PATHFAST™

LIFE SAVING

PRESEPSIN –
The Sepsis Biomarker
A short monograph

LSI Medience Corporation
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Sepsis is a worldwide healthcare problem

Sepsis is estimated to affect more than 30 million people worldwide every year, potentially leading to 6 million deaths (1). The burden of sepsis is most likely highest in low- and middle-income countries. Sepsis is the most common cause for readmissions to the hospital costing more than $2 billion per year (2). The number of hospital admissions for sepsis following healthcare-associated and community-acquired infections increased up to three-fold over the last decade. In comparison, hospital admissions for stroke and myocardial infarction remained stable over the same period (Fig. 1; 3). Sepsis is the number 1 cost of hospitalization in the U.S. consuming more than $24 billion each year. The average cost per hospital stay for sepsis is $18,400, double the average cost per stay compared to all other conditions (4). Moreover, it is estimated that 3 million newborns and 1.2 million children suffer from sepsis globally every year (5). Three out of ten deaths due to neonatal sepsis are thought to be caused by resistant pathogens (6). Furthermore, one in ten deaths associated with pregnancy and childbirth is due to maternal sepsis with over 95% of deaths occurring in low- and middle-income countries (7). Totally, one million newborn deaths are associated with maternal infection, such as maternal sepsis, each year (8).

What is sepsis?

Sepsis is a serious medical condition caused by an overwhelming immune response to infection. The body releases immune chemicals into the blood to combat the infection. Those substances trigger widespread inflammation, which leads to blood clots and leaky blood vessels. As a result, blood flow is impaired, organs are deprived of nutrients and oxygen and organ damage can be the final outcome. Common symptoms of sepsis are fever, chills, rapid breathing and heart rate, rash, confusion, and disorientation (9).

In 1991, an earlier sepsis definition, Sepsis-1, was established as “systemic inflammatory response to documented/suspected infection. Patients who met two or more of the SIRS criteria fulfilled the definition of the SIRS. Sepsis which is complicated by organ dysfunction was termed “severe sepsis”, which could progress to "septic shock" (10).

A 2001 SSC task force expanded the list of diagnostic criteria, resulting in the introduction of the Sepsis-2 definition (4). However, the definitions of sepsis and septic shock remained unchanged for more than two decades (11). In 2016 the task force compared traditional SIRS criteria to other methods, including the Logistic Organ Dysfunction System (LODS) and Sequential Organ Failure Assessment (SOFA) scoring. The authors recommended the use of SOFA scoring to assess the severity of organ dysfunction in a potentially septic patient and redefined sepsis, known as “Sepsis-3” and the SOFA score used as criteria for the diagnosis of sepsis. Since 2016, SCCM/ESICM recommended a simplified method termed “quick SOFA” to facilitate fast identification and risk assessment of patients at admission. To build up a SOFA score takes time and needs additional laboratory data and is therefore not easy to use for urgent clinical decisions. The definition and diagnosis criteria for “septic shock” were also revised (Fig. 2; 12, 13).

Fig. 1: Hospital admissons for sepsis in comparison to Stroke or Acute myocardial infarction (AMI)

Fig. 2: Relationship between Sepsis-2 and Sepsis-3 classification

Sepsis: systemic inflammatory response syndrome. Adapted from Carneiro et al., 2017 (13)
**Sepsis diagnosis: Time is survival**

Management of sepsis is a complicated clinical challenge requiring early recognition and management of infection, hemodynamic complications and other organ dysfunctions. The Surviving Sepsis Campaign (SSC) is a joint international program to reduce mortality caused by sepsis (11). Delays in sepsis recognition and slow initiation of treatment in multiple settings have been associated with worse outcomes, while early evidence-based treatment has been shown to improve survival (Fig. 3; 3, 12, 14). As the Surviving Sepsis Campaign’s messages evolved, the 1-hour bundle of care treatment has been introduced being a valuable tool for caregivers’ application upon recognition of sepsis/septic shock using a new diagnostic criteria (15). This bundle was reduced from 6 and 3 hours to finally 1 hour to enable more rapid interventions for adult sepsis and septic shock patients. Initiation of the sepsis treatment is critical to reduce mortality from sepsis and septic shock (Fig 4; 15).

The 1-hour bundle consists of the measurement of lactate and the obtaining of blood cultures prior to the administration of antibiotics, broad-spectrum antibiotics, or the application of intravenous fluids and vasopressors. A rapid and reliable biomarker at the point of care for the detection of sepsis which is applicable directly in the ICU or ER can support the diagnosis of sepsis (15).

**Fig. 3: Correlation of mortality rate caused by sepsis and time to effective antibiotic treatment**

![Graph showing correlation of mortality rate caused by sepsis and time to effective antibiotic treatment](adapted from World Sepsis Day by lindgruen-gmbh.com)

**Fig. 4: Scheme for detection of sepsis patients**

![Diagram showing scheme for detection of sepsis patients](qSOFA: quick Sequential Organ Failure Assessment, SOFA: Sequential Organ Failure Assessment, CRP: C-reactive protein; Adapted from Singer et al., 2016 (15))

\[\text{Suspected infection patient} \rightarrow \text{qSOFA} \geq 2? \rightarrow \text{Suspected sepsis} \]
\[\text{Assessment of organ dysfunction} \rightarrow \text{SOFA} \geq 2? \rightarrow \text{Monitoring} \]
\[\text{Sepsis} \rightarrow \text{Septic shock} \]

\[\text{Time is survival} \]

- 6 h
- 3 h
- 1 h
Medical scores and biomarkers for sepsis

Clinical scores like the Acute Physiology and Chronic Health Evaluation II (APACHE-II), Sequential Organ Failure Assessment (SOFA) score, Simplified Acute Physiology Score 2 (SAPS-2) are widely used scores in the ICU (16). The systemic inflammatory response syndrome (SIRS) criteria has been considered to be central to the diagnosis of sepsis, promoting the importance of inflammation for many years (17). SIRS criteria are composed of four symptoms (body temperature, respiratory rate, white blood cell and heart rate). When at least 2 out of 4 criteria are present, these patients are regarded as SIRS condition.

