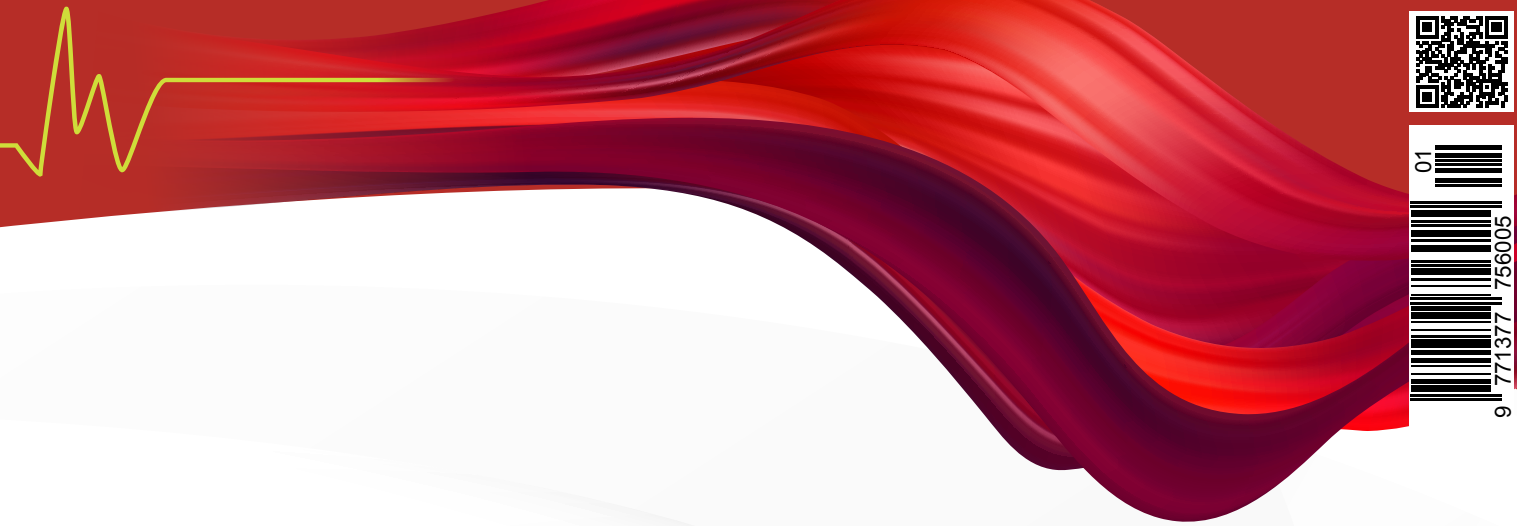


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Biomarkers

Biomarkers are quantifiable indicators of physiological or pathological processes in the body. They can be useful in establishing a diagnosis, assessing disease progression and a patient's condition and guide therapeutic interventions. However, a great deal could still be done to further improve the utilisation of biomarkers in critical care.

Biomarkers can help identify early signs of disease, leading to timely interventions and improved patient outcomes. Also, it may be more efficient to identify patients likely to benefit from certain treatments and tailor therapy per individual patient needs using biomarkers. In addition, biomarkers can help predict outcomes such as disease recurrence and mortality so that clinicians can make informed decisions. Finally, an important benefit of biomarkers could be reduced healthcare costs as clinicians could avoid unnecessary treatment and/or interventions.

While all these are important, it is essential to remember that not all biomarkers are created equal. Some may not have the desired sensitivity or specificity; therefore, their use should be in conjunction with other clinical and laboratory data.

Biomarkers can be more effectively utilised in intensive care by improving standardised protocols for biomarker testing and interpretation. This is essential as biomarkers may vary in measurement, interpretation and clinical significance. Better access to specific biomarkers can also help clinicians use them more routinely in critical care settings. Additional training to understand complex and often difficult-to-interpret biomarker data can provide clinicians with the necessary expertise to utilise these data effectively. Research can also play an important role in identifying and validating new biomarkers that are sensitive, specific and clinically relevant.

In this issue, our contributors discuss the use of **Biomarkers** in critical care and where and how biomarkers can provide valuable diagnostic, prognostic and therapeutic value. As always, if you would like to get in touch, please email JLVincent@icu-management.org.

Jean-Louis Vincent

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Biomarkers for ARDS What is New?

Despite several biomarkers having been studied for diagnosis and/or prognosis of acute respiratory distress syndrome (ARDS), their extensive use has not been established. Better knowledge of the pathophysiology of ARDS and acute lung injury (ALI) may help develop new biomarkers.

Acute respiratory distress syndrome (ARDS) is characterised by non-cardiogenic pulmonary oedema and respiratory failure (Matthay et al. 2019) and is diagnosed by clinical parameters defined in the last Berlin definition (Ranieri et al. 2012). The presence of an acute insult, bilateral opacities in thoracic images, hypoxaemia despite receiving a positive end-expiratory pressure or continuous positive airway pressure higher or equal to 5 mmHg, and the absence of a cardiogenic cause are required for ARDS diagnosis (Bernard and Artigas 2016). Different insults or causes have been described as associated with ARDS (Bos and Ware 2022). ARDS is not always developed despite the presence of these conditions and also can vary according to the aetiology. While only 30% of severe pneumococcal pneumonia develop ARDS (Cilloniz et al. 2018), almost all patients admitted to ICU with COVID-19 developed ARDS (Ceccato et al. 2022). Different virulence factors, inflammatory responses, and their interaction may explain this.

Epithelial and endothelial barrier disruption and damage may be variable in ARDS and could be impaired with mechanical stretch (Matthay et al. 2012; Ware and Matthay 2000). These phenomes activate the inflammatory and coagulation pathways leading to the first phase of ARDS named exudative. A second phase is named proliferative where resolutions of ARDS are started. A third fibrotic phase is variable and is not always developed. It is related to the duration of mechanical ventilation (Ware and Matthay 2000).

Calfee et al. (2014) have described two sub-phenotypes of ARDS. Unbiased latent class analysis of clinical and biomarker characteristics of ARDS patients demonstrated hypo-inflammatory

and hyper-inflammatory groups. These have different clinical and biological features and different responses to therapy. In the hyper-inflammatory group, there is a higher level of inflammatory biomarkers, higher vasopressor use, lower serum bicarbonate, higher prevalence of sepsis, higher mortality, and fewer ventilator and organ failure-free days, compared to the hypo-inflammatory group. Bos et al. (2017) identified two phenotypes in the MARS cohort as well. Levels of inflammatory, coagulation and endothelial activation proteins expression were higher in the reactive cohort, instead uninflamed have lower levels of markers. Currently, the PHIND study (NCT04009330) aims to evaluate a point-of-care assay to prospectively identify phenotypes at the bedside.

The identification of an accurate diagnostic, a predictive or prognostic marker for ARDS would significantly improve our understanding of this heterogeneous disease. Recent progress in several areas of biomarkers research, including advances in the development of point-of-care testing technologies, has the potential to transform the application of biomarkers at the bedside for diagnosis, risk stratification, molecular phenotyping, and monitoring therapeutic response (Bernard and Artigas 2016; Ware and Calfee 2016). Nevertheless, the heterogeneity in features, underlying causes, different phases, and phenotypes makes it hard the identification of biomarkers to predict clinical outcomes or personalise treatment. Several studies have looked into markers of epithelial and endothelial injury, coagulation, and inflammation and have shown a combination of clinical predictors with biomarkers that were better at predicting mortality compared to either clinical or biomarkers alone (Ware et al. 2010; Fremont et al. 2010; Calfee et al. 2011).



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Systemic and Local Biomarkers

A combination of seven biomarkers including the receptor for advanced glycation end-products (RAGE), procollagen peptide III (PCP III), brain natriuretic peptide (BNP), angiotensin-2 (Ang-2), interleukin-8 (IL-8), tumour necrosis factor- α (TNF- α) and interleukin-10 (IL-10) were superior to clinical diagnosis for the diagnosis of ARDS in severe trauma with an area under the curve ROC (AUCROC) of 0.86 (Fremont et al. 2010). The combination of markers for lung epithelial injury, collagen deposition, cardiac dysfunction, endothelial activation/injury, and inflammation allows an accurate diagnosis of acute lung injury (ALI) in these selected populations.

In a posthoc analysis of two clinical trials in patients with ARDS, measures of intercellular adhesion molecule-1 (ICAM-1), von Willebrand factor, IL-8, soluble tumour necrosis factor receptor-1, and surfactant Protein-D (SP-D) improved the prognosis of risk of death at the moment of enrolment to the study (Calfee et al. 2011).

In septic patients, a panel including inflammatory and epithelial injury markers (RAGE, SP-D, Club Cell Protein-16[CC-16], IL-8, and IL-6) were useful for the diagnosis of ARDS in a case-control study. The combination of markers showed higher AUC than each marker, indicating the potential value of combining lung epithelial and inflammatory markers for the diagnosis of ARDS (Ware et al. 2013).

Elevated levels of interleukin-18 (IL-18), a cytokine activated by inflammasomes, were observed elevated in patients with ARDS (traumatic or sepsis ARDS) and correlated with the severity and mortality of patients (Dolinay et al. 2012).

Direct lung injury mainly caused by pneumonia and aspiration is characterised by more severe lung epithelial and less severe endothelial injury and inflammation with a higher level of SP-D and RAGE and a lower Ang-2 compared with indirect ARDS (Calfee et al. 2015). Indirect ARDS is characterised by higher severity scores and a high number of organ failures compared with direct ARDS, even though mortality is similar (Luo et al. 2017). Ang-2 levels showed better accuracy than other endothelial dysfunction biomarkers in patients with ALI and sepsis, and the highest levels were found in patients with non-pulmonary sepsis. Ang-2 also may predict the onset of ALI before clinical signs and identify patients with a high risk to develop ARDS (Agrawal et al. 2013). On the other hand, a greater plasma level of RAGE, a marker of injury of alveolar cell type I, was correlated with a high lung injury score and lower compliance and was associated with poor outcomes in patients who did not receive protective mechanical ventilation parameters. Also, the levels of the soluble form of RAGE inversely correlate with alveolar fluid clearance, and a decrease in the measures was observed after the resolution of lung injury and alveolar fluid clearance was restored in an in vivo model (Calfee et al. 2008; Jabaudon et al. 2015). Serum sRAGE concentrations are elevated in COVID-19 patients and may predict independently of other variables the need for invasive mechanical ventilation (Lim et al. 2021). Endothelial injury and dysfunction have great interest in other areas such as cardiovascular diseases or oncology. Further studies should

evaluate the impact of other endothelial markers studied in other conditions (Balistreri 2022).

SP-D levels are correlated with pulmonary oedema measured by radiographic assessment of lung oedema (RALE) or lung ultrasound score (LUS) irrespective of the cause of ARDS. sRAGE and Ang2 were associated with pulmonary oedema as well but were not associated when subgroups were analysed separately.

Eight plasma biomarkers were included to differentiate between the two subphenotypes described by Calfee et al. (2014): SP-D, von Willebrand factor antigen, soluble intracellular adhesion molecule 1 (sICAM-1), IL-6 and IL-8, soluble tumour necrosis factor receptor (TNFR1), plasminogen activator inhibitor-1 (PAI-1) and protein C. Bos et al. (2017) included a selection of 4 biomarkers IL-6, interferon-gamma, Ang 1/2, and PAI-1 to cluster ARDS into biological phenotypes (reactive and uninflamed) with different mortality rates. The stability of ARDS phenotypes has been shown over the first three days of enrolment in two clinical trials (Delucchi et al. 2018), and they respond differently to fluid management strategies (Famous et al. 2017). These findings have the potential to transform the way we approach patients with ARDS, selecting patients who may benefit from specific therapeutic strategies and tailoring the treatment for every single patient.

There is a difference between the systemic reaction indicated by biological phenotypes and the local alveolar reaction emphasising the importance of phenotyping the alveolar compartment in future research. Recently, a study showed that phenotypes according to plasma or bronchoalveolar levels had minimal overlap (Sathe et al. 2023). Moreover, Heijnen et al. (2021) observed a non-difference in levels of biomarkers between subphenotypes reactive or uninflamed/hypo-inflammatory or hyper-inflammatory. In other critically ill conditions such as VAP, the difference in biomarkers were observed in bronchoalveolar lavage fluid (BALF) but not in serum (Morris et al. 2010). A theory that may explain this phenomenon is the compartmentalised immune response (Morris et al. 2022). This theory may change the way of measuring biomarkers for pulmonary conditions.

Exhaled Breath Markers

Markers of endothelial, epithelial injury, protein-rich pulmonary oedema, and systemic or alveolar host response could be measured through a heat moisture exchange filter (Bastarache et al. 2021; McNeil et al. 2018). Nevertheless, this technique still requires validation.

Measures of samples from exhaled breath analysing volatile organic compounds using gas-chromatography and mass spectrometry could be a non-invasive, real-time approach to diagnosing changes in lung inflammation, or bacterial overgrowth. Through gas chromatography and mass spectrometry, metabolites can be detected in exhaled air of patients. In a study including more than 100 patients, octane, acetaldehyde, and 3-methyl heptane were identified as biomarkers of ARDS (Bos et al. 2014; Bos 2018) and showed a moderate-good accuracy (AUC ROC 0,78-0,80) for the diagnosis of ARDS compared to cardiopulmonary oedema or pneumonia.

MicroRNA

MicroRNA (miRNA) can be easily measured and hence are potential diagnostic and therapeutic targets in ARDS (Cardinal-Fernández et al. 2016). Plasma levels of miRNA-146a and miRNA-155 significantly increased in sepsis and sepsis-induced ALI. Pro Inflammatory related miRNAs miR-34a, miR-132, miR-155, miR-15a, miR-21, miR-27b, and miR-146a were described in LPS induced ALI. Some of them stimulate the NF- κ B signalling pathway. Also, several miRNAs may be associated with endothelial injury such as miR-887-3p, miR-34a-5p, or miR-1246. In at-risk ARDS patients, Zhu et al. (2017) demonstrated that miRNA-181a, miRNA-92a, and miRNA-424 were protective biomarkers, and in addition to Lung Injury Pulmonary Score can improve the risk estimate of ARDS. During the COVID-19 pandemic a signature based on 2miRNA, miR-192-5p, and miR-323a-3p, may predict the survival probability with an AUCROC of 0.80 (de Gonzalo-Calvo et al. 2021).

Extracellular Vesicles

The rapidly developing field of study of extracellular vesicles

(EVs) and their natural features such as their high biocompatibility and low immunogenicity, the increased specificity to target cells or tissues, the ability to cross biological barriers, the use of endogenous cellular machinery of loading and their capacity to mirror the composition and the metabolic status of their source cells, could make EVs valuable biomarkers of injury, and targets or vehicles for new therapies.

the rapidly developing field of study of extracellular vesicles could make them valuable biomarkers of injury and targets or vehicles for new therapies

When lung cells are subjected to external stimuli, such as hypoxia, inflammatory factors, or pathogens, they may alter the amount and the composition of the EVs they secrete, and this is crucial for ARDS progression and development (Ye et al. 2020). These changes that can be detected in the blood and bronchoalveolar lavage fluid (BALF) of ARDS patients, may provide new strategies for the aetiological diagnosis of ARDS and also predict the progression of this syndrome.

On the one hand, it has been demonstrated that serum/plasma EVs of patients with ARDS have a strong potential to guide clinical decisions on early intervention measures to block the development of lung inflammation leading to ARDS since they reflect contributions from most systemic tissues (Hu et al. 2022). A study carried out in patients with severe pneumonia revealed that the combined expression of exosomal miR-126, miR-27a, miR-146a, and miR-155 in plasma, predicted the development of ARDS with an AUCROC of 0.909 (95 % CI 0.815 –1) (Wu et al. 2019). In addition, Sun et al. (2012) demonstrated that EVs containing nitrated sphingosine-1-phosphate receptor-3 (S1PR3) shed into the circulation during inflammatory lung states represented a novel ALI biomarker linked to disease severity and

outcome. The high heterogeneity that characterises serum EVs, also spurs new diagnosis opportunities, as in the case of a study performed in 2022, where the monitoring of the dynamics of serum EVs subsets (classified by size, concentration, and surface marker profile) distribution in the plasma of COVID-19 patients highlighted their predictive value and their correlation with the immune responses during COVID-19 progression (Yim et al. 2022).

On the other hand, changes in specific EVs markers in BALF samples may also be used as diagnostic tools in lung injury, particularly when it is due to external stimuli, such as respiratory pathogens (Hu et al. 2022). It has been demonstrated that the EVs from BALF of patients with pulmonary infection had a higher expression of miR-17-5p and miR-193a-5p in contrast with control patients, turning them into a new biomarker for pneumonia. Similarly, Letsiou et al. (2021) revealed that EVs carrying mitochondrial serve as diagnostic biomarkers of lung injury associated with microbial infection and Mahida et al. (2022) observed that the presence of CD14+/CD81+ BALF EVs is enriched in patients with sepsis-induced ARDS and an elevated count of this marker is associated with increased mortality in these patients as well as the presence of EVs containing the mRNA of phospholipase-IIA A2 (sPLA2-IIA) which is, not only a marker of early-phase ARDS but also a tracer of spatiotemporal events characterising the propagation and exacerbation of the syndrome (Kitsiouli et al. 2021).

A more exhaustive study of differentially expressed markers and the validation of specific transcripts of EVs present in both, plasma and BALF of ARDS patients, is necessary to implement them in the clinic as definitive biomarkers for a more efficient stratification of ARDS aetiologies and thus, offering a more precise and early intervention.

