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RESEARCH ARTICLE

Pancreatic Stone Protein Measurement to Screen and Diagnose Sepsis in the Context of the Surviving Sepsis Campaign Recommendations.

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ABSTRACT

Sepsis occurs yearly in 48.9 million people worldwide of whom 11 million will die. Sepsis is defined as a life-threatening dysregulated reaction of the body in response to a bacterial infection, leading to organ dysfunction. The Surviving Sepsis Campaign made numerous recommendations for sepsis diagnosis and treatment using an evidence-based medicine approach. Frequently, levels of evidence of these recommendations are poor and lack clear clinical guidance. Interestingly, these guidelines strongly recommend, with a moderate quality of evidence, screening of nosocomial sepsis in acutely ill hospitalized high-risk patients. The definition of acutely ill and high-risk patients is not specified, nor it is indicated which tools should be used. The diagnosis of infection and the subsequent administration of antibiotics relies solely on rapid clinical assessment, as recommended by the Best Practice Statement. Again, the elements used for clinical assessment are poorly defined, encompassing patient history, clinical examination, and unspecified tests for both infectious and non-infectious causes of acute illness. In the real world and based on these recommendations, only 30 to 40% of empiric broad-spectrum antibiotic administrations are appropriate, contributing to the emergence of antimicrobial resistant bacteria, toxicity related to antibiotic administration, and costs. The aim of this review article is to show that the use of biomarkers, such as the Pancreatic Stone Protein, could be the specific tests and tools to help the clinician to diagnose and manage sepsis. Over 600 peer-reviewed publications have studied the physiology of Pancreatic Stone Protein and more than 50 evaluated its usefulness to screen for the development of nosocomial sepsis and diagnose sepsis.

Keywords: Sepsis, Septic shock, infection, bacterial infection, biomarker, pancreatic stone protein, organ failure, antibiotics, antimicrobial resistance

Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection,[1] and is a major public health threat causing 11 million deaths per year among 48.9 million cases worldwide.[2] This places sepsis as the second leading cause of death in adults after cardiovascular disease and the leading cause of death in children. Sepsis and septic shock can be prevented if diagnosed and treated early using an appropriate treatment, particularly a rapid administration of antibiotics. Mortality from sepsis increases by 8% per hour of delayed appropriate administration of antibiotics.[3] Two global campaigns have been launched by the Global Sepsis Alliance and the Surviving Sepsis Campaign (SSC) to improve sepsis care and survival rates. Sepsis and septic shock (a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality) are serious illnesses usually requiring management in an intensive care unit (ICU) and is very costly.[1] Sepsis-related costs in US hospitals surpass 24 billion US$ annually, making sepsis the most expensive disease to manage.[4] The diagnosis of sepsis is currently based on the 2016 Sepsis-3 definition.[1] According to Sepsis-3, sepsis is defined a dysregulated inflammatory response with organ dysfunction caused by a bacterial infection. Therefore, the diagnosis of sepsis is the sum of 3 components: infection + inflammation + organ failure. The latest international recommendations for the diagnosis and treatment of sepsis were published in October 2021 by the SSC.[5] These recommendations are assessed using an evidence-based medicine approach, often revealing a regrettable insufficiency in the level of supporting evidence. Additionally, due to a paucity of data and comprehensive studies, many SSC recommendations remain conceptual and lack specific guidance for clinical practice.

SEPSIS DIAGNOSIS STEWARDSHIP

According to the SSC 2021 recommendations,[5] the diagnosis of suspected infection is based on rapid clinical assessment *(including history and clinical examination, tests for both infectious and non-infectious causes of acute illness. Best Practice Statement*). The diagnosis of inflammation is based on a clinical score dating from 1992 (SIRS score), and that of organ failure on clinical scores (National Early Warning Score [NEWS], Modified Early Warning Score [MEWS]−*Strong recommendation, moderate-quality evidence*). The Sepsis-3 definition proposes the Sequential Organ Failure Assessment (SOFA) score as a tool to characterize organ failure and predict mortality but not to manage the patient.[1] The quick SOFA (qSOFA) proposed in 2016 is no longer recommended in 2021 (*moderate-quality evidence*). Therefore, sepsis diagnosis requires clinical assessment for infection and clinical scores for inflammation and organ failure. In the literature, there is frequent confusion between the diagnosis of infection, inflammation, organ failure, and or sepsis. The biomarkers classically used in sepsis, such as C-reactive protein (CRP), Procalcitonin (PCT), and lactate, each have specific properties. CRP is a biomarker of inflammation (*not SSC recommended*), PCT of infection (*against use*) and lactate is for organ failure (*weak recommendation, low-quality evidence*). Note, the use of PCT plus clinical evaluation in deciding when to stop antimicrobials, when compared to relying on clinical evaluation alone is weakly recommended (*very low quality of evidence*). Individually none of these three biomarkers are a biomarker of sepsis; instead, the combination of the three biomarkers (PCT + CRP + lactate) could lead to the diagnosis of sepsis. However, to date, no studies have compared the sensitivity and specificity of this biomarker combination to the combination of rapid clinical assessment and clinical scores (SIRS, NEWS, MEWS, SOFA) recommended by the SSC in 2021.[5] In practice, clinicians (in Switzerland) use biomarkers more frequently (89.7% measure circulating blood leucocytes, 92.3% CRP, 84.6% PCT, and 100% lactate in case of suspicion of sepsis) than clinical scores (35.9% use the Sepsis-3 definition alone, 34.2% calculate the qSOFA, and 44.7% the SOFA score).[6] Hence, a comparison of combined clinical vs combined biomarker sepsis diagnosis would be a useful and pragmatic study. Initiating broad-spectrum antibiotics in patients with suspected infection, based on the current combined clinical assessment, results in unnecessary treatments (empiric broad spectrum antimicrobial) in 60 to 70% of patients who do not ultimately have confirmed infection and sepsis. An issue due to similarities in clinical signs between viral and bacterial infections and inflammatory processes.[7] This is problematic since antibiotics are associated with secondary toxic effects and will contribute to the development of antimicrobial resistance (AMR). It has recently been estimated that 4.95 million (3.62–6.57) deaths yearly were associated worldwide with AMR.[8] To address the issue, ten golden rules for optimal antibiotic use in the hospital setting were published in October 2023 by the Worldwide Antimicrobial Resistance National/International Network Group (WARNING),[9] including *Prescribing antibiotics when they are truly needed*, *Prescribing the appropriate antibiotic(s) at the right time*, *Supporting surveillance Hospital Acquired Infections HAIs and AMR, monitoring of antibiotic use, consumption, and the*

quality of prescribing. But, like the SSC recommendations, it remains unclear how these rules are to be applied by the clinician. In 2019, two working groups of the European Society of Clinical Microbiology and Infectious Disease (ESCMID), ESGAP (Antimicrobial Stewardship) and ESGMD (Genomic and Molecular Diagnostics), proposed 7 roles that an infectious disease consultant can play in managing sepsis diagnosis, including the *selection of relevant rapid diagnostic tests for clinical practice to improve infection management and antibiotic prescribing behaviour*.[10] However, specific recommendations for which rapid tests to select are still lacking.

