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PATHFAST™ Presepsin

<REAGENT FOR PATHFAST>

60 Tests

English

▪ Intended Use

PATHFAST Presepsin is a product for in-vitro diagnostic use with the in vitro diagnostic (IVD) automated analyser PATHFAST for the quantitative measurement of presepsin in human heparinized or EDTA whole blood and plasma. PATHFAST Presepsin is intended to be used:

- as an aid in the diagnosis and prognosis of sepsis,
- in the assessment of the degree of septic severity,
- in the risk stratification of critically ill septic patients,
- by laboratory technician, nurse or physician,
- in hospital including emergency room, doctor's office and clinical laboratory.

PATHFAST Presepsin is a device for near patient testing (NPT).

▪ Summary

CD14 is a glycoprotein expressed on the surface membrane of monocytes/ macrophages (mCD14) and serves as a receptor for complexes containing the pathogen associated molecular patterns, such as lipopolysaccharides (LPS) and LPS binding protein (LBP) complexes. mCD14 co-localizes with toll-like receptor 4 (TLR4). Upon binding of the LBP and LPS complex, CD14 activates the TLR4-specific proinflammatory signalling cascade thereby starting the inflammatory reaction of the host against infectious agents. The soluble CD14 (sCD14) is released into circulation by shedding from the cell membrane. However, protease activity generates also another sCD14 molecule called sCD14 subtype (sCD14-ST) or presepsin (1-3). Presepsin levels were found significantly higher in septic patients than in apparently healthy individuals as well as in patients with SIRS (systemic inflammatory response syndrome) (3). Presepsin secretion is also related to phagocytosis and cleavage with lysosomal enzymes (4). Presepsin levels were elevated earlier than IL-6 and D-dimer along with occurrence of blood bacteria in a rabbit cecal ligation and puncture (CLP) model (5).
The determination of the presepsin concentration can be used in emergency room (ER) and intensive care units (ICU) as shown by clinical studies, not only for diagnosis (6-9) and prognosis (10-12) of sepsis, but also to monitor the course of the disease and the responses to therapeutic interventions (13-21).

▪ Test principle

The PATHFAST Presepsin procedure is based on chemiluminescent enzyme immunoassay (CLEIA) and MAGTRATION. All required components for performing the testing are packed in one reagent cartridge. By loading PATHFAST Presepsin into the in vitro diagnostic system PATHFAST, presepsin can be accurately quantified within 17 min. In this procedure, alkaline phosphatase labelled anti-Presepsin polyclonal antibody (PoAb) and anti-Presepsin monoclonal antibody (MoAb) coated magnetic particles are mixed with the sample. Presepsin contained in the specimen binds to the anti-Presepsin antibodies forming an immunocomplex with enzyme labelled antibody and antibody coated magnetic particles. After removing the unbound enzyme labelled antibody, a chemiluminescent substrate is added to the immunocomplex. After a short incubation, the luminescence generated by enzyme reaction is detected. The presepsin concentration in the specimen is calculated by means of a standard curve.
*"MAGTRATION" is technology of B/F separation where magnetic particles are washed in a pipette tip and is a trademark or registered trademark of Precision System Science Co., Ltd.

▪ Package composition of materials provided

Reagent cartridge 6 cartridges x 10 trays
The reagent cartridge consists of 16 wells. All wells with the exclusion of the sample well (# 1) and counting well (# 10) are covered with an aluminium seal having a bar code. All reagents for the test are filled in each well of the reagent cartridge. Do not reuse a reagent cartridge. This is designed for single use only.

Wells	Form	Ingredient	Quantity	Source
# 1	Empty	Sample well	-	-
# 2	Liquid	Alkaline phosphatase conjugated anti-Presepsin PoAb, Na azide (< 0.1%)	50 µL	Microorganism Rabbit
# 7	Liquid	anti-Presepsin MoAb coated magnetic particles	50 µL	Mouse
# 13	Liquid	Chemiluminescent substrate, CDP-Star	100 µL	-
# 11	Liquid	Sample dilution buffer Na azide (< 0.1%), Triton X-100 (< 0.1%)	50 µL	-
# 3, 4, 5	Liquid	Washing buffer Na azide (< 0.1%), Triton X-100 (< 0.1%)	400 µL	-
# 1, 6, 8, 9, 10, 12, 14, 15, 16 are empty wells. "CDP-Star" is a trademark or registered trademark of Applied Biosystems, LLC.				