Conclusion

Despite several biomarkers having been studied for diagnosis and/or prognosis of ARDS, their extensive use have not been established. Despite the fact that it could be useful to identify phenotypes, it is still unknown how biomarker measures may

change in clinical practice. Further studies are warranted to determine if biomarkers may be used to identify differential diagnoses, aetiologies, prognosis, phenotypes, development of VILI, and therapeutic targets. Meanwhile, better knowledge of the pathophysiology of ARDS and ALI may help us to develop new biomarkers.

Conflict of Interest

None. ■

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Introduction

Septic shock is a subset of sepsis, with circulatory collapse and metabolic dysfunction associated with high mortality. Worldwide, 48.9 million people develop sepsis each year, and 11 million die of septic shock (Rudd et al. 2020).

The definition of sepsis has evolved over time. In 1992, in the first set of definitions, sepsis was defined as a suspected bacterial infection associated with a systemic inflammatory response syndrome (SIRS) (Bone et al. 1992). In 2003, sepsis was defined as a suspected bacterial definition associated with a more complete SIRS definition (Levy et al. 2016). In 2016, a third set of definitions of sepsis was proposed: sepsis was defined as a bacterial infection causing organ dysfunction (Singer et al. 2016). Since October 2021, the latest set of sepsis definitions was proposed by the Surviving Sepsis Campaign (SSC) (Evans et al. 2021). Sepsis was defined as a bacterial infection associated with a dysregulated response of the body with SIRS and organ dysfunction. Guidelines for the management of sepsis were first proposed by the SSC in 2004 (Dellinger et al. 2004); they have since been revised regularly, with the latest update published in October 2021 (Evans et al. 2021).

The Diagnosis of Sepsis

In adults and in children, the diagnosis of sepsis is based on an early diagnosis of a bacterial infection and the identification of a dysregulated response of the body with organ dysfunction (Evans et al. 2021; Weiss et al. 2020). There are two different diagnostic

Sepsis Diagnosis: Clinical Signs, Scores, and Biomarkers

A checklist of criteria to assess the usefulness of a biomarker to be integrated into sepsis guidelines.

approaches and two different therapeutic approaches to be made in parallel: the control of infection with antimicrobials and the source of infection, and the treatment of the dysregulated response of the body and organ dysfunction, with volume resuscitation, organ support, and adjuvant therapies.

Diagnosis of (suspected) infection

In the case of (suspected) sepsis, it is recommended to confirm or rule out bacterial infection and to continuously reassess the infectious diagnosis, to initiate, modify or stop antibiotic therapy (Evans et al. 2021). Unfortunately, bacterial cultures take between 24 and 48 hours to give meaningful results to the clinician and do not help to make decisions as to start antibiotics or not. They may also be false negatives due to prior antibiotic therapy or inadequate sampling. It is, however, a strong recommendation in the sepsis management guidelines that antibiotic therapy should be initiated as soon as possible, at least less than 45 to 60 minutes after suspicion of sepsis (Evans et al. 2021). Initiating broad-spectrum antibiotics in all patients with suspected sepsis will result in unnecessary treatments in 60 to 70% of patients who end up not having sepsis, in part because signs are similar between severe viral and bacterial infections and also with severe inflammatory processes (Klein Klouwenberg 2015).

Biomarkers have been extensively studied to help diagnose rapid bacterial infection in patients with suspected sepsis. They may be used to increase specificity to restrict antibiotic treatment only to patients with a bacterial infection. In addition, they should have a good negative predictive value to rule out a bacterial infection in patients with suspected sepsis and prevent unnecessary antibiotic treatments. The matrix presented in **Table 1** describes four clinical

conditions: adequately treated sepsis, inadequate sepsis treatment at risk for aggravation, unnecessary antibiotic therapy at risk of bacterial resistance, and adequate no (or suspended) antibiotic therapy.

Once antibiotic therapy has been initiated, it should be reassessed daily (pursue, modify or stop) based on the results of bacterial cultures and clinical evolution (Evans et al. 2021).

Biomarkers sepsis diagnosis matrix		Clinical evaluation/suspicion	
		SEPSIS Infection	NO SEPSIS No infection
Biomarkers-based antibiotics	Positive biomarkers Antibiotics	Accurate management (True positive)	Inadequate treatment Risk of AMR (False positive)
	Negative biomarkers No Antibiotics	Inadequate treatment Risk of septic shock (False negative)	Accurate management (True negative)

Table 1. Biomarker-based antibiotics and sepsis diagnosis matrix

Diagnosis of dysregulated response of the body

The diagnosis of dysregulated response of the body is based on SIRS criteria and/or organ dysfunction according to the SSC 2021 guidelines (Evans et al. 2021). SIRS score evaluate three non-specific clinical parameters: temperature, heart rate, and

respiratory rate, as well as two laboratory results: circulating blood leukocytes and PaCO². The dysregulated organ response is based on two clinical scores, the National Early Warning Score (NEWS) and the Modified Early Warning Score (MEWS) (strong recommendation, moderate quality evidence) (Evans et al. 2021). The gold standard for the dysregulated organ response is the Sequential Organ Failure Assessment (SOFA) score which assesses the function of six organs impacted by sepsis (lung, circulation/heart, brain, liver, kidney, coagulation), combining five clinical parameters and four laboratory results. The qSOFA (quick SOFA) is a simple and fast version of the SOFA which takes < 5 minutes. However, the 2021 SCC guideline suggested that the qSOFA should no longer be used (Evans et al. 2021). In paediatrics, the organ failure score is the Pediatric Logistic Organ Dysfunction (PELOD) score which assesses the function of six organs (Goldstein et al. 2005).

Clinical Signs, Scores, and Biomarker

The consequence of the four different definitions of sepsis, the absence of a gold standard specific test for early diagnosis, and the change in clinical scores to be used have led to confusion among clinicians. More than half of the clinicians use a mixture of all these scores (Ventura 2021); 89.7% measure circulating blood leukocytes, 92.3% CRP, 84.6% PCT, and 100% lactate in case of suspicion of sepsis. Only 35.9% use the Sepsis-3 definition alone, 34.2% still calculate the qSOFA, and 44.7% use the complete SOFA score. This indicates that in daily practice, clinicians use more biomarkers than scores. The ideal biomarker of infection and sepsis should have a sensitivity similar to the non-specific, highly sensitive clinical approach but should carry a better specificity, with a very good negative predictive value to rule out infection and sepsis. Ideally, biomarkers should be able to detect sepsis even before clinical suspicion, which is only possible by routine monitoring (daily measurements) in hospitalised patients at high risk for nosocomial sepsis. This is

the concept of pre-symptomatic diagnosis of nosocomial sepsis. Finally, a biomarker should be able to help with the decision of antibiotic de-escalation, coupled with clinical evaluation.

One or more biomarkers should help in the diagnosis of sepsis and nosocomial sepsis in the three chronological phases: the pre-sepsis or pre-symptomatic phase (with daily monitoring of hospitalised patients at risk), the clinical onset of sepsis phase, and the post-sepsis phase (Table 2).

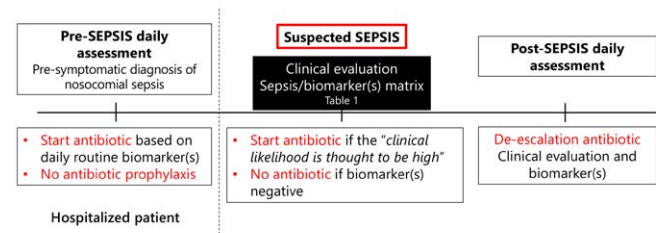


Table 2. Sepsis phase

Discussion

It is fundamental to carry out future clinical studies on sepsis biomarkers analysing their specificity (PPV and NPV with cut-offs), their capacity to make a pre-symptomatic diagnosis, and their potential in the de-escalation of antibiotics. We propose a checklist (Table 3) with the basic requirements that biomarkers of sepsis should meet and a standard protocol for biomarker sepsis studies so that future studies can be comparable and can answer the urgent questions raised by the major public health problems of sepsis and antimicrobial resistance. This standard protocol should include three specific protocols according to the three phases of sepsis (pre-sepsis, sepsis, post-sepsis) the studies would like to investigate.

Conclusion

Both classical sepsis and infection biomarkers and new biomarkers

should be studied or re-studied using a standardised approach to determine which biomarker(s) answer(s) clinicians' questions. The biomarker result should be obtainable within 45 to 60 minutes to initiate (or not) antibiotic therapy quickly, as required by the SSC 2021 guidelines (Evans et al. 2021) for adults and the SSC 2020 for children (Weiss et al. 2020). A point-of-care test (POCT), with a 10-20 minute dosing time, can allow such a rapid result, and it must be able to fulfil to a large extent the ASSURE criteria (Affordable, Sensitive, Specific, User-friendly, Rapid, Equipment free) for a sepsis diagnosis test (Bissonnette and Bergeron 2010). Economic studies should also be able to determine the financial consequences of sepsis biomarker testing on public health costs. The objective of all these studies could allow one or several infection and sepsis biomarkers that tick all the boxes on the checklist (Table 3) to be included in the next adults and paediatrics international Surviving Sepsis Campaign guidelines. ■

Ideal criteria for a sepsis biomarker	
Affordable	
Price 10-50 US\$	<input type="checkbox"/>
Economic study published	<input type="checkbox"/>
Sensitive	
Standard protocolized study	<input type="checkbox"/>
As high as clinical symptoms	<input type="checkbox"/>
Pre-symptomatic diagnosis	<input type="checkbox"/>
Antibiotic de-escalation	<input type="checkbox"/>
Specific	
Standard protocolized study	<input type="checkbox"/>
Cut-off and VPP > 90%	<input type="checkbox"/>
Cut-off and VPN > 90-95%	<input type="checkbox"/>
TP, TN, FP, FN rate	<input type="checkbox"/>
Sepsis/AMR Matrix	<input type="checkbox"/>
User-friendly testing	
	<input type="checkbox"/>
Rapid	
Results in 45-60 minutes	<input type="checkbox"/>
Dosing time 10-20 minutes	<input type="checkbox"/>
Equipment free (or light)	
Point of Care testing POCT	<input type="checkbox"/>
Pediatrics	
Capillary blood	<input type="checkbox"/>
Blood volume 30-50 ul	<input type="checkbox"/>
Certified	
European IVDR	<input type="checkbox"/>
FDA 510K	<input type="checkbox"/>
Australia	<input type="checkbox"/>

Table 3: Checklist - Tick the box: Ideal criteria for a sepsis biomarker

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Point-of-View articles are the sole opinion of the author(s) and they are part of the ICU Management & Practice Corporate Engagement or Educational Community Programme.

References

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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. 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

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*.

(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 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

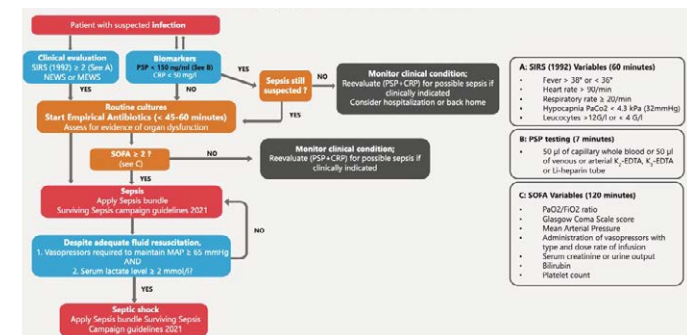


Figure 1. Proposal for modifying the 2021 Surviving Sepsis Campaign Guidelines definition with the inclusion of rapid measurement of PSP and CRP

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**).

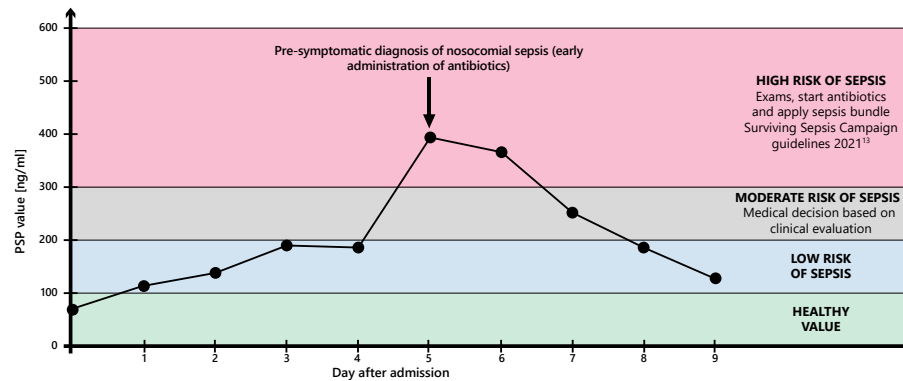


Figure 2. Pre-symptomatic diagnosis of nosocomial sepsis. Daily routine PSP monitoring of nosocomial sepsis.

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 (Jirí 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).

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

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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Biomarkers in Sepsis

This article describes the application of existing and emerging biomarkers in the diagnosis and management of sepsis and pneumonia.

adverse outcomes through the implementation of antibiotic de-escalation, and even in those with positive cultures, it may be possible to reduce the duration of therapy (Gupta et al. 2016; Kethireddy et al. 2018; Nanna Panday et al. 2019). In addition, current clinical and laboratory-based scoring systems lack sensitivity and specificity to guide clinicians in triage decision making and prognostication (Churpek et al. 2017; Freund et al. 2017; Raith et al. 2017; Wang et al. 2022). To aid in these dilemmas, clinicians have turned to biomarkers, defined as molecules that can be objectively measured and evaluated as an indicator of underlying biological processes (Biomarkers Definitions Working Group 2001). The ideal biomarker in sepsis would aid in one or more of the following domains: 1) antibiotic initiation, and differentiation between bacterial infection, viral infection, and sterile inflammation; 2) antibiotic treatment duration; and 3) prognostication (Pierrakos et al. 2020). In this review we discuss these specific applications for the following existing and emerging biomarkers: procalcitonin, presepsin, pentraxin-3, and pancreatic stone proteins in sepsis. Finally, we discuss these biomarkers in comparison, as well as their multimodal application in sepsis.

Procalcitonin

Procalcitonin (PCT) is a protein precursor of calcitonin produced by the parafollicular C cells of the thyroid glands (Table 1) (Becker et al. 2004). In response to inflammation, PCT synthesis behaves as an acute phase reactant and is activated in peripheral tissues such as the kidney and liver, followed by subsequent increases in serum levels, up to 100,000 times normal levels, in the setting of bacterial infection (Christ-Crain and Müller 2007). This increase tends to be specifically

observed in response to bacteria, but less so with viruses. Bacterial toxins and host cytokines appear to increase PCT levels, whereas molecules produced in response to viruses attenuate PCT production (Becker et al. 2004; Christ-Crain and Müller 2007; Christ-Crain and Müller 2005). Given this property, PCT has been widely studied as a biomarker in sepsis, especially in relation to lower respiratory tract infections (LRTI). It has been evaluated in all aspects of biomarker application as previously described, which include guiding antibiotic initiation, determining antibiotic duration, and prognostication. Currently, its most relevant clinical utility is in guiding antibiotic duration, while its usefulness in other applications remains in debate. In current sepsis guidelines, it is recommended to use PCT, along with clinical data, to guide duration of therapy, and not for determining when to start therapy.

Diagnosis and Antibiotic Initiation

The use of PCT to guide antibiotic initiation has been studied in several randomised controlled clinical trials (RCT), with a majority in pulmonary infections and respiratory diseases that include chronic obstructive pulmonary disease (COPD) exacerbations. These trials used serial measurements of PCT levels to determine the initiation or discontinuation of antibiotics, compared with standard practice, at the time the RCTs were conducted. Results of these trials have been conflicting. For example, two of the larger trials, the ProHOSP and the ProACT trial produced different results. The ProHOSP trial showed that a PCT based algorithm significantly shortened the average number of antibiotic days (5.7 vs 8.7 days), for respiratory infection, whereas the ProACT trial did not show a meaningful difference (4.2 vs 4.3 days) (Schuetz et al. 2009;

Introduction: The Need for Bio-markers in Sepsis

Sepsis is defined as a dysregulated host response to infection that results in life threatening organ dysfunction. It carries an estimated 30-day mortality rate of 24.4% and increases to 34.7% in patients who develop shock (Singer et al. 2016; Bauer et al. 2020). A main pillar in sepsis management is the early initiation of antibiotics. However, inappropriate use of broad-spectrum antibiotics can lead to antimicrobial resistance and even increase mortality (Kumar et al. 2009; Rhee et al. 2020; Teshome et al. 2019). Identification of the 30.6% to 56.4% of patients with culture negative sepsis could prevent these

Huang et al. 2018). An argument supporting the ProHOSP trial is that the ProACT trial was conducted nearly a decade after the ProHOSP trial when standard practice had already incorporated shorter antibiotic durations. This can be seen in the difference in average antibiotic days between the two RCTs. Nonetheless, other clinical outcomes such as adverse events and infection relapse were not significantly different between the trial groups.

Additional areas of ambiguity include varying levels of acceptable thresholds for antibiotic initiation. A level of ≥ 0.25 $\mu\text{g/L}$ has been used as a general cut-off for bacterial infections; however studies in respiratory infections have demonstrated that no specific value adequately predicted bacterial infection (Self et al. 2017; Musher and Thorner 2014; Schuetz et al. 2017). As a result, professional guidelines such as the surviving sepsis campaign, and pneumonia treatment guidelines from the Infectious Disease Society of America (IDSA)/American Thoracic Society (ATS), as well as the European Respiratory Society (ERS) have recommended against the reliance on PCT in guiding antibiotic initiation (Torres et al. 2017; Metlay et al. 2019; Kalil et al. 2016). Furthermore, while PCT can be specifically elevated in response to bacterial infection, false elevations can be observed in sterile inflammation. Examples include, but are not limited to pancreatitis, trauma, surgery, burns, and cardiac arrest (Mimoz et al. 1998; Annborn et al. 2013; Meisner et al. 1998; Kylänpää-Bäck et al. 2001).