In summary, as mentioned above, the current approach to initiating antibiotic therapy, based on a combination of a rapid clinical assessment (and the use of unspecified tests) and clinical scores (tools), is unsatisfactory.[7] It is, therefore, urgent to define which tests and tools could improve current practice and accurate antibiotic administration (antimicrobial stewardship). The use of a combination of classic biomarkers CRP + PCT + lactate (vs. clinical combined sepsis diagnosis) or other biomarkers (tests) and scores (tools) should therefore be evaluated.

NOSOCOMIAL SEPSIS SCREENING (PRE-SYMPTOMATIC DIAGNOSIS)

Nosocomial infections, i.e., hospital-acquired infections (HAI), occur in 7 to 8% of hospitalized patients in Europe,[11] and 56% of those patients admitted to the ICU.[12] The WHO estimated 1.4 million nosocomial infections in 2016 and forecasted 10 million yearly deaths in 2050.[13] The main causes of HAI are bacteria with AMR and are frequently related to a poor adherence to infection control and prevention programs. In an epidemiological study published in 2020,[14] the proportion of nosocomial sepsis, i.e., hospital-acquired sepsis (HAS) among all hospital-treated sepsis cases, was 23.6% (95%CI, 17–31.8%). In the ICU, 24.4% (95%CI, 16.7– 34.2%) of cases of sepsis with organ dysfunction were acquired during ICU stay, and 48.7% (95%CI, 38.3–59.3%) had a hospital origin. The pooled hospital incidence of HAS with organ dysfunction per 1,000 patients was 9.3% (95%CI, 7.3–11.9%). Mortality of ICU patients with HAS with organ dysfunction was 52.3% (95%CI, 43.4–61.1%). The study concluded, "*There is an urgent need to improve the implementation of global and local infection prevention and management strategies to reduce its high burden among hospitalized patients*."

In this context, the first recommendation in the latest SSC 2021 guidelines proposes,[5] "*For hospitals and health systems, we recommend sepsis screening for acutely ill and high-risk patients. Strong recommendation, moderate quality of evidence*". But it is not defined how screening should be carried out. The definition of acutely ill and high-risk patients is not specified, but classical suggestions can be found in the literature (Table 1).

Table 1: Categories of hospitalized acutely ill and high-risk patients of nosocomial sepsis.[15,16]

Hospital stay > 5 days in patient with ≥ 2 co-morbidities
Emergency and abdominal surgery
Trauma patient with open fracture
Intensive care unit patient
Patient with catheters and drainage
Invasive mechanical ventilation
Parenteral nutrition

According to SSC 2021 guidelines,[5] "*There is wide variation in diagnostic accuracy of these screening tools with most having poor predictive values, although the use of some was associated with improvements in care processes. A variety of clinical variables and tools are used for sepsis screening, such as SIRS criteria, vital signs, signs of infection (unspecified tests), qSOFA or SOFA score, NEWS, or MEWS. Machine learning may improve the performance of screening tools. The pooled area under the receiving operating curve (AUROC−0.89 - 95%CI, 0.86−0.92) was higher for machine learning than the AUROC for traditional screening tools such as SIRS (0.70), MEWS (0.50), and SOFA (0.78). Screening tools may target patients in various locations, such as inpatient wards, emergency departments, or ICUs. A pooled analysis of three Randomized Clinical Trials (RCTs) did not demonstrate a mortality benefit of active screening (Relative risk RR 0.90; 95% CI, 0.51−1.58).*" Numerous studies have been carried out on a wide range of biomarkers (PCT, CRP, Pancreatic Stone Protein [PSP], Presepsin, leukocytes, Interleukin-6 [IL6], monocyte distribution width, etc.) to screen for early sepsis when first symptoms appear.

CURRENT SEPSIS BIOMARKERS

In 2020, a literature review listed studies on 258 different biomarkers of sepsis,[17] with 9 of them showing better performance than classical CRP and PCT. Unfortunately, 31% of the biomarkers had been the subject of only one publication, and most of them had been studied in less than 5 studies. Only 16% of the studies answered a clinical question, which is fundamental for biomarkers. In 2009, the *International Sepsis Forum Colloquium on Biomarkers of Sepsis* proposed to develop a systematic framework for the identification and validation of biomarkers of sepsis, and to promote collaboration between investigators, the biomarkers industry, and regulatory agencies.[18] For the organization, a biomarker of infection, inflammation, organ failure, and/or sepsis can have 5 clinical uses, i.e., 1) diagnose, 2) screen, 3) monitor, 4) stratify risk, and 5) use them as surrogate endpoints. Table 2 summarizes the current SSC 2021 approach to screen,[5] diagnose, and monitor sepsis. However, the question of whether a single specific biomarker (tool/test) exists that simultaneously and specifically detects infection, inflammation, organ failure, and thus sepsis remains unanswered. It seems unlikely given the complexity of immunological and inflammatory responses in sepsis.

Table 2: Current SSC 2021 recommendation to screen, diagnose, and monitor sepsis.[5]

Surviving sepsis campaign **SCC 2021**[5]	**Early Screening** In acutely ill and high-risk hospitalized patient (Table 1)	**Rapid Diagnosis** At time of clinical suspicion	**Monitoring** Treatment efficacy
Infection	*No recommendation*	**Rapid clinical assessment with Tests**[b] *Best Practice Statement* **Against PCT** *Weak recommendation* *Very low-quality of evidence*	**Clinical evaluation with Tests**[b] **+ PCT** *Weak recommendation* *Low-quality of evidence*
+ Inflammation	*No recommendation*	**SIRS score** *Strong recommendation* *Moderate quality of evidence*	*No recommendation*
+ Organ failure	*No recommendation*	**NEWS, MEWS, SOFA** *Strong recommendation* *Moderate quality of evidence* **Lactate** *Weak recommendation* *Low-quality of evidence*	**Lactate** **Capillary refill time** **Dynamic parameters**[c] *Weak recommendation* *Low-quality of evidence*
= Sepsis	**Tools**[a] *Strong recommendation* *Moderate quality of evidence*	**Rapid clinical assessment with Tests**[b] + **NEWS, MEWS, SOFA lactate**	**Clinical evaluation with Tests**[b] **+ PCT + Lactate + Capillary refill time + Dynamic parameters**[c]

Tools[a]: Variables analysis by manual methods or automated use of the electronic health record HER analysis (with or without artificial intelligence). Variables include scores, vital signs, signs of infections (unspecified tests), and others. **Tests**[b] (unspecified): biomarkers, radiological exams, other. **Dynamic parameters**[C]: response to passive leg raising or fluid bolus, stroke volume SV, stroke volume variation SVV, pulse pressure variation PPV, or echocardiography. **Abbreviation**: Systemic Inflammation Response Syndrome SIRS, National early warning score NEWS, Modified early warning score MEWS, Sequential organ failure assessment SOFA, quick SOFA qSOFA, Procalcitonin PCT.

Based on the analysis of the current situation, it seems necessary to use new or alternative biomarkers as the missing unspecified tools and tests in the current SSC recommendations.[5] To illustrate this search, we will review the current literature on the sepsis biomarker PSP. The aim is to see if PSP could be used as a tool and/or a test to be included in the next SSC recommendations.

Methods

SEARCH STRATEGY AND SELECTION CRITERIA

A literature search was performed on PubMed databases using pancreatic stone protein, PSP, PSP/reg, regenerating protein (REG1), lithostatine, and infection and sepsis as keywords and/or MeSH Terms. The search was specified for human and animal fundamental/physiological research and human adult clinical trials (ED and ICU) published until October 2023, that evaluated the

performance of PSP as a biomarker of infection and/or sepsis.