Calibrator 1 (CAL-1)	2.0 mL x 1 bottle (liquid)
Calibrator 2 (CAL-2)	For 1.2 mL x 2 vials (lyophilized)
Calibrator diluent	1.2 mL x 2 bottles (liquid, Na azide < 0.1%)
MC ENTRY CARD	1 sheet
Instruction for use	1 sheet
CONTROL DATA SHEET	1 sheet

Materials required but Not Provided
PATHFAST Analyser (Product #: 300929) and consumables
PATHFAST TIP (Product #: 300936)
PATHFAST WASTE BOX (Product #: 300950)
PATHFAST Presepsin Control (Product #: PF0201C)
PATHFAST SAMPLE DILUENT 2 (Product #: PF02D)

▪ Precautions and warnings

1. Do not peel off the aluminium seal of the reagent cartridge.
2. Handle the reagent cartridge by holding the edge of it and do not touch the aluminium seal or the black well with your fingers.
3. When the reagent cartridge is dropped and damaged, do not use it.
4. Avoid contamination of saliva in the black well.
5. Avoid contamination of foreign substances such as fungi, bacteria and detergent into the specimen.
6. After a certain period of storage or shipment, there may be some reagents adhered to the aluminium seal. If such a condition is observed, gently tap the cartridge on the table before use.
7. Store the reagent cartridges in an upright position at all times.
8. Used reagent cartridges contain bodily fluids. Handle with appropriate care to avoid skin contact and injection.
9. Azide can react with copper and lead used in some plumbing systems to form explosive salts. When disposing of azide-containing materials, they should be flushed away with large volumes of water.
10. Dispose of all measured reagents and materials according to the standard disposal method. For example, autoclave at 121 °C for 20 minutes. Follow general precautions and handle all components as if capable of transmitting infectious agents.
11. The PATHFAST reporting system contains error codes to warn the operator of specific malfunctions. Any reports containing such error codes should be held for follow-up. See the PATHFAST operator's manual.
12. Patient samples may contain heterophilic antibodies that could react in immunoassay to give a falsely high or low result. This assay has been designed to minimize interference from heterophilic antibodies. Nevertheless, complete elimination of this interference from all patient specimens cannot be guaranteed. A test result that is inconsistent with the clinical picture and patient history should be interpreted with caution.
13. The results should be evaluated in context of all laboratory findings and the total clinical status of the patient. In cases where the laboratory results do not match the clinical picture or history, additional tests should be performed.
14. When any serious incident occurs in relation to the product, report to the manufacturer and the competent authority in which the user and/or the patient is located.

Storage and expiration
1. Store at 2 - 8 °C.
2. Store the cartridge tray with the label side up.
3. Avoid water damage during storage.
4. Do not open the cartridge tray until just before use.
5. Avoid contamination and exposure to direct sunlight.

6. CAL-1 can be used until the expiration date after opening.
7. CAL-2 is stable for 14 days at 2 - 8 °C and 6 months at -20 °C or lower after reconstitution.
8. The expiration date is listed on each reagent cartridge and kit box label.
9. Do not use reagents beyond the indicated expiration date.

Sample collection
Use whole blood or plasma collected with qualified collection tube containing Na-heparin, Li-heparin or EDTA.
When collecting samples, dispense whole blood from the primary collection tube and avoid long-term shaking such as blood cell counting (22). Avoid vigorous mixing, including vortex mixing and long gentle mixing. Before processing mix, and then centrifuge at 2500 - 3000 x g for 10 minutes all previously frozen specimens and those stored longer than 12 hours.

Sample stability
Whole blood sample must be stored at 2 to 25 °C and analysed within 4 hours after collection.
EDTA and heparin plasma samples are stable under the conditions below:

2 to 25 °C:	24 hours
-20 °C or lower:	2 months (freeze only once)

Sample volume: 100 µL

▪ Preparation and procedure
Refer to the PATHFAST operator's manual for detailed information of the analyser operation.