Antibiotic Duration

Recent data support the use of PCT in guiding antibiotic duration. Three RCTs involving critically ill sepsis patients – the PRORATA, SAPS, and PROGRESS TRIALS – have shown that serial measurements, with decreasing PCT levels, can be used as a safe metric for antibiotic discontinuation in conjunction with best clinical judgment (Bouadma et al. 2010; de Jong et al. 2016; Kyriazopoulou et al. 2021). The trials used ≤ 0.5 $\mu\text{g/L}$ or an 80% reduction from baseline level as a guide for antibiotic discontinuation. All three trials found a significantly shorter antibiotic duration with PCT-guided treatment. The PRORATA trial showed no significant difference in mortality

and re-infection risk. However, in the SAPS and PROGRESS trials, significant mortality reductions at 28 days (also reduction in 1-year mortality for the SAPS trial) were observed. Furthermore, the PROGRESS trial, which was initially designed to assess the aetiology behind the mortality reduction observed in the SAPS trial, found reduction in long-term adverse outcomes with PCT-guided treatment such as acute kidney injury, and diarrhoea. However, colonisation by multidrug resistant organisms (MDRO) was similar between the two groups.

Prognostication

The prognostic value of PCT had been primarily evaluated in LRTIs and can be valuable in clinical practice when combined with other risk prediction models. Initial PCT elevations, and more so, up trending levels have been associated with increased mortality or treatment failure in patients with LRTI. These findings were observed in a meta-analysis of 14 trials, as well as in several observational studies (Kutz et al. 2015; Boussekey et al. 2006; Bloos et al. 2011). Much like in antibiotic initiation, no cut-off value for a single measurement had been specifically associated with poor outcomes. Furthermore, studies have reported conflicting results as to whether PCT levels are truly predictive of mortality (Ryoo et al. 2019). A possible approach may be to use serial measurements for prognostication, which can potentially carry more value as has been the case in guiding antibiotic duration.

Presepsin

Presepsin is an emerging immunological biomarker that is a soluble form of CD14. CD14 is a surface glycoprotein and member of the Toll-like receptors, expressed by macrophages and monocytes, with affinity to bacterial ligands such as lipopolysaccharide (Xiao et al. 2022). In the presence of bacterial pathogens, presepsin levels increase early, as it is a by-product of the innate immune response (Chenevier-Gobeaux et al. 2015). This is particularly advantageous in identifying bacterial sepsis early in the disease course (Leli et al. 2016; Wu et al. 2017). While it is currently not widely available, presepsin has been evaluated in guiding the diagnosis of bacterial sepsis,

antibiotic duration, and sepsis prognosis.

Diagnosis of Bacterial Sepsis

Presepsin has the potential to distinguish bacterial infections from non-bacterial infections as a cause of sepsis, based on several observational studies. Higher presepsin levels have been associated with bacterial sepsis compared to non-bacterial sepsis, consistent with its underlying biology (Pugni et al. 2015; Masson et al. 2015; Liu et al. 2013; Endo et al. 2012). Threshold values indicative of bacterial sepsis were reported in the 600 ng/L range, with reported sensitivity of 87.8% and specificity of 81.3% (Endo et al. 2012). However, the range of values varies across studies, as well as its predictive value (Azim 2021). Therefore, at this time there are no guidelines or recommendations for an accepted discriminant value until further studies are conducted.

Antibiotic Duration

Much like PCT, presepsin has potential value for improving antibiotic stewardship and contributing to decisions to escalate or de-escalate antibiotic therapy. In an unrandomised, multicentre trial in China of 656 patients, a presepsin-guided treatment protocol was compared to standard of care (Xiao et al. 2022). Antibiotic therapy was discontinued when levels reached below 350 pg/mL or decreased by $\geq 80\%$ from baseline. There were no significant differences in 28-day mortality, and the presepsin group had a significant reduction in antibiotic days compared to standard of care (14.54 vs 11.01 days). In contrast to decreasing levels, persistently elevated or rising presepsin concentration has been associated with inadequate treatment and persistent positive blood cultures (Masson et al. 2015; Liu et al. 2013; Endo et al. 2012; Azim 2021; Kweon et al. 2014). Therefore, in addition to antibiotic de-escalation, presepsin might be able to be used to escalate therapy when clinically appropriate.

Prognostication

Presepsin also has potential in prognostication in sepsis, such as predicting mortality, disease severity, and adverse

outcomes. Initially elevated levels or persistently increasing levels have been associated with adverse outcomes across multiple studies (Masson et al. 2015; Kweon et al. 2014; Kim et al. 2017). These include the development of acute kidney injury, increased lengths of hospitalisation, increased ventilator days, increased vasopressor duration, decreased infection clearance, and mortality.

Overall, additional studies are needed to support presepsin's potential clinical applications. Nonetheless, the current available data show a promising future for this biomarker in guiding sepsis management.

Pentraxin 3

Pentraxin 3 (PTX3) is involved in the innate immune response as it is produced by dendritic cells, monocytes, and macrophages (along with many others) upon stimulation of the pro-inflammatory cytokines TNF α and IL-1 β , or damage-associated molecular patterns (Magrini et al. 2016). PTX3 can then promote inflammation through complement activation and opsonisation but also attenuate the immune response by binding P-selectin on neutrophils, decreasing their recruitment to sites of inflammation (Bottazzi et al. 2010; Deban et al. 2010). PTX3 can be an ideal biomarker in sepsis as levels increase with disease severity, for example from systemic inflammatory response syndrome (SIRS) to septic shock (Muller et al. 2001).

Diagnostic Applications

As an acute phase protein, PTX3 can aide in clinical diagnosis of sepsis. In patients who presented to the emergency department (ED), PTX3 was found to be elevated in patients with severe sepsis compared to those without severe sepsis (median value 16.7 ng/mL vs 4.9 ng/mL, $p < 0.001$) and a cut-off value of 14.1 ng/mL was associated with a higher odds of having severe sepsis (odds ratio 6.77, 95% CI 3.64 – 12.59, $p < 0.001$) (Uusitalo-Seppala et al. 2013). In a study of 213 intensive care unit (ICU) patients with sepsis and septic shock PTX3 correlated well with higher lactate, the Acute Physiology and Chronic Health Evaluation II (APACHE II) and the

Sequential Organ Failure Assessment (SOFA) score. On day 1 of ICU care, a cut-off value of 5 ng/mL and 9 ng/mL for septic shock provided a sensitivity of 98 and 93% but only a specificity of 79 and 45% indicating that this can be a good test in ruling out these disease states (Hamed et al. 2017).

While existing and emerging biomarkers hold promise in guiding sepsis management, no biomarker is perfect and yields variable predictive capabilities in its diagnostic and prognostic utilities

Prognostic Applications

Elevated levels of PTX3 have shown prognostic utility in predicting future organ failure and disease severity (Huttunen et al. 2011; Bastrup-Birk et al. 2013). Multiple studies have shown that elevated PTX3 levels were associated with worse mortality in patients with sepsis and septic shock (Uusitalo-Seppala et al. 2013; Bastrup-Birk et al. 2013; Chen et al. 2021; Jie et al. 2017; Perez-San Martin et al. 2020). A recent meta-analysis has confirmed the association of elevated PTX3 levels and mortality (hazard ratio 2.09; 95% CI 1.55 – 2.81 $p < 0.001$, AUC 0.73; 95% CI 0.7 – 0.77 $p < 0.001$); however there was high heterogeneity in the studies analysed and the optimal cut-off value for mortality prediction remains uncertain (Wang et al. 2022).

In summary, PTX3 appears to be a useful biomarker in predicting disease severity and mortality. However, more well balanced and larger studies should be performed before any definitive conclusions can be made.

Pancreatic Stone Protein

Pancreatic stone protein (PSP) is a molecule secreted primarily by the pancreas, but also in other parenchymal cells during the stress response (Terazono et al. 1988). It was formerly identi-

fied as two separate molecules, lithostathine and regenerating protein 1. However, they were later found to be similar and eventually renamed PSP (Terazono et al. 1988). The various functions of PSP remain under investigation and continue to be unravelled. However, it has been recognised to play a role in inflammation and the innate immune response, such as activation of polymorphonuclear cells (Eggimann et al. 2019). Concentrations of PSP have been observed to increase in response to stress and trauma, especially when the inciting event leads to infection and sepsis (Reding et al. 2017). Given this property, PSP has been studied both as a diagnostic biomarker to identify sepsis, and as a prognostic marker to evaluate treatment response.

Diagnosis of Sepsis

The utility of PSP comes from its potential for the early identification of sepsis, even before the onset of clinical signs and symptoms. Serial serum measurements of PSP increase leading up to nosocomial sepsis with elevated levels being detected as early as five days prior (Pugin et al. 2021). Similarly, in a study involving burn patients, PSP showed a steep rise 72 hours prior to the development of sepsis and was able to differentiate between septic and non-septic patients (Klein et al. 2021). At the point of admission, PSP can be highly accurate in the diagnosis of sepsis with infection compared to patients without infection (AUC 0.839; 95% CI 0.773 – 0.904), and those with sepsis compared to a non-infectious SIRS (AUC 0.91; 95% CI 0.86 – 0.96) (Garcia de Guadiana-Romualdo et al. 2017; Llewelyn et al. 2013). A recent systematic review and patient level meta-analysis showed that PSP has moderate diagnostic accuracy for the discrimination of septic vs non-septic patients with a specificity of 0.83 and sensitivity of 0.66 using a cut-off of value of 44.18 ng/mL (Prazak et al. 2021). Finally, the implementation of a PSP decision tree model in patients with suspected sepsis led to a reduction in healthcare costs in the ED and ICU compared to the standard of care. This indicates that PSP has utility in not just sepsis diagnosis but also in healthcare cost reduction (Schneider et al. 2022).

Prognostication

In a prospective cohort study, Que et al. (2012) studied whether PSP drawn within 24 hours of admission could predict in-hospital mortality. Median levels of PSP were elevated in patients who died, compared to those that survived (397 ng/mL vs. 216.1 ng/mL, $p < 0.02$). However, the overall prognostic accuracy was moderate at best and the prognostic accuracy for in-hospital mortality was poor (AUC 0.65; 95% CI 0.51 – 0.80). The poor prognostic accuracy of PSP can be improved with the addition of a clinical severity score measure such as the APACHE II or the Simplified Acute Physiology Score II (SAPS II) (Que et al. 2015). Further research involving large cohorts of patients with sepsis and septic shock are needed to further clarify the prognostic implications of PSP.

Comparison of PCT, Presepsin, PTX3, and PSP

Since PCT is one of the earlier and most studied biomarkers in sepsis and LRTI, its utility has been compared to the newer and emerging biomarkers. Liu et al. (2013) examined the prognostic accuracy of presepsin compared to PCT in the context of patients presenting to the ED with SIRS. They found that using a cut-off value of 317 pg/mL for presepsin produced a sensitivity of 70.8% and specificity of 85.8% compared to a sensitivity of 60% and specificity of 77.7% for PCT (cut-off value of 0.25 ng/mL). These findings are divergent from a recent prospective observational study of 420 patients with non-infectious organ failure, sepsis, and septic shock where PCT (cut-off 0.51 ng/mL, sensitivity 75.5%, specificity 93%) was marginally better at differentiating patients with sepsis compared to non-infectious organ failure than presepsin (cut-off 582 pg/mL, sensitivity 70.1%, specificity 89.4%) (Lee et al. 2022).

PTX3 has shown comparable accuracy for sensitivity and specificity for the diagnosis of septic shock compared to PCT (PTX3; AUC 0.73, 95% CI 0.66 – 0.80 vs PCT; AUC 0.73, 95% CI 0.65 – 0.80) but is slightly worse when it comes to the diagnosis of sepsis (PTX3; AUC 0.68, 95% CI 0.58 – 0.78 vs PCT; AUC 0.79, 95% CI 0.70 – 0.88) (Chen et al. 2021). PTX3 and PCT perform equally well for 28-day mortality prediction

in patients with a diagnosis of sepsis but ultimately perform worse compared to clinical scores such as the APACHE II (Hu et al. 2018).

When compared to PCT, PSP performs equally well in distinguishing patients with sepsis from those without (Pugin et al. 2021). A patient level meta-analysis found that both PCT and PSP perform equally well in diagnosing hospitalised patients with an infection, with superior accuracy when both biomarkers were combined (Prazak et al. 2021).

Multi-Marker Application in Sepsis

While existing and emerging biomarkers hold promise in guiding sepsis management, no biomarker is perfect and yields variable predictive capabilities in its diagnostic and prognostic

utilities. As with every clinical tool, biomarkers play a role as adjuncts to broader clinical assessments in helping us predict clinical outcomes. Combining biomarkers together with existing predictors, such as the SOFA score, may have promise in improving predictive performance in both the diagnostic and prognostic arenas.

Mearelli et al. (2018) evaluated the performance of predictive models incorporating multiple serum biomarkers including PCT, phospholipase A₂ group IIA (sPLA₂GIIA), presepsin, soluble interleukin-2 receptor α (sCD25), and soluble triggering receptor expressed on myeloid cell (sTREM-1) to determine whether patients had infectious vs non-infectious SIRS. The model was trained on 947 adults presenting to the ED of five Italian university hospitals and validated in 185 adults.

Biomarker	Properties	Diagnostic Ability	Prognostic Utility
Procalcitonin	<ul style="list-style-type: none"> - Protein precursor of calcitonin, produced by parafollicular C cells. - Acute phase reactant, levels are higher in bacterial than viral infections. 	<ul style="list-style-type: none"> - Cut-off value of ≥ 0.25 $\mu\text{g/L}$ can help distinguish bacterial from viral respiratory infections. - Current IDSA/ATS and ERS guidelines recommend against using this solely to guide antibiotic initiation. 	<ul style="list-style-type: none"> -Reduction of more than 80% from initial values can help guide antibiotic discontinuation. -Elevated or persistently increasing values are associated with increased mortality.
Presepsin	<ul style="list-style-type: none"> - Soluble form of CD14. - Levels increase in setting of bacterial pathogens. 	<ul style="list-style-type: none"> -Higher levels in bacterial sepsis compared to non-bacterial sepsis. 	<ul style="list-style-type: none"> - Can be used to determine antibiotic duration.
Pentraxin- 3	<ul style="list-style-type: none"> - Secreted by cells within the innate immune system upon stimulation by pro-inflammatory cytokines. - Levels track with disease severity. 	<ul style="list-style-type: none"> - Elevated in patients with severe sepsis. - Higher levels correlate with elevated lactate, APACHE II, and SOFA score. - Highly sensitive for ruling out sepsis and septic shock. 	<ul style="list-style-type: none"> -Elevated levels can predict mortality, disease severity, acute kidney injury, and ventilator days.
Pancreatic Stone Protein	<ul style="list-style-type: none"> - Secreted by the pancreas. - Levels increase in stress and trauma. - Plays a role in the innate immune response. 	<ul style="list-style-type: none"> -Able to identify sepsis up to 5 days prior to onset. - Identifies sepsis from non-infectious inflammation. 	<ul style="list-style-type: none"> - Moderate prognostic accuracy for in-hospital mortality but improves when combined with clinical measures (e.g. APACHE II).

Table 1. Current and Emerging Biomarkers in Sepsis

Abbreviations: APACHE II (Acute Physiology and Chronic Health Evaluation II), SOFA (Sequential Organ Failure Assessment), IDSA (Infectious Disease Society of America), ATS (American Thoracic Society), ERS (European Respiratory Society).

The patients were stratified into low, intermediate, and high probability of infection based on a predictive nomogram, and the models were assessed in each group. In the intermediate probability group, the multi-marker model had the highest predictive capability in identifying infectious SIRS, yielding an area under the receiver operating characteristic curve (AUROC) of 0.85 (95% confidence interval 0.778-0.923) for patients with sepsis or septic shock. The individual biomarkers showed lower AUROCs ranging from 0.56 to 0.77 (Mearelli et al. 2018).

A combination of biomarkers and clinical features was also studied in predicting prognosis in patients with sepsis. Kim et. al (2017) evaluated a combination of SOFA score, white blood cell count, C-reactive protein, PCT, presepsin, galectin-3, soluble suppression of tumourigenicity 2 (sST2) in

157 patients with either sepsis or septic shock. The predictive performance of the model improved with stepwise addition of each biomarker in addition to the SOFA score. The multi-marker approach with SOFA showed an AUROC of 0.769 (95% confidence interval 0.695 – 0.833) vs SOFA score alone with an AUROC of 0.615 (95% confidence interval 0.535 – 0.692). Although this study was limited by its small sample size, the initial results pave a way for future research to re-evaluate the multi-marker approach further.

Conclusion and Future Directions

As the role of biomarkers in sepsis continues to evolve, current evidence lends strong support for the diagnostic and prognostic utility of PCT, presepsin, PTX3, PSP, and their combination with other existing clinical predictors in patients with sepsis

and septic shock. In assessing the literature, it is key to focus on whether data are being used for sepsis diagnosis, prognosis, or to determine duration of therapy. Further research involving these biomarkers should focus on determining the optimal cut-off levels for the diagnosis of sepsis, and the development of clinical decision tools that incorporates these biomarkers to aid clinicians in predicting and improving outcomes in these patients.