STUDY OBJECTIVES

The first objective is to review the physiology and the pathophysiological mechanisms of PSP in sepsis. The second is to classify PSP studies according to the 5 clinical questions: 1) diagnose, 2) screen, 3) monitor, 4) stratify risk, and 5) use them as surrogate endpoints, that the biomarker is expected to address for the 3 components of sepsis: infection, inflammation, organ failure. This review will show whether PSP could be one of the unspecified tools and/or tests currently lacking in the current SSC recommendation (Table 2). The third objective is to review the different technologies used to measure PSP. The fourth is an economic analysis of PSP use. Finally, we will discuss to what extent the existing data support the inclusion of PSP as a tool and/or test in the current SSC recommendations and its practical application in sepsis diagnosis stewardship in 2024.

Results

PHYSIOLOGY OF PANCREATIC STONE PROTEIN

Pancreatic Stone Protein is secreted mainly by the pancreas, has been the subject of > 600 publications since the 1970s, and has been extensively investigated for its role in the exocrine and endocrine function of the pancreas. These investigations are summarized in a recent publication.[19] Originally called lithostathine, PSP was discovered by different teams performing research on pancreatitis.[20] Lithostathine was hypothesized to be secreted by acinar cells in the duodenum and was believed to inhibit the formation of pancreatic stones by an inhibition of calcium carbonate crystal precipitation in the pancreatic juice. It was, therefore, renamed PSP,[21] but this proposed function turned out to be inaccurate,[22] and the name "stone" did not align with its function.

Simultaneously, other teams performing research on diabetes identified a protein isolated from beta-cells of the islets of Langerhans with potential beta cells regenerative activity, which they named islet-derived regenerating protein, the REG1 and REG family protein.[23] Surprisingly, lithostathine (PSP) and REG1 proteins were found to be almost identical,[24] even though one is involved in the exocrine function, and the other in the endocrine function of the pancreas. The correct name of the PSP is, therefore, PSP/REG1 or PSP/reg, but for reasons of habit and simplification, the name PSP has been commonly used. It should also be noted that the exocrine and endocrine functions of the pancreas are not totally independent, and acinar cells play an important role in the development and maintenance of islets of Langerhans betacells.[25]

However, the function of PSP, a 16 KDa 144 amino acid glycoprotein released in the duodenum, and digested in the duodenum by trypsin into an exocrine 14 KDa PSP 133 amino acid glycoprotein (lacking an eleven amino acid N-terminal peptide),[25] has not been fully elucidated despite numerous investigations.[26] This digested 14 KDa PSP is insoluble and therefore cannot be reabsorbed in the digestive tract. The 16 KDa PSP measured in the blood is therefore not a reflect of the PSP secreted by the pancreas in the duodenum.

PHYSIOPATHOLOGY OF PANCREATIC STONE PROTEIN IN INFECTION AND SEPSIS

In 1993, a study showed that the 14 KDa exocrine PSP form had the ability to immobilize and aggregate bacteria by binding to them,[27] but not the 16 KDa PSP form. Consequently, this property is related to the antibacterial activity of pancreatic juice but not the blood activity of PSP during infection or sepsis.

In 2002, it was demonstrated that blood levels of 16 KDa PSP transiently elevated in animals following stress induced by anaesthesia, even in the absence of pancreatic lesions. In response to this finding, Graf and Keel evaluating their newly developed Research Use Only (RUO) enzyme-linked immunosorbent assay (ELISA) technology on healthy individuals and patients with severe trauma.[28] The objective of this investigation was to investigate whether the 16 KDa PSP could function as an acute-phase protein (APP) in patients with nonpancreatic trauma. In this study of 83 patients, PSP plasma levels increased slightly after trauma (22.8 ng/ml vs. healthy controls 10.4 ng/ml) but increased significantly in patients who developed infection (111.4 g/ml) and sepsis (146.4 ng/ml). In contrast, CRP, IL-6, and PCT increased during the early phase after severe trauma, but these values did not differentiate between septic and non-septic patients. Since the pancreas was not damaged on imaging (CT-scan), and amylase and lipase plasma levels were unchanged, it was postulated that the increase in blood PSP was not caused by the release of damaged acinar cells into the bloodstream but possibly by intestinal cells (enterocytes) or through an unclear mechanism.

PANCREATIC STONE PROTEIN CLINICAL STUDIES FOR INFECTION AND SEPSIS

Searching for clinical studies of PSP and infection or sepsis in PubMed, we identified 1 prospective multicenter study,[29] 20 prospective observational studies (Table 3 and 4), 2 meta-analyses,[30,31] 2

literature reviews,[32,33] 1 economic study,[34] 2 technology study,[35,36] 1 case report,[37] 3 Covid-19 studies,[38-40] 1 book chapter,[41] 2 point-of-view articles.[42,43] From the PubMed citations, we excluded 8 children studies,[44-51] 3 neonate studies,[52-54] 1 post-mortem study,[55] 1 study in women for pregnancy-related disease,[56] 1 PSP and diabetes study,[57] 2 study protocols,[58,59] 1 letter,[60] 1 editorial,[61] 4 comments,[62-65] and 1 published erratum.[66]

PANCREATIC STONE PROTEIN FOR RAPID DIAGNOSIS OF INFECTION AND SEPSIS

For rapid diagnosis of infection at the time of clinical suspicion, we identified eight studies in different settings (Table 3).[28,36,67-72] Five of these were analyzed in a meta-analysis.[28,30,67,69,71,72] In this latter study, the median PSP value in infected patients was 81.5 ng/ml (IQR 30.0–237.5) compared to uninfected patients, 19.2 ng/ml (IQR 12.6–33.57) using a RUO ELISA. With a cut-off of 44.18 ng/ml, the sensitivity and specificity of PSP for the diagnosis of infection (AUROC 0.81 – 95%CI, 0.78-0.85) were higher than that of CRP (99.05 mg/l - AUROC 0.77 – 95%CI, 0.73-0.80) and PCT (0.20 ng/ml, AUROC 0.78 – 95%CI, 0.74-0.82). The combination of CRP plus PSP further enhanced its diagnosis performance (AUROC 0.90 – 95%CI, 0.87-0.92), with a higher sensitivity of 0.81 (0.77-0.85) and a higher specificity of 0.84 (0.79-0.90) for discriminating infection from non-infection compared to other biomarkers or combination of biomarkers. Adding PCT did not further improve the performance of the test.