The third international consensus definitions for sepsis and septic shock (Sepsis-3) changed the definition of sepsis, where SOFA score (Tab. 1) should be used as the diagnostic criteria and quick SOFA (qSOFA) for non-ICU patients (3). qSOFA criteria (Tab. 2) shall be used as a warning system to draw attention to clinicians to perform further investigation for organ dysfunction (15).

Blood culture is considered as the most important test (the Gold standard) for the diagnosis of sepsis. However, it usually takes a day or more for microorganism cultivation and the positive blood cultures rate is not sufficient enough to determine the infection.

Creatine protein (CRP), an acute phase protein increased at inflammatory states, is routinely used in patients with suspected infection. CRP however will be elevated for reasons other than bacterial infections such as burns, severe trauma and autoimmune diseases. Since formation of CRP is triggered by cytokines it will rise late (18).

Assicot et al. reported first in 1993 that Procalcitonin (PCT) specifically increased in bacterial infection (19). PCT becomes essential for diagnosis of sepsis and for guiding their therapy and monitoring (20). In 2016, the SCCC committee recommended to measure PCT for antimicrobial therapy guidance.

Next to CRP and PCT, many other biomarkers have already been evaluated at both hyper-inflammatory and immunosuppressive states like e.g. Leucocyte count, IL-6, IL-8, IL-10, PD-1/PDL-1, IL-1, CD64, TREM-1 and others (Fig. 5, 15, 21). Unfortunately, an ideal single biomarker has not yet been identified.

---

Tab. 1: Sequential (Sepsis-related) Organ Failure Assessment Score (SOFA-Score)

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Objective measurement</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiration</td>
<td>PaO2/FIO2</td>
<td>≥400</td>
<td>&lt;400</td>
<td>&lt;300</td>
<td>&lt;200*</td>
<td>&lt;100*</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Platelets (cells/mm³)</td>
<td>&gt;150,000</td>
<td>&lt;150,000</td>
<td>&lt;100,000</td>
<td>&lt;50,000</td>
<td>&lt;20,000</td>
</tr>
<tr>
<td>Liver</td>
<td>Bilirubin, mg/dL</td>
<td>&lt;1.2</td>
<td>1.2 - 1.9</td>
<td>2.0 - 5.9</td>
<td>6.0 - 11.9</td>
<td>&gt;12.0</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>MAP (mm Hg) or vasopressor</td>
<td>MAP ≥70</td>
<td>MAP &lt;70</td>
<td>DPA ≤5</td>
<td>DPA 5.1 - 15</td>
<td>DPA &gt;15</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>GCS</td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
<td>3-6</td>
</tr>
<tr>
<td>Renal</td>
<td>Creatinine, mg/dL or urine output</td>
<td>&lt;1.2</td>
<td>1.2-1.9</td>
<td>2.0-3.4</td>
<td>3.5-4.9</td>
<td>&lt;500 mL/d</td>
</tr>
</tbody>
</table>

Tab. 2: Quick SOFA (qSOFA) for diagnosis of suspected sepsis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low blood pressure</td>
<td>SBP ≤100 mm Hg</td>
</tr>
<tr>
<td>High respiratory rate</td>
<td>≥22 breaths per min</td>
</tr>
<tr>
<td>Altered mentation</td>
<td>Glasgow coma scale &lt;15</td>
</tr>
</tbody>
</table>

Adapted from Singer et al., 2016 (15)

Fig. 5: Sequential stages of sepsis

SIRS: Systemic Inflammatory Response Syndrome, IL: Interleukin, DC: Cluster of differentiation, sTREM1: Soluble triggering receptor expressed on myeloid cells-1, CARs: Chimeric antigen receptor, PD-1: Programmed cell death protein 1, PDL-1: Programmed Death Ligand 1, BTLA: B- and T-lymphocyte attenuator, CTLA-4: cytotoxic T-lymphocyte-associated Protein 4; Adapted from Singer et al., 2016 (15)
sCD14-ST is a 13k Da fragment derived from cleavage of CD14, a glycoprotein of 55 kDa anchored to the membrane of monocytes, macrophages and polymorphic neutrophils. CD14 acts as a receptor for lipopolysaccharide (LPS) complexes and the specific LPS binding protein (LBP). It can bind to peptidoglycans and other surface structures present in both Gram-Positive and Gram-Negative bacteria. Once bound to the LPS-LBP complex, it activates the intracellular inflammatory response of the Toll-Like receptor 4 (TLR4)/MD2-complex, triggering the host’s inflammatory cascade against the infectious pathogenic agent. Phagocytosis and activity of plasma proteases (lysosomal enzymes, cathepsin D) result in the formation of the fragment sCD14 subtype, in particular the 13 kDa fragment of sCD14-ST known as Presepsin (Fig. 6, 22). The half life of the molecule in plasma is 4-5 hours, compared to 12-24 hours for PCT, allowing more effective and earlier management of the pharmacological treatment (93). Presepsin was shown to be generated during the immune response. In sepsis patients, infected microorganisms are digested by the activities of monocytes or macrophages called phagocytosis. During phagocytosis, CD14 molecules are also digested by intracellular lysosomal enzymes, such as cathepsin D, resulting in the fragmentation of CD14. The N-terminal CD14 fragment (Presepsin), is circulated again into blood which was shown by in vitro analysis (35, 36).

In addition to the phagocytosis- and receptor model, several hypotheses are proposed in terms of Presepsin production because of the findings that Presepsin was produced even in patients with a very low number of white blood cells (WBC). Presepsin is metabolized through the kidneys and excreted with the urine (36). So far, the biological activity of Presepsin remains unknown.

**Fig. 6: Schematic production of Presepsin**

TLR: Toll-like-receptor, LPS: Lipopolysaccharides, LBP: LPS-binding protein, MD-2: Molecular dynamic-2, PSEP: Presepsin, CD: Cluster of differentiation, PCT: Procalcitonin; Mod. from C. Chenevier-Gobeaux et al., 2015 (22)
Measurement of Presepsin

Presepsin can easily be measured from whole blood, plasma or serum with the compact PATHFAST™ analyzer at the point of care or in the lab. The PATHFAST™ Presepsin immunoassay is based on chemiluminescence technology and shows excellent precision. No interference was observed from bilirubin, hemoglobin, lipids, triglyceride, or rheumatoid factors. Presepsin can be measured from 20 pg/mL to 20,000 pg/mL without dilution (24). The fully automated procedure takes less than 17 minutes and it requires only 100 µl samples.