Conflict of Interest

Dr Di Pan and Dr William Whalen have no conflict of interest to declare. Dr Michael S Niederman has been a consultant to Thermo Fisher, but has no other relevant disclosures. ■

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Biomarkers of Infection in the Intensive Care Unit

Biomarkers are an area of rapid discovery in critical care medicine today. They have the potential to improve our ability to identify and manage patients at increased risk of organ failure and death. This article provides an overview of biomarkers of infection in the intensive care unit.

The heterogeneity of sepsis makes its identification challenging in the acute setting. As is common with many critical illnesses, rapid diagnosis and rapid institution of therapy are necessary to reduce mortality. The administration of active antibiotics is one of the principal modifiable risk factors for mortality in the septic patient, with the benefits most pronounced in the patient with shock (Kumar et al. 2006; Taylor et al. 2021). Conversely, our ability to identify the potentially infected patient remains imperfect. Approximately 40% of adult inpatients with features of the systemic inflammatory response syndrome are not infected (Comstedt et al. 2009), and a third of patients who receive broad-spectrum antibiotics in emergency settings for suspected sepsis do not have bacterial infections (Shappell et al. 2021). As the slow-moving pandemic of antimicrobial resistance (AMR) continues to challenge health systems around the world, critical care clinicians are becoming aware of the risks of antibiotic overuse, both in terms of increased rates of AMR and as a potential cause of direct patient harm (Vaughn et al. 2019).

At the bedside, we rely on a variety of features to identify sepsis. The term “biomarker” generally refers to some manner of laboratory assay to assist in this identification as well as to guide therapy. Biomarkers do not need to be laboratory-based, of course; fever and leukocytosis are biomarkers, and indeed the absence of fever has been associated with delayed recognition and worse outcomes in sepsis (Kaukonen et al. 2015; Dias et al. 2021). The inadequacy of our existing biomarkers, however, has led investigators to study other assays in an attempt to improve our diagnostic abilities.

Procalcitonin (PCT) is produced by parafollicular cells of the thyroid and by neuroendocrine cells in the lungs and gut, the production of which is increased in the presence of tumour necrosis factor alpha (TNF- α), interleukin (IL)-1 and IL-6 and inhibited by interferon gamma (IFN- γ). As TNF- α , IL-1, and IL-6 are associated with bacterial infections and IFN- γ with viral infections, it has been postulated that PCT can serve as an effective biomarker for bacterial infection (Assicot et al. 1993). PCT is clearly associated with disease severity in infected patients, with elevated levels corresponding to increased risk for 28-day mortality, the need for invasive ventilation, and shock requiring vasopressors (Self et al. 2016; Huang et al. 2008); Ramirez et al. 2011; Bloos et al. 2011). The Multicenter Procalcitonin Monitoring Sepsis (MOSES) study, a randomised trial of PCT-guided therapy conducted in 13 US hospitals, evaluated patients admitted to the ICU with sepsis and septic shock. Those participants with decreases in PCT levels $\leq 80\%$ at 4 days had an increased risk of death compared with those patients whose PCT levels declined $>80\%$ (PPV for death, 29.5%; NPV 81.1%) (Schuetz et al. 2017). Similarly, declines in PCT of 80% or more from admission baselines are associated with decreased rates of in-hospital death (Schuetz et al. 2013).

Durations of antibiotic therapy in patients with sepsis are often arbitrary and may appear to be simple multiples of the numbers of days in a week or fingers on a human hand (Spellberg and Rice 2023). PCT-guided algorithms have been shown to be effective

tools to personalise the duration of antimicrobial therapy in patients with bacterial infections in the ICU. The PRORATA and SAPS II trials demonstrated overall reductions in antibiotic treatment durations (from 14.3 to 11.6 days, and from 9.3 to 7.5 days, respectively) in critically ill patients without negative effects on mortality (Bouadma et al. 2010; de Jong et al. 2016). These results have not been consistent across all studies, with some trials demonstrating either no significant benefit or increased usage of broad-spectrum therapy using PCT guidance (Jensen et al. 2011; Shehabi et al. 2014). Some of these inconsistencies may be due to differences in the algorithm used, however. In the 2014 study by Shehabi et al. for example, the cut-off PCT value for antibiotic discontinuation was 0.1 ng/mL, lower than the 0.25-0.5 ng/mL levels used in other trials, while the 2011 study by Jensen et al. permitted not only antibiotic cessation with lower levels of PCT but antibiotic broadening and intensification with increasing levels. Like any algorithm, the outputs matter as much as the inputs.

Attempts have been made to use PCT to distinguish between viral and bacterial causes of community-acquired pneumonia (CAP). When integrated into a diagnostic strategy that included the use of commercially available multiplex molecular testing for common viral and bacterial pathogens, patients with CAP in one prospective study who had both low serum PCT levels (≤ 0.1 ng/mL) and testing that identified only viruses received fewer antibiotics and had shorter hospitalisations than the comparator

group. However, a large observational study in the United States was unable to identify a PCT cut-off level that safely excluded bacterial disease in patients with CAP, with a negative predictive value for bacterial pathogens of only 82.4%, even at PCT levels of <0.1 ng/mL, considerably lower than the more routine cut-off levels of 0.25–0.5 ng/mL. High levels of PCT may occur in patients with purely viral pneumonias, with murine models indicating that the suppression of PCT expression by IFN- γ may be overcome by high IL-6 levels in severe disease (Gautam et al. 2020; Carbonell et al. 2021). Similar findings have been noted in patients with 2019 coronavirus disease (COVID-19), dengue, malaria, and candidaemia, suggesting that PCT may be more closely linked to an infection's severity than to the nature of the inciting pathogen (Tong-Minh et al. 2022; Thanachartwet et al. 2016; Cortegiani et al. 2019; Hesselink et al. 2009).

The data for PCT usage as a biomarker appears strongest for its use as a tool for individualised antibiotic cessation. In 2019, a patient-level meta-analysis of 13 randomised trials of PCT-guided treatment durations in patients with bacteraemia described overall reductions in antibiotic days without increased mortality (Meier et al. 2019). In order to be effective, however, PCT guidance needs to be a part of an integrated antimicrobial stewardship programme with institutional support.

Other than lactate, C-reactive protein, and leukocytosis, procalcitonin is likely the most widespread sepsis biomarker in current usage. However, additional novel markers are an area of active investigation. Proadrenomedullin is a precursor of adrenomedullin, a product of vascular endothelial cells with varied effects on the cardiovascular system including vasodilator and diuretic functions. The majority of proADM studies utilise measurements of a middle region of the peptide (MR-proADM) without known biological activity. MR-proADM is predictive of organ injury and death in the emergency department (ED) and ICU settings, correlating well with Sequential Organ Failure Assessment (SOFA) scores (similar to PCT but with perhaps greater precision) (Piccioni et al. 2021). Unlike PCT, MR-proADM lacks the ability to discriminate between viral and bacterial pathogens and

indeed is not specific for infection per se; rather, MR-proADM is best viewed as a marker of impending organ failure independent of aetiology, including in patients with heart failure (Maisel et al. 2011) and in the perioperative setting (Schoe et al. 2015). The theoretical benefit of MR-proADM, accordingly, may be in its ability to detect patients at high risk of decompensation early, with a hope for potential early intervention and improved outcomes.

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Presepsin is a N-terminal fragment of soluble CD14 (sCD14), a Toll-like receptor (TLR) molecule that identifies pathogen-associated molecular patterns as a key component of the innate immune system. Among CD14's specific biological functions is as a coreceptor for the binding and recognition of lipopolysaccharide (LPS), or endotoxin, a key component and virulence factor on the outer membrane of gram-negative bacteria. As such, presepsin may be somewhat more specific for gram-negative than gram-positive bacterial infections, although it is elevated in both (Massan et al. 2015). Similar to PCT, presepsin declines with effective antibiotic therapy and has utility in distinguishing bacterial sepsis from other causes of organ failure and shock (Kweon et al. 2014). A meta-analysis of nine studies suggested that its discriminative properties are insufficient to rule out infection in a high-risk patient, however, despite a relatively high AUROC of 0.85–0.89 (Wu et al. 2015). However, the upregulation and expression of presepsin may occur rapidly than that of PCT, suggesting that its utility in an acutely decompensating patient could be superior (Ulla et al. 2013).

Pancreatic stone protein (PSP) is a 14 kDa polypeptide synthesised by the exocrine pancreas that functions as an acute phase reactant

in the setting of tissue damage, possibly promoting repair after injury (Duseti et al. 1995). Despite this apparently nonspecific trigger, PSP elevations seem to be relatively specific for infection compared with other inflammatory insults, including burns and chronic obstructive pulmonary disease exacerbations (Klein et al. 2021; Scherr et al. 2013). Similar to presepsin, PSP upregulation occurs earlier than PCT and may precede the formal diagnosis of sepsis (Niggemann et al. 2021). As the data supporting PSP are largely observational, its utility in direct management remains to be determined.

Perhaps most exciting in contemporary biomarker research is the monocyte distribution width (MDW). Along with neutrophils, cells of the monocyte-macrophage lineage respond early to new infections. The MDW does not require a new assay to measure; rather, it is a parameter readily available (although not routinely reported) when obtaining a standard complete blood count (CBC), or haemogram, with a leukocyte differential. Multiple observational studies have demonstrated an increased sensitivity for the diagnosis of sepsis in the emergency department with the use of MDW, often combined with SOFA scores or total leukocyte counts, with the cut-off for an abnormal MDW usually >20.0 (Jo et al. 2022; Kim et al. 2022; Hausfater et al. 2021; Woo et al. 2021; Cusinato et al. 2022). MDW appears to be pathogen-agnostic and does not distinguish between bacterial and viral causes of sepsis, with evidence for elevations in severe influenza and SARS-CoV-2 infections (Badaki-Makun et al. 2022). Similarly, elevated MDWs in trauma patients at the time of ICU admission are associated with the risk of future multiorgan failure (Marcos-Morales et al. 2022). Although MDW similarly lacks prospective validation in an interventional trial, its advantages seem clear: MDW could provide rapidly actionable data that do not require additional diagnostic testing beyond a routine CBC, avoiding the attendant delays in results. Biomarkers are an area of rapid discovery in critical care medicine today. I will make a small editorial assertion here: the best biomarkers in the ICU are the eyes, ears, hands, and brain of a skilled intensivist. Despite this, these markers have the potential to improve our ability to

identify and manage patients at increased risk of organ failure and death. Further prospective interventional trials are needed to determine which biomarkers, and in which combinations, will best serve our patients' needs.

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Tachycardia in Sepsis: Friend or Foe?

An overview of tachycardia in sepsis, the importance of rate control and the beneficial effects of beta-blockers.

Sepsis and Tachycardia – Aetiologic Factors

During sepsis, the sympathetic nervous system plays a key role in maintaining cardiac output and blood pressure. This is achieved through changes in heart rate, contractility, and vascular tone. The proper function of the baroreflex system is important for maintaining haemodynamic homeostasis. Tachycardia (increased heart rate) in the early phases of sepsis becomes a crucial mechanism for compensating the decrease in stroke volume (SV) and indicates the efficacy of baroreflex activity. Adequate volume resuscitation often decreases heart rate due to the compensatory origin of tachycardia (Morelli et al. 2016).

Tachycardia is very common in septic patients in the ICU. In septic shock, the baroreflex response is often impaired due to high levels of catecholamines, leading to a hyper-adrenergic state. This results in persistent tachycardia even after adequate fluid resuscitation in many septic shock patients, which is a sign of excessive sympathetic stimulation (Baygin and Kararmaz 2018).

Patients who were tachycardic 24 hours after starting norepinephrine infusion have a three-time higher risk of death than those without tachycardia. This may be due to an exhausted compensatory reflex mechanism. Persistent tachycardia can harm the heart by increasing oxygen demand, reducing diastolic filling, and causing direct cardiotoxicity (Domizi et al. 2020).

Studies report that the incidence of atrial fibrillation (AF) in septic patients is nearly 25.5%. This number increases to 31.6% for those in the ICU. Patients who have AF during sepsis have a higher five-year risk of hospitalisation for heart failure, ischaemic stroke and death compared to those without AF (Vélez-Gimón 2021).

Heart failure (low left ventricular ejection fraction) and sepsis, independently, increase the risk of arrhythmias. AF is a common supraventricular arrhythmia in sepsis, accounting for up to 70% of cases. Rate control is the preferred treatment in ICU patients, as

the majority will convert back to normal sinus rhythm once their acute illness has been resolved. A study of critically ill patients with AF showed that 81% returned to normal sinus rhythm via rate control alone (Jones et al. 2021).

Landiolol is a first-line treatment for patients with cardiac dysfunction with limited effect on blood pressure and inotropy

Limitations of Standard of Care

The conventional approach for the management of AF in septic patients with pre-existing heart failure may be the use of agents which are considered haemodynamically favourable (e.g., amiodarone and digoxin). However, current evidence suggests beta-blockers appear to be a better choice.

Sepsis causes overstimulation of adrenergic receptors, which contributes to cardiac dysfunction. Treatment with beta-blockers offers several benefits, such as attenuation of inflammatory cytokines, improvement of cardiac function, counteraction of metabolic dysregulation, prevention of negative consequences from sympathetic overstimulation and prevention of dobutamine-induced ventricular arrhythmias in decompensated heart failure with ejection fraction less than 35%. Given the benefits, it is suggested that chronic beta-blockers be continued in sepsis and heart failure (Jones et al. 2021).

The beneficial effects of beta-blockers in sepsis are due to the normalisation of the hypermetabolic state and the modulation of the immune system. The use of epinephrine and dobutamine in septic shock patients is linked to higher in-hospital mortal-

ity (Hasegawa et al. 2021). A study showed that beta-blockers reduced mortality compared to calcium channel blockers, digoxin, and amiodarone when used for intravenous intervention for 48 hours (Walkey et al. 2016).

Even among beta-blockers, there are certain limitations in critically ill patients with cardiac dysfunction. For example, esmolol has a negative inotropic effect and causes hypotension. Metoprolol has the same drawback, and combined with its late onset of action and an unpredictable effect, may not be the best choice.

Landiolol - A New Kind of β_1 -antagonist

Landiolol is a β_1 -antagonist with limited effects on blood pressure and heart pump function because of its pure S-enantiomer molecular structure. It has a favourable safety profile for patients with renal and hepatic comorbidities due to inactive metabolites and the breakdown by plasma esterases. Landiolol is metabolised mainly by pseudocholinesterases and carboxylesterases and not by CYP450. It has two inactive metabolites (M1 and M2) and does not require dose adjustment for patients with renal dysfunction. It is mainly excreted in urine and has excellent efficacy even at low doses, with a low volume distribution and lower risk of toxicity. Landiolol, due to the highest cardioselectivity (β_1/β_2 -selectivity = 255:1) has a minimal impact on respiratory function and β_2 -receptor-mediated coronary hyperaemia.

A study was conducted across 54 hospitals to investigate the efficacy and safety of landiolol for the treatment of sepsis-related tachyarrhythmias. A total of 151 patients with sepsis and persistent tachyarrhythmia were randomised into two groups, with 76 receiving landiolol and standard therapy (landiolol group) and 75 receiving only standard therapy (control group), where 33% of the control group received antiarrhythmics. In the study, the mortality rate in the landiolol group was 12%, resulting in

an absolute reduction of 8% and a relative reduction of 40% in the risk of death. Additionally, landiolol was found to be effective and safe regardless of patient characteristics, such as septic shock, low LVEF, acidosis, and acute renal failure. Patients with respiratory infections receiving landiolol had a lower mortality rate at 28 days compared to the control group. The results suggest that landiolol effectively controls heart rate and reduces the risk of death (Matsuda et al. 2020; Kakikhana et al. 2020).

In another study of 61 patients with severe sepsis, landiolol was found to decrease heart rate in septic patients without causing negative effects on haemodynamics. The study found that landiolol administration resulted in a high rate of conversion to sinus rhythm, potentially due to its direct suppressive effect on sympathetic activity (Okajima et al. 2015).

Cost Effectiveness of Using Landiolol

There is sufficient evidence to establish that sepsis and septic shock are associated with cardiovascular problems, including tachyarrhythmia, myocardial injury, and changes in vascular endothelial function. Tachycardia and AF, if treated with less effective agents such as amiodarone, can increase the use of healthcare resources and costs (Krumpl and Walter 2022).

A study was conducted to analyse the cost-effectiveness

of landiolol use instead of the standard of care treatment for tachyarrhythmias in septic patients in intensive care units. The authors also looked at the long-term health economic effects of sepsis and the elevated mortality rates after discharge for patients with new-onset AF during sepsis. Findings show that patients with sepsis-related tachyarrhythmia have higher mortality rates, complications, longer hospital stays, increased need for ventilation and higher costs, including hospitalisation and ICU costs. Using landiolol for the management of sepsis-related tachyarrhythmias resulted in an estimated lifetime cost of 58,100.71€ per patient and a gain of 4.02 quality-adjusted life-years (QALYs). The standard of care treatment resulted in 60,935.11€ per patient and 3.55 QALYs. Landiolol showed a cost savings of 2,834.40€ and a gain of 0.47 QALYs or 5.63 months in perfect health. The major source of cost reduction was found to be the reduced need for ICU care (Krumpl and Walter 2022).

Conclusion

The above discussion and clinical evidence highlight the benefits of rapid control of heart rate in patients with tachycardia and AF. Landiolol is a first-line treatment for patients with cardiac dysfunction with limited effect on blood pressure and inotropy. It has a favourable safety profile for patients with renal and hepatic

comorbidities and is compatible with pulmonary disorder patients due to its super-cardioselectivity. ■

Key Points

- Tachycardia is common in sepsis patients in the ICU.
- Studies report that the incidence of atrial fibrillation in sepsis patients is nearly 25.5%.
- Rate control is the preferred treatment in ICU patients, as the majority will convert back to normal sinus rhythm once their acute illness has been resolved.
- Sepsis causes overstimulation of adrenergic receptors, which contributes to cardiac dysfunction. Treatment with beta-blockers offers several benefits.
- Landiolol, due to the highest cardioselectivity (B1/B2=255:1) has a minimal impact on respiratory function and B2-receptor-mediated coronary hyperaemia.
- Landiolol is a B1-antagonist with limited effects on blood pressure and heart pump function. Landiolol owns a well tolerated safety profile.