The three studies not included in the meta-analysis showed that 1) PSP could differentiate an exacerbation of bacterial from other and viral origin in 200 patients with COPD[70]; 2) identify a bacterial origin in 114 febrile neutropenic patients[68]; and 3) diagnose infection in an unselected cohort of 105 patients admitted to the emergency department (ED).[36] A combination of a PSP cut-off value of 33.9 ng/mL by RUO ELISA, and the presence of purulent sputum had a specificity of 97% in identifying patients with pathogenic bacteria in sputum culture. In contrast, PSP levels below 18.4 ng/mL, and non-purulent sputum, ruled out positive bacterial sputum culture with a sensitivity of 92%.[70] When analyzing the capability of PSP and PCT to diagnose infection in cancer patients with febrile neutropenia, PSP using a cut-off value of 29 ng/ml by RUO ELISA (AUROC 0.751 – 95%CI, 0.662-0.840) demonstrated a lower performance than PCT (AUROC 0.901 – 95%CI, 0.846-0.955). However, PSP differentiated infected neutropenic patients with a median cut-off at 58 ng/ml (31-101) vs. 26 ng/ml (15-49), p<0.001 in non-infected patients. Recently, a new Chinese technology has been proposed to measure PSP, based on aldehyde nanoparticle-based amplified luminescent proximity homogeneous assay [AlphaLISA], and tested in 105 patients admitted to the ED.[36] The correlation between PSP values measured by RUO ELISA vs. AlphaLISA is not known. In this latter study, PSP (126.4 ng/ml - AUROC 0.91 - 95%CI, 0.84-0.98) was better than PCT (0.185 ng/ml - AUROC 0.79 - 95%CI, 0.67-0.91) and CRP (17.35 mg/l – AUROC 0.89 – 95%CI, 0.79-0.99) to diagnose infection. PSP (198.5 ng/ml - AUROC 0.85 – 95%CI, 0.76-0.95) was also better at differentiating infected vs. septic patients (PCT 1.05 ng/ml - AUROC 0.69 – 95%CI, 0.57-0.83) and CRP (98.15 mg/l - AUROC 0.78 – 95%CI, 0.66-0.89). The combination of PSP + CRP + PCT provided the best AUROC to differentiate healthy and infected patients (AUROC 1.0), as well as infected and septic patients (AUROC 0.92 – 95%CI, 0.84-0.99).

Apart from this latter publication, we identified 7 studies for rapid diagnosis of sepsis (Table 3).[28,29,36,67,70,71,73-75] Keel et al. were the first to show that the performance of PSP was higher in nosocomial sepsis occurring in 83 ICU patients with trauma.[28] Llewelyn et al. showed in 219 patients admitted to the ICU that PSP (cut-off value 30 ng/ml RUO ELISA – AUROC 0.91 – 95%CI, 0.86-0.96) was better than PCT (1.0 ng/ml - AUROC 0.84 – 95%CI, 0.77-0.91) for the diagnosis of sepsis.[71] In the ED, PSP (96.6 ng/ml RUO ELISA – AUROC 0.87 – 95%CI, 0.81-0.94) also performed better than PCT (2.02 ng/ml - AUROC 0.82– 95%CI, 0.74-0.90) for sepsis diagnosis (n=152). Since 2020, four studies have used a new nanofluidic dosing technology to measure PSP,[35] the only test certified to date (abioSCOPE®, Abionic, Switzerland). The correlation between RUO ELISA and abioSCOPE® PSP values has been established: abioSCOPE® ng/ml = 4.6 x RUO ELISA ng/ml + 30 ng/ml - 95%IC 0.39-0.59.[76] This will be further discussed in the section on technology.

In a recent European multicenter study involving 14 centers and 243 participants,[29] it was shown that the diagnostic accuracy of PSP to diagnose sepsis was similar, with a cut-off value of 290.5 ng/ml for PSP measured using abioSCOPE® (AUROC 0.75 – 95%CI 0.67-0.82), CRP, 167.2 mg/l - AUROC 0.77 – 95%CI 0.69-0.84), and PCT(0.94 ng/ml - AUROC 0.75 – 95%CI 0.680.82. The combination of CRP plus PSP had the best diagnosis accuracy with an AUROC of 0.79 – 95%CI, 0.72-0.86. The addition of PCT did not further improve the diagnostic performance. In another study involving

357 patients,[73] with obvious clinical infection or sepsis, PSP measured at home by paramedics differentiated patients with confirmed bacterial infection (median PSP abioSCOPE® 131 ng/ml, IQR 83-205) from those with sepsis (PSP 156 ng/ml, IQR 90-286), p=0.016.[73] Unfortunately, the absence of a control group without infection precluded determining the negative predictive value or PSP cut-offs as guidance for antibiotic therapy initiation. Similarly, in a study performed in 156 patients admitted to the ED with suspected sepsis,[74] the PSP was used to differentiate patients without infection or uncomplicated infections from patients with sepsis. By combining patient age (< 50 years old) with PSP (excluding Covid-19 patients), the positive predictive value (PPV) was 100% and negative predictive value (NPV) was 84.4% using a PSP cut-off value of 199 ng/ml. Among 40 patients with abdominal infections such as cholecystitis, appendicitis, or diverticulitis, the median PSP level on admission for patients with sepsis was 162 ng/dL (86.75–254.25) vs. 74.5 ng/dL (47.25–141.25) for patients without sepsis (p = 0.037).[75]

Table 3: Positioning PSP studies for early screening, rapid diagnosis and to monitor treatment efficacy.

Pancreatic Stone Protein studies	**Early Screening** In acutely ill and high-risk hospitalized patient (Table 1)	**Rapid Diagnosis** At time of clinical suspicion	**Monitoring** Treatment efficacy
Infection	**Intensive Care Unit** • Trauma[28] • Post cardiac surgery[69] • Severely burns[77]	**Intensive Care Unit** • Unselected patient[71] • Trauma[28] • Post cardiac surgery[69] • Major abdominal surgery[72] **Emergency department** • Unselected[36,67] • Febrile neutropenia[68] • Exacerbations of COPD[70] **Meta-analysis**[30]	*On-going multicenter study*
+ Inflammation	-	-	-
+ Organ failure	-	-	-
= Sepsis	**Intensive Care Unit** • Multicenter study[29] • Trauma[28] • Post cardiac surgery[69] • Severely burns[77,78]	**Intensive Care Unit** • Unselected patient[29,71] • Trauma[28] • Post cardiac surgery[69] • Major abdominal surgery[72] • *On-going multicenter study*[79] **Emergency department** • Unselected[36,67,74] • Infectious abdominal diseases[75] **Out-of-hours Primary Care** • Unselected[73]	*On-going multicenter study*

PANCREATIC STONE PROTEIN FOR EARLY NOSOCOMIAL INFECTION AND SEPSIS SCREENING

After the initial study by Keel et al. ,[28] several studies showed that measurement of plasma PSP could detect infection and sepsis up to 3 to 5 days before the first symptoms appeared (pre-symptomatic diagnosis of nosocomial sepsis).[29,69,77] In an unselected population of cardiac surgery patients,[69] "*post-operative serum PSP levels were significantly associated with the presence of infection in both the on-pump and off-pump setting*." PSP (48.1 ng/ml RUO ELISA – AUROC 0.76 – 95%CI, 0.62-0.88) was better than CRP (AUROC 0.53) and leucocytes (AUROC 0.64) in predicting infection at Day 2.

In a cohort of 90 severely burned patients,[77] "*PSP daily measurement differentiated between sepsis, infection, and sterile inflammation from day 3 onward with an area under the curve of up to 0.89 (p< 0.001). PSP demonstrated a highly discriminatory ability to timely identify evolving sepsis and septic shock in patients with acute severe burns. Its steep increase allows sepsis detection up to 72 hours before clinically overt deterioration, thus outperforming CRP and PCT based protocols for sepsis diagnosis*". These results prompted the launch of an ICU prospective multicenter study with 14 centers in Europe, and 243

patients included, using the new abioSCOPE® technology.[29] Results showed that "*serial PSP measurement demonstrated an increase of this marker days preceding the onset of signs necessary to diagnose sepsis clinically. PSP started to increase 5 days before the clinical diagnosis of sepsis, compared to 3 and 2 days, for PCT and CRP, respectively*". Interestingly, in this study, all patients with sepsis already had PSP values above 300 ng/ml 3 days before sepsis and above 450 ng/ml on the day of sepsis, compared to the non-sepsis group who had PSP values under 200 ng/ml.