Reagent preparation
1. Reagent cartridge: Ready to use.
2. CAL-1: Ready to use. (Limited to use with reagent of the same lot.)
3. CAL-2: Transfer the whole volume of one bottle of calibrator diluent into one vial of CAL-2. Do not use different lots of calibrator diluent to dissolve CAL-2. Stand for 15 minutes at room temperature after the reconstitution. Mix gently and ensure that calibrator is completely dissolved. (Limited to use with reagent of the same lot.)

Installation of master calibration curve
1. Installation of a master calibration curve is necessary when a new reagent lot is used.
2. Install the master calibration curve by reading the bar code on MC ENTRY CARD, which is enclosed in each package, with the hand-held bar code reader of PATHFAST.

User calibration
1. User calibration is necessary when a new reagent lot is used after installation of the master calibration curve from MC ENTRY CARD.
2. User calibration is also necessary every 4 weeks after the first user calibration. (MC ENTRY CARD is not required.)
3. The calibrators, CAL-1 and CAL-2, must be tested both in duplicate. Therefore, 4 reagent cartridges, two for CAL-1 and two for CAL-2 are necessary for user calibration.
4. Place the reagent cartridges in the cartridge rack, and then dispense approximately 100 µL of CAL-1 and CAL-2 in sample wells to load onto PATHFAST.
5. Push the START button of PATHFAST and perform assay for the calibration.

Quality Control assay (QC assay)
1. QC assay is indispensable for assuring validity of sample results. QC assay is performed after every calibration to check the calibration curves and to obtain data from QC samples for quality control. After each calibration, with each new shipment of previously calibrated test kit, or whenever the institution wishes to verify the performance of the system, analyse two levels of quality control material with known concentrations of presepsin.
2. Good laboratory practice recommends the use of appropriate quality controls. It is recommended to follow national, federal, and local guidelines for quality control. If controls do not perform as expected, do not use the test results. Repeat the test or call your authorized PATHFAST distributor for technical service.

Sample assay
1. Place the reagent cartridge in the cartridge rack, then dispense approximately 100 µL of sample into a sample well of a cartridge.
2. Load the cartridge rack onto PATHFAST and push the START button of PATHFAST to perform sample assay.

Note
1. When a whole blood sample is used, the whole blood contained in a blood collection tube should be mixed gently just before dispensing. (Do not use a vortex mixer.) After dispensing the whole blood sample and loading the cartridge on PATHFAST, the assay must be started immediately.
2. When fibrin threads or clots and other insoluble materials are present in the plasma sample, such material must be removed by centrifugation or filtration.
3. When samples are left for more than 5 minutes after dispensing into a sample well, a lower result will be obtained analysing whole blood because of blood sedimentation and a higher result will be obtained analysing plasma because of increasing presepsin concentration by evaporation.
4. When a whole blood sample is used, input of an individual haematocrit value of the sample in PATHFAST is optional.
5. Samples with result above 20000 pg/mL should be diluted with sample diluent (Product #: PF02D) and retested if a quantitative result is desired or alternatively, they can be reported as > 20000 pg/mL. The recommended dilution is 1:5.

・Specific performance data
Representative performance data on the PATHFAST are given below.

Metrological traceability
The calibrator for PATHFAST Presepsin is traceable to in-house standard material assigned by amino acid analysis (23).

Precision (repeatability)
Precision was assessed with whole blood and plasma samples at each 4 concentration levels. The samples were tested in 20 replicates. The following results were obtained.

Whole blood	Mean (pg/mL)	S.D. (pg/mL)	C.V. (%)
Level-1	76.8	6.06	7.9
Level-2	2061	57.2	2.8
Level-3	8793	324.8	3.7
Level-4	17198	478	2.8

Plasma	Mean (pg/mL)	S.D. (pg/mL)	C.V. (%)
Level-1	66.6	4.30	6.5
Level-2	1987	67.4	3.4
Level-3	8147	203	2.5
Level-4	15851	428	2.7

Precision (reproducibility)
Plasma samples at 4 concentration levels within the measurement range were assayed in duplicate in each run, 2 runs per day, for 20 days with 1 reagent lot on 1 instrument, for a total of 40 runs. The within-run and total coefficient of variations (C.V.) were calculated with standard deviations (S.D.) according to the CLSI EP5-A2 protocol. The following results were obtained.