Disclaimer

Point-of-View articles are the sole opinion of the author(s) and they are part of the ICU Management & Practice Corporate Engagement or Educational Community Programme.

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Biomarkers in Sepsis Present and Future

A biomarker defines a measurable indicator of a patient's medical situation that can be measured precisely and accurately. Biomarkers provide value for diagnosis, prognosis, early disease detection, risk stratification, suitable treatment (theragnostic), and trial improvement for patients with sepsis or presumed sepsis.

Introduction

Sepsis is characterised by a dysregulated immune response that leads to organ dysfunction (Arina and Singer 2021). Host response biomarkers take part in a critical role in diagnosis, early detection of organ dysfunction, risk stratification, prognosis, and patient managing, including antibiotic stewardship (Huang and Ramirez 2020). Biomarkers may also be useful for trial improvement to recognise suitable patients and/or risk categorisation for an intervention.

An extensive range of biomarkers, measured by a host of different technologies, are being explored to distinguish a systemic inflammatory response syndrome (SIRS) rapidly, which is a disproportionate defensive body's response to a damaging stressor (for example, infection, trauma, surgery, acute inflammation, ischaemia or reperfusion, or cancer) (Chakraborty and Burns 2022) or prompt detection of infection-triggered organ failure (sepsis).

These biomarkers embrace measurement of acute-phase proteins, cytokines, chemokines, damage-associated molecular patterns (DAMPs), endothelial cell markers, leukocyte surface markers, non-coding RNAs, micro-RNA, and soluble receptors, as well as metabolites and alterations in gene expression (transcriptomics). Biomarkers may assist in stratifying septic patients into biological phenotypes, for example, hyperinflammatory versus immunosuppressive.

Lately, the advancement of biomarkers in the intensive care unit (ICU) has been vast. However, only a few are commonly used in clinical procedure: procalcitonin (PCT), and, newly, Mid-region fragment of pro-adrenomedullin (MR-proADM). Others are under

investigation with encouraging results: pancreatic stone protein (PSP), soluble Triggering Receptor Expressed on Myeloid Cells (sTREM), and presepsin (Table 1).

Procalcitonin

PCT has been extensively investigated as a decision-making aid in critically ill patients with sepsis. PCT, a 116-amino acid precursor hormone of calcitonin, is the most analysed biomarker in sepsis. Its production is caused by systemic inflammation due to severe infection in response to various pro-inflammatory signals (Becker et al. 2008). The Research Committee of the Surviving Sepsis Campaign (SSC) believes research in biomarkers in sepsis as a priority for future years (Coopersmith et al. 2018) and the 2021 SSC guidelines suggest the measurement of PCT levels to help shortening the duration of antimicrobial treatment (Evans et al. 2021).

PCT and diagnosis

PCT had similar performance in guessing positive sepsis results with AUROC values of 0.75 and 0.73, respectively (Mihajlovic et al. 2017). A cut-off value of 1.1 ng/ml [sensitivity of 77% and specificity of 79%; area under the receiver operating characteristic curve of 0.85 (95% CI 0.81–0.88)] could be used for diagnosis of sepsis, depending on pre-test probability (Wacker et al. 2013). Another study gave AUROC values of 0.87 for PCT in predicting bacteraemia (Leli et al. 2016). Plasma concentrations of PCT were gradually higher in sepsis and septic shock than in non-septic patients. PCT was slightly superior to presepsin in one more study of septic patients admitted to intensive care (Enguix-Armada et al. 2016).



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PCT and prognosis

In patients with septic shock and multiorgan dysfunction, a sustained high concentration of PCT is associated with significantly lower survival. PCT clearance could be a useful tool for monitoring the clinical evolution of the patients and the prognosis can be assessed by PCT clearance at 48h (Ruiz-Rodríguez et al. 2012).

Procalcitonin-guided antimicrobial stewardship in sepsis helps individual assessments on the duration of antibiotics, treatment approaches, and diagnostic interventions (Saeed et al. 2019). In earlier studies, procalcitonin assistance in the intensive care unit improved clinical results and diminished the length of stay, with no associated problems (Iankova et al. 2018; Balk et al. 2017). Adding up, studies are describing the mortality advantages of procalcitonin guidance. In a prior meta-analysis (Lam et al. 2018) the positive effects of a procalcitonin-guided strategy for de-escalation in decreasing the threat of death were found. Also, in another study, procalcitonin-guided therapy in patients with sepsis reduced mortality (Wirz et al. 2018).

PCT guided therapy

Changes in PCT plasma concentrations have been helpful to distinguish patients with a reasonable response to antimicrobial treatment and have their therapy de-escalated. A decrease to levels < 0.5 ng/ml or by at least 80-90% of the peak in combination with clinical progress can be applied to support the clinical decision to lessen antimicrobial coverage, thus escaping from antibiotic-related adverse effects (de Jong et al. 2016).

PCT-guided de-escalation

PCT-guided de-escalation algorithms rely on the early evidence demonstrating that patients with positive progress and satisfactory reaction to antibiotic treatment have a rapid decline in PCT concentrations (Harbarth et al. 2001). In at least three meta-analyses, PCT-guided algorithms have been efficient and secure to de-escalate antibiotics in sepsis and septic shock, with no side effects on patient results (Wirz et al. 2018; Lam et al. 2018).

Previous studies revealed patients with lower respiratory tract infections can often be de-escalated when PCT concentra-

tions are low, provided that medical assessment supplements biomarker measurements. A patient-level meta-analysis of 2,910 patients demonstrated that PCT guidance reduced antibiotic treatment period to 5.7 days from 6.2 days in controls ($p < 0.0001$) (Wacker et al. 2021). In another randomised study of 1,546 ICU patients, PCT guidance lessened the duration of antibiotic therapy. It improved the number of antibiotic-free days matched to control, though the number of ventilator-associated pneumonia (VAP) patients was not specified (Kim et al. 2019). Numerous observational studies have shown the absence of utility of PCT measurements in VAP diagnosis. The primary reason for explaining these conclusions was that another non-infectious diseases or infections out of the lung can raise PCT concentrations in patients on mechanical ventilation. The recent ERS/ESICM/ESCMID/ALAT guidelines (Gibot et al. 2012) suggest that PCT can be helpful to guide treatment duration or extend it in several circumstances, such as inappropriate antibiotic treatments, infections caused by multidrug-resistant or extensively drug-resistant microorganisms.

Some analyses do not promote the use of PCT-guided de-escalation in sepsis. However, these studies have incorporated in non-septic or non-critically ill patients with lower respiratory tract diseases (Huang et al. 2018).

Mid-Region Fragment of Pro-adrenomedullin

Mid-region fragment of proadrenomedullin (MR-proADM) quickly suggests concentrations of adrenomedullin, a potent vasodilator agent with immune-modulating and metabolic properties that rises in sepsis. MR-proADM is synthesised in different tissues, including the adrenal cortex, kidney, lung, blood vessels, and heart. It has biological assets, including vasodilating, inotropic, diuretic, natriuretic, and bronchodilating. In one study, mid-regional pro adrenomedullin (MR-proADM) was an independent prognosticator of five different organ dysfunctions (respiratory, coagulation, cardiovascular, neurological, and renal), compared to lactate which predicted three (coagulation, cardiovascular and neurological), PCT two (cardiovascular and renal) and C-Reactive protein (CRP) none (Martín-Fernández et al. 2021).

MR-proADM most precisely recognised patients with a high

likelihood of further disease progression compared to other biomarkers and clinical scores (Schuetz 2015). A total of 1089 individuals with either sepsis (142) or septic shock (977) were included in a randomised controlled study. The MR-proADM level within the first 24 h after sepsis diagnosis was associated with 7-day mortality (AUROC 0.72, $p < 0.001$) and 90-day mortality (AUROC 0.7, $p < 0.001$). Patients with declining PCT levels

but persistently high MR-proADM levels on day-1 or day-4 had a substantially higher mortality risk of 19.1 (8.0–45.9) and 43.1 (10.1–184.0), respectively; MR-proADM identifies disease severity and treatment response more accurately than established biomarkers and scores, adding additional information to facilitate rapid clinical decision-making and improve personalised sepsis treatment (Elke et al. 2018). Adult patients hospitalised in ICU had

their bioactive-MR-proADM levels measured in this retrospective observational study. This study comprised a total of 1867 patients, 632 septic patients, and 267 septic shock patients. The median bioactive-ADM was 74 pg/mL in sepsis patients, 107 pg/mL in septic shock, and 29 pg/mL in non-septic patients. The association of elevated bioactive-ADM and mortality in sepsis patients and the ICU population resulted in O.R.s of 1.23 and 1.22, respectively (Lundberg et al. 2020).

Newly, the association has been reported between a higher clearance of MR-proADM levels during ICU stay and favourable outcomes, with survivors displaying a blood plasma concentration fall to 1.65 nmol/L 48 hours after admission and lower levels on day five compared to non-survivors. The role of MR-proADM in the early identification of severe cases at higher risk of organ dysfunction has been evaluated, irrespective of the location of the infection source. Furthermore, MR-proADM is used to aid clinical decisions regarding the use of hospital and ICU resources, having the highest predictive value for mortality compared to PCT, CRP, Sequential Organ Failure Assessment (SOFA) scores, and lactate (Baldirà et al. 2020).

In conclusion, MR-proADM is a good applicant in the prompt identification of sepsis patients with moderate illness severity but at threat of mortality and is a reliable marker of mortality danger and disease severity along time in sepsis (Andaluz-Ojeda et al. 2017).

Pancreatic Stone Protein

Pancreatic stone protein (PSP) is a 14 kDa insoluble polypeptide encoded by a single transcript of the reg gene, resulting in a 144-amino acid length glycoprotein, structurally similar to C-type lectin-like proteins (Jin et al. 2011) which are calcium-dependent glycan-binding proteins involved in the process of cell to cell and host-cell interaction, including adhesion and signalling receptors in homeostasis and innate immunity as well leukocyte and platelet trafficking in inflammatory responses (Varki et al. 2009). The role of PSP in the immune and inflammatory response to infection prompted its identification as a potential biomarker of infection and sepsis since a pivotal observation was accidentally made in rat experiments by the group of Rolf Graf in which PSP was found

Biomarker	Utility
Presepsin	Initial diagnosis and sepsis risk stratification
	Potential marker to distinguish Gram (+) and Gram (-) bacterial infection
sTREM-1	Sepsis indicator
	An early distinction between sepsis and SIRS
	Septic shock prediction
	Theragnostics, Precision Medicine
PCT	PCT clearance for monitoring clinical evolution and prognosis
	Measurement of PCT levels to support shortening the duration of antimicrobial therapy
	Guided de-escalation
	Mortality benefits of procalcitonin guidance
PSP	Identification of sepsis
	Prognostic tool
MR-proADM	Discrimination of survivors and non-survivors
	Identified patients with a high likelihood of further disease progression
	Higher clearance of MR-proADM levels during ICU stay and favourable outcomes
	Organ dysfunction biomarker

Table 1. Relationship of biomarkers and clinical utility

MR-proADM: Mid-region fragment of pro-adrenomedullin; PSP: Pancreatic Stone Protein; PCT: procalcitonin; sTREM-1: soluble TREM-1

to be an indicator of systemic stress (Graf et al. 2002).

PSP as a diagnostic tool for sepsis

PSP demonstrates a significant interaction between time and presence of sepsis suggesting that besides a fixed cut-off value (as in standard ROC curve analysis) the time-related kinetics of PSP has a crucial role in the identification of sepsis when considering the time-dependency of the infectious/septic event (Pugin et al. 2021). In a meta-analysis, the results of PSP were better than CRP or PCT for the diagnosis of community acquired infections in the emergency department and surgical infections after cardiac surgery (Prazak et al. 2021).

In a multicentric international prospective observational clinical study conducted in 14 ICUs in France, Switzerland, Italy, and the United Kingdom where adult patients at risk of nosocomial sepsis were included, clinical sepsis diagnosis was associated with an increase in biomarkers value over the 3 days preceding this diagnosis [PSP ($p = 0.003$), PCT ($p = 0.025$) and CRP ($p = 0.009$)] , of note that PSP started to increase 5 days before the clinical diagnosis of sepsis. So, serial PSP measurement demonstrated an increase of this marker the days preceding the onset of signs necessary to clinical diagnose sepsis (Pugin et al. 2021).

PSP as a prognostic tool

PSP has shown good performance in the prognosis of septic patients. PSP was evaluated in a cohort of 101 patients with VAP; the highest values were obtained in non-survivors (Boeck et al. 2011). In another study, PSP was the only biomarker significantly increased in non-survivors (Que et al. 2012). In patients with septic shock, PSP was substantially higher in non-survivors in the first six hours after diagnosis and on the second day of admission to the ICU (Guadiana-Romualdo et al. 2019). In another study performed in 249 septic patients, higher PSP values were linked with clinical severity and non-survivors (Que et al. 2015).

Presepsin

Presepsin is a biomarker to identify sepsis, but its prognostic value has not been exhaustively reviewed. Known as soluble CD14 subtype, is a 13-kDa glycoprotein cleavage N-terminal

fragment of CD14, released into circulation after activation of a pro-inflammatory signal cascade on contact with infectious agents (Wright et al. 1990). The diagnostic accuracy of presepsin in sepsis was established by a meta-analysis (Zhang et al. 2015) where eleven studies fulfilled the inclusion criteria; the overall diagnostic sensitivity of presepsin for sepsis was 0.83 (95% CI: 0.77–0.88), and specificity was 0.78 (95% CI: 0.72–0.83) but the major design deficits of the included studies were lack of prespecified thresholds and patient selection bias. Another meta-analysis (Yang et al. 2018) encompassed a total of 10 studies and 1617 patients were involved. Presepsin levels in the first sampling (within 24 hours) were considerably lower among survivors as matched with non-survivors: the pooled SMD between survivors and non-survivors was 0.92 (95% CI: 0.62–1.22) in the random effects model ($I^2 = 79%$, $P < 0.01$). In subgroups, separated by the sepsis severity or study site, pooled SMD was consistently noting higher presepsin levels in non-survivors. A meta-analysis with 19 studies included (19 observational studies and no randomised controlled trials) that had enrolled 3012 patients, showed that the diagnostic accuracy of procalcitonin and presepsin in identifying infection was similar and that both were useful for early diagnosis of sepsis and subsequent reduction of mortality in critically ill adult patients (Kondo et al. 2015). Presepsin also has been demonstrated to have predictive value for circumstances other than sepsis such as cardiac surgery (Bomberg et al. 2017), haemophagocytic syndrome (Nanno et al. 2016), or renal failure (Nagata et al. 2015).

Soluble Triggering Receptor Ex-pressed on Myeloid Cells-1

The Triggering Receptor Expressed on Myeloid Cells (TREM) family includes several isoforms that share low sequence homology with each other and have only one immunoglobulin-like domain. Engagement of TREMs triggers a signalling pathway leading to intracellular calcium mobilisation, actin cytoskeleton rearrangement and activation of transcriptional factors. TREM-1 was first detected on both human and murine myeloid cells, especially neutrophils, mature monocytes and macrophages. Its expression at the cell-surface of these effector cells is significantly enhanced

in skin, biological fluids and tissues infected by Gram-positive or Gram-negative bacteria as well as by fungi (Bouchon et al. 2001). The activation of TREM-1 by its still unidentified ligand in the presence of Toll-like receptor 2 (TLR2) or TLR4 ligands amplifies the production of proinflammatory cytokines. Additionally, activation of these TLRs upregulates TREM-1 expression (Bleharski et al. 2003). Thus, TREM-1 and TLRs collaborate to produce an inflammatory response. Besides its membrane-anchored form, a soluble form of TREM-1 (sTREM-1) is released and can be measured in several body fluids.

sTREM-1 and the diagnosis of septic shock

The newest meta-analysis on sTREM-1 as a diagnostic biomarker of sepsis in adult patients was published in 2012 (Wu et al. 2012). Its assumption was that plasma sTREM-1 had a moderate diagnostic performance in distinguishing sepsis from sterile inflammatory response and was not enough for sepsis identification, especially when pre-test probability of SIRS was high.

sTREM-1 as a prognostic marker of infection

In 63 consecutive septic patients, plasma sTREM-1 concentrations were measured sequentially (Gibot et al. 2005). The baseline plasma sTREM-1 concentration was higher in survivors and was found to be an independent factor associated with good outcome. In a meta-analysis, sTREM-1 plasmatic levels had a moderate prognostic meaning in evaluating the mortality of infection in adult patients (Su et al. 2016). In a cohort of 190 septic ICU patients, sTREM-1, PCT, leucocyte surface expression of CD64 and clinical severity scores were analysed. sTREM-1 was noticed to be the best prognostic biomarker amongst those studied (Charles et al. 2016).

sTREM-1 as a target molecule for adjuvant treatment of sepsis

Blockade of TREM-1 reduces inflammation and improves survival in animal models of bacterial sepsis. Nangibotide is a 12 amino-acid peptidic fragment derived from TREM-Like Transcript-1 (TELT-1), a receptor protein of TREM-1 family. Nangibotide can bind to TREM-1 ligand and modulate the amplification of the immune response caused by the activation of TREM-1 in sepsis.