PANCREATIC STONE PROTEIN FOR MONITORING INFECTION AND SEPSIS TREATMENT EFFICACY

In contrast to PCT and CRP, there are no studies on monitoring infection and sepsis treatment efficacy with PSP as an aid to antibiotic de-escalation decisions.

PANCREATIC STONE PROTEIN FOR INFECTION, ORGAN FAILURE, AND SEPSIS RISK STRATIFICATION AND TO SURROGATE ENDPOINT

Thirteen studies investigated risk stratification: disease severity, SOFA score, vasopressor support, renal replacement therapy, risk of readmission, progression to organ failure, mechanical ventilation, treatment escalation, and surrogate endpoints: length of stay, mortality for infection, organ failure, and sepsis (Table 4). A meta-analysis of five studies (n=678) was recently published,[31,67,71,72,80,81] and showed that risk thresholds based on the Youden index to discriminate mild infection from severe infection or septic shock were 61.7 ng/ml for PSP using the RUO ELISA, 125.9 mg/l for CRP and 1.1 ng/ml for PCT. PSP (AUROC 0.80 - 95%CI, 0.75–0.85) and PCT (AUROC 0.79 - 95%CI, 0.74–0.84) performed better than CRP (AUROC 0.56 - 95%CI, 0.50–0.63). The prediction of 28-day mortality was also better with PSP (AUROC 0.69 – 95%CI, 0.64-0.74) than with PCT (AUROC 0.61 - 95%CI, 0.56-0.66) and CRP (AUROC 0.52 - 95%CI, 0.47-0.57). A study in ventilator-associated pneumonia (VAP) patients (n=101) showed that PSP was correlated with the SOFA score from VAP onset (Spearman rank correlation coefficient $r = 0.49$, $p < .001$) up to day 7. PSP at VAP onset was elevated in non-survivors (n = 20, 117.0 ng/ml by RUO ELISA, 36.1-295.3) compared to survivors (36.3 ng/mL, 21.0-124.0) p= 0.011. The AUROC of PSP to predict mortality was 0.69 at VAP onset and 0.76 at day 7. PSP also proved superior to CRP, ferritin, and fibrinogen in sepsis diagnosis (AUROC 0.862), treatment escalation (AUROC 0.689), and prediction of readmission (AUROC 0.899) among patients (n=40) with intra-abdominal infections.[75] In COPD exacerbation, admission PSP was predictive of 2-year mortality.[70] In 107 ICU patients,[82] PSP at Day 1 (AUROC 0.65 - 95%CI, 0.51-0.80) was higher than for CRP (0.44 – 95%CI, 0.29-0.60) and PCT (0.46 – 95%CI, 0.29 to 0.61) in predicting in-hospital mortality. In patients with septic shock, PSP was the only biomarker associated with in-hospital mortality (p=0.049). The risk of mortality increased continuously for each ascending quartile of PSP. In 141 ICU patients,[83] PSP was correlated with the SOFA score ($p<0.001$). Significant differences were observed in PSP levels between patients with and without MODS ($p<0.05$) and between survivors and non-survivors of sepsis ($p<0.01$). A strong correlation was observed between circulating PSP and vasopressor support at admission ($r = 0.496$; $p < 0.001$), long-term administration of vasopressors ($r = 0.545$; $p < 0.001$), mechanical ventilation ($r = 0.607$; $p < 0.01$), or renal replacement therapy (RRT) ($r = 0.360$; $p = 0.015$). Although the literature showed that PSP was not a marker of viral infection, three studies were carried out with the abioSCOPE® in patients infected with SARS-CoV2, two in the ED,[38,39] and one in the ICU.[40] In the study performed in the ED (n=173),[38] PSP ≥ 90.5 ng/ml was predictive of 7-day mortality with an AUROC (0.83 - 95%CI, 0.74-0.92) identical to CRP (136.5 mg/l - AUROC 0.83 - 95%CI, 0.79-0.93), but better than the qSOFA (AUROC 0.7 – 95%CI, 0.57083). In 55 patients admitted to the ED,[39] PSP accurately identified patients requiring prolonged hospitalization (AUROC 0.80) but not at risk of death (AUROC 0.59). A small ICU study with 21 patients enrolled showed better mortality prediction with PSP (AUROC 0.83 – 95%CI, 0.73-0.93) than with PCT (AUROC 0.65 – 95%CI, 0.53-0-76) and CRP (AUROC 0.58 – 95%CI, 0.43-0.70).[40]

Table 4: Positioning PSP studies for risk stratification and to surrogate endpoint.

Pancreatic Stone Protein studies	**Risk stratification** Prognosis, disease severity, progression to multiples organ failure, other.	**Surrogate endpoint** Length of stay, mortality, other.
Infection	**Hospitalized Patient** • Meta-analysis[31] • Intra-abdominal infection[75] **Intensive Care Unit** • Unselected patients[71,72,80,81 80,82] • Ventilator-associated pneumonia[84] • COVID-19[40] **Emergency Department** • Unselected patient[67] • COVID-19[38,39]	**Hospitalized Patient** • Meta-analysis[31] • Intra-abdominal infection[75] **Intensive Care Unit** • Unselected patients[71,72,80-82] • Ventilator-associated pneumonia[84] • COVID-19[40] **Emergency Department** • Unselected patient[67] • Exacerbations of COPD[70] • COVID-19[38,39]
+ Inflammation	-	-
+ Organ failure	**Intensive Care Unit** • Unselected patient[81,83,84]	-
= Sepsis	**Hospitalized Patient** • Meta-analysis[31] • Intra-abdominal infection[75] **Intensive Care Unit** • Unselected patient[71,72,80-82,84] **Emergency Department** • Unselected patient[67]	**Hospitalized Patient** • Meta-analysis[31] • Intra-abdominal infection[75] • Intensive Care Unit • Unselected patient[71,72,80,81 82] **Emergency Department** • Unselected patient[67]

PANCREATIC STONE PROTEIN TECHNOLOGY

Until 2020, PSP plasma levels were determined using RUO ELISA technique. This technique was used in all clinical studies from 2009 to 2020. Since 2020, PSP could be accurately measured using the 5 minutes rapid, point of-care abioSCOPE® diagnostic platform, using a nanofluidic technology (CE certified 2020 and FDA registered) and the PSP-abioKIT® (Europe CE certified In Vitro Diagnostic Regulation IVDR 2022, Australia and Malaysia registration, Swissmedic, FDA 510K expected Q2 2024, Abionic, Epalinges, Switzerland). The measurement of plasma PSP levels has become very robust and accurate using this novel nanofluidic precision technique, coupled with high affinity and highly specific antibodies.[35] Several classical ELISA kits with results obtained within 2 to 3 hours are used and commercialized in China.[46,48,83] In addition, the new Chinese AlphaLISA technology calibrated using an ELISA technic can also deliver results in 5 minutes.[36]

PANCREATIC STONE PROTEIN ECONOMIC STUDY

A 2021 independent US economic study showed that the use of PSP at a hypothetical price of 52 US$ could save the US healthcare system US$7 billion a year.[34] "*The rapid PSP test was found to reduce costs by US$1,688 per patient in the ED and US$3,315 per patient in the ICU compared to standard of care. Cost reductions were primarily driven by the specificity of PSP in the ED and the sensitivity of PSP in the ICU*".

