ICU
MANAGEMENT & PRACTICE

2023
VOLUME 23
ISSUE 1

Biomarkers

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Sepsis Diagnosis: Pancreatic Stone Protein in Adults, Children, and Neonates

The potential use of Pancreatic Stone Protein (PSP) in adults, children, and neonates based on concepts and checklist criteria for an ideal sepsis biomarker described in the article Sepsis Diagnosis: Clinical signs, Scores, and Biomarkers in this issue of ICU Management & Practice.

Pancreatic Stone Protein in Adults

First described in the 1970s, pancreatic stone protein (PSP) was only evaluated as a potential biomarker in sepsis in 2000 (Graf 2020). Since then, laboratory, animal, and clinical studies have accumulated on PSP, with over 600 studies now published. A recent review suggested PSP was an early biomarker of sepsis (Eggimann et al. 2019), confirmed by a second review (Fidalgo et al. 2022), including a multicentric study (Pugin et al. 2021) and a meta-analysis (Prazak et al. 2021). PSP has been used to diagnose and characterise sepsis even in severe inflammatory states without infection, such as in trauma patients (Keel et al. 2009; Klein et al. 2020), postoperative patients (Klein et al. 2020) such as post-cardiac surgery patients (Klein et al. 2015), severely burned patients (Klein et al. 2021a), and in ARDS (Klein et al. 2021b).

Diagnosis of Infection and Sepsis With PSP in Adults

A meta-analysis (Prazak et al. 2021) suggests that PSP is more sensitive and specific than CRP and PCT to diagnose infection. The combination of CRP with PSP further enhances its accuracy, with higher sensitivity and specificity. In a multicentric study (Pugin et al. 2021), the diagnostic accuracy of PSP, CRP and PCT for sepsis were similar, but the combination of CRP plus PSP had the best accuracy.

In this study, the cut-off of PSP to detect infection was lower than that for sepsis (Prazak et al. 2021). Until 2020, PSP levels were determined using an ELISA technique. Since 2020, PSP could be accurately measured using the rapid (<10 minutes), point-of-care abioSCOPE® diagnostic platform using a nanofluidic technology and the PSP-abioKIT®. In healthy subjects, PSP measured using the PSP-abioKIT® is under 44 ng/ml. In patients without infection or sepsis but with co-morbidities, PSP is under 88 ng/ml. The PSP cut-off for the diagnosis of infection was 233.3 ng/ml and 290.5 ng/ml for sepsis. All patients with sepsis had PSP values > 300 ng/ml already three days before sepsis and > 450 ng/ml on the day of sepsis, compared to the non-sepsis group who had PSP values under 200 ng/ml. A study with infection or sepsis managed in outpatient clinics showed that PSP measured performed at home can differentiate patients with confirmed bacterial infection from those with sepsis (Loots et al. 2022). In a study performed in the emergency room patients with suspicion of sepsis, PSP was used to differentiate patients without infection or uncomplicated infections from patients with sepsis. Combining patient age with PSP, the PPV is 100% and NPV 84.4% for PSP < 199 ng/ml (Van Singer et al. 2021).

Potential Use of Combining CRP and PSP

PSP may be integrated into the definition of sepsis in a severely burned patient (Niggemann et al. 2021). We propose that PSP and CRP could be added to the 2021 SSC guidelines (Evans et al. 2021). PSP plus CRP have the potential to increase the rapid diagnosis accuracy of bacterial infection and sepsis and help to start antibiotics as soon

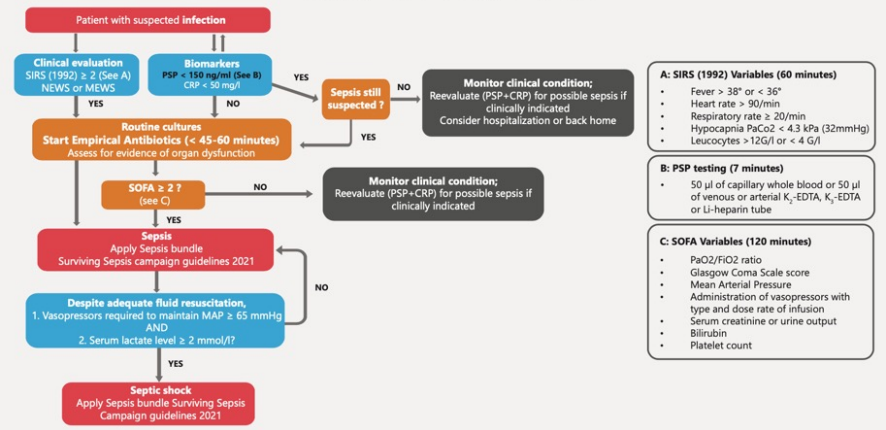

Figure 1. Proposal for modifying the 2021 Surviving Sepsis Campaign Guidelines definition with the inclusion of rapid measurement of PSP and CRP

as possible. They may prove useful to rule out diagnosis of sepsis based on good NPV and prevent unnecessary broad-spectrum antibiotic therapy (**Figure 1**). PSP levels < 150 ng/ml are associated with a good NPV and allow to decide not to start antibiotics, particularly when combined with a plasma CRP value < 50 mg/l.