In pre-clinical animal studies performed in peritonitis with

septic shock patients, analogues of Nangibotide showed an improvement of inflammatory response and organ function, cardiovascular status, and survival (Derive et al. 2012; Derive et al. 2013). In a recent phase IIa clinical trial that investigated the safety and tolerability of three doses of Nangibotide in septic shock, Nangibotide-treated patients improved organ function biomarkers. This effect was bigger in the subgroup of patients with high circulating soluble TREM-1 (sTREM-1) levels. A phase 2b clinical trial, ASTONISH, evaluated its efficacy, safety, and tolerability in patients with septic shock, specially focused on the high sTREM-1 subgroup (ClinicalTrials.gov Identifier NCT04055909) (Francois et al. 2021). The results suggest a therapeutic potential

of Nangibotide in septic shock patients with excessive activation of the TREM-1 pathway confirming also that the soluble TREM-1 biomarker predicts response to Nangibotide treatment.

Conclusion

The use of sepsis biomarkers for individualising treatments is promising. Recent progress in several areas of biomarkers research can transform the application of biomarkers as a chip at the bedside for diagnosis, predictive and prognostic enrichment in clinical studies, risk stratification, molecular phenotyping, and monitoring therapeutic response in more personalised medicine.

Statement of Ethics

We complied with the guidelines for human studies, and our research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written informed consent to publish this case was obtained and it was recorded in the medical history. Information revealing the subject's identity was avoided.

Conflict of Interest

None. ■

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The Footprints of a Gigantic Hound – Biomarkers in Intensive Care

Biomarkers hint at the pathophysiology behind a clinical entity, leading to better treatments. Access to biomarker testing may improve drug discovery in clinical trials, responses at the bedside and personalised patient management.

The human body is a construct of chemical fires – each with a characteristic smoke signal. The smoke signals are borne to the clinician in the form of biomarkers – some more specific than others. A biomarker we are all used to employing is the humble CRP (C-reactive protein). However, its utility is limited by its lack of specificity – for example, it increases postoperatively, and there is a lag in its peak. Only day 3 CRP is a prognostic marker in ICU (Devran et al. 2012). We would prefer an admission biomarker. In the setting of planned high-risk surgery, we would appreciate a baseline biomarker for predicting complications.

A biomarker is an objective measure of a biological process – ideally, it is sensitive to the process, correlates with extent or severity, specific to that process, with a predictable half-life and available in minimally invasive media such as serum or urine – a brain biopsy is impractical for routine analysis.

In addition to diagnosing and prognosticating, biomarkers are able to hint at the pathophysiology behind a clinical entity, leading to better treatments. A clear example of this is the repurposing of tocilizumab in severe COVID-19 (Abani et al. 2021). An example where a biomarker does not demonstrate this is the monumental presence of IL-6 and TNF α in sepsis, but the failure of drug therapy targeting these cytokines (Fisher et al. 1996). That said, the success of IL-6 blockade in severe COVID-19 may indicate it is only a cohort of patients with very deranged inflammatory responses who benefit, and this is where access to biomarker testing may improve drug discovery in trials and responses at the bedside.

Acute Respiratory Distress Syndrome

The explosion of research surrounding the coronavirus pandemic

has led to serious developments regarding the use of biomarkers for both phenotyping and prognosticating in serious respiratory failure/Acute Respiratory Distress Syndrome (ARDS).

Ferritin is one such biomarker. Whilst traditionally seen as an iron-chelating protein associated with inflammation (an acute phase protein), its roles in inflammation are also causal. For example, there is evidence it affects the inflammasome – a protein assembly inside cells which produces IL-1, part of the innate immune system and a key player in viral immunity. The inflammasome is also an assembly that can be primed according to genetics (receptor mutations cause familial Mediterranean fever (Van Gorp et al. 2016) or metabolic disease such as diabetes (Wan et al. 2019) – possibly contributing to poorer outcomes in these patients. There is clear evidence in particular that ferritin is associated with poor pulmonary status in COVID-19 pneumonitis – those above the 25th percentile had worse respiratory status (Carubbi et al. 2021) and was an independent risk factor for ARDS development (Gandini et al. 2020). Moreover, inflammasome activation can have a double hit with respect to pulmonary involvement – exacerbating ventilator-associated damage (Kuipers et al. 2012).

Bench-side ferritin itself has been shown *ex vivo* to increase IL-1 production by macrophages as well as increased gene expression of the inflammasome receptor (NLRP3) (Ikeda et al. 2014). Additionally, proteomic analysis shows that the heavy units of ferritin in sera increase peripheral blood monocyte proliferation, as well as levels of the cytokines IL-1, 6 and TNF α (Ruscitti et al. 2020). Thus, the ferritin axis is likely to be causal in addition to associated with higher inflammation. Indeed, this was confirmed

bedside in COVID-19 patients, where it was associated with worse mortality and higher levels of inflammasome activation (Mehta et al. 2022).

Meanwhile, there is hope with respect to biomarkers like ferritin, we can identify subphenotypes of heterogenous disease syndromes. This leads to enrichment in clinical trials (improving efficacy of successful drug development) and hopefully personalised patient management. Calfee et al. (2012) have led the way with sub-phenotyping ARDS. In particular, there is the emergence of a hyperinflammatory phenotype. This phenotype is particularly high in IL-6 (Santa Cruz et al. 2021) and has a poor outcome. Moreover, IL-6 levels putatively predict tocilizumab response in COVID-19 (Galván-Román et al. 2021). A concise commentary on sub-phenotyping is available here (Shankar-Hari and McAuley 2017). Meanwhile, the development of a bedside test to detect IL-6 is being trialled in ICU patients with COVID-19 and has been under development (Fischer et al. 2019).

Acute Kidney Injury

Acute kidney injury/failure (AKI) complicates 30-50% of intensive care admissions (Case et al. 2013), can lead to protracted periods on organ support, and progress to permanent chronic kidney failure requiring permanent dialysis. It is also associated with increased mortality. As a result, it is vital to be able to prognosticate or predict this course of organ failure, both early in admission and even prior to the insult – such as planned surgery. A significant proportion of AKI may be preventable, with a significant impact on patients and healthcare systems. KDIGO/RIFLE criteria rely on serum creatinine is generally used; however, there is a delay in its

elevation. Moreover, it is also affected by haemodynamic changes in illness rather than pure renal injury itself. However, a recent expert consensus has identified biomarkers as predictive agents in managing this important condition (Ostermann et al. 2020).

Two biomarkers of note are NGAL (neutrophil-associated ligand) and TIMP2.IGFBP7 and each shall be explained in turn.

Neutrophil gelatinase-associated lipocalin was first identified in neutrophils, though it is found in numerous human tissues and is actively reabsorbed in the proximal tubule. In the setting of kidney injury, it is actively secreted by the distal tubule and accumulates in urine. Evidence shows it is statistically significant at 12 hours – it has an AUC of 0.82, a sensitivity of 70% and a specificity of 90%, and remains so at 24 and 48 hours (Khawaja et al. 2019). It forms part of innate immune defences by binding to iron chelators in microbes and preventing them from utilising Fe (Goetz et al. 2002). This is a well-honed strategy in innate immunity where ferritin has a similar role, underscoring the fact that anaemia is a functional consequence of inflammation. The vital importance of this somewhat paradoxical strategy was demonstrated in the death of a laboratory worker with subclinical haemochromatosis, falling ill to an attenuated strain of yersinia pestis (bubonic plague), which had been inactivated by modulating its iron transport system (Frank et al. 2011).

NGAL has been slightly more equivocal (Törnblom et al. 2020) than TIMP2.IGFBP7, however, and is recommended in an expert consensus where lower levels are not associated with a high risk of AKI progression, and high levels able to predict RRT (Nisula et al. 2014). An NIHR cost analysis indicated point-of-care tests were cost-effective and could be used in a community setting; important considerations with respect to current UK healthcare forecasts regarding ‘hospital at home’.

Meanwhile TIMP2.IGFBP7 checks two proteins, both of which are cell cycle arrest markers. TIMP2 binds metalloproteinases (Escalona et al. 2020), whilst IGFBP7 binds insulin growth factor with high affinity and has significant interactions with type VI collagen and tissue proliferation (Jin et al. 2020). Clinical trials have quite conclusively shown they are of singular utility in predicting renal and survival outcomes as well as the need for RRT post-surgery. The mechanism of increased urinary presence of this marker (for which there are combined assays) showed

accumulation is particularly due to reduced re-absorption and distal tubular damage (Johnson and Zager 2018) rather than stress-induced gene expression changes alone, which aids its renal injury specificity.

the explosion of research surrounding COVID-19 has led to developments regarding the use of biomarkers for both phenotyping and prognosticating in ARDS

For example, in septic patients, urinary TIMP2.IGFBP7 at baseline and following resuscitation predicted three times the risk of AKI if positive following resuscitation or a reduced risk if baseline positive became negative (Fiorentino et al. 2020). This would help plan care or possibly detect adequacy of resuscitation.

Furthermore TIMP2.IGFBP7 positivity can predict survival even within an AKI cohort – in a series of >700 patients, TIMP2.IGFBP7 positivity meant survival of 34%, almost half that of the negative-at-baseline AKI group (67% survival) (Xie et al. 2019).

Of equal interest, this set of biomarkers can indicate, even prior to surgery, risk of AKI and RRT. In elective cardiac patients, TIMP2.IGFBP7 at baseline had an AUC of 0.8, increasing to 0.93 with serum creatinine and TIMP2.IGFBP7 added post-operatively.

Neuroprognostication

Cardiac arrest surviving to discharge is approximately 18% (Nolan et al. 2014), with a portion of those undergoing a period of neurological assessment in the intensive care unit. The loss of neurological function is complex to examine and often causes controversy in national media, as well as consternation to families and clinicians. Recent European Resuscitation Council and European Society of Intensive Care Medicine guidelines (Nolan et al. 2021) suggest the additional use of the biomarker neuron-specific enolase to aid with decision-making (though it does not replace

the other clinical investigations such as formal brainstem testing).

Enolases are glycolytic enzymes, and ENO2 is the gene coding for the isoform found in neurons. Upregulation of glycolysis is traditionally seen as a cellular stress response, and ENO2 expression is upregulated in inflammation in neurons (Liu et al. 2018). Several investigations have demonstrated that serial measurements in NSE correlate with both short (Wihersaari et al. 2019) and longer-term outcomes, with AUCs that exceed 0.8 or even 0.9 in younger patients, though this drops with age and a longer period until resuscitation.

Sepsis

Sepsis is defined as a dysregulated immune response to an infection, with the clinical entity defined by Sepsis-3 criteria (Singer et al. 2016). Heterogenous host responses are conferred in a constellation of ways – from variations in PAMPs (pathogen-associated molecular patterns), DAMPs (damage associated molecular patterns), innate immune proteins, receptors and cells, and similar for the adaptive response – proving complex to study and examine. A multitude of sepsis biomarkers are elegantly reviewed by Barichello et al. (2022).

Of note, pentraxin-3 and angiopoietin serve diagnostic and prognostic potential sequentially. Pentraxin 3 is a fluid phase pattern recognition molecule – these are ancient serum proteins released in response to a range of pathogenic features (CRP is also a pentraxin) – from whole organisms to gram-negative wall components and influenza agglutinins (Doni et al. 2019). They are able to opsonise, activate complement, bind to a range of follow-on receptors in the innate and adaptive pool, and interact with tissue repair and coagulation proteins via interactions with fibrinogen-like and collagen-like binding sites – which are prolifically re-used across inflammatory, repair, and clotting pathways. Significantly SNPs in this gene relate to susceptibility for aspergillus, tuberculosis and pseudomonas.

In combination with lactate, IL-6 and procalcitonin, pentraxin 3 produces a marker of 28-day mortality more accurately than the SOFA score for sepsis patients (Song et al. 2020). Moreover, pentraxin-3 correlates with SOFA, APACHE II, DIC, elevated creatinine, and 90-day outcome. Overall it was superior to PCT (Chen et al. 2021). It has also been shown to be a better marker

of severity and death than IL-6 (Hamed et al. 2017) and is capable of discriminating between sepsis and septic shock (Chen et al. 2021) – cut-off values could allow for automatic flagging to ICU/vasopressor review. Highly recent meta-analyses have confirmed its viability as a biomarker (Wang et al. 2022).

Another emerging biomarker is angiotensin-2. This was first identified as a potential marker of sepsis severity some decades ago, with an emphasis on vascular reactivity (Davis et al. 2010). Its role as an antagonist to the endothelial stabilising receptor Tie has now been clarified (Aslan et al. 2014). It thus contributes to the vasodilatory and capillary leak aspects of a systemic inflammatory response. In particular, the ratio of angiotensin 2 to the Tie agonist angiotensin 1 (Seol et al. 2020) has been proposed as a prognostic marker. The angiotensin/Tie axis is proven disturbed in sepsis patients with AKI (Aslan et al. 2014), and moreover, angiotensin 2 differentially prognosticates between infectious and non-infectious causes of ARDS. Intriguingly, there is a difference in the rate of decline of angiotensin 2 levels with conservative vs liberal fluid therapy (Calfee et al. 2012).

In addition to the above, an antibody with specificity for ang2 has been used successfully to treat an experimental murine model

of sepsis, with improvements in vascular permeability and survival (Hauschildt et al. 2020).

Hand in hand with biomarker-based phenotypes comes a requirement for point-of-care testing – something that seems a distance away at present but has been negotiated in the past

Conclusion

Biomarkers are now reaching clinical guidelines and assisting decision-making. They are also being used to identify cohorts in trials. This is likely to lead to better homogeneity within trial groups and enhance efficacy in the development of new drug treatments – being able to group phenotypes with biomarkers is a process known as enrichment that may hasten drug development and fulfil the growing expectation that medicine can be personalised.

The use of biomarkers in prognosticating is also an objective measurement that may feel less emotionally laden for friends and relatives, though all clinical features must be considered in such scenarios.

Using biomarkers at baseline to better aid decision making, such as that for elective surgery, may reduce iatrogenic delivered injury and reduce the burden of elective decisions on high-dependency clinical areas.

Hand in hand with biomarker-based phenotypes comes a requirement for point-of-care testing – something that seems a distance away at present but has been negotiated in the past for example, Haemocue, INR, blood glucose and even pregnancy tests. IL-6 bedside testing is being trialled (Fischer et al. 2019; Oeschger et al. 2019).

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Conflict of Interest

None. ■

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Utility of Biomarkers in Obstetric Patients With Preeclampsia

Preeclampsia is a complex syndrome whose complications bear an impact on perinatal morbidity and mortality. Angiogenic biomarkers may significantly impact both the decision to admit patients and risk stratification and may also help guide patient management and level of care.

to maladaptation of the uterine spiral arteries with restricted trophoblast invasion (8-18 weeks). These alterations can lead to poor placental perfusion, which is associated with a complex interaction between a “stressed” syncytiotrophoblast and a “susceptible” maternal cardiovascular system, potentially leading to inflammatory, immunological and haemodynamic effects which may or may not have maternal and foetal organ consequences (Cerderia et al. 2018).

For more than a century, the most common form to diagnose preeclampsia has been through documentation of elevated blood pressure; nonetheless, there are many patients with neurological (eclampsia), hepatic (HELLP syndrome: haemolysis, elevated liver enzymes and thrombocytopenia) or other manifestations which do not critically elevate the blood pressure. International guidelines usually recommend suspecting and making the diagnosis by means of clinical parameters and past medical history, arguing that it is a low-cost screening approach, although at the expense of poor detection (MacDonald et al. 2022). Currently, however, the biomarkers related to syncytiotrophoblastic stress play an important role for the differential diagnosis in difficult cases, as well as in prediction of its development and prognosis (Cerderia et al. 2018).

a low detection rate (sensitivity) for preterm preeclampsia (40%) and term preeclampsia (35%) (Magee et al. 2022). Definitive prediction of this syndrome still remains unclear; the proposed tools that are considered effective are also considered complex and expensive. Nevertheless, an early detection should prompt the clinician to make efforts of further preventing this disease. It should also prompt the clinician to consider the potential costs of short and long-term adverse perinatal outcomes resulting from preeclampsia (Magee et al. 2021) (Table 1).

1. Timely work-up: before 28 weeks' gestation for early preeclampsia and before 36 weeks' gestation for late preeclampsia.
2. Clinicians should understand that many of these biomarkers are present in pregnancies with preeclampsia, but some of them have not been studied in pregnant patients without preeclampsia. This validation is necessary.
3. Generating new evidence in this area is essential.
4. In practice, the use of biomarkers (e.g. sFlt-1/PlGF) has the ability of ruling out disease in suspected patients.
5. Despite the growing literature, availability of most biomarkers is low in resource-constraint settings.

Table 1. Considerations of preeclampsia biomarkers

Prediction of Preeclampsia

Classically, guidelines recommended to make the diagnosis of preeclampsia through assessment of risk factors and mere clinical manifestations; however, this simple approach is at the expense of

Multiple tools have been proposed for the prediction of preeclampsia development, including clinical measurements, ultrasonographic and laboratory parameters. Laboratory biomarkers

Preeclampsia is one of the main causes of maternal and foetal morbimortality, with a global incidence of 3-5%, and is a frequent reason for admission to the Intensive Care Unit (ICU) (Drogue 2015). Preeclampsia is the result of deficient placentation due



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that have been evaluated in relation to this disease include proinflammatory agents, derivatives of lipid metabolism and oxidative stress, molecules of maternal organ dysfunction and molecules of fetoplacental function (Magee et al. 2021) (Table 2).