Discussion

PHYSIOLOGY OF PANCREATIC STONE PROTEIN

In the current environment, there are 2 different PSPs with the same name, the 16KDa endocrine form, formerly known as REG1, and the 14KDa exocrine form, formerly known as lithostathine. In healthy patients, PSP measured in the blood is only the 16 KDa PSP produced by pancreatic beta-cells.[85]

In 2017, immunohistochemical analysis indicated that in healthy subjects, PSP is predominantly produced by the pancreas, followed by the duodenum, jejunum - including enterocytes and Paneth cells, ileum, blood, specifically fundic cells of the stomach, colon, kidney, and liver.[86] Serum PSP levels increase in pancreatic diseases, such as acute and chronic pancreatitis, as well as various gastrointestinal conditions.[87] In remains unclear whether it is the production by the beta-cells that increases and/or whether it is the damaged acinar cells that release PSP into the bloodstream. The frequencies of increased serum PSP levels were as follows: 79% in acute pancreatitis, 44% in chronic pancreatitis, 42% in pancreatic cancer, 100% in chronic renal failure, 33% in gastric cancer, 11% in peptic ulcer, 18% in gallstone, 19% in liver cirrhosis, and 17% in diabetes mellitus.[85] Among non-pancreatic diseases, chronic renal failure under RRT presented significantly higher serum PSP than other disease groups, except for acute pancreatitis. Some

of the patients with myocardial infarction, cardiac failure, perforation of the gastro-intestinal tract, or ileus in ICU seemed to have presented increased PSP in serum and urine.[88] In acute pancreatitis, PSP serves as the best prognostic marker (AUROC 0.827) for clinical outcomes surpassing other classical clinical (Ranson) and radiological (Balthazar) scores.[89] It was shown that PSP slightly correlated with HbA1c ($r=0.547$, $p<0.001$), glomerular filtration rate ($r=-0.502$, $p<0.001$), serum creatinine ($r=0.492$, $p<0.001$), urinary albumin ($r=0.620$, $p<0.001$), and blood pressure ($r=0.479$, $p<0.001$).[57] The origin of this increase, in the absence of pancreatic or intestinal lesions, was likely related to stress and beta-cell activation, rather than the release of PSP from non-damaged acinar cells. Table 5 provides a list of situations where PSP should be interpreted with caution for the diagnosis of infection and sepsis and highlights cases in which monitoring PSP kinetics is recommended or should not be interpreted.

Table 5: Relative and absolute limitation of Pancreatic Stone Protein PSP values interpretation.

PSP relative limitation Interpret PSP with caution - follow PSP kinetics	**PSP absolute limitation** PSP not interpretable
Diabetes	Acute and chronic pancreatitis
Moderate acute and chronic renal failure • Creatinine ≤170 µmol/l	Severe acute and chronic renal failure • Creatinine > 170 µmol/l
Gastrointestinal disease	Renal Replacement Therapy (RRT)
Abdominal surgery	Pancreatic cancer

For renal insufficiency, the cut-off of > 170 µmol/l (≥ 2 points on the SOFA score) corresponding to moderate to severe insufficiency is based on a subgroup analysis from a clinical study but remains to be confirmed by a dedicated study. In the case of RRT, there are no specific studies analyzing PSP kinetics. It can be postulated that since PSP is a 16 KDa protein, like PCT (13 KDa) but not CRP (115 KDa), it should be eliminated by dialysis filters that filter out molecules of < 35-40 KDa.[65] Even though clinical experience does not show a significant drop in PSP during renal replacement therapy (RRT), and in the absence of a study, we propose not to interpret PSP during RRT, like PCT.

PHYSIOPATHOLOGY OF PANCREATIC STONE PROTEIN IN INFECTION AND SEPSIS

As mentioned, PSP (REG1 protein) is secreted by beta-cells, and we hypothesize that during sepsis PSP would be secreted by beta-cells and not by acinar cells as previously thought. A review article mentioned that PSP had a regenerative activity for pancreatic beta-cells,[25] and the link between immunity and insulin secretion was established.[89] Immunohistochemical studies on human cadavers showed that it is the 16KDa undigested PSP that increases during sepsis and not the 14KDa digested form secreted by the acinar cells.[86] Therefore, the hypothesis is that immune activation following infection, and/or a dysregulated immune reaction in the context of sepsis, induced the secretion of PSP 16 KDa by beta-cells. Studies are needed to confirm or refute this hypothesis.

The reason why PSP increases during infection and sepsis is probably due to induction by pro- and anti-inflammatory cytokines, as shown in different publications.[28,88] Further, studies show that there is a link between immune activation and beta-cell responses,[90] between sepsis and insulin,[91] and between beta-cell stress and PSP.[92]

PSP was initially described as an acute-phase protein (APP) as well in subsequent clinical studies and literature reviews.[28] APP are inflammatory markers produced by the liver that exhibit significant changes in serum concentration during acute and chronic inflammation.[93] Cytokines such as IL-6, IL-1, tumour necrosis factor-alpha (TNF-alpha), and interferon-gamma are responsible for inducing APP production by the liver. APPs may cause effects such as fever, anaemia, anorexia, somnolence, lethargy, and cachexia. APPs can be classified as positive or negative, depending on their blood concentrations during inflammation. Positive APP are upregulated, and their concentrations increase during inflammation. They include CRP, ferritin, fibrinogen, hepcidin, and serum amyloid A. Negative APP are downregulated, and their concentrations decrease during inflammation, and they include albumin, prealbumin, transferrin, retinol-binding protein, and antithrombin. Interestingly, PSP is not produced by the liver, and can therefore not be considered as an APP. PSP does not increase during inflammation, as demonstrated in numerous clinical studies.[69,77,94,95] The function of PSP in sepsis remains to be elucidated. The study of Keel et al. showed that PSP not only binds to polymorphonuclear neutrophils (PMNs),[28] but also activates PMNs and microcirculatory failure by decreasing CD62L (an L-selectin expressed on the PMN surface that is shed

after activation of the binding process) and increasing CD11b (a beta-2 integrin expressed on the PMN surface which enables PMNs to adhere to blood vessels).

As a reminder, PCT is a pro-hormone (Calcitonin) normally produced in the thyroid C-cells, and is therefore not considered as an APP. During inflammation, infection and sepsis, the production of PCT follows a pathway which are not fully understood. The function of PCT is not clearly identified either. The presence of PCT in the serum of thyroidectomized patients during bacterial infection supports the notion that an organ other than the thyroid is the source of PCT in bacterial sepsis. Some studies suggest a ubiquitous expression of the calcitonin gene in response to sepsis, while others suggest that specific organs like pituitary, neuroendocrine cells in the lungs, intestine, splanchnic area, liver, or hypothalamus are the source of PCT in sepsis.[96] PCT has many limitations and interpretation of PCT levels can be difficult in patients with severe trauma, major burns, multi-organ failure, renal failure, islet cell tumours and medullary thyroid carcinoma, cellular injury of any kind, direct tissue, or ischemia-reperfusion injury without infection, and other). Highly elevated bilirubin and triglycerides also interfere with PCT level measurement.[96] CRP is an APP synthesized by the liver under the action of inflammatory cytokine such IL-6 but also T lymphocytes, NK cells and macrophages. CRP binds to damaged tissue, to nuclear antigens and to certain pathogenic organisms in a calcium dependent manner.[97] The function of CRP is felt to be related to its role in the innate immune system. CRP binds to Fc receptors and acts as an opsonin for various pathogens. Interaction of CRP with Fc receptors leads to the generation of proinflammatory cytokines that enhance the inflammatory response. CRP provides early defence and leads to a proinflammatory signal and activation of the humoral, adaptive immune system.[97]

PANCREATIC STONE PROTEIN FOR RAPID DIAGNOSIS OF INFECTION AND SEPSIS

A study conducted at home by paramedics showed that biomarkers do not provide any additional value compared to clinical assessment for diagnosing clinically obvious infection and sepsis.[73] Since the indication for measuring the biomarker is clinical suspicion of sepsis or infection, the biomarker's sensitivity cannot surpass the clinical suspicion.

