Health Policy Advisory Committee on Technology

Technology Brief

PATHFAST Presepsin chemiluminescent enzyme immunoassay for the diagnosis and prognosis of sepsis

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This Brief was commissioned by Queensland Health, in its role as the Secretariat of the Health Policy Advisory Committee on Technology (HealthPACT). The production of this Brief was overseen by HealthPACT. HealthPACT comprises representatives from health departments in all States and Territories, the Australian and New Zealand governments and MSAC. It is a sub-committee of the Australian Health Ministers’ Advisory Council (AHMAC), reporting to AHMAC’s Hospitals Principal Committee (HPC). AHMAC supports HealthPACT through funding.

This Brief was prepared by Benjamin Ellery and Jacqueline Parsons from Adelaide Health Technology Assessment, University of Adelaide.
Summary of findings

Sepsis is a severe and life-threatening complication of infection, and identifying it early may improve outcomes and save lives. As the gold-standard for diagnosing sepsis, blood culture, takes several days, many biomarkers are being investigated that can improve the speed at which sepsis can be diagnosed. Limited, low-level evidence on presepsin showed moderate diagnostic performance, with the caveat that it should not be used in isolation from other clinical factors to diagnose sepsis. No studies investigating the impact of presepsin result on treatment or outcomes were identified.

HealthPACT Advice

The PATHFAST Presepsin assay is one of many tests either developed, or in development, for the rapid detection of sepsis. There is insufficient evidence demonstrating the superiority of presepsin over tests such as procalcitonin. In addition, there is little evidence that demonstrates the use of presepsin results in changes in clinical behaviour when treating patients with suspected sepsis.

HealthPACT does not support public investment in the PATHFAST Presepsin assay in clinical practice, and recommends no further research is warranted at this time.
<table>
<thead>
<tr>
<th><strong>Technology, Company and Licensing</strong></th>
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<tr>
<td><strong>Register ID</strong></td>
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<td><strong>Technology name</strong></td>
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<td><strong>Patient indication based</strong></td>
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</table>

**Description of the technology**

Presepsin (formerly known as CD14), is a glycoprotein receptor occurring on the surface of macrophages and monocytes.¹ Presepsin binds to lipopolysaccharide (LPS) complexes and LPS binding protein (LPB), which triggers activation of toll-like receptor 4 (TLR4), thereby inducing the production of several pro-inflammatory cytokines. Following presepsin activation by bacterial products, the CD14 complex is released into the bloodstream as its soluble form (sCD14). sCD14 is in turn cleaved by a plasma protease to generate a sCD14 fragment called sCD14-subtype (sCD14-ST). Plasma levels of sCD14 can be measured using an automated chemiluminescent assay. The PATHFAST Immunoanalyzer, using the PATHFAST Presepsin reagent kit, has been commercially marketed for this purpose. This point-of-care testing method can provide results within minutes."² Unfortunately, no image of the technology has been included in this Brief as multiple permission requests to the developer were unsuccessful.

**Company or developer**

Mitsubishi Chemical Europe GmbH (Dusseldorf, Germany) is responsible for the European distribution of the PATHFAST Presepsin reagent kit and PATHFAST Immunoanalyser platform required for point-of-care (POC) testing based on the presepsin biomarker. Mitsubishi Chemical Europe is a subsidiary of Mitsubishi Chemical Holding Corporation (Tokyo, Japan), as is LSI Medience (Tokyo, Japan), responsible for the distribution of the technology in other parts of the world.

**Reason for assessment**

Sepsis affects a large patient group with significant morbidity and mortality.³ Early identification leading to commencement of timely antimicrobial intervention is considered a priority in the management of sepsis, given that delays in treatment are associated with worse prognosis.³⁻⁵

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¹ See the section Disease description and associated mortality and morbidity for details.
Stage of development in Australia

- [ ] Yet to emerge
- [ ] Established
- [ ] Experimental
- [x] Investigational
- [ ] Established but changed indication or modification of technique
- [ ] Should be taken out of use
- [ ] Nearly established

Licensing, reimbursement and other approval

Several representatives of Mitsubishi Chemical/LSI Medience in Europe and Japan were contacted for information on the licensing and regulatory approval of PATHFAST Presepsin. The management of sales and marketing for LSI Medience (Tokyo, Japan) responded that that PATHFAST Presepsin is CE marked and mainly distributed in Europe.\(^b\) Indeed, the technology has been predominantly trialled in Europe as well as in Asia.\(^c\) No evidence was located to suggest that PATHFAST Presepsin is available outside these regions, and LSI Medience indicated that it is not distributed in Australia at the present time.\(^d\)

Australian Therapeutic Goods Administration approval

- [ ] Yes
- [x] No
- [ ] Not applicable

ARTG number(s): Not applicable

Technology type: Diagnostic; prognostic

Technology use: Early diagnosis; prognosis

Patient Indication and Setting

Disease description and associated mortality and morbidity

Sepsis is a life-threatening condition in which the immune system responds to *infection* in a way that causes damage to the body’s tissues and organs.\(^6,7\) This immune response, known as systemic inflammatory response syndrome (SIRS), may occur in the absence of infection (e.g. following severe trauma, burns and as a result of autoimmune conditions). Therefore, the septic patient is defined as having both an infection and SIRS. Clinically, differentiating between sepsis and non-infectious SIRS may be challenging, especially due to the time required to confirm infection using traditional culture techniques. Research on various biomarkers to aid in the clinical management of sepsis versus SIRS is ongoing, given the difficulty in promptly differentiating between the two conditions with similar, if not identical, clinical presentations.\(^6-8\)

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\(^b\) Personal communication with sales and marketing representative of LSI Medience, email response received 4 January 2016.