In addition to Presepsin, the PATHFAST™ reagent menu offers several other STAT assays which can be used in sepsis diagnosis such as D-Dimer, NT-proBNP, hs-cTnI, CK-MB and hs-CRP. All assays are provided in economical pre-calibrated unit-use cartridges. Up to six samples can be tested in parallel in one single run. Whole blood samples should be measured within 4 hours after collection. Plasma can be stored in the refrigerator for 3 days or may be frozen. The stability of whole blood and plasma is shown in Tab. 3. Complete Blood Count (CBC) mixing leads to unspecifically increased Presepsin values, probably caused by shear forces, whereas mixing on roller mixers or inverting mixing does not increase PSEP values (25).

Low sample volume use is an ideal property especially for pediatrics where it is sometimes difficult to obtain a sufficient amount of blood from the neonates. In whole blood samples, the effect of hematocrit can be corrected automatically or manually. There is excellent correlation between whole blood and plasma results (24). PATHFAST™ assays show no biotin interference since utilized monoclonal antibodies are alka-line phosphatase conjugated instead. Running a sample on PATHFAST™ is simple and does not require special skills.

<table>
<thead>
<tr>
<th>Specimens</th>
<th>Store condition</th>
<th>Stability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole blood (Heparin, EDTA)</td>
<td>Room temperature</td>
<td>Within 4 hours</td>
</tr>
<tr>
<td>Heparin-plasma</td>
<td>Refrigerator (-2 to 8 °C)</td>
<td>Within 3 days</td>
</tr>
<tr>
<td></td>
<td>Freezer (&lt;-20 °C)</td>
<td>One year</td>
</tr>
<tr>
<td>EDTA-plasma</td>
<td>Refrigerator (-2 to 8 °C)</td>
<td>Within 3 days</td>
</tr>
<tr>
<td></td>
<td>Freezer (&lt;-20 °C)</td>
<td>One year</td>
</tr>
</tbody>
</table>
Okamura et al. reported the Presepsin values from the measurements of heparinized plasma and whole blood samples from 127 healthy volunteers. Presepsin concentrations ranged from 105-333 pg/ml in plasma and for whole blood, 98.3-314 pg/ml, respectively (23).

Another study reported the reference interval for Presepsin with overall reference limits of 55-184 pg/ml determined from two hundred individuals (120 females, median 39 years (18-75), which values were a little lower than the values previously reported. No significant differences between males and females were shown. Also, no influence by age was shown (37). Several studies described higher reference ranges of neoptanes than those for adults (see neonatal section). The accuracy of PATHFAST™ Presepsin was evaluated by Endo et al. in 2012. The cut off value of Presepsin for discrimination of bacterial and nonbacterial infectious diseases was determined to be 600 pg/ml, with clinical sensitivity and specificity of 87.8% and 81.4%, respectively. The area under the receiver operating characteristic curve (AUC) was 0.908 (38).

Lu et al. compared biomarkers among sepsis, severe sepsis and septic shock patients. AUC values for Presepsin, PCT, CRP and WBC to differentiate sepsis from non-infectious SIRS were 0.954, 0.874, 0.859 and 0.723, respectively. The cut off of Presepsin for discrimination of sepsis and nonbacterial infectious SIRS was determined to be 407 pg/ml (39). Yamamoto et al., evaluated Presepsin accuracy with the sepsis-3 definition criteria with the cut off value of 508 pg/ml (AUC = 0.88) (40).

Recently, several systematic reviews and meta-analysis reports describe specificity and sensitivity of Prespsin (41, 42, 43, 44, 45, 46, 47, 48). Kondo et al. included 18 studies from 12 counties and evaluated Presepsin diagnostic accuracy for sepsis as the AUC was 0.87 [95% CI 0.84 to 0.90], where the AUC of PCT was 0.84 [95% CI 0.81 to 0.87]. They concluded that the overall diagnostic performance of PCT and P-SEP for infection were comparable (Tab. 4, 48).