In the context of clinical suspicion, the biomarker is used to confirm the diagnosis (specificity) but not to detect an already suspected clinical situation (sensitivity). It is the specificity that is of interest, as it enables clinicians to decide whether to give antibiotics (PPV) or not (NPV). The administration of antibiotics should occur within one hour of admission to the ED, with a *strong recommendation but low-quality evidence* in cases of septic shock and a *strong recommendation but very low-quality evidence* in cases of sepsis without shock.[5] Consequently, the test result, in this case, PSP, must also be obtained within less than one hour. All PSP and other biomarkers clinical studies wrongly determined cut-offs and AUROCs to obtain the best sensitivity and specificity combination. Cut-offs for the best specificity should have been determined without taking sensitivity into account. In the absence of this analysis, it is difficult to determine the precise cut-off that would allow for the initiation of antibiotics with a low rate of false negatives. Moreover, it seems illusory to find a magic cut-off, for PSP or any other biomarker, with 0% infection or sepsis if it is not reached and 100% infection and sepsis if it is exceeded. It has been correctly proposed in a recently submitted article,[98] that 4 cut-off points (NPV) should be determined (not only for PSP) to differentiate between 5 levels of risk of infection or sepsis (very low < 10%, 10-20% low, 20-50% moderate, 50-80% high, > 80% very high). This stratification could aid clinicians in making care decisions (Table 6). In situations of clinical suspicion, the sepsis test/biomarker should help to confirm (PPV) or exclude (NPV) infection as recommended by the SSC guidelines. *For adults with suspected sepsis without shock, we recommend rapid assessment of the likelihood of infectious versus non-infectious causes of acute illness, per Best Practice Statement.* The decision not to give antibiotics to prevent the development of AMR bacteria is therefore based on the NPV.[99] The consequences of not giving antibiotics to a patient with sepsis can be immediately more severe (8% increase in mortality per hour of delay) than starting a broad spectrum empirical antibiotic therapy,[3] which can be stopped after 24-48 hours depending on the microbiological documented infection (MDI) or clinical documented infection (CDI) including lab tests, radiological finding and clinical evaluation. Based on the literature review and pending the final results of a multicenter study in the USA in 550 patients,[79] we propose an NPV approach in cases of clinical suspicion, where a PSP value < 50 ng/ml indicates very low risk of sepsis, 50-100 ng/ml indicates a low risk, 100-150 ng/ml signals a moderate risk, 150-200 ng/ml indicates a high risk, and > 200 ng/ml points to a very high risk (Table 6). The use of PSP, in combination with other biomarkers such as CRP, PCT, lactate, etc. and/or scores, could represent the missing unspecified test in the SSC recommendations and thus already be used in

clinical practice to decide "To give or not to give antibiotics?". Subsequent interventional studies could then confirm the benefits for patients, potentially influencing future international recommendations.

Table 6: Proposed Pancreatic Stone Protein PSP values and cut-offs for nosocomial sepsis early screening and to diagnose or rule out sepsis at the time of clinical suspicion.

Risk of sepsis Pancreatic Stone Protein PSP Value		**Early screening** In acutely ill and high-risk hospitalized patient (Table 1) *PSP positive predictive value*	**Rapid diagnosis of sepsis** At time of clinical suspicion *PSP negative predictive value*
Very High	>80%	> 300 ng/ml	> 200 ng/ml
High	50-80%	200-300 ng/ml	150-200 ng/ml
Moderate	20-50%	150-200 ng/ml	100-150 ng/ml
Low	< 20%	100-150 ng/ml	50-100 ng/ml
Very Low	<10%	< 100 ng/ml	< 50 ng/ml

Literature reviews and clinical experience show that PSP does not increase, or increases only minimally,[74] with viral infections such as SARS-CoV2, or with toxic shock syndrome. It is, therefore, probable that PSP has a high degree of specificity for classic gram-negative bacterial sepsis. A dozen studies are in progress across different settings, including ICU, hospital wards, primary care in low-income countries, to evaluate the use of PSP in suspected infection and/or sepsis. However, the behavior of PSP during fungal infection has not yet been specifically studied.

PANCREATIC STONE PROTEIN FOR EARLY NOSOCOMIAL INFECTION AND SEPSIS SCREENING

Following a couple of publications, including a multicenter study,[29] and a position paper with a conceptual guidelines,[41] a number of ICUs in many countries have proposed to measure PSP daily to screen acutely ill and high-risk patients (Table 1), assessing the risk of nosocomial sepsis, as strongly recommended by the SSC.[5] In this screening situation, sensitivity and PPV are more important than specificity. Studies must, therefore, determine PPV cut-offs to help starting sepsis therapy early, perhaps even before clinical suspicion. Based on the literature review and an European multicentric study,[29] we propose a PPV screening PSP value of < 100 ng/ml for very low risk of sepsis, 100-150 ng/ml for low risk, 150-200 ng/ml for moderate risk, 200-300 ng/ml for high risk, and > 300 ng/ml for very high risk (Table 6).

PSP could, therefore, fill the gap in current screening SSC recommended tools, with or without the help of electronic health record analysis. A case report of a long ICU stays for a postoperative intra-abdominal infection and sepsis illustrated well the rapid kinetics of PSP and the concept of pre-symptomatic diagnosis of nosocomial sepsis.[37] Approximately, fifteen PSP studies are currently underway to screen for nosocomial infection and/or sepsis in hospital wards, or in the ICU, examining patients with burn, ventilator-associated pneumonia, Covid19, liver transplants and failure, ECMO, ARDS, and cardiac surgery. A study comparing PSP with Mid-Regional ProAdrenomedulin (MD-proADM) in screening nosocomial sepsis is also underway. MD-proADM is considered to be a marker of organ failure regardless of its origin and is, therefore, not specific to sepsis. MD-proADM is used only for risk stratification (triage) and to predict mortality (surrogate endpoint) in the ED,[100] and in the ICU.[101] To the best of our knowledge, MD-proADM studies have not been performed in the context of diagnosis, screening, and monitoring of infection and sepsis. A recent study showed that in 70 cases of febrile neutropenia in children, PSP was more specific (82%) and sensitive (84%) than MDProADM (70% and 74%) in differentiating infections with or without sepsis.[51]

Interventional studies are required to establish the evidence level for PSP in nosocomial sepsis screening. Table 7 summarizes the role of PSP and other biomarkers in the SSC recommended tools and scores for screening, diagnosing, and monitoring.