\(^c\) See section on “International utilisation” for details.

\(^d\) Personal communication with sales and marketing representative of LSI Medience, email response received 4 January 2016.
Data on the population incidence of sepsis and mortality caused by sepsis are lacking; most studies reporting on sepsis incidence and/or mortality are based on cases that develop subsequently to admission to intensive care units (ICUs), which does not take into account sepsis cases that initially occur outside the emergency setting. Some studies report evidence that the incidence of sepsis has been increasing, while mortality from sepsis is decreasing, and in 2014, a large observational study (n=101,064) found that the mortality due to sepsis had decreased by as much as 17 per cent within the period from 2000 to 2012.

A cohort study published in 2004 documented the incidence of severe sepsis in 23 ICUs in 21 Australian and New Zealand hospitals. During the three-month period from May to July 1999, each hospital collected data for all ICU admissions of at least 48 hours duration. During this period there were 5,878 admissions. Of these, 3,543 (3,338 patients; mean age 55.9±20.2 years) met the criteria for inclusion in the analysis; each patient was screened for severe sepsis. In total, 691 (20.7%) experienced 752 episodes of severe sepsis, the equivalent of 11.8 (95% CI 10.9, 12.6) patients with severe sepsis per 100 ICU admissions. Of the 691 patients with severe sepsis, 183 (26.5%) died in ICU, 224 (32.4%) died within 28 days of diagnosis and 259 (37.5%) died in hospital. These data were used to calculate the annual incidence of severe sepsis in adult patients admitted to all Australian and New Zealand ICUs in Australia and New Zealand based on the estimated total Australian and New Zealand population (17,359,776 people) at the time. The calculated annual incidence was 0.77 (95% CI 0.76, 0.79) per 1,000 population. Note that this study did not indicate whether or not sepsis was the verified cause of all deaths. However, this does not affect the estimates of incidence given that all the patients, whether they survived or not, had sepsis at some point. Mortality specific to sepsis is discussed below.

In 2007, a retrospective study reported on the outcomes of patients with sepsis admitted via emergency departments to ICUs in Australia and New Zealand between 1997 and 2005. During the study period, the number of ICUs contributing data increased; in the final year, 101 ICUs (82% of all Australian and New Zealand ICUs) provided data. Admission and mortality outcomes for patients are shown in Table 1.
Kaukonen and colleagues published the results of a large retrospective observational study which included data on 101,064 patients with severe sepsis who were admitted to Australian and New Zealand ICUs between 2000 and 2012.\textsuperscript{11} This study found that the proportion of severe sepsis admissions out of all ICU admissions increased from 7.2 per cent in 2000 (2,708/35,012 patients) to 11.1 per cent in 2012 (12,512/100,286 patients). In contrast, mortality from sepsis decreased from 35 per cent (95% CI 33.2, 36.8) in 2000 to 18.4 per cent (95%CI [17.8, 19.0], \(p<0.001\)) in 2012, representing an overall decrease of 16.7 per cent (95% CI 14.8, 18.6), an absolute yearly decrease of 1.3 per cent and a relative risk reduction of 47.5 per cent (95% CI 44.1, 50.8) for the study period. Adjusted analysis for severity of disease and confounders indicated that the statistically significant reduction in mortality was maintained for the study period with an odds ratio of 0.49 (95% CI [0.46, 0.52], \(p<0.001\)) in 2012, using 2000 as the year of reference.\textsuperscript{11}

**Speciality**

Emergency care; immunology; infectious disease and microbiology; haematology

**Technology setting**

General hospital

**Impact**

**Alternative and/or complementary technology**

Based on available published evidence\textsuperscript{12, 13} and medical expert opinion\textsuperscript{e}, clinical assessment remains the accepted standard for identifying and managing sepsis in Australia. PATHFAST Presepsin would be best placed to act as complementary testing method alongside standard clinical assessment. Blood culture is considered the gold standard method for the detection of microorganisms in the bloodstream; however, it has limited usefulness for early detection of sepsis because it usually requires several days to

\textsuperscript{e} Personal correspondence via email with two senior intensive care clinicians (10 November 2015; 14 November 2015).
obtain results.⁸ Many biomarkers for sepsis have been proposed; of note, procalcitonin (PCT) which has been trialled in 11 Australian centres,⁹ is an alternative biomarker for sepsis. However, at the present time, it is considered that there is insufficient evidence for public funding of PCT testing in the Australian healthcare setting.⁸ This issue is further discussed under Other considerations.

Current technology
Clinical assessment and, to some extent, testing for sepsis based on PCT.

Diffusion of technology in Australia
PATHFAST Presepsin is not commercially available in Australia, nor were any Australian studies investigating the technology found.