Sample	Mean (pg/mL)	Within-run precision		Total precision	
		S.D. (pg/mL)	C.V. (%)	S.D. (pg/mL)	C.V. (%)
Level-1	445	19.8	4.4	20.0	4.5
Level-2	882	25.9	2.9	37.8	4.3
Level-3	4801	154	3.2	197	4.1
Level-4	19292	753	3.9	956	5.0

Analytical sensitivity
Limit of blank (LoB): 2.53 pg/mL
Limit of detection (LoD): 8.86 pg/mL
Limit of quantitation (LoQ): 38.4 pg/mL (C.V. 10%)

Linearity
Presepsin antigen was spiked into plasma at 4 concentration levels (3629, 9462, 15453, 22975 pg/mL). The samples were serially diluted with 5 or 10-fold and assayed. The recovery rate against the theoretical value was within 86 - 105% up to 20000 pg/mL.

Assay range: 20 - 20000 pg/mL
The assay range was set from the results of LoD and linearity.

High dose hook effect
Presepsin antigen was spiked into plasma at the concentration of approximately 4000000 pg/mL. The samples were diluted with plasma and assayed. There was no high dose hook effect for the samples with their presepsin values up to 4000000 pg/mL.

Analytical specificity
Interference of endogenous substances
The following factors were found to have an effect of less than 10% on the assay at the concentrations indicated in parentheses.

Free bilirubin	(40 mg/dL)
Conjugated bilirubin	(40 mg/dL)
Lipemia	(2000 FTU)
Triglyceride	(1000 mg/dL)
Haemoglobin (haemolysis)	(600 mg/dL)
Rheumatoid Factor	(500 IU/mL)

Interference of exogenous substances

The following drugs which might be used in target patients were found to have an effect of less than 10% on the assay at the concentrations indicated in parentheses.

Acetaminophen	(20 mg/dL)
Acetylsalicylic Acid	(65.2 mg/dL)
Allopurinol	(4.0 mg/dL)
Ampicillin	(5.3 mg/dL)
Ascorbic Acid	(6 mg/dL)
Atenolol	(1 mg/dL)
Caffeine	(10 mg/dL)
Captopril	(5 mg/dL)
Digoxin	(0.61 µg/dL)
Dopamine	(65 mg/dL)
Erythromycin	(20 mg/dL)
Furosemide	(6.0 mg/dL)
Methyldopa	(2.5 mg/dL)
Nifedipine	(6 mg/dL)
Phenytoin	(10 mg/dL)
Theophylline	(25 mg/dL)
Verapamil	(16 mg/dL)
Protein(Albumin)	(4 g/dL)
Imipenem	(2.0 mg/dL)
Cefotaxime	(200 mg/dL)
Vancomycin	(4.0 mg/mL)
Noradrenaline	(4 µg/mL)
Dobutamine	(25.0 µg/mL)

Cross-reactivity

PATHFAST Presepsin has no significant cross-reactivity with sCD14 (9.09 µg/mL).

Correlation between samples of Na-heparin plasma and other sample matrices

x	y		n	Slope	Intercept	r
Na-heparin Plasma	Plasma	EDTA-2K	104	0.989	-26.7	0.983
	Whole blood	Na-heparin	104	1.01	11.6	0.979
		EDTA-2K	104	1.02	-48.9	0.976

The regression equation was calculated by Passing-Bablok fit.

Expected values

1. Reference range

Study-1:

Using PATHFAST Presepsin assay, the reference interval for presepsin in 230 healthy individuals was determined to be: (95% interval ranging from the 2.5th to 97.5th percentile) 82.4 - 327 pg/mL. The reference range of presepsin is independent from age and gender.

Age

	All	< 30 years	30 - 39 years	40 - 49 years	50+ years
Mean	155	152	158	146	164
S.D.	54.2	54.5	38.7	48.4	66.7
Median	145	141	150	136	152
97.5th percentile	327	332	270	265	346
n	230	55	46	63	66

Gender

	All	Males	Females
Mean	155	152	159
S.D.	54.2	54.4	54.1
Median	145	142	148
97.5th percentile	327	328	318
n	230	126	104

Study-2:

Presepsin concentrations were measured in EDTA plasma samples obtained from healthy individuals (n = 119) and patient with sepsis (n = 99). ROC analysis revealed a cut off value of 337 pg/mL for discrimination between healthy individuals and patients with sepsis.