**How to interpret Presepsin values?**

Tab. 4: Presepsin Meta-analysis

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Number of participants</th>
<th>Mean/median age</th>
<th>Study design</th>
<th>Sepsis definition</th>
<th>Cut off value</th>
<th>Prevalence</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ali, 2016 (76)</td>
<td>Egypt</td>
<td>51</td>
<td>49.8</td>
<td>Prospective</td>
<td>Sepsis-3</td>
<td>0.85</td>
<td>907</td>
<td>0.647</td>
<td>60.6%</td>
</tr>
<tr>
<td>Balci, 2003 (77)</td>
<td>Turkey</td>
<td>89</td>
<td>58</td>
<td>Prospective</td>
<td>Sepsis-1</td>
<td>2.415</td>
<td>–</td>
<td>0.461</td>
<td>85.4%</td>
</tr>
<tr>
<td>Bauer, 2016 (78)</td>
<td>USA</td>
<td>219</td>
<td>59</td>
<td>Prospective</td>
<td>Sepsis-1</td>
<td>0.74</td>
<td>–</td>
<td>0.551</td>
<td>73.1%</td>
</tr>
<tr>
<td>Behnes, 2014 (79)</td>
<td>Germany</td>
<td>116</td>
<td>62</td>
<td>Prospective</td>
<td>Sepsis-2</td>
<td>–</td>
<td>530</td>
<td>0.705</td>
<td>–</td>
</tr>
<tr>
<td>Çakir Madenci, 2014 (80)</td>
<td>Turkey</td>
<td>37</td>
<td>40</td>
<td>Prospective</td>
<td>ABA 2007*</td>
<td>0.759</td>
<td>542</td>
<td>0.393</td>
<td>75.4%</td>
</tr>
<tr>
<td>Endo 2012 (30)</td>
<td>Japan</td>
<td>185</td>
<td>66</td>
<td>Prospective</td>
<td>Sepsis-2</td>
<td>0.5</td>
<td>600</td>
<td>0.622</td>
<td>86.1%</td>
</tr>
<tr>
<td>Enguix-Armada 2016 (81)</td>
<td>Spain</td>
<td>388</td>
<td>63</td>
<td>Prospective</td>
<td>Sepsis-2</td>
<td>0.28</td>
<td>101.6</td>
<td>0.634</td>
<td>92.3%</td>
</tr>
<tr>
<td>Gibot 2004 (82)</td>
<td>France</td>
<td>76</td>
<td>60</td>
<td>Prospective</td>
<td>Sepsis-1</td>
<td>0.6</td>
<td>–</td>
<td>0.618</td>
<td>83.0%</td>
</tr>
<tr>
<td>Godnic 2015 (83)</td>
<td>Slovenia</td>
<td>47</td>
<td>N.A.</td>
<td>Retrospective</td>
<td>Sepsis-2</td>
<td>3.12</td>
<td>413</td>
<td>0.851</td>
<td>57.5%</td>
</tr>
<tr>
<td>Klouche 2016 (84)</td>
<td>France</td>
<td>144</td>
<td>58</td>
<td>Prospective</td>
<td>Sepsis-1</td>
<td>0.5</td>
<td>466</td>
<td>0.694</td>
<td>80.0%</td>
</tr>
<tr>
<td>Leli 2016 (85)</td>
<td>Italy</td>
<td>92</td>
<td>73</td>
<td>Prospective</td>
<td>Sepsis-1</td>
<td>4.4</td>
<td>843.5</td>
<td>0.281</td>
<td>84.0%</td>
</tr>
<tr>
<td>Miglietta 2015 (86)</td>
<td>Italy</td>
<td>145</td>
<td>64.4</td>
<td>Retrospective</td>
<td>Sepsis-1</td>
<td>0.88</td>
<td>–</td>
<td>0.625</td>
<td>85.7%</td>
</tr>
<tr>
<td>Romualdo 2014 (87)</td>
<td>Spain</td>
<td>226</td>
<td>67</td>
<td>Prospective</td>
<td>Original</td>
<td>0.45</td>
<td>729</td>
<td>0.164</td>
<td>75.7%</td>
</tr>
<tr>
<td>Selberg 2000 (88)</td>
<td>Germany</td>
<td>33</td>
<td>47.9</td>
<td>Prospective</td>
<td>Sepsis-1</td>
<td>3.3</td>
<td>–</td>
<td>0.667</td>
<td>86.4%</td>
</tr>
<tr>
<td>Takahashi 2016 (89)</td>
<td>Japan</td>
<td>103</td>
<td>68</td>
<td>Prospective</td>
<td>Sepsis-1</td>
<td>0.85</td>
<td>658</td>
<td>0.85</td>
<td>78.8%</td>
</tr>
<tr>
<td>Ugarte 1999 (90)</td>
<td>Belgium</td>
<td>190</td>
<td>62</td>
<td>Prospective</td>
<td>Sepsis-1</td>
<td>0.6</td>
<td>–</td>
<td>0.584</td>
<td>67.6%</td>
</tr>
<tr>
<td>van der Geest 2016 (91)</td>
<td>Netherlands</td>
<td>301</td>
<td>57</td>
<td>Prospective</td>
<td>Original</td>
<td>1.41</td>
<td>–</td>
<td>0.505</td>
<td>65.1%</td>
</tr>
<tr>
<td>Wong 2013 (92)</td>
<td>France</td>
<td>270</td>
<td>61</td>
<td>Prospective</td>
<td>Not described</td>
<td>0.5</td>
<td>–</td>
<td>0.537</td>
<td>88.3%</td>
</tr>
<tr>
<td>Yang 2016 (93)</td>
<td>China</td>
<td>300</td>
<td>64</td>
<td>Prospective</td>
<td>Sepsis-1</td>
<td>0.4475</td>
<td>–</td>
<td>0.357</td>
<td>83.2%</td>
</tr>
</tbody>
</table>

PCT: Procalcitonin, P-SEP: Presepsin; *American Burn Association Consensus Criteria; Adapted from Kondo et al., 2019 (51)
In clinical studies performed in Peru and Germany, cut off values were established. For healthy individuals the normal values of Presepsin are below 200 pg/mL. A Presepsin cut off value of 622 pg/ml excludes 30 day mortality by a Negative Predictive Value (NPV) of 98.5% (28). Based on the Presepsin values measured in the study patients with different disease severity degrees (SIRS, sepsis, severe sepsis or septic shock) and the close relationship between Presepsin and outcome decisions thresholds for risk stratification could be established (Tab. 5, 22, 26).

In Germany, another study examined the diagnostic and prognostic validity of Presepsin in 140 emergency patients. Similar decision thresholds could be identified for diagnostic differentiation of sepsis grades and mortality prediction in septic patients presenting at the Emergency Room (ER). The determination of Presepsin at presentation allowed reliable risk stratification already at the earliest time point in patients suspected for sepsis. Moreover, the Presepsin concentration during anti-microbial therapy was related to the patient’s outcome (Tab. 6, 27).

Recommendation

For a risk assessment in adult patients, threshold values given in Tab. 5 and 6 may be used. For final diagnosis, Presepsin results may support clinical findings but should not be used as a sole decision criteria.

### Tab. 5: Diagnosis of sepsis by Presepsin

<table>
<thead>
<tr>
<th>Presepsin (pg/mL)</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 200</td>
<td>Exclusion of sepsis</td>
</tr>
<tr>
<td>200-300</td>
<td>Systemic infection not probable</td>
</tr>
<tr>
<td>300-500</td>
<td>Systemic infection (sepsis) possible</td>
</tr>
<tr>
<td>500-1000</td>
<td>Significant risk of the systemic infection progression (severe sepsis), increasing risk of unfavorable outcome</td>
</tr>
<tr>
<td>≥ 1000</td>
<td>High risk of the systemic infection progression (severe sepsis/septic shock). High risk for mortality after 30 day comparable with a SOFA score ≥ 8</td>
</tr>
</tbody>
</table>

Adapted from Carpio et al., 2015 and Chenevier-Gobeaux, 2015 (22,26)