International utilisation

<table>
<thead>
<tr>
<th>Country</th>
<th>Level of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trials underway or completed</td>
</tr>
<tr>
<td>Italy</td>
<td>✓</td>
</tr>
<tr>
<td>Germany</td>
<td>✓</td>
</tr>
<tr>
<td>Japan</td>
<td>✓</td>
</tr>
<tr>
<td>Spain</td>
<td>✓</td>
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<tr>
<td>China</td>
<td>✓</td>
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<tr>
<td>Korea</td>
<td>✓</td>
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<tr>
<td>Serbia</td>
<td>✓</td>
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<tr>
<td>Turkey</td>
<td>✓</td>
</tr>
</tbody>
</table>

Cost infrastructure and economic consequences
LSI Medience (Tokyo, Japan) have advised that PATHFAST Presepsin is not available in Australia, but did provide costs of the technology in Japan. The cost of the required platform, i.e. the PATHFAST Analyzer, is ¥3.9 million (AU $45,300) and the cost of the presepsin reagents is ¥192,000 (AU $2,200).⁹ Given the limited cost information and the non-availability of the technology for the Australian market, no discussion of potential economic impact is provided here.

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⁸ Calvary Hospital (Adelaide, SA), Concord Hospital (Concord, NSW), Epworth Hospital (Richmond, Victoria), John Hunter Hospital (New Lambton Heights, NSW), Liverpool Hospital (Liverpool, NSW), Nambour General Hospital (Nambour, QLD), Prince Charles Hospital (Chermside, QLD), Prince of Wales Hospital (Randwick, NSW), Queen Elizabeth Hospital (Woodville, SA), Royal Darwin Hospital (Tiwi, NT), Wollongong Hospital (Wollongong Hospital, NSW).


⁹ Personal communication with sales and marketing representative of LSI Medience, email response received 4 January 2016.
Ethical, cultural, access or religious considerations

No specific issues were identified.

Evidence and Policy

Safety and effectiveness

Zhang and colleagues recently conducted a meta-analysis (level III-1 diagnostic accuracy evidence\(^1\)) reporting on the diagnostic accuracy of presepsin using the PATHFAST platform to differentiate between sepsis and SIRS.\(^14\) The meta-analysis included a total of eight studies involving 1,815 patients with systemic inflammation. Only studies including a defined reference standard\(^1\) were eligible for inclusion. Data from the included studies were independently extracted in duplicate and the pooled diagnostic accuracy of presepsin calculated using bivariate meta-analysis. A summary receiver operating characteristic curve (SROC) analysis was also undertaken. All studies were critically appraised using a revised tool for Quality Assessment of Diagnostic Accuracy Studies (QUADAS) and also grouped according the Sackett and Haynes classification of diagnostic studies. The Sackett and Haynes classification\(^15\) groups studies of diagnostic accuracy as either ‘Phase 1’, ‘Phase 2’ or ‘Phase 3’. Phase 1 studies compare the difference in test results between patients with the target disorder and healthy controls; Phase 2 studies examine how the index test differentiates between patients with and without the target disorder; Phase 3 studies assess the test’s real-life performance in patients in whom the disorder is suspected. The potential for publication bias was assessed using Deek’s funnel plot. The characteristics and main results of the individual studies included in the meta-analysis, as extracted by Zhang et al, are shown in Table 2.

Based on the methods outlined, the authors reported that two of the included studies were Phase 2 studies which they referred to as ‘Group 1’ and six were Phase 3 studies, referred to as ‘Group 2’ (see Table 2). It was reported that on average, “the overall QUADAS scores of all studies met 10 of the 14 criteria, which suggests that the studies were of high quality.” According to the Deek’s funnel plot, no significant publication bias was detected (p=0.31).

Zhang et al reported pooled sensitivity and specificity of 0.86 (95%CI 0.79, 0.91) and 0.78 (95%CI 0.68, 0.85), respectively. The SROC analysis indicated an area under the curve (AUC) of 0.89 (95%CI 0.86, 0.92). The positive likelihood ratio (LR+) and negative likelihood ratio (LR-) are in clinical terms more useful measures than sensitivity and specificity, were 3.8 (95%CI 2.6, 5.7) and 0.18 (95%CI 0.11, 0.28), respectively. The LR+ and LR- respectively indicate that a positive presepsin test result correlates with a clinical scenario in which

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\(^1\) The level of evidence was determined based on the details of included studies reported in the published meta-analysis. This was not checked against publications of the original studies.

\(^3\) While the only definitive sepsis diagnosis involves the presence of SIRS in addition to a positive culture result, it was not reported whether the included studies adhered to this strict definition of “reference standard”. It is possible that diagnosis by clinical assessment alone may have constituted the reference standard in some studies.
there is a *small* increase in the likelihood of sepsis (compared to baseline probability) and a negative presepsin test result corresponds to a *minimal* decrease in the likelihood of disease. Starting with a hypothetical pre-test probability 20 per cent, the authors found that the use of presepsin in the detection of sepsis increased the post-test probability to 48 per cent when the results were positive and reduced the post-test probability to four per cent when the results were negative. These results suggest that despite sensitivity approaching 90 per cent and a good overall accuracy (AUC 0.89), the presepsin test performs poorly for ruling in sepsis among patients who have a positive test. The 48 per cent post-test probability of having sepsis among test-positive patients is translates approximately to a one-in-two chance of making a true-positive diagnosis. However, presepsin testing can rule out sepsis with 96 per cent probability given that the post-test probability of a test-negative patient having sepsis is four per cent, indicating good ability of the presepsin test to rule out sepsis.