Pre-Symptomatic Diagnosis of Nosocomial Sepsis in Adults

A multicentric study in severely ill patients (Pugin et al. 2021) confirmed that daily measurement of PSP may be used for pre-symptomatic diagnosis of nosocomial sepsis. It is proposed not to initiate antibiotic therapy if PSP levels are < 200 ng/ml. It also seems safe not to perform additional blood or radiological tests. It can also be proposed to start empirical broad-spectrum antibiotic therapy if PSP levels are > 300 ng/ml. If PSP is in a zone of moderate risk of sepsis (200-300 ng/ml), the management decision is based on clinical evaluation **(Figure 2**).

PSP in Neonatal Sepsis

In 2013, PSP levels were measured in 137 infants with a gestational age of > 34 weeks admitted with suspected early-onset neonatal sepsis (Schlapbach et al. 2013). A bio-score combining PSP and PCT was the best predictor and resulted in a NPV of 100% and a PPV of 71%. In 2016, a study on neonates showed a 96.2% sensitivity, an 88.5% specificity, and a 95.8% PPV to diagnose sepsis for an AUC of 0.87 (Rass et al. 2016). In 2017, a study of 119 neonates admitted with suspected sepsis showed significantly higher PSP levels in the infected group compared to the control group at all time points (Wu R et al. 2017).

PSP in the Diagnosis of Infection and Sepsis in Children

In a study (Jiří et al. 2014), PSP levels were significantly higher in patients with a PELOD score of 12 or higher or those with MODS. Serum levels of PCT and PSP were higher in children with acute osteomyelitis than those non-infected (Cui et al. 2017), and the combination of PCT with PSP further enhances its accuracy. In a study (Peng et al. 2015) PSP levels in the sepsis and severe sepsis groups were significantly higher than in the control group, on day 1 after PICU admission. In 2023, a study including 180 septic children and 100 control shows that PSP has a significant diagnostic value in evaluating critically ill patients with sepsis and detecting sepsis severity (Saleh et al. 2022).

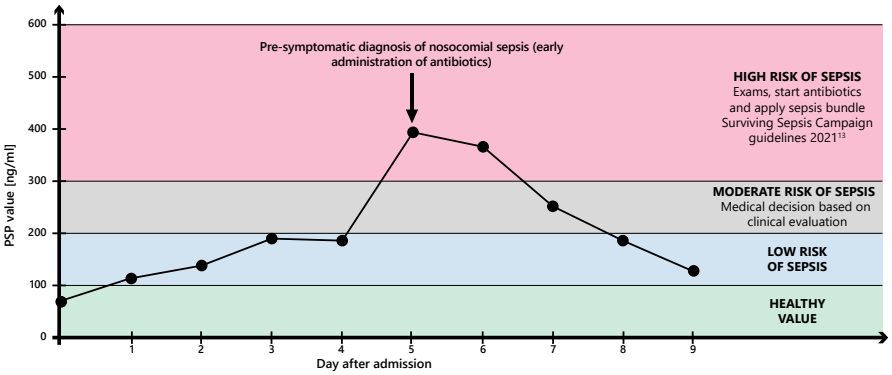

Figure 2. Pre-symptomatic diagnosis of nosocomial sepsis. Daily routine PSP monitoring of nosocomial sepsis.

Agenda for Further Research

An economic study published in 2022 (Schneider et al. 2022) shows that measuring PSP (US$ 52 per test) in adults at admission reduces costs by US$ 1,688 per septic patient in the emergency department and US$ 3,315 per septic patient in the ICU compared to standard of care. The national saving in the US could be up to US$ 7 billion per year.

Conclusion

In adults and children, the combination of CRP with PSP, allows high accuracy in the early diagnosis of infection and sepsis, with a potentially sufficiently high NPV (above 90%, even higher in neonates) to rule out infection and sepsis. PSP increases at least 48 to 72 hours in adults before clinical signs of sepsis, allowing pre-symptomatic diagnosis of nosocomial sepsis. The good NPV of the PSP could demonstrate its usefulness in the decision not to start antibiotic therapy or not to perform complementary exams and help solve the major public health problem of antimicrobial-resistant bacteria in hospitals and ICUs. Measuring PSP in adults at admission reduce costs per septic patient in the ED in the ICU compared to the standard of care. PSP combined with CRP in adults and PCT in paediatrics could fulfil most of the checklist criteria for an ideal sepsis biomarker (**Table 1**).

Sepsis Biomarker - Pancreatic Stone Protein PSP		
Affordable		
Price 10-50 US$	☑	30 - 40 US$
Economic study published	☑	Health Economic Review
Sensitive		
Standard protocolized study	☑	45 studies and 20 in progress
As high as clinical symptoms	☑	
Pre-symptomatic diagnosis	☑	
Antibiotic de-escalation	☑	Study in progress
Specific		
Standard protocolized study	☑	45 studies and 20 in progress
Cut-off and VPP > 90%	☑	
Cut-off and VPN > 90-95%	☑	
TP, TN, FP, FN rate	☑	
Sepsis/AMR Matrix	☑	
User-friendly testing	☑	Plug-and-play easy use POCT
Rapid		
Results in 45-60 minutes	☑	
Dosing time 10-20 minutes	☑	10 minutes
Equipment free (or light)		
Point of Care testing POCT	☑	
Pediatrics		
Capillary blood	☑	
Blood volume 30-50 ul	☑	
Certified		
European IVDR	☑	
FDA 510K	☐	Expected for Q4 2023
Australia	☑	

Table 1. Pancreatic Stone Protein (PSP) checklist as proposed in the article *Sepsis Diagnosis: Clinical signs, Scores, and Biomarkers in this issue of ICU Management & Practice*

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References

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