### Tab. 6: Presepsin decision thresholds at admission of 30 days outcome

<table>
<thead>
<tr>
<th>Risk stratification</th>
<th>Very low</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
<th>Very high</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presepsin (pg/mL)</td>
<td>&lt;200</td>
<td>200-300</td>
<td>300-500</td>
<td>500-1000</td>
<td>≥1000</td>
</tr>
<tr>
<td>Low grade sepsis, n (%)</td>
<td>3 (3.5)</td>
<td>9 (10.6)</td>
<td>18 (21.1)</td>
<td>29 (34.1)</td>
<td>26 (30.6)</td>
</tr>
<tr>
<td>Severe sepsis, n (%)</td>
<td>0</td>
<td>0</td>
<td>5 (12.5)</td>
<td>11 (27.5)</td>
<td>24 (60.0)</td>
</tr>
<tr>
<td>Septic shock, n (%)</td>
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<td>0</td>
<td>0</td>
<td>4 (26.7)</td>
<td>11 (73.3)</td>
</tr>
<tr>
<td>30-day death, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5 (21.7)</td>
<td>18 (78.3)</td>
</tr>
</tbody>
</table>

Adapted from Spanuth et al., 2011 (27)
Specificity and sensitivity of Presepsin

Early sepsis marker

One of the Presepsin advantages is the quick response against the onset of sepsis. A case study at Iwate Medical University compared the sepsis biomarkers Presepsin, PCT and CRP after a colon perforation with septic shock. Presepsin showed a high concentration level spontaneously at the infectious event and decreased in parallel with the APACHE II score. On the other hand, IL-6, CRP and Procalcitonin elevated one day after the onset of disease (Fig. 7).

Low influence from burns, trauma and medical surgery

Because CRP and PCT are inflammatory biomarkers, it is well known they are affected by burns, severe trauma, or surgical operations other than the sepsis status. Presepsin values are less affected by such cases. A typical case report of a severe burn patient indicated that IL-6, CRP and PCT increased in the first period (day 0 to 5) due to burn inflammation whereas Presepsin did not. When this patient became septic, Presepsin increased earlier than the other markers and showed a peak at the septic shock. After polymyxin B-immobilized fiber column (PMX-DHP) therapy on day 8 Presepsin decreased as expected whereas IL-6, PCT and CRP decreased delayed and did not reflect clinical course correctly (Fig. 8). Hoshino et al. also showed, in severe trauma patients with Injury Severity Scores ≥16, a significant increase of PCT on day 1 after trauma while Presepsin concentration was neither elevated at day 0 nor day 1. This result strongly indicated that Presepsin was useful to diagnose sepsis in severe trauma patients (28).
In the case study by Shozushima et al., a 51-year-old patient was taken to hospital with extensive burns covering 76% of his body. The laboratory data on arrival included an elevated white blood cell (WBC) count of 38,880/µL, and a diagnosis of SIRS was made. Since no elevation of the Presepsin value (281 pg/ml) or PCT value (0.98 ng/ml) was observed on arrival and the blood cultures were negative, there was no suspicion of sepsis at that time.

Presepsin (in orange) and other markers in post-traumatic patients following a serious burn were considered. It is well-known that Presepsin values does not change after the trauma and there is an early increase in the values of Presepsin by day 2 following the occurrence of a bacterial infection confirmed by a positive blood culture of day 5. Effectiveness of anti-biotic treatment is shown at day 13 (Fig. 9, 24).

Fig. 10: Time course of plasma concentrations of Presepsin and Procalcitonin during ICU stay by survival status

Adapted from Masson et al., 2014 (29)

Evolution of Presepsin levels over time in survivors was significantly different from that in deceased patients in the ICU. PCT levels decreased rapidly and similarly in both survivors and non-survivors whereas Presepsin clearly differentiates already after 24 hours between the two cases. In comparison to survivors, Presepsin levels in non-survivors stayed constantly high over the time period observed. Conversely, PCT levels fell rapidly and similarly from day 1 to 7 in survivors and non-survivors. Presepsin appears as an early marker of mortality with better prognostic performance than PCT and can be used as an aid in risk stratification strategies in septic patients (Fig. 10, 29).

Patients with decreasing levels of Presepsin over 7 days in ICU were more likely to have received an early appropriate first-line empirical antibiotic therapy on day 1 than those with increasing levels (29).

Prognosis and monitoring with Presepsin
In a multicentric study in Japan with 140 patients observed over a 7-day period, Presepsin and other biomarkers used in sepsis were investigated in sepsis patients over the clinical course. All markers declined over time in patients with predicted favorable outcome according to SOFA or APACHE II scores. Unlike other biomarkers, only Presepsin values showed a tendency to stay elevated in the group of patients with unfavorable outcomes.

A clear difference in the development of Presepsin and PCT values during the course of treatment could be demonstrated with sepsis patients who got antimicrobial treatment after diagnosis of sepsis. Presepsin showed a clear trend towards lower values in survivors over the period from 0–72 h observation time while non-survivors reached very high values. PCT, in contrast, though also much higher in non-survivors, showed only a marginal decline after 24 hours in the survivors (Fig. 11, 30).

**Recommendation**

For ICU patients, a baseline cut off for Presepsin of approximately 1,000 pg/ml may be used which may increase with progression of disease and severity of organ failure. For final diagnosis, Presepsin results may support clinical findings but should not be used as a sole decision criteria for severity of organ damage.

**Fig. 11: Course of biomarkers over time**

IL: Interleukin, CRP: C-reactive protein, PCT: Procalcitonin; Adapted from Endo et al., 2014 (30)
Organ dysfunction and Presepsin

According to the Sepsis 3 definition, organ dysfunctions are main symptoms of sepsis which indicates that Presepsin concentration reflects the severity of sepsis. Masson S et al. demonstrated the association of Presepsin concentration at baseline with the incidence of new organ failures. Presepsin concentration at baseline (946 ng/L) increased with the SOFA score, the number of prevalent organ dysfunctions or failures, and the incidence of new respiratory, coagulation, liver, cardiovascular and kidney system events (Fig. 12, 31). The concentration decreased over 7 days in ICU patients with negative blood cultures. Presepsin increased with inappropriate antibiotic therapy. Baseline Presepsin was independently associated and correctly reclassified with the risk of ICU and 90-day mortality (31).