The authors noted some limitations of their data analysis in the discussion of their paper. Notably, they reported that they were unable to determine the optimised presepsin concentration cut-off because they could not obtain the raw data to map the SROC curve. The optimised cut-off value was retrospectively determined based on the SROC curve presented in each original study, and these cut-off points were highly variable despite all studies having used the PATHFAST assay. The authors further explained that the variance may be attributable to the study design, especially with respect to patient inclusion criteria, acknowledging that chronic renal failure, history of resuscitation and trauma are all factors that may lead to “falsely” elevated presepsin levels, suggesting that presepsin is not particularly specific for infection. These issues have been noted elsewhere in the literature, along with the finding that even advanced age may have a profound bearing on the levels of detectable presepsin in blood.

A further issue which requires attention in interpreting the results of the meta-analysis is the high levels of observed heterogeneity; $I^2$ values associated with the pooled sensitivity and pooled specificity were 90.5 per cent and 91.8, respectively. Meta-regression indicated that consecutive recruitment, sample size and setting significantly accounted for the heterogeneity of sensitivity.

Zhang et al concluded that presepsin has good overall diagnostic accuracy. This finding was countered with appropriate advice, in light of the limitations of the data, that presepsin cannot be regarded as a single definitive test for sepsis diagnosis and that clinicians should comprehensively evaluate each patient rather than relying on a single biomarker-based approach. They further recommended the continuous re-evaluation of patients with systemic inflammation.

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$k$ It cannot be determined how the authors decided on 20 per cent for the pre-test probability. The figure may be attributable to the authors own clinical experience, but this has not been made clear in the text of the paper.
Another meta-analysis, published by Tong and colleagues in 2015, reported on pooled measures of diagnostic accuracy from eleven studies including 3,106 subjects\(^1\) (level III-1 diagnostic accuracy evidence\(^1\)). Based on the reported methods, the data extraction and quality appraisal were the same as for the meta-analysis reported by Zhang et al\(^{14}\) (i.e. duplicate extraction and appraisal using QUADAS); however details were lacking about the methods used to conduct the meta-analysis for pooled sensitivity, specificity and likelihood ratios. An SROC analysis was performed based on the pooled sensitivity and specificity values. With the exception of the one study, Tong et al included all the studies which were included in the meta-analysis by Zhang et al, and four additional studies, indicating a large degree of overlap between the two meta-analyses.

The results presented by Tong et al were not dissimilar to those reported by Zhang et al.\(^{14}\) Overall sensitivity, specificity, LR+ and LR- were 0.83 (95%CI 0.77, 0.88), 0.81 (95%CI 0.74, 0.87), 4.43 (95%CI 3.05, 6.43) and 0.21 (95%CI 0.14, 0.30), respectively. The AUC was calculated to be 0.89 (95% CI 0.86, 0.92), the point estimate and confidence interval being identical to the report by Zhang et al. Tong and colleagues also performed a meta-regression with the object of accounting for the high level of heterogeneity observed for the pooled estimates of sensitivity, specificity, LR+ and LR-, which were associated with \(\hat{I}^2\) values of 85.5, 82.7, 75.5 and 84.4 per cent, respectively. They reported that they didn’t find any covariates of significance, and therefore couldn’t draw conclusions about the source of the heterogeneity.

Tong et al concluded that although presepsin showed good diagnostic accuracy overall, testing for sepsis using this biomarker should not occur in the absence of testing with other markers including PCT\(^m\), C-reactive protein and white blood cells. In agreement with Zhang and co-workers, they emphasised the importance of the clinical context for each patient, noting age and kidney dysfunction as key factors associated with elevated presepsin.\(^{17}\)

\(^1\) The level of evidence was determined based on the details of included studies reported in the published meta-analysis. This was not checked against publications of the original studies.

\(^m\) It should be noted that PCT for the diagnosis for sepsis has been previously rejected for public funding in Australia on the basis of insufficient evidence. Refer to the section on Other considerations for further details.
Table 2  Diagnostic accuracy studies included in the meta-analysis by Zhang et al 2015