Placental Proteins

Pregnancy-associated plasma protein-A (PAPP-A) and alpha-fetoprotein (AFP) have both been associated with adverse perinatal outcomes, including preeclampsia. When combined, an AFP/PAPP-A ratio of >10 resulted in an increased relative risk for preeclampsia, although with poor statistical power (MacDonald et al. 2022).

Placental and endothelial RNA

RNAs derived from placental microvilli (mRNAs, miRNA, Gata2, mir-574-5p, mir1972 and mir-4793) associated with preeclampsia have been identified in maternal circulation; however, a systematic review concluded that it is difficult to draw firm conclusions regarding their usefulness in preeclampsia prediction, given

Biomarker	Trend	Sensitivity (%)	Specificity (%)	AUC
PlGF	↓	62	60	ND
PP13	↓	44	80	0.83
Endothelin-1	↑	96.8	51	ND
PAPP-A	↓	11-23	ND	ND
NGAL	↑	ND	ND	0.75
S-Eng	↑	63	57	ND
Activin A	↑	20	ND	0.59
Inhibin A	↑	16-35	ND	ND
sFlt-1/PlGF	↑	38-58.2	95	ND

Table 2. Biomarkers of the first and second trimesters of pregnancy (MacDonald et al. 2022; Griffin and Shennan 2014). ND: Not determined.

some limitations in adjustments for clinically relevant variables (MacDonald et al. 2022). Some substances derived from endothelial dysfunction, such as those derived from nitric acid metabolism (asymmetric dimethylarginine) and pro-endothelin 1, have been shown to bear alterations in pregnancies with preeclampsia, although with a modest predictive effect; therefore, their routine use is not currently recommended (MacDonald et al. 2022).

Circulating angiogenic proteins

Currently, these are considered the most promising biomarkers for the prediction and diagnosis of preeclampsia. They can be used as screening tools in the first trimester of pregnancy, even in twin pregnancies (Drogüe et al. 2015). In subsequent stages of pregnancy (>20 weeks' gestation), angiogenic factors have been associated with prediction of early preeclampsia, which is in turn associated with a higher risk of complications (Cerdeira et al. 2018). Placental dysfunction in preeclampsia causes altered expression of placental proteins with potential endothelial damage (Drogüe et al. 2015). The FLT-1 protein-encoding gene produces a complete transmembrane receptor (rFlt-1) that binds to vascular endothelial growth factor (VEGF) and to placental growth factor

(PlGF). Under certain conditions, a soluble form of this transmembrane receptor (sFlt-1) is released, which lacks cytoplasmic domains and acts as a decoy receptor for VEGF and PlGF in the circulation, preventing their angiogenic function (Cerdeira et al. 2018) (Figure 1).

Preeclampsia Diagnosis

With classical clinical diagnosis (elevated blood pressure after 20 weeks' gestation, plus proteinuria), positive predictive value is deemed at 20% (Cerdeira et al. 2018). Reference ranges and cut-off points for the diagnosis of preeclampsia using the sFlt-1/PlGF ratio have been documented: ≥ 85 for early preeclampsia (20–33.6 weeks gestation) and ≥ 110 for late preeclampsia (34–36.6 weeks gestation). In addition, a sFlt-1/PlGF ratio of ≤ 33 has been observed to perform well for exclusion of preeclampsia diagnosis (Cerdeira et al. 2018).

Regarding PlGF, cut-off levels for the diagnosis of preeclampsia have been defined as positive when they are below the fifth percentile adjusted for gestational age (<36 pg/ml), with sensitivity of 100% (95% CI 86–100) and specificity of 96% (95% CI 85–99) for early onset preeclampsia (Cerdeira et al. 2018). These biomarkers are important to accurately rule out preeclampsia, given their high negative predictive values. This feature allows for reduction in the number of admissions and/or unnecessary

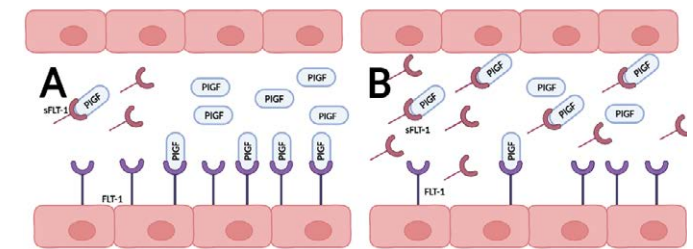


Figure 1. sFlt-1/PlGF ratio in preeclampsia. A) Normal sFlt-1/PlGF ratio: transmembrane FLT-1 receptors (purple) allow signalling of second messengers when stimulated by PlGF (pro-angiogenesis); a ratio of low sFlt-1 to high PlGF is maintained. B) Abnormal sFlt-1/PlGF ratio: high concentrations of sFlt-1 (pink) block second messenger signalling by binding to circulating PlGF (anti-angiogenesis); a ratio of high sFlt-1 to low PlGF is maintained.

interventions, thus permitting a better allocation of resources (Cerdeira et al. 2018).

The determination of these biomarkers is useful for making differential diagnoses of patients with clinical presentations similar to preeclampsia (Cerdeira et al. 2018), some of which are frequent causes of admission to the ICU, such as chronic or acute kidney disease, hypertension, gestational thrombocytopenia, thrombocytopenic purpura, hyperaldosteronism, hyperparathyroidism, pheochromocytoma or paraganglioma, Cushing's syndrome, or obstructive sleep apnoea (Phinder-Puente et al. 2022).

Prediction of Complications

In a retrospective study that included 1,379 patients, it was shown that the levels of lactic dehydrogenase, liver enzymes, and creatinine were directly related to an increase in protein levels in a 24-hour urine collection above 5g. This relationship also includes other data such as HELLP syndrome, preterm birth, and oligohydramnios (Yildiz and Yilmaz 2022); nevertheless, international guidelines have discarded their usefulness in the prediction of adverse perinatal outcomes (Ukah et al. 2017). Furthermore, liver function tests (such as AST, ALT and LDH) have been reported to be moderate predictors of maternal and foetal complications (Ukah et al. 2017).

Corominas and colleagues (2022) demonstrated that a serum uric acid concentration less than 1.5 mg/dl is a useful, accessible, and inexpensive tool for the exclusion of preeclampsia diagnosis during the first trimester of pregnancy, with a high sensitivity. Uric acid levels should be monitored during pregnancy to assist in the identification and prediction of preeclampsia.

During the second half of pregnancy, angiogenic markers appear to be particularly useful in the short-term prediction of potential development of severe forms of the disease such as HELLP syndrome and eclampsia. The PROGNOSIS study (Prediction of Short-Term Outcome in Pregnant Women with Suspected Preeclampsia Study) found that a sFlt-1/PlGF ratio of <38 could rule out preeclampsia in the following 7 days, with a negative predictive value of 99.3% (95% CI 97.9–99.9), sensitivity of 80% (95% CI 51.9–95.7) and specificity of 78.3% (95% CI

74.8–81.7). This high negative predictive value indicates that women with suspected preeclampsia are unlikely to develop this disease, allowing for rationalisation of treatment and promoting patient reassurance (Sroka and Verlohren 2021).

It has been observed that pregnant patients with an elevated sFlt-1/PlGF ratio are prone to developing adverse perinatal events: placental abruption, acute pulmonary oedema, eclampsia, small-for-gestational-age (SGA) newborns, intrauterine growth restriction, hypertransaminasaemia and haematological alterations such as thrombocytopenia. This ratio's performance as a prediction tool of complications is superior compared to elevated blood pressure (Rana et al. 2013).

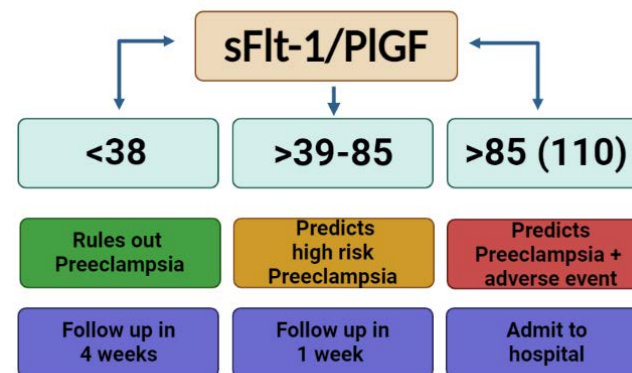


Figure 2. Utility of the sFlt-1/PlGF ratio in clinical practice.

A sFlt-1/PlGF ratio of <38 rules out preeclampsia, with a negative predictive value of 94.3% over 4 weeks. Women with suspected preeclampsia and sFlt-1/PlGF ratio ranging from 38 to 85 should be classified as at high risk for developing preeclampsia. In these patients, a one-week follow-up is suggested, depending on other clinical findings. In women with pregnancies >34 weeks' gestation, the sensitivity and specificity of a sFlt-1/PlGF ratio of ≥ 110 are 58.2% and 95.5%, respectively, being clearly associated with an increase in perinatal adverse events; thus, these patients must be followed up in the hospital (Cerdeira et al. 2018). The stan-

dard use of this ratio increases the risk of early delivery (with a mean of 17 days), in addition to increasing the risk of imminent delivery, although no association of altered sFlt-1/PlGF ratios with development of preterm labour has been found (Sroka and Verlohren 2021) (Figure 2).

Other biomarkers of maternal organ function, such as NT-proBNP, can predict complications such as preeclampsia-related preterm birth (<34 weeks gestation), with a cut-off point of >70 ng/l. If the NT-proBNP value is greater than 219 ng/L, it could surrogate a value similar to the sFlt-1/PlGF ratio for the prediction of early preeclampsia (Stepan et al. 2020; Alvarez-Fernandez et al. 2016).

Low PlGF levels were consistently associated with caesarean delivery due to foetal compromise, as well as with neonatal ICU admission, and foetal death (Alvarez-Fernandez 2016). Although attempts have been made to predict the severity of hypertensive disorders of pregnancy with haematological markers such as neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, platelet distribution width, and aspartate aminotransferase-to-platelet ratio, their clinical significance in the prediction of severe forms of preeclampsia have not been demonstrated yet (Ozkan et al. 2022).

Superimposed Preeclampsia

The sFlt-1/PlGF ratio is higher in patients with preeclampsia compared to women with normal pregnancies or women with chronic hypertension and gestational hypertension. In women with pre-existing chronic hypertension, when this ratio is higher, it accurately predicts which patients will develop preeclampsia (mainly early preeclampsia) (Stepan et al. 2020). Some authors have recognised that there is an economic impact with the use of biomarkers in preeclampsia, especially in patients at high risk for developing the disease; in this regard, there is currently no evidence for endorsement of the universal use of these biomarkers (Cerdeira et al. 2018). In women with chronic kidney disease and chronic hypertension, PlGF levels <12 pg/mL identified superimposed preeclampsia requiring delivery within the next 14 days. Importantly, PlGF levels were similar between healthy controls and women with chronic kidney disease who did not

develop superimposed preeclampsia (Bramham et al. 2016).

Potential Interventions

In a pilot study, Thadhani and colleagues (2016) used an extracorporeal apheresis system to remove sFlt-1 from the maternal circulation of women with preeclampsia, which was safe and prolonged pregnancy up to 15 days.

Conclusions

Preeclampsia is a complex syndrome whose complications bear an impact on perinatal morbidity and mortality. Angiogenic biomarkers may significantly impact both the decision to admit patients and risk stratification and may also help guide patient management and level of care. From the study of these biomarkers, it can be concluded that the classic definition of preeclampsia (de

Angiogenic Factors	Clinical Parameter	Adverse Pregnancy Outcome
>sFlt-1/PlGF or <PlGF alone	Hypertension	Preeclampsia**
>sFlt-1/PlGF	Seizure	Eclampsia
	Liver enzymes/platelets/LDH/epigastric pain	HELLP syndrome
	Chronic hypertension / chronic kidney disease	Superimposed preeclampsia
	Ultrasonography	Foetal growth restriction

Table 3. Redefinition of preeclampsia syndrome, including angiogenic biomarkers.

** It has been suggested to update the definition of preeclampsia as follows: Heterogeneous maternal syndrome characterised by hypertension + de novo imbalance in angiogenic biomarkers (Stepan et al. 2020).

novo hypertension plus proteinuria after 20 weeks' gestation) is outdated and is mainly based on historically described clinical conditions that precede eclamptic seizures. This vision has a low predictive value for defining such a heterogeneous pregnancy disorder with potential for multi-organ damage (Table 3).

Conflict of Interest

None. ■

Abbreviations

sFlt-1:	Soluble fms-like tyrosine kinase-1
sEng:	Soluble endoglin
TGF-β:	Transforming growth factor beta
PAAP-A:	Pregnancy-associated plasma protein-A
AFP:	Alpha-fetoprotein

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Introduction

Catalonia is one of the autonomous communities of northern Spain. It has a surface area of 32,114 m² and a population of 7,747,709 inhabitants. The Emergency Medical System (known in Spanish as the Sistema de Emergencias Médicas, SEM) is part of CatSalut, the Catalan Health Service, and is the public entity that provides support services for medical emergencies in the

The Role of the Paediatrician in the Coordination Centre

Since 2017, the Medical Emergency System of Catalonia has included a paediatrician specialised in critical care at its coordination centre. Their duties are to manage the coordination of interhospital transfers and provide telephone support for paediatric and neonatal emergencies. Here we present our experience and the challenges that we have encountered.

region. As of 1995, it has two advanced life support ground units that are specialised in paediatric and neonatal transport, located at the Vall d'Hebron University Hospital and the Sant Joan de Déu University Hospital, which operate 24 hours a day, 365 days a year. It also has a specialised paediatric and neonatal aerial unit that is operated by personnel from the Parc Taulí and Santa Creu i Sant Pau university hospitals in Sabadell and Barcelona respectively, plus a nurse paediatric basic life support unit during the winter months. The team is composed of more than 60 professionals, including paediatricians and nurses with training in paediatric and neonatal care and medical emergency technicians specialised in paediatrics.

Since the creation of the paediatric SEM, more than 30,000 children have been transferred, among which approximately 40% were neonates. Around 95% of the activity corresponds to interhospital transfers, involving the stabilisation and transfer of critically ill or injured children to receiving hospitals that can handle their level of complexity. As of several years ago, these teams also respond to incidents in homes, public areas, and primary care centres when they are required to accompany the regional intermediate or advanced life support units. Since 2019, these units can also transfer critically ill patients who are connected to ECMO devices.

The paediatric SEM's activity is managed from the SEM coordination centre, who receives the request for patient transfer, coordinates the transfer to the appropriate hospital centre, and

assigns the proper health transport resource.

The Paediatrician as Part of the SEM Coordination Centre

Up to 2017, the activity of the paediatric SEM was managed by SEM professionals from the coordination centre who were not specialised in paediatrics. That year, the SEM Health Coordination Centre began having a paediatric physician on call 24 hours a day, 365 days a year. Since then, that role has become key for coordinating resources, providing both telephone support for healthcare teams in the region and guidance in paediatric emergencies.

This task is carried out by the same paediatricians who are part of the aforementioned paediatric advanced life support units. Thus, they are knowledgeable not only about serious medical conditions, but also about the particularities of initial medical attention outside of health centres and transport. This new facet of their work has been a challenge for these professionals, who up to then had provided only on-site medical support.

Tasks of the Paediatrician in the Coordination Centre

1. Managing interhospital transfers: coordination and assessment

Initially, they directly managed the transfers for patients ≤ 6 years of age and provided support for the interhospital transfer team for patients > 6 years of age. They now currently manage transfers for patients < 16 years of age.

When a call comes in from a health centre for the transfer of

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Images of the paediatrician in the coordination centre of the Medical Emergency System of Catalonia

a paediatric or neonatal patient, it will firstly be routed to a call centre operator who will request the basic information needed. Next, it will be immediately transferred to the coordinating paediatrician, who will evaluate the patient's situation, assess the possible additional treatment measures, and decide on the most appropriate destination centre and transportation resource. It is worth noting that the transport may not always be performed by a paediatric unit, depending on the availability, coordination, and time dependence of the medical condition.

2. Telephone support for emergencies

The other function of the coordinating paediatrician is to provide support for consultations that may require specialised care due to their complexity and severity. These may be:

- Calls made by citizens which have first been screened by professional call managers (non-paediatric physicians or nurses). These are usually calls flagged by the system as high priority (Priority 0), where the reason for the call is a serious situation, such as unconsciousness, severe breathing difficulty, and/or other life-threatening circumstances.
- Consultations from SEM healthcare teams caring for paediatric patients or other professionals from healthcare centres.

In all of these cases, we collaborate with other members of

the coordination centre to send, if necessary, the proper resource as determined by the evaluation made.

How the Paediatrician Collaborates From the Coordination Centre in Paediatric and Neonatal Emergencies

The fact that paediatricians with specific training in paediatric and neonatal emergencies and critical care can remotely assess the initial stabilisation of these patients provides an additional point of support from the healthcare system. In the execution of these tasks, the information transferred is the fundamental element.

With respect to the information on the patient's clinical situation, some basic, structured information on the physical examination and vital signs is requested, in addition to that regarding the treatments and additional diagnostic tests already performed. This information is used to evaluate the situation and enable the professionals to suggest additional measures (whether treatment-related or diagnostic), if any are needed. If, due to the patient's condition, the coordinating paediatrician decides to immediately send one of the paediatric ground units, they will alert the sending centre and offer them guidance. The ground unit

will then also contact the sending centre directly to determine the patient's situation and be able to suggest measures that will continue following their arrival.

This bi-directional and regulated communication in emergency situations will always be systematic (following the ABCDE sequence), concise, objective (using scores, particular vital signs, etc.), specific (i.e. specifying the units of the analytical parameters), and cross-checked when sensitive information is being sent (meaning that it should be repeated by the other person to ensure that the information was correctly understood, i.e. for a dose of medication).