Presepsin is metabolized rapidly through the kidneys and was reported to be affected by kidney failure. Nagata et al. studied Presepsin values in patients with various chronic kidney disease (CKD) stages. Even if patients were not infected by any pathogens, Presepsin values were increased by the decrease of glomerular filtration rate (GFR) values. Moreover, Presepsin values elevated extensively among the patients who received hemodialysis (HD), so other cut off values need to be used (32). Another study reported the median of Presepsin in hemodialysis treated and that the optimal cut off value was 2,083 pg/ml (33). Acute kidney injury (AKI) is one of the major complications in sepsis patients. Takahashi et al. showed that the diagnostic accuracy for infectious diseases in patients with AKI was even higher than that in patients without AKI, however, the cut off value for diagnosis of sepsis among AKI patients should be changed. Plasma levels of neutrophil gelatinase-associated lipocalin (NGAL), a kidney dysfunction marker, was used to be classified into non-AKI (<150 ng/mL) and AKI (≥150 ng/mL) groups. AUCs of Presepsin were higher than those of PCT in non-AKI and AKI groups (AKI group PSEP 0.83 vs. PCT 0.72 / non-AKI group PSEP 0.75 vs. PCT 0.67). The optimal cut off values of Presepsin for AKI and Non-AKI patients were 828 pg/mL and 694 pg/mL, respectively (Fig. 13, 34). Presepsin seems to be a useful biomarker for bacterial infections in AKI patients but different thresholds should be applied (34).

Recommendation

AKI patients without infections and Non-AKI patients with infections show similar cut off values (about 600 pg/ml) which reflects the influence of the organ damage to the Presepsin level. When AKI patients get an additional infection, cut off values can even rise up to 1,200 pg/ml, whereas Non-AKI patients without infection show normal cut off values of approximately 300 pg/ml (see also Tab. 5 and 6).

For final diagnosis, Presepsin results may support clinical findings but should not be used as a sole decision criteria severity of organ damage.
Pathogens and Presepsin

Due to the Presepsin production mechanism build up from CD14 by the mechanism of phagocytosis, the specificity of microorganisms was investigated. Endo et al. initially reported that there were no significant differences in Presepsin levels between the Gram-positive and Gram-negative bacterial infection groups (2,881 ± 4,374 and 2,641 ± 3,709 pg/ml, respectively; P = 0.5320) and several other reports support this result. Rabensteiner J et al., examined 300 patients consecutively included 100 for Gram-positive and Gram-negative bacteremia, 50 for candidemia and 50 for controls. The median of Presepsin of Gram-positive, Gram-negative and candidemia were 1078, 1295 and 2293 pg/mL, respectively (Fig. 14; 49).

Ugajin et al., examined the Presepsin levels in pneumonia patients and revealed that Presepsin levels were different between Gram-positive and Gram-negative bacteria. These differences may be related to the difference of species, or sepsis severity (50).

Qi et al. examined the usefulness of differentiating active pulmonary tuberculosis (APTB) from bacterial community acquired pneumonia (BCAP). Presepsin concentrations in APTB patients were slightly increased, and may be helpful for initial discrimination between APTB and BCAP. This is probably caused by PSEP levels and the low immunogenicity by Mycobacterium tuberculosis (52).

There is little information about virus infection. Arai et al. analyzed for a cohort study of patients undergoing allogeneic hematopoietic cell transplantation and reported that patients with hemophagocytic syndrome (HPS) and bacteremia (n=19) showed higher levels of Presepsin. No correlation between Presepsin and CMV (cytomegalovirus) reactivation (n=12) could be shown (53). Moreover, a study with febrile children showed that Presepsin values in patients with Influenza A did not elevate in contrast to other bacterial infections or Kawasaki diseases (54).
Lippi et al. investigated the usefulness of Presepsin and Procalcitonin in the context of invasive fungal infections. Invasive fungal infections are a major healthcare issue accounting for approximately 20% of all sepsis cases. Classic fungal diagnostics are serologic testing, measurement of 1,3-beta-D-glucan, mannan antigen or anti-mannan antibodies and molecular biology. These findings lead the way to developing diagnostic algorithms based on results of both biomarkers Procalcitonin and Presepsin.

Concomitantly increased values of these biomarkers could be suggestive of bacterial sepsis or mixed infection. Non-diagnostic values of both biomarkers may enable the ruling out of sepsis of bacterial or fungal origin. A disproportionate increase of Presepsin values combined with normal or only modestly elevated Procalcitonin concentration may be suggestive of invasive fungal infections (Fig. 15; 55).

Moreover, Bamba et al. evaluated cases of fungal bloodstream infections and found elevated Presepsin levels correlated with increased SOFA score. They also showed that Presepsin increased by incubation with blood and Candida sp. in vitro (51).
Application of Presepsin in a clinical setting

Since the first publications of clinical use of Presepsin in 2005, about 240 papers from various categories (as of June/2019), such as ED (47 papers), ICU (22 papers), hematology (15 papers), neonates (24 papers) and others were published during the last 14 years (Fig. 16).

Other than sepsis, clinicians are interested in Presepsin in terms of specificity for bacterial infection including local infection. Due to the high interest in the clinical use of Presepsin, more publications will follow.

Neutropenia

Febrile neutropenia (FN) remains one of the major complications during chemotherapy in patients with solid tumors or hematological malignancies. FN is basically defined as having an oral temperature ≥38.3 or ≥38°C for more than 1 h with absolute neutrophil count (ANC) <500 cells/μL or the reduction to 500 cell/μL in the next 24-48 h. The mortality rate is higher and it is difficult to predict or to detect those mali-cious events at an earlier point in time. Koizumi et al. showed Presepsin values in FN patients were not significantly associated with the absolute WBC count and the median plasma Presepsin level was 456.5 pg/mL even with a low WBC count below 100/μL. This data revealed that Presepsin values were increased in the case of FN in spite of the Presepsin production mechanism. One case study described a 48 year old male patient with B-cell leucaemia who received chemotherapy. On day 10 he experienced infection with K. pneumonia. Plasma Presepsin level was already elevated one day prior to FN onset whereas CRP was not increased at that time (Fig. 17, 56)

Ebisawa et al. studied Presepsin and Procalcitonin response time after the onset of fever, and showed that Presepsin has an advantage for early detection (from 1 to 18 hours) with the AUC of 0.8188, where PCT has little elevation (AUC=0.6354) (57).

Nanno et al. reported higher median values of Presepsin (>1935 pg/mL) with hemaphagocytic syndrome (HPS) and Presepsin values were significantly associated with the 90-day mortality (58).