<table>
<thead>
<tr>
<th>Study, design, and country</th>
<th>Clinical setting</th>
<th>Severity of sepsis</th>
<th>Control patients</th>
<th>Prevalence of sepsis (%)</th>
<th>% male</th>
<th>Mean age ± SD/median age (range)</th>
<th>Cut-off (pg/mL)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Group 1” studies*</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kweon 2014, Korea Prospective DA study</td>
<td>ED</td>
<td>Sepsis, severe sepsis, septic shock</td>
<td>25 patients without SIRS</td>
<td>61.9</td>
<td>50.0</td>
<td>61.2 (20-91)</td>
<td>430</td>
<td>87.7</td>
<td>82.2</td>
</tr>
<tr>
<td>Liu et al 2013, China Prospective DA study with CR</td>
<td>ED</td>
<td>Sepsis, severe sepsis, septic shock</td>
<td>100 healthy controls</td>
<td>79.2</td>
<td>66.3</td>
<td>79.4 (58-78)</td>
<td>317</td>
<td>70.8</td>
<td>85.8</td>
</tr>
<tr>
<td>“Group 2” studies**</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Vodnik 2013, Serbia Prospective DA study</td>
<td>ED</td>
<td>Sepsis, severe sepsis, septic shock</td>
<td>70 healthy controls</td>
<td>50</td>
<td>58.3</td>
<td>54.4±15.5</td>
<td>630</td>
<td>100</td>
<td>93</td>
</tr>
<tr>
<td>Endo 2012, Japan Multicentre prospective DA study</td>
<td>ED and ICU</td>
<td>NR</td>
<td>No</td>
<td>62.1</td>
<td>59.5</td>
<td>71.8 (17-98)</td>
<td>600</td>
<td>87.8</td>
<td>81.4</td>
</tr>
<tr>
<td>de Guadiana Romualdo 2014, Spain Prospective DA study</td>
<td>ED</td>
<td>NR</td>
<td>No</td>
<td>16.4</td>
<td>58.4</td>
<td>67±26</td>
<td>729</td>
<td>81.8</td>
<td>63</td>
</tr>
<tr>
<td>Study, design, and country</td>
<td>Clinical setting</td>
<td>Severity of sepsis</td>
<td>Control patients</td>
<td>Prevalence of sepsis (%)</td>
<td>% male</td>
<td>Mean age ± SD/median age (range)</td>
<td>Cut-off (pg/mL)</td>
<td>Sensitivity (%)</td>
<td>Specificity (%)</td>
</tr>
<tr>
<td>---------------------------</td>
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</tr>
<tr>
<td>Ishikura 2014, Japan Prospective DA study</td>
<td>ED</td>
<td>Sepsis, severe sepsis, septic shock</td>
<td>No</td>
<td>52.4</td>
<td>53.7</td>
<td>67.2±17.3</td>
<td>647</td>
<td>93</td>
<td>76.3</td>
</tr>
<tr>
<td>Ulla 2013, Italy Multicentre prospective DA study</td>
<td>ED</td>
<td>Sepsis and septic shock</td>
<td>No</td>
<td>56.1</td>
<td>61.4</td>
<td>64.4 (19-99)</td>
<td>600</td>
<td>78.9</td>
<td>61.9</td>
</tr>
<tr>
<td>Behnes 2014, Germany Prospective DA study</td>
<td>ICU</td>
<td>Sepsis, severe sepsis, septic shock</td>
<td>60 patients without SIRS</td>
<td>84.4</td>
<td>63.1</td>
<td>65.9 (20-88)</td>
<td>530</td>
<td>90</td>
<td>60</td>
</tr>
</tbody>
</table>

CR = consecutive recruitment; DA = diagnostic accuracy; ED = emergency department; ICU = intensive care unit; NR, not reported; SIRS = systemic inflammatory response syndrome

*Group 1 refers to studies denoted as “Phase 2” according to Sackett and Haynes classification of diagnostic accuracy studies.

**Group 2 refers to studies denoted as “Phase 3” according to Sackett and Haynes classification of diagnostic accuracy studies.
The potential prognostic value of presepsin has also been assessed in a number of recent studies.\textsuperscript{18-22} All these studies were retrospective cohort studies (level III-3 prognostic evidence). Of these five studies, all compared the prognostic performance of presepsin against other biomarkers available for sepsis prognostication, while Liu et al\textsuperscript{20} and Endo et al\textsuperscript{18} also considered the prognostic benefit of presepsin against established clinical parameters for the prognosis of sepsis. A description of the two identified prognostic studies that compared presepsin against other biomarkers and clinical parameters is provided below.

The Chinese study by Liu et al\textsuperscript{20} enrolled patients (n=859) meeting at least two diagnostic criteria for SIRS. The aim of the study was to determine the early prognostic value of plasma presepsin levels, as measured by the PATHFAST Presepsin assay using the PATHFAST Immunoanalyzer (Mistubishi Chemical Medience Corporation, Tokyo, Japan), compared with PCT levels and clinical measures including the Mortality in Emergency Department Sepsis (MEDS) score and Acute Physiology and Chronic Health Evaluation II (APACHE II) score in septic patients in an emergency department setting. Findings were as follows:

- the AUC\textsuperscript{14} of presepsin level for predicting 28-day mortality in septic patients was 0.66 versus 0.66, 0.72 and 0.72 for PCT, MEDS score and APACHE II score, respectively (no significant difference for all comparisons);
- plasma presepsin levels in septic patients were significantly higher in non-survivors than in survivors at 28-day follow-up, 748 pg/mL (95%CI 385, 1386 pg/mL) versus 412 pg/mL (95%CI 243, 744 pg/mL), respectively (p<0.001);
- based on binary logistic regression analysis, presepsin, MEDS score and APACHE II score were found to be independent predictors of severe sepsis, but PCT was not;
- the regression analysis indicated that presepsin, MEDS score, APACHE II score and PCT were independent predictors of septic shock and 28-day mortality;
- Spearman correlation analysis indicated positive correlations of presepsin with PCT, MEDS score and APACHE II score (Spearman’s coefficient, ρ = 0.50, 0.42 and 0.29, respectively);
- notably, and not surprisingly, the addition of MEDS score and APACHE II score to the risk prediction models presented by the authors resulted in increased prognostic accuracy compared to presepsin alone, e.g. a significant difference in observed 28-day mortality (AUC\textsubscript{presepsin} = 0.66 vs AUC\textsubscript{presepsin+MEDS} = 0.73 and AUC\textsubscript{presepsin+APACHEII} = 0.73, p<0.05 for both comparisons).