Table 7: Positioning of Pancreatic Stone Protein PSP in the tools[a] and tests[b] recommended by the Surviving Sepsis Campaign SSC 2021[5].

Pancreatic Stone Protein + Surviving sepsis campaign 2021[5]	**Screening** In acutely ill and high-risk hospitalized patient (Table 1)	**Rapid diagnosis** At time of clinical suspicion	**Monitoring** Treatment efficacy
Infection	**PSP** + Tools[a]	Rapid clinical assessment with Tests[b] **PSP + CRP**	Clinical evaluation with Tests[b] + PCT
+ Inflammation	-	SIRS score	-
+ Organ failure	-	NEWS, MEWS, SOFA, Lactate	Lactate Capillary refill time Dynamic parameters[c]
= Sepsis	**PSP** + Tools[a]	Rapid clinical assessment with Tests[b] **PSP + CRP** + NEWS, MEWS, SOFA, lactate	Clinical evaluation with Tests[b] + PCT + Lactate + Capillary refill time + Dynamic parameters[c]

Tools[a]: Variables analysis by manual methods or automated use of the electronic health record HER analysis (with or without artificial intelligence). Variables include scores, vital signs, signs of infections (unspecified tests), and others. **Tests**[b] (unspecified): biomarkers, radiological exams, other. **Dynamic parameters**[c]: response to passive leg raising or fluid bolus, stroke volume SV, stroke volume variation SVV, pulse pressure variation PPV, or echocardiography. **Abbreviation**: Systemic Inflammation Response Syndrome SIRS, National early warning score NEWS, Modified early warning score MEWS, Sequential organ failure assessment SOFA, quick SOFA qSOFA, Pancreatic Stone Protein PSP, C-Reactive Protein, Procalcitonin PCT.

PANCREATIC STONE PROTEIN FOR MONITORING INFECTION AND SEPSIS TREATMENT EFFICACY

The SSC 2021 recommends[5]: *For adults with an initial diagnosis of sepsis or septic shock and adequate source control where the optimal duration of therapy is unclear, we suggest using procalcitonin AND clinical evaluation to decide when to discontinue antimicrobials over clinical evaluation alone. Weak recommendation, low quality of evidence.* The case report demonstrated PSP's potential in assessing treatment efficacy for post-operative abdominal infection and sepsis.[37] Ongoing multicenter and prospective studies are evaluating the role of PSP role in antibiotic de-escalation, with results anticipated early 2024.

PANCREATIC STONE PROTEIN FOR INFECTION, ORGAN FAILURE, AND SEPSIS RISK STRATIFICATION AND TO SURROGATE ENDPOINT.

The studies on biomarkers, including PSP, primarily serve risk stratification and future prediction, with limited clinical or practical utility beyond triage and disease severity evaluation. They can help to test the hypothesis of clinical utility and justify further research on diagnosis, screening, and monitoring. PSP levels increase in correlation with organ failure (SOFA score), and a recent meta-analysis showed that PSP kinetics correlated with disease severity and showed a progressive increase from moderate infection to septic shock.[31] This correlation was stronger for PSP (AUROC 0.80) than for PCT (AUROC 0.79) and CRP (AUROC 0.56). Serial PSP monitoring could substitute CRP daily monitoring, as suggested by sepsis screening studies. Overall, PSP outperformed other biomarkers (PCT, CRP, IL-6) and traditional scores (APACHE II, SOFA) in predicting mortality. However, the outcomes of these risk stratification and surrogate endpoint studies do not align with the tools and tests missing from the SSC recommendations and do not directly address practical clinical questions.

PANCREATIC STONE PROTEIN TECHNOLOGY

A correlation between the PSP levels measured by the RUO ELISA and the abioSCOPE® can be used to compare PSP studies before and after 2020 (abioSCOPE® ng/ml = 4.6 x RUO ELISA ng/ml + 30 ng/ml - 95%CI, 0.39-0.59).[76] In healthy subjects, PSP measured using the abioSCOPE® was under 44 ng/ml (median 42 ng/ml, 5-95% percentiles 27-61 ng/ml, lowest/highest 23-74 ng/ml). In patients without infection or sepsis but with co-morbidities, PSP was under 88 ng/ml. The PSP cut-off for the diagnosis of bacterial infection in the meta-analysis was 233.3 ng/ml (44.2 ng/ml multiplied by 4.6 + 30 ng/ml) and 290.5 ng/ml for sepsis in the multicentric study. The correlation between values obtained with RUO ELISA vs. Chinese ELISA vs. AlphaLISA vs. abioSCOPE® and the type (specificity) of antibodies used is unknown, making it difficult to compare the values and cut-offs of the various studies. In October 2023, Abionic

and LASCCO (Epalinges, Switzerland) announced a licensing agreement with Fapon Biotech In. (Guangdong, China) for PSP sepsis diagnosis in China. Under this agreement, Fapon will develop and commercialize PSP chemiluminescent immunoassay (CLIA) analyzer within the Chinese market. It is anticipated that the PSP assay will soon become standardized worldwide to ensure proper result interpretation and application cut-off. Previous PSP studies using RUO ELISA, now obsolete, for establishing infection/sepsis cut-off age-dependent values in 372 healthy patients,[102] and in 440 healthy pregnant women,[103] should not be used as a reference without correction.

PANCREATIC STONE PROTEIN AND ECONOMIC STUDY

In addition to the benefits for patients in terms of reduced incidence of sepsis and development of nosocomial infections due to AMR bacteria, the use of PSP has the potential to deliver substantial savings for the healthcare system. A saving of 7 billion US$ per year on the US healthcare system would correspond to a reduction of around 30% from current sepsis costs,[34] accounting for 24 billion US$ per year.[4]

Conclusion

This review underscores a new fundamental shift in the understanding of physiology and pathophysiology related to PSP. PSP levels measured in blood is the reflect of PSP secreted by beta-cells, not pancreatic acinar cells. PSP and is no more considered as an acute phase protein. Clinical experience shows that PSP increases mainly in Gram-negative bacterial sepsis, but not in viral infections or toxic shock syndrome. PSP can be used at the patient's bedside to screen acutely ill and high-risk patients for nosocomial sepsis, in line with SSC recommendations for unspecified missing tools. In cases of suspected sepsis, PSP can also be one of the unspecified missing tests recommended by the SSC to diagnose infection, and to help decide "To give or not to give antibiotics?", and thus address the two major threats of sepsis and AMR.[42] Interventional, impact studies are essential to establish evidence using PSP levels for inclusion in future SSC recommendations. PSP is not used yet, nor studied in monitoring the efficacy of sepsis treatment and guiding antibiotic de-escalation. A multicenter study addressing these critical issues is ongoing. PSP is a marker of the severity of infection and sepsis, and is predictive of organ failure and 28-day mortality. PSP could also replace the SOFA score as a tool, which measures organ failure and predicts mortality. With international certifications for PSP measurement - in Europe, Australia, Switzerland, Malaysia, and soon China and the USA - using innovative nanofluidic technology, standardizing PSP values and cut-offs in clinical practice is now feasible and ready to implement in the clinical setting. The simplicity of point-of-care measurement of whole blood PSP, its rapidity (5 minutes), and cost-effectiveness at the patient's bedside offer a significant advantage in reducing the development of sepsis in patients at risk, to combat the development of AMR bacteria, and to significantly lower sepsis costs by approximately 30%.

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