2. Decision Threshold of Presepsin in Early Risk Stratification

Presepsin at admission of 30 days outcome (20)

Presepsin (ng/L)	< 200	200 - 300	300 - 500	500 - 1000	> 1000
Sepsis Progression and mortality risk	Very low	Low	Moderate	High	Very high
Sepsis, n (%)	6 (8)	7 (10)	22 (30)	21 (28)	18 (24)
Severe sepsis / Septic shock, n (%)	1 (3)	1 (3)	2 (5)	6 (15)	30 (75)
30-day death, n (%)	1 (4)	1 (4)	3 (13)	5 (21)	14 (58)

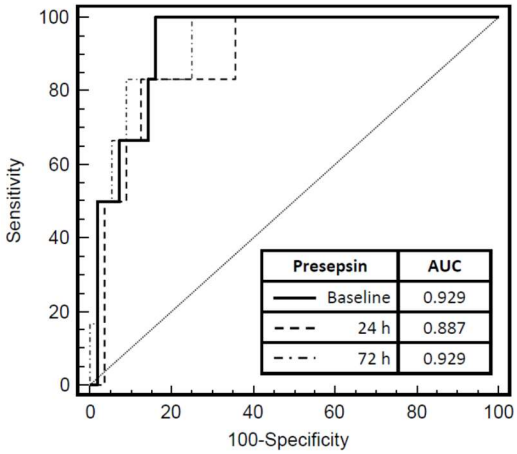
3. Sepsis-3 Criteria and Presepsin

In 2016 the Surviving Sepsis Campaign Guideline (SSCG) recommend the use of Sequential Organ Failure Assessment (SOFA) scoring to assess the severity of sepsis known as "Sepsis-3" and the SOFA score used as criteria for the diagnosis of sepsis (24). The area under the curve (AUC) values of presepsin to distinguish sepsis (with a change in SOFA score of 2 or more) without shock from non-sepsis were 0.90 (95% CI, 0.76 - 0.96). According to the AUC value, the sensitivity, specificity, PPV, NPV, and accuracy of presepsin to diagnose septic shock/sepsis using a cut off value of 508 pg/mL were 87%, 86%, 93%, 76%, and 87%, respectively (9).

4. Prognostic power

In patients suspicious for sepsis at presentation who developed sepsis during hospitalization the presepsin values were determined at baseline and compared to the 30 days mortality. Kaplan-Meier survival analysis showed that patients with presepsin values in the highest quartile (> 1858 pg/mL) revealed a mortality risk of > 60% (p = 0.0005) within 30 days after admission to hospital. Whereas the mortality in patients with presepsin values in the lower quartiles was below 20%.

The figure below represents the results of the ROC analysis regarding the prognosis of mortality using the presepsin values at baseline, 24 hours and 72 hours after presentation. The prognostic power of presepsin at baseline and at 72 hours after presentation are comparable (AUC = 0.929).



The expected value/reference values may vary from laboratory to laboratory and from country to country depending on various factors. It is therefore recommended for each institution to establish corresponding reference values. We recommend each laboratory to establish its own reference values.

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Symbols
LSI Medience Corporation uses the following symbols and signs in addition to those listed in the EN ISO 15223-1:2021 (Medical devices - Symbols to be used with information to be supplied by the manufacturer - Part 1: General requirements).

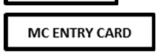
This symbol means “Device for near patient testing”.
(Symbols for self-testing and near-patient testing under the IVD Regulation 2017/746/EU. MedTech Europe. Dec. 13, 2018)

: Reagent cartridge

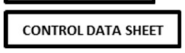
: Calibrator 1

: Calibrator 2

: Calibrator diluent



: Entry card for master calibration curve



: Datasheet for control

* PATHFAST: JP Registered Trademark No.5982733

Summary of safety and performance is available from:
European Database on Medical Devices (EUDAMED).

Contact for technical assistance
www.pathfast.eu/contact

LSI Medience Corporation
1-2-3 Shibaura, Minato-ku,
Tokyo 105-0023, Japan

PHC Europe B.V.
Nijverheidsweg 120, 4879 AZ, Etten-Leur,
Netherlands