Fig. 16: Applications of the biomarker Presepsin

Fig. 17: Time course of Presepsin, CRP and WBC in a chemotherapy patient

Presepsin elevates one day prior to CRP

WBC: White Blood Cells, CRP: C-reactive protein, MEPM: Meropenem; Adapted from Koizumi et al., 2017 (56)
Differentiation between SIRS and sepsis in surgical patients is of crucial significance. Inflammatory biomarkers are commonly measured in clinical practice, however, CRP and PCT are influenced by non-specific systemic inflammatory response (24). Presepsin is expected to be specific for bacterial infection at perioperative periods because of less response against burns and trauma (23). Takahashi G. presented that in comparison to CRP and WBC, Presepsin shows no unspecific increase via surgical interventions in the case of spinal scoliosis surgery (personell communication) (n=12) (Fig. 18).

Popov et al. evaluated the prognostic values of Presepsin in cardiac surgery. During study periods 19 out of 51 patients (37%) developed sepsis in which the most frequent complication was ventilator-associated pneumonia (n=12). Presepsin values showed significant differences between with and without infectious complications during the first day after the operation. Presepsin dynamics in the postoperative period were found with an increase of Presepsin levels associated with higher risk of infection. When Presepsin levels were persistently higher than the normal values, more than 50% of patients (21/42 58.3%) acquired infectious complications (59). Another study from Germany also revealed high prognostic value in cardiac surgery patients. 856 patients were studied prospectively. Preoperative plasma concentrations of Presepsin, Procalcitonin, NT-proBNP, Cystatin C and the the additive European System of Cardiac Operative Risk Evaluation 2 were compared to mortality at 30 days, 6 months and 2 years. Thirty-day mortality was 3.2%, 6-month mortality was 6.1%, and 2-years mortality was 10.4% across the population. The median of pre-operative Presepsin concentrations was significantly higher in 30-day nonsurvivors than in survivors: 842 pg/ml versus 160 pg/ml difference. The results were similar for 6-month and 2-years mortality. Presepsin also provided better discrimination than Cystatin C, N-terminal pro-hormone natriuretic peptide, or Procalcitonin. An elevated preoperative plasma Presepsin concentration is an independent predictor of postoperative mortality in elective cardiac surgery patients and is a stronger predictor than several other commonly used biomarkers and scores (Tab. 7; 60).

A researcher group from Italy recruited 35 cadaveric organ transplant recipients and 35 abdominal surgery patients and measured Presepsin after surgery. Presepsin levels were very high in the case of blood culture positive group (n=50) and 33 patients which received initial empiric antibiotic therapy, where Presepsin values decreased to the threshold level at T3 (144h after operation). Four patients who died due to sepsis showed increased Presepsin values within 28 days from admission (61).

Tab. 7: Comparison of Presepsin with further risk factors

<table>
<thead>
<tr>
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<th>ROC analysis to predict 30-day mortality (n=852)</th>
<th>P-value vs. AUC of preoperative Presepsin</th>
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<tr>
<td></td>
<td>AUC</td>
<td>95% CI</td>
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<tr>
<td>Preoperative</td>
<td></td>
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<tr>
<td>Presepsin, mg/dL</td>
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<td>0.81–0.96</td>
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<td>Leukocytes, ×10⁹/L</td>
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<td>0.45–0.71</td>
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<tr>
<td>Procalcitonin, ng/ml</td>
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<td>0.48–0.69</td>
</tr>
<tr>
<td>Age, years</td>
<td>0.73</td>
<td>0.64–0.81</td>
</tr>
<tr>
<td>EuroSCORE 2</td>
<td>0.74</td>
<td>0.65–0.83</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL</td>
<td>0.77</td>
<td>0.69–0.84</td>
</tr>
<tr>
<td>Cystatin C, mg/dL</td>
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<td>0.64–0.87</td>
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<td>Presepsin, pg/mL</td>
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<td>0.77–0.93</td>
</tr>
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</table>

Adapted from Bomberg et al., 2017 (60)
Pneumonia

Some reports show the usefulness of Presepsin measurement for pneumonia patients (62, 50, 52, 73, 74). Klouche et al. pointed out that among ICU-admitted patients, Presepsin values in severe pneumonia group were significantly higher than in non-infectious group, and Presepsin reflected prognosis as well (Fig. 19; 62). Ugajin et al. also showed that Presepsin values at admission predicted 30-day mortality rate using cut off 470 pg/ml (Fig. 20; 50).

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![Image of a child with a toy]
Endo et al. showed in a multicenter prospective study (n=207) that Presepsin could be produced even by local infection. The cut off value of Presepsin for discrimination of bacterial and nonbacterial infectious diseases was determined to be 600 pg/ml, of which the clinical sensitivity and specificity were 87.8% and 81.4%, respectively. The sensitivity of blood culture was 35.4%; that for Presepsin was 91.9%. Moreover, there were no significant differences in Presepsin levels between the blood culture-positive and -negative groups (Fig. 21; 38).

Salina et al. (95) from a study with acute pancreatitis (SAP) patients and septic complications point to Presepsin as an early marker for supporting diagnosis of SAP.

Lin et al. showed the relationship between the severity of acute cholangitis (AC) and Presepsin values. 119 AC patients were classified from Grade I to III using the TG13 criteria, Presepsin values were increased with severity (Fig. 22; 63).
Imagana et al. studied the usefulness of Presepsin for the identification of septic arthritis (SA) from osteoarthritis (OA). The mean blood level of Presepsin was 529.4 ± 470.8 pg/ml in the SA group and 136.4 ± 52.4 pg/ml in the OA group. Interestingly, the diagnostic accuracy was significantly improved using synovial fluid (Fig. 23; 64).

Another scientific report provided information regarding different causes of pleural effusions. Presepsin values were significantly higher in the case of empyema, which was caused by infection (65). Presepsin values are higher in pleural fluids than in blood, strongly suggesting that Presepsin was produced at infectious loci (28).

Titova et al. (96) found in hemodialysed patients with pneumonia and sepsis three times higher levels of Presepsin compared to other hemodialysed patients w/o sepsis.

Abudeev et al. (94) reported Presepsin use in cerebrospinal fluids (CSF) to support diagnosis of nosocomial infections of the central nervous system.

