the glass capillary tube in contact with the tear film at the lid margin or from the inferior fornix (near the lateral or medial canthus) with the glass microcapillary tube. As needed, gently retract the lower eyelid to expose the inferior cul-de-sac. Place the microcapillary tube into the tear lake at the inferior medial or lateral canthal region. Tears are drawn into the microcapillary tube by microcapillary action by establishing contact with the tear film. Ensure the microcapillary is completely filled. The utilization of a slit-lamp or a handheld light may be useful to visualize sample fill.

Note: Use a new microcapillary tube for collecting each tear sample (one for each eye) and dispose of the microcapillary tube after the tears are transferred to the diluent vial. The rubber bulb is reuseable.

Step 3: After each collection the sample is transferred into a diluent vial. Insert the micropipette tip under the diluent surface and squeeze the bulb. You should see bubbles evolving. Pull the microcapillary tube out of the diluent vial before releasing compression of the bulb. Replace the green cap on the diluent vial and mix by rocking the vial 3-5 times. Remove and discard the green cap and replace it with the attached dropper tip. Set the vial aside and repeat Steps 1-3 for the next eye.

Step 4: Once the samples are ready, remove TEST CASSETTE from its foil pouch and place it into the open READER tray.

Step 5: Holding the dropper vial vertically above the appropriate cassette port, add two (2) drops of diluted sample from the corresponding diluent vial to port labeled OS for the left eye and port labeled OD for the right eye.

Step 6: Gently slide the tray with the TEST CASSETTE into the READER until it clicks into place and press [TIMED SCAN] button on the touch screen.

Step 7: After 8 min countdown, the READER displays the result for the left eye under [OS Strip] tab and the result for the right eye under [OD Strip] tab.

• If the control values are valid, the patient values are also acceptable. If the control values are invalid the run is unacceptable. Retest the patient.

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ASSESSMENT OF RESULTS

To evaluate the patient lactoferrin level, assess the following:

1. The reader display for the control must be valid.
2. If the patient value is >1.2 mg/mL, this indicates a normal tear lactoferrin level.
3. If the patient value is <0.9 mg/mL, this indicates an abnormal lactoferrin level and appropriate therapeutic action should be taken.
4. If the patient value is between 0.9 and 1.2 mg/mL, the patient should be retested on the next visit, since in the early stages of KCS the values can fluctuate strongly.
   - If, on retesting, the patient value is still between 0.9 and 1.2 mg/mL, it may be assumed that the tear lactoferrin concentration for this patient is within the lower range of normal.

- If, on retesting, the patient value is <0.9 mg/mL, the patient appears to be in the initial stages of lacrimal gland dysfunction, and appropriate monitoring and therapeutic steps should be taken.

5. The lower the tear lactoferrin concentration, the worse the lacrimal gland dysfunction.

LIMITATIONS OF THE PROCEDURE

The physician should consider the results obtained with this system as additional information to that obtained from patient history, clinical presentation, other assays, etc. Patients may have diminished lactoferrin levels but are not presenting with KCS, and conversely, patients may have normal lactoferrin levels but are presenting with symptoms of KCS. KCS cannot be diagnosed as the single disease state when lactoferrin levels appear to be diminished, nor should it be ruled out when levels appear to be normal. Apart from KCS, a decrease in tear lactoferrin has been reported in a number of other diseases. Most reports in which a substantial decrease of lactoferrin was reported dealt with the acute phase of various infections, accompanied by excessive tearing. These conditions, however, are not likely to be confused with KCS. Decreased levels of lactoferrin have been reported in acute adenovirus conjunctivitis,[32] acute giant papillary conjunctivitis,[33] acute herpes simplex infection,[34] acute post-operative infection,[35] severe protein malnutrition[36] and trachoma.[37]

Normal lactoferrin levels have been reported in acute dendritic keratitis,[38] chronic blepharitis,[39,40] chronic conjunctivitis,[41] chronic giant papillary conjunctivitis (GPC),[33] diabetes,[42] meibomianitis,[43] ocular allergy,[44] ocular pemphigoid[45] and rheumatoid arthritis.[44]

The T-POC LACTOFERRIN IMMUNOASSAY test procedure must be closely followed.

PERFORMANCE CHARACTERISTICS OF THE TEST

Precision: Using a 0.25 mg/mL standard, the precision of the T-POC LACTOFERRIN ASSAY SYSTEM averaged 10% CV. Using a 2.5 mg/mL standard, the precision of the LACTOFERRIN ASSAY SYSTEM averaged 15% CV.

Dynamic range: The T-POC LACTOFERRIN ASSAY SYSTEM can accurately measure human lactoferrin concentrations between 0.25 and 2.5 mg/mL.

Interference: The following levels of human tear proteins do not cross-react or interfere with the T-POC LACTOFERRIN ASSAY SYSTEM:
IgA: 0-5.0 µg/mL; IgG: 0-5.0 µg/mL; IgE: 0-25 µg/mL; Albumin: 0-25 mg/mL; Lysozyme: 0-2.5 mg/mL; Transferrin: 0-250 mg/mL.

Clinical data:

Normal population with >0.9 mg/mL tear lactoferrin:	85/86	98.8%
Normal population with <0.9 mg/mL tear lactoferrin:	1/86	1.2%
Severe KCS patients with <0.9 mg/mL tear lactoferrin:	20/24	83.3%
Severe KCS patients with >0.9 mg/mL tear lactoferrin:	4/24	16.7%

Quality control:

Quality Control: U.S. CLIA Regulation requires that 2 controls be run on each day of patient sample testing and when there is a change of lot number. Refer to the corresponding package insert for controls.
External controls are available but not provided with the testing kit. Perform quality control testing per your laboratory protocol. The lab may implement an IQCP protocol. Refer to the laboratory IQCP plan for QC testing frequency.

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SYMBOL GLOSSARY


Manufacturer


Use-by date

Batch code

Catalog number

In Vitro diagnostic medical device


Consult instruction of use


Do not re-use

Temperature limit

Contains sufficient for 2 tests

Contains sufficient for 100 tests

Unique device identifier

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AP0054.1 OPH-008-10052023-v1