\textsuperscript{14}As a general ‘rule’, an AUC in the range 0.5 to 0.7 is considered the basis for a marginally useful test, an AUC of 0.7 to 0.9 would be indicative of a good test, and a test with AUC >0.9 can be considered as excellent. In this instance, an AUC of 0.66, for example, corresponds to a 66 per cent probability that the presepsin test will correctly predict 28-day mortality of a given patient selected at random. Refer here for further details.
To interpret, the findings of Liu et al suggest that plasma presepsin levels are marginally more useful for determining sepsis severity and the prediction of 28-day survival among SIRS patients compared to clinical assessment scores. These results also indicate that presepsin compares favourably to PCT as a prognostic marker for sepsis. The use of presepsin may have some capacity to impact effective risk stratification, particularly if used in combination with established clinical parameters for sepsis prognosis, though the cost of the technology (see relevant previous section) may not justify such a small clinical benefit. Though not explicitly stated in the conclusions, this study echoes the conclusions of other authors that their “preliminary findings provide a solid basis for future, more extensive evaluation of presepsin as a biomarker for... sepsis.” This conclusion is countered by the understanding that further insight is required in terms of “the pathophysiological conditions associated with presepsin release, both in experimental models of sepsis and in well-characterized patients...” and that “clinical indications for presepsin should be confirmed and validated in large-scale, independent cohorts of unselected patients with severe sepsis or septic shock.” Given the study was conducted among an Asian population, it is uncertain whether these results would be equally applicable to patients sampled from populations of another race.

A Japanese multicentre study \( (n=103) \) by Endo et al\(^{18} \) investigated the prognostic use of presepsin for patients diagnosed with sepsis \( (n=40) \), severe sepsis \( (n=32) \) or septic shock \( (n=31) \) according to American College of Chest Physicians/Society of Critical Care Medicine criteria. Plasma presepsin levels, determined using the PATHFAST Presepsin assay (Mitsubishi Chemical Medience, Tokyo, Japan), were compared with plasma PCT, interleukin-6 (IL-6), and CRP levels at admission to ICU/emergency department, and after one, three, five and seven days. The reference points for comparison were clinical indicators of sepsis severity, i.e. Sequential Organ Failure Assessment (SOFA) score, and APACHE II score; these parameters were used to classify patients according to prognostic risk group, either favourable or unfavourable, and levels of presepsin, PCT, IL-6 and CRP were compared between the prognostic groups. Biomarker levels and clinical scores, as measured at admission, are summarised in Table 3.
Table 3  Clinical and biological data of each prognosis group on admission by SOFA and APACHE II score