Shiota et al. reported (33) severe local infection during critical limb ischemia (CLI) patients who received hemodialysis. As mentioned above, hemodialysis affects the Presepsin baseline; however, Presepsin values were significantly increased in non-healing group where bacterial infections were strongly suspected. This study indicated the possibility to detect infection even when receiving hemodialysis (Fig. 24; 33).

Presepsin has also been studied in other cases than sepsis or infectious diseases. Tanimura et al. researched the clinical significance of Presepsin levels in patients with systemic lupus erythematosus (SLE). Elevated plasma Presepsin levels were correlated with disease activity of SLE, suggesting inappropriate monocyte or neutrophil activation in the pathophysiology of SLE exacerbation (66). Moreover, Presepsin was linked to early identification of severe acute pancreatitis (SAP). Presepsin levels showed obviously higher levels in SAP patients than in healthy individuals (67). Acute myocardial infarction could also be a state of inflammation with activated monocytes.

Caglar et al. examined Presepsin levels in patients with acute ST elevation myocardial infarction (STEMI). Plasma Presepsin and troponin levels were significantly higher in patients with STEMI than controls (1988.89 ± 3101.55 vs. 914.22 ± 911.35 pg/ml, p = 0.001 and 3.46 ± 3.39 vs. 0.08 ± 0.43 ng/ml, p = 0.001, respectively). The cut off value for Presepsin of 447 pg/ml was found to detect STEMI with 87.5% sensitivity, 44% specificity, 60% positive predictive value and 78.5% negative predictive value. Presepsin levels were found to be significantly elevated in patients with STEMI together with high-sensitivity troponins (68).

Other diseases that might affect Presepsin levels

OA: osteoarthritis, SA: septic arthritis; Adapted from Imagana et al., 2019 (64)

Adapted from Shiota et al., 2016 (33)
Neonatals

Sepsis is one of the most significant syndromes for mortality and morbidity in the neonatal population. The diagnostic validity of Presepsin in neonatal sepsis has been evaluated in numerous clinical studies. Pugni et al. enrolled 684 healthy neonates for evaluation of reference ranges for Presepsin. The Presepsin median value in term infants was 604 pg/mL whereas, in preterm infants the Presepsin median value was slightly higher (620 pg/mL). The normal reference ranges of Presepsin observed were higher than those seen in healthy adults (69).

Generally, neonatal sepsis is classified either as early onset sepsis (EOS) occurring in the first 72 h of life or late onset sepsis (LOS) which occurs at day 4 or after birth. Poggi et al. prospectively studied preterm newborns (<32 wk. gestational age) with LOS and non-infected controls. Presepsin was higher in the LOS than in the control group at enrollment (1295 vs. 562 pg/mL) throughout the evaluation period. The area under the ROC curve was 0.972. P-SEP achieved the best accuracy for prediction of probable sepsis at the cut off of 885 ng/L (Fig. 25; 70).

Montaldo et al. studied preterm neonates (<34 wk. gestational age) who were admitted to NICU by 6 hours of age with suspicion of sepsis. Presepsin values are significantly higher in the EOS group than those in the uninfected group at every time interval, and the highest accuracy was achieved at 24 h after birth with the AUC score 0.97 using the cut off value of 788 pg/mL. Importantly, CRP as well as PCT are influenced by the physiological change during the first day of life, so cut off points should be determined in a time-dependent manner (71).

Recently, two meta-analysis for the diagnostic accuracy of Presepsin in neonatal sepsis were published. Bellos et al. selected 11 clinical study publications with a total number of 783 neonates. The pooled sensitivity of Presepsin for the prediction of neonatal sepsis was 0.91, the pooled specificity was 0.91 and the diagnostic odds ratio was 170.28 (95% CI 51.13-567.11). Head-to-head comparison with AUC values of CRP (0.9748 vs. 0.8580) and PCT (0.9596 vs. 0.7831) revealed that Presepsin was more accurate in detecting neonatal sepsis. The cut off values from each publication were categorized into 650, 650-850, 850 pg/mL as listed in Table 8 which indicated that the diagnostic efficacy was maximized (AUC 0.99) when the Presepsin cut off value in neonates ranged from 650-850 pg/mL (72). Ruan et al. (75) also showed superior diagnostic accuracy of Presepsin for neonatal sepsis diagnosis when compared with simultaneous use of CRP and PCT (AUC = 0.99 vs AUC = 0.96) (75).

Recommendation

A preliminary cut off value of ≤650 pg/ml for exclusion of sepsis seems to be appropriate for neonates. Presepsin values ≥850 pg/ml indicate a bacterial infection.

For final diagnosis, Presepsin results may support clinical findings but should not be used as a sole decision criteria for severity of organ damage.
The major advantage of the assessment of Presepsin is its capacity to predict the severity of a bacterial infection. Presepsin correlates significantly with the degree of severity of the infection as its quantitative results increase proportionally. In fact, the studies reveal maximum correlation with the SOFA score values (clinical scoring used most frequently to evaluate organ failure). Higher values on the first day of monitoring are closely associated with a higher incidence of new organ failure and hemodynamic instability in the first 24 hours.

Presepsin concentration increased with the SOFA score, the number of prevalent organ dysfunctions or failures, and the incidence of new failures of the respiratory, coagulation, liver, and kidney systems. Presepsin is an early predictor of host response and mortality in septic patients. Changes in concentrations over time reflect the appropriateness of antibiotic therapy.

In addition, the measurement of Presepsin can be done by an easy procedure that takes less than 17 min with PATHFAST™.

Since only one single biomarker is not enough for a reliable diagnosis or prognosis of disease, support of Presepsin determination could be used in combination with other biomarkers and standard methods of infection diagnosis like e.g. medical scores for increased accuracy.

The different performance efficiency values may be due to the heterogeneity established in all the different studies. Possible factors for heterogeneity might be study strategy (prospective or not), clinical setting (ED, ICU), type of patients (adults or neonate), reference for sepsis criteria and even the type of sample (plasma or whole blood) for measurement of Presepsin. The better knowledge of conditions, that influence the levels of Presepsin, might enable reducing the false positive rate of infection diagnosis and inappropriate treatments. Recommended cut off values reflect the up-to-date information from clinical studies and may be used as an orientation.

Future studies are necessary, for the identification of these conditions and the determination of cut off values for the detection of different types of infections in different groups of patients would also be effective in the clinical application of this biomarker.


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