<table>
<thead>
<tr>
<th>Analysis by SOFA score favourable/unfavourable</th>
<th>Total (n=53)</th>
<th>SOFA favourable group (n=27)</th>
<th>SOFA unfavourable group (n=26)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean±SD)</td>
<td>73.7±14.7</td>
<td>72.9±17.8</td>
<td>74.5 (10.9)</td>
<td>0.7</td>
</tr>
<tr>
<td>Sex, n (%) male</td>
<td>32 (60.4)</td>
<td>20 (74.1)</td>
<td>12 (46.2)</td>
<td>0.04</td>
</tr>
<tr>
<td>Sepsis severity, N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>14</td>
<td>9</td>
<td>5</td>
<td>NA</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>19</td>
<td>11</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Septic shock</td>
<td>20</td>
<td>7</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>APACHE II score (median [IQR])</td>
<td>21.0 (17.7–29.0)</td>
<td>20.0 (16.2–24.0)</td>
<td>26.5 (19.0–31.1)</td>
<td>0.05</td>
</tr>
<tr>
<td>SOFA score (median [IQR])</td>
<td>9.0 (6.0–11.0)</td>
<td>7.0 (6.0–10.0)</td>
<td>9.0 (6.0–11.0)</td>
<td>0.54</td>
</tr>
<tr>
<td>Presepsin, pg/mL (median [IQR])</td>
<td>1523 (1014–2615)</td>
<td>1512 (962–2490)</td>
<td>1539 (1022–2863)</td>
<td>0.93</td>
</tr>
<tr>
<td>PCT, ng/mL (median [IQR])</td>
<td>17.9 (2.7–80.9)</td>
<td>27.3 (3.2–97.5)</td>
<td>16.2 (1.8–66.7)</td>
<td>0.53</td>
</tr>
<tr>
<td>IL-6, pg/mL (median [IQR])</td>
<td>1972 (287–25 297)</td>
<td>1972 (271–18 809)</td>
<td>1555 (331–58 547)</td>
<td>0.70</td>
</tr>
<tr>
<td>CRP, mg/dL (median [IQR])</td>
<td>13.0 (8.5–24.3)</td>
<td>13.7 (8.1–24.0)</td>
<td>12.1 (8.8, 25.6)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Analysis by APACHE II score favourable/unfavourable</th>
<th>Total (n=51)</th>
<th>APACHE favourable group (n=20)</th>
<th>APACHE unfavourable group (n=31)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean±SD)</td>
<td>75.6±12.7</td>
<td>72.3±15.4</td>
<td>77.8±10.2</td>
<td>0.12</td>
</tr>
<tr>
<td>Sex, n (%) male</td>
<td>32 (62.7)</td>
<td>15 (75.0)</td>
<td>17 (54.8)</td>
<td>0.15</td>
</tr>
<tr>
<td>Sepsis severity, N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>13</td>
<td>7</td>
<td>6</td>
<td>NA</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>18</td>
<td>6</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Septic shock</td>
<td>20</td>
<td>7</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>APACHE II score (median [IQR])</td>
<td>22.0 (19.0–29.0)</td>
<td>20.5 (17.4–24.0)</td>
<td>26.0 (19.0–29.8)</td>
<td>0.22</td>
</tr>
<tr>
<td>SOFA score (median [IQR])</td>
<td>9.0 (6.0–11.0)</td>
<td>7.0 (6.0–9.6)</td>
<td>9.0 (6.0–11.0)</td>
<td>0.21</td>
</tr>
<tr>
<td>Presepsin, pg/mL (median [IQR])</td>
<td>1523 (1025–2490)</td>
<td>1420 (962–2490)</td>
<td>1539 (1022–2863)</td>
<td>0.15</td>
</tr>
<tr>
<td>PCT, ng/mL (median [IQR])</td>
<td>18.2 (3.6–90.3)</td>
<td>18.7 (3.3–88.5)</td>
<td>18.1 (5.31–90.2)</td>
<td>0.8</td>
</tr>
</tbody>
</table>
The reported interquartile ranges for all biomarker levels at the time of admission were notably wide. Biomarker levels and clinical prognostic scores measured on Day 1, Day 3, Day 5 and Day 7 were reported graphically and it is not possible to accurately read values from the graphs provided. However, the author’s qualitative report of the graphical results indicated that:

- among the SOFA favourable group, presepsin levels on Day 3 and Day 7 were significantly lower than levels on admission (p<0.001 for Day 3 and Day 7 compared to admission);
- in the SOFA unfavourable group, presepsin levels on Day 7 were not significantly lower than those on admission;
- PCT, IL-6 and CRP levels in both SOFA groups were significantly lower on Day 7 compared to levels on admission (p<0.001 for PCT, IL-6 and CRP on admission versus Day 7);
- the 28-day mortality rate was significantly higher in the SOFA unfavourable group (6/26 [23%]) than the SOFA favourable group (1/27 [3.7%])(p=0.04);
- in the APACHE II favourable group, presepsin levels on Day 3 and Day 7 were significantly lower than levels on admission (p<0.001 for Day 3 and Day 7 compared to admission);
- in the APACHE II unfavourable group, presespin levels on Day 7 were not significantly lower than those on admission;
- PCT, IL-6 and CRP levels in both APACHE II groups were significantly lower on Day 7 compared to levels on admission (p<0.001 for PCT, IL-6 and CRP on admission versus Day 7);
- the 28-day mortality rate was significantly higher in the APACHE II unfavourable group (6/31 [19%]) than the APACHE II favourable group (0/20)(p=0.04).

These findings among a small patient sample from a Japanese population provide preliminary evidence suggesting the better prognostic performance of presepsin over earlier established biomarkers intended for the same purpose, but without a clear indication of the
variability of the estimates, conclusions about the prognostic usefulness of presepsin require caution. Given the study was small, it is likely that confidence intervals associated with the estimates would be large. The authors note that presepsin may well be more robustly predictive for sepsis than PCT. Indeed, systematic evidence\(^2^3\) suggests PCT does not reliably discriminate between sepsis and other acute inflammatory conditions without infection. In this sense, presepsin may represent a better method to help differentiate prognostic risk compared to PCT, as the latter may be elevated due to non-infectious conditions such as SIRS. However, larger, more rigorous studies including Asian and non-Asian patients are still required to provide guidance on the appropriate clinical place, if any, for presepsin as a prognostic biomarker for sepsis.

Furthermore, studies that demonstrate that the use of the PATHFAST Presepsin assay results in changes to clinical management appear to be lacking, and until such studies are available the value of adopting this test into routine clinical practice will be in question. Indeed, determining the ability of the test to provide early differentiation between sepsis and non-infectious inflammatory conditions such as SIRS should be a priority for any future research in the investigation of presepsin as a sepsis biomarker. If this question can be clarified, the value of PATHFAST Presepsin as a supplementary tool in clinical decision-making, particularly for determining which patients have the greatest potential to benefit from immediate commencement of antimicrobial therapy, and avoiding prophylactic antibiotics where truly not indicated, will be better understood.

**Economic evaluation**

None identified.

**Ongoing research**

A search of ClinicalTrials.gov identified an observational study (NCT02052895) that was completed in September 2015; the purpose of the study was to evaluate the diagnostic accuracy of presepsin levels to discriminate between sepsis and SIRS. It would appear that the results of this study are yet to be published.

The Australian New Zealand Clinical Trials Registry was also searched for any relevant forthcoming literature; however no additional studies were identified.

**Other issues**

Experts with clinical and research experience in critical care/intensive care were contacted to assist in preparing this Brief. Of the two Australian clinicians who responded, one stated that he had no specific knowledge of PATHFAST Presepsin\(^1^5\) and the other indicated (to the best of her knowledge) that of the numerous biomarkers being evaluated for sepsis, presepsin has received little interest among clinicians in Australia, and that PATHFAST is only

\(^1^5\) Personal correspondence via email, 10 November 2015.
“being used as a research tool (overseas).”\textsuperscript{16} It was further asserted that PCT is the only sepsis marker for which there is proven validity/acceptance. Notably, it was subsequently found that this clinician was an investigator in a randomised trial supported by industry (Roche Diagnostics, Thermo Fisher Scientific, and BioMérieux) that compared the outcomes for septic patients who were managed on the basis of clinical assessment plus testing for PCT levels with patients who were assessed using standard clinical criteria alone.\textsuperscript{24} The connection between industry and the trial this clinician was involved in represents a potential conflict of interest and source of potential bias against the PATHFAST system in favour of PCT, and may provide some indication as to why specific advice regarding PATHFAST was not forthcoming.

It is noteworthy that in the November 2011 assessment report\textsuperscript{17} to determine eligibility of PCT testing for public funding, the Medical Services Advisory Committee (MSAC) found that:

- there is an obvious need for early, accurate diagnosis of sepsis (and severe bacterial infection);
- sepsis and severe bacterial infection are currently managed based on clinical judgment in conjunction with results of existing direct tests (blood culture; microscopy and culture of urine, sputum or cerebrospinal fluid) and indirect testing methods (C-reactive protein; erythrocyte sedimentation rate; white cell count and differential; chest x-ray);
- the introduction of PCT aims to supplement not substitute standard medical assessment for clinical presentation of suspected sepsis;
- the accuracy of PCT testing is unknown given the lack of a validated reference standard;
- there is little evidence to suggest that PCT rises earlier or is more accurate than clinical assessment in predicting serious bacterial infection;
- PCT is safe, but appears to have no impact on hospitalisation, length of hospital stay or overall mortality;
- some evidence suggests a possible reduction in antibiotic prescribing associated with PCT testing, but there was significant heterogeneity in the results, making it difficult to determine whether this had a downstream impact on the prevalence of antibiotic resistance in the community (consequently MSAC concluded that adherence to

\textsuperscript{16} Personal correspondence via email, 14 November 2015.
\textsuperscript{17} November 2011 assessment of PCT measurement by the Medical Services Advisory Committee, available here: \url{http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1139-public}.
guidelines on appropriate antibiotic prescribing is more likely to impact on antibiotic resistance than an introduction of PCT testing;  

- PCT testing is not cost saving from a health care perspective compared to no PCT testing, and that there was potential for high volume use with the current wording of the proposed Medicare Benefits Schedule (MBS) item descriptor and that the number of repeat tests outlined in the assessment report is likely to be an underestimation of the number of tests that may actually be ordered (particularly in an ICU setting);  

- and that the data used to estimate the volume of use per year was also likely to be an underestimation and concluded that the total cost of $17 million per year was considered to be a gross underestimate, especially given that PCT testing may be used in a wider range of clinical scenarios than originally considered in the assessment.

These findings resulted in MSAC’s recommendation to the health minister that the currently available evidence is insufficient to support public funding for the measurement of PCT in serum or plasma for the diagnosis of life-threatening infections and sepsis, and monitoring the course and control of antibiotic therapy.

Industry involvement does not appear to have been source of potential bias among the meta-analyses included in this Brief. However, without a thorough examination of all studies contributing data to the meta-analysis described, it is not possible to categorically exclude the possibility of further industry influence on the findings. One study (Liu et al) included for prognostic evidence was supported by National Clinical Key Speciality Construction Project Funds and 2012 Beijing City Outstanding Doctoral Dissertation Funds, while the remaining prognostic evidence study was in part contributed by Mitsubishi Chemical Medience Corporation (Tokyo, Japan).

**Number of studies included**

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the HealthPACT web site.

Total number of studies: 4

Total number of Level III-1 studies: 2 (diagnostic accuracy)

Total number of Level III-3 studies: 2 (prognostic)

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18 Based on the available evidence for presepsin as a marker for sepsis (i.e. evidence of downstream impact on the decision for or against antibiotic therapy is lacking), it seems reasonable to conclude that this finding with respect to PCT is applicable to presepsin also.
Search criteria to be used

**MeSH terms**
- Sepsis; Systemic Inflammatory Response Syndrome; Bacterial Infections; Luminescent Measurements; Biological Markers; Humans; English

**Text terms**
- Presepsin; sepsis; soluble CD14 subtype; sCD14-ST; chemiluminescent immunoassay; biomarker; bacterial infection

**References**