Later, if the patient does indeed need to be transferred, the proper healthcare resource will be chosen after carefully considering different factors. These factors are mainly:

- Clinical condition of the patient and their current and/or foreseeable needs: For example, a stable patient for whom advanced lifesaving measures are not foreseen to be needed in the next few hours can be transferred by conventional means (transport technicians); this also applies to term neonates who present good thermoregulation and whose weight is > 2.5 kg.

- Availability of resources: It should be kept in mind that the paediatric units cover all of Catalonia and Andorra. If the units are busy or response times are very long, it will be necessary to propose to the centre sending the patient that a non-paediatric transport unit be used, justifying the reason for this.
- Time dependence: When faced with certain medical conditions for which it is completely impossible for the centre of origin to offer the treatment needed, the fastest resource should be chosen, as long as it is possible to ensure the stabilisation of the patient prior to and during the transport. Lastly, the coordinating paediatrician will select the receiving centre according to the needs they feel that patient has, taking into consideration the information given and the availability of each centre. If possible, they will also consider the preferences of the centre of origin and how close the family lives. For some medical conditions, the distribution guidelines established by CatSalut will be followed.

How Much Activity Have the Paediatricians at the Coordination Centre Had Since 2017?

Since 2017, when these paediatricians started to work at the coordination centre, more than 175,956 interhospital transfers have been handled, of which 7,806 were neonatal transfers and 16,469 were paediatric transfers (4.4% and 9.35% of the total transfers, respectively). Managing transfers for paediatric patients has been done by the coordinating paediatrician, along with the professionals who were in charge of this function before 2017 (non-paediatric physicians and nurses). The most frequent reasons for transfer were respiratory pathologies, infectious pathologies, and being born premature. **Figure 1** shows the transfers per year and in it we can observe a decrease in paediatric activity

that coincides with the SARS-CoV-2 pandemic. Less paediatric pathologies were recorded during this time, a phenomenon which is already well known.

As regards telephone support for paediatric consultations, between 2017 and 2021 more than 642,761 calls were taken. Of these, 25,775 (4%) were flagged as Priority 0. They were sent to the coordinating paediatrician and the other consultation, medical, and nursing professionals.

Future Challenges

The SEM, in collaboration with the paediatric units, has identified several challenges in its efforts to provide more efficient patient care and management and adapt to the new needs of the system.

- Protocolisation of the management of calls flagged as Priority 0, to avoid both the coordinating paediatrician having to take non-emergency calls and them not receiving these emergency calls at all.

- Direct participation in the paediatric palliative care network, helping to cover its transfer needs.
- Definitively establishing a telemedicine programme using a videoconferencing platform to be able to evaluate patients with the aid of real-time images.
- Better guidance for the centres sending patients and better management of the distribution of patients requiring transport, with full information on the resources available at each centre for paediatric or neonatal care.
- Homogenisation of the initial support, regardless of the patient's location in the region.

Conclusion

The role of the paediatrician at the coordination centre is becoming increasingly important within the SEM as a professional specialised in paediatric and neonatal critical care. These physicians not only assess the initial stabilisation of this kind of patient, whether at a private home or at healthcare centres, they also play an essential role in managing the resources of the Catalan healthcare system, as regards both transportation units and the centres receiving patients. Overall, the general opinion of these last 5 years is very positive, with the service being well-perceived by the professionals using it. The fact that the coordinating paediatricians are the same professionals that work in the specialised advanced support units has improved territorial equality in patient care and fostered a model focused on the child and their family.

Conflict of Interest

None. ■

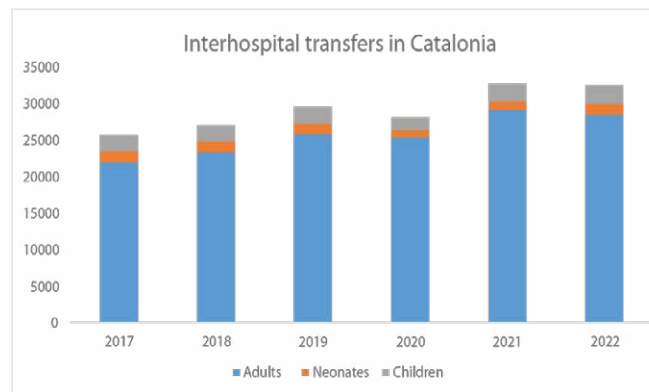


Figure 1. Interhospital transfers in Catalonia



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As the COVID-19 pandemic hit mankind, many healthcare systems worldwide faced a widely unprecedented shortage of personnel, pharmaceuticals, equipment and/or protective gear. Subsequently, many scientific societies developed and promulgated guidelines for managing the respective scarcities properly within their realms. Despite a noteworthy yet conceivable variability between these guidelines, a few principles matched widely (Meier 2022; Sarmiento et al. 2022; White and Lo 2021; Dufner 2021; White and Lo 2020; Sprung et al. 2020; Jöbges and Biller-Andorno 2020), namely:

- Treating patients equally and individually;
- Maximising the benefits achievable under the circumstances prevailing, mostly as maximising the number of lives saved;
- Giving priority to patients with the best odds of success (whereby the parameters to determine the odds included but were not limited to medical history, comorbidities, frailty, and the present health status at admission).

Other principles, such as giving priority to healthcare workers or mitigating structural health inequities, were not met with the same common approval. It was evident, though, that the usual deontological focus of care had to be switched to a utilitarian

New German Law: Ex-post Triage Criminalised

What will be the consequences of the new German law of criminalising ex-post triage? Will it result in more legal disputes, ethical dilemmas and preventable deaths? Or will it achieve its goal?

approach in times of scarcity.

At the same time, most guidelines – including the German one (Marckmann et al. 2020) – stated explicitly that certain personal characteristics were not to be considered with regard to the allocation of scarce resources, particularly sex, ethnicity, (chronological) age, religious affiliation, disabilities, solvency, and the alleged social value.

most guidelines stated that personal characteristics were not to be considered with regard to the allocation of scarce resources, particularly sex, ethnicity, (chronological) age, religious affiliation, disabilities, solvency, and the alleged social value

However, German leagues of persons with disabilities challenged the German guidelines, unanimously adopted by eight German specialist societies, before the German Supreme Court, the “*Bundesverfassungsgericht*”. The Court stated that the rights of persons with disabilities might be violated by the guidelines and ruled that the German parliament pass a law to preserve the rights of persons with disabilities and prevent their being disadvantaged to a sufficiently effective degree (1 BvR 1541/20, December 16, 2021).

The German parliament has recently pulled off this new law (§ 5c IfSG, in the version dated December 20, 2022), which has

been integrated into the national Infectious Diseases Protection Act, “*Infektionsschutzgesetz*”. The new law is remarkable at least for three stipulations, namely:

1. Ex-post triage is explicitly criminalised;
2. The allocation of scarce resources must refer to the patients’ short-term survival. At the same time, some factors in assessing the odds of short-term survival are forbidden to use.
3. The decision-making process as to the allocation of scarce resources must include “experts” regarding (all) comorbidities and/or disabilities that the patient concerned is suffering from (independent of his/her present health status).

First, to better assess the benefit of life-sustaining, yet at times scarce treatment modalities, treatment in an emergency room or intensive care unit is worth trying for a certain period agreed upon beforehand. Such time-limited trials are an appropriate means to better understand the course of disease in individual patients, elucidate a patient’s wishes and values, and reduce the prognostic uncertainty as to survival (Vink et al. 2018). If the status of the patient concerned does not improve during the trial period agreed upon, the therapeutic goal is regularly changed from cure to comfort, and life-sustaining therapies are limited. Criminalising the implementation of this procedure, coined “ex-post triage”, will *de facto* install a first-come-first-served rule for prioritisation and lead to more preventable deaths (Bartenschläger et al. 2022), as patients with better odds will be denied life-sustaining resources in favour of others already treated with them, however with worse odds. This rule will also affect patients with disabilities, whose representatives had challenged the guidelines in the first place.

Second, the new law states that allocation decisions may only

concern the odds of short-term survival. However, several factors that clearly influence it, such as (physiologic) age, disabilities, or frailty, may not be used for its assessment. This is a *contradictio in terminis*.

Third, the need to summon a potentially great number of (perhaps self-appointed) experts prior to an urgent decision regarding the allocation of scarce resources is a cloistered regulation allegedly typical for unabashed parliamentarians.

Formally, the new law only applies to scarcity situations regarding communicable diseases and has therefore been integrated into the national Infectious Diseases Protection Act. However, the criminalisation of ex-post triage might be transferred to other scenarios using a conclusion by analogy. Then, in fact, Germany would side with Israel in this respect, where physicians are

forbidden to withdraw life-sustaining therapies (Steinberg and

the new law will result in what it was meant to prevent: more legal disputes, more ethical dilemmas and more preventable deaths

Sprung 2006). Besides, Germany would be one of the very few countries explicitly installing a first-come-first-served rule for the allocation of scarce resources – in fact, not only in intensive

care units.

In summary, the new law will result in what it was meant to prevent: more legal disputes, more ethical dilemmas, and, most alarmingly, more preventable deaths. Physicians will shun from making proportionate decisions as to the extent of treatment for fear of legal repercussions and laymen's pressure. For the sake of their professional integrity, though, physicians should firmly uphold the right to their own professional judgement – also in times of scarcity.

Conflict of Interest

None. ■

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From the Other Side: Humanising Critical Medicine

Support in intensive care has undergone unprecedented development, with proven technology and protocols, but at the same time, it constitutes an environment that often makes empathy and humanisation difficult. This article reviews current concepts of care for critically ill patients from the point of view of health providers who were also patients in some circumstances.

Introduction

Being a patient in an intensive care unit (ICU) can represent one of the most painful experiences a human being can endure. Several reports mention that post-ICU survivors remember this period as the most unpleasant of their lives. On the other hand, there are reports that intensivists are not trained to mitigate patient pain or family grief, so this support requires a different skill set. This is how Curtis et al. affirm that this set of skills does not receive the appropriate attention by the intensivists (López et al. 2018).

Support in intensive care has undergone unprecedented development, with proven technology and protocols, but at the same time, it constitutes an environment that often makes empathy and humanisation difficult. Effective empathy implies being vulnerable to the grief and tragedy experienced by patients and their families without losing objectivity and rationality in effective work with all patients. It is important to address the current status of humanisation. Many successful interventions in the patient's condition are applied without considering the patient's comfort, generating an incorrect perception in the patient or their family of the care received. This article reviews current concepts of care for critically ill patients from the point of view of health providers who were also patients in some circumstances.

Subjection

The systematic use of restraint should be avoided. This measure generates a greater risk of delirium and can cause nerve and muscle injuries, ulcerations and scars, even with psychological sequelae.

Reduce the use of restraint, and avoid violating the welfare of patients. Patients who remained in the ICU with restraint report that the worst memories of their stay were caused by the physical and psychological suffering generated (Iglesias et al. 2012).

Body grooming

The cleaning of patients represents one of the most common care, but it involves friction of the skin, which could cause skin lesions and consequently more pain. The fragility of the skin of critically ill patients should be considered, and alternatives should be available, for example, wet towels with chlorhexidine, which have been used to reduce the inconveniences of friction and drying (Díaz and Turégano 2019). It is advisable to discuss with the patient their wishes and preferences, and personal hygiene should be carried out at a time that does not interrupt night-time sleep or interferes with other nursing activities. It is not clear whether chlorhexidine body wash decreases the risk of nosocomial infections, length of stay in the ICU, or mortality (Lewis et al. 2019); therefore, its use cannot be generally recommended.

Noise, Light and Infrastructure

These are factors that can alter comfort, rest, and sleep, having a negative impact on physical, psychological and behavioural aspects. Sound level monitoring strategies should be implemented, such as adjusting the volume of alarms differentially day or night, using earplugs during rest hours, and trying to maintain environmental comfort, avoiding loud voice tones (Ruidiaz and Fernández 2020).

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The World Health Organization suggests maintaining up to 45 dB during the day and 35 dB at night. It should be considered that keeping units closed generates unpleasant periods of anguish and anxiety in such a way that following the European Regulations for interior lighting, it is recommended to maintain lighting with light levels between 100-1,000 lux during the day and 20 lux at night. Infrastructure designs with windows with access to natural light and individual cubicles are suggested (Heras 2017).

Environmental temperature

In the daily routine of the units, the physical environment is often not considered even though it is a determining factor in the recovery of patients. A large number of patients report that they feel cold, regardless of the environmental temperature, probably in relation to metabolic, haemodynamic disorders, and medication, among others, so adequate shelter should be sought (Ferrer et al. 2021). It is essential for the ICU to offer safety and comfort to the patient from the environment. It has been recommended that the humidity be between 50% to 60% and the temperature between 22°C and 24°C (Gomes 2003). Maintaining these levels helps to avoid the negative effects of hypothermia. It is essential that the patient can have their space and privacy.

Dream

The rest period and especially the night sleep of patients are usually altered during their stay in the ICU. It can be altered by the sequence of scheduled care, such as internal transfers, x-rays,

bathing, or position changes. These measures must be appropriate to the patient's needs and, if possible, agree on the most suitable time to perform them. Sleep disruption could lead to disturbances in cognition, respiratory, immune, metabolic function, anxiety, and pain and be a risk factor for delirium. Simple interventions to promote ICU patient sleep could be reducing noise at night, developing protocols for exposure to day and night light favouring relaxation techniques such as music therapy, and reviewing the use of corticosteroids and beta-blockers that reduce the efficacy of sleep. Ventilatory strategies that promote sleep should also be considered as pressure support (Bosma et al. 2007).

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Chest x-ray

Chest radiography is a daily element in the units for the comprehensive evaluation of the patient and the evolutionary follow-up of the patient's clinical situation (Chico et al. 2011). However, it entails numerous dangers to which the patient is subjected as mobilisation in clinical states of cardiovascular or respiratory liability, exposure to ionising radiation and even risk from a cost-benefit perspective. For this reason, it is recommended that pulmonary imaging control in patients under mechanical ventilatory support and/or cardiopulmonary diseases be individualised with a periodicity according to their clinical condition and evolutionary status (Graat et al. 2005). Anstey et al. (2014), in their proposal for high-value care in the ICU, propose to personalise the studies, avoiding unnecessary routines and repetitions of imaging and laboratory studies. Ultrasonography may be a more frequent follow-up alternative.

Secretion of aspirations

Abundant secretions represent one of the biggest problems when

assisting a critically ill patient, for which reason they suffer continuous trauma that causes discomfort, pain, and stimulation of cough reflexes with invasive ventilatory decoupling. We recommend the incorporation of mechanical respiratory physiotherapy techniques, such as patient mobilisation, posture changes, breathing exercises, cough stimulation and even measures that increase expiratory volume such as continuous positive airway pressure (CPAP) among others (Arias et al. 2022).

Thirst

Another condition that constitutes a stressful factor for the ICU patient may be secondary to common disorders such as hypernatraemia, hyperglycaemia, or the patient's inability to drink fluids, and may be present in up to 23% of patients. This condition is common in patients with negative fluid balance; therefore, attention should be paid to maintaining the moisture of the mouth and lips, providing a lip moisturiser, and assessing the contribution of ice water (Lana et al. 2018).

Pain

This sensation should be objectified through scales since it is common for the intensity of pain to be underestimated. Strategies that suggest its level should be evaluated for patients who can communicate using a visual or numeric analogue scale. In the case of patients without communication skills, the Behavioural Pain Scale can be considered. In addition, the eCASH (early comfort using analgesia, minimal sedatives) protocol described by Dr Vincent can be an alternative to optimise our humanised care, prioritising effective pain relief through multimodal analgesia, minimising the use of opioids and benzodiazepines (Vincent et al. 2016).

There are vascular lesions related to the administration of fluids and intravenous medication, so the FDA (Food and Drug Administration) has described at least 250 types of mechanical and infectious complications (Mermel et al. 2001) that cause pain in patients. Therefore, multiple punctures for taking laboratory tests should be avoided. Thus, the American Thoracic Society has suggested the placement of an intra-arterial catheter if more than three arterial gas samples are necessary.

Similarly, routine vascular device and dressing changes should

be avoided if there is no evidence of contamination (Rickard et al. 2021).

The use of ultrasound prevents bloody procedures from becoming recurrent and prevents the appearance of complications such as bruising, reduces channelling times and increases the success rate and safety (Agencia de Evaluación de Tecnologías Sanitarias de Andalucía 2014).

Position changes constitute common episodes of pain and stress with the associated immediate physiological consequences of vasoconstriction, glycaemic imbalance, and increased oxygen consumption. A simple way described to identify this degree of stress could be the perfusion index of the oximeter, which could suggest the need to deepen the analgesia of the patient who is sedated (Hasanin et al. 2017), although it is not a validated method.

Delirium

It has been described as altered consciousness with fluctuations in attention. The patient describes it as incongruous, unreal thoughts with hallucinations. In addition to producing a longer stay in the ICU, it generates post-traumatic stress, so risk factors must be quickly identified in addition to promoting early mobilisation and exercise, stimulating night sleep, restarting basic psychiatric medication, and avoiding the use of benzodiazepines (Alvarez et al. 2022). Distraction is important, so the patient's tastes, contact with the family, and walks outside the unit must be taken into account since they comfort and reassure the patient.

Anguish

Being a hospitalised ICU patient can generate emotional reactions such as anxiety, anguish, depression, or the well-known

post-intensive care syndrome caused by noise, external light that inhibit sleep, or difficulty in patient communication due to the use of mechanical ventilation. In addition, the stay in the critical unit is a negative experience, with the suffering of the individual due to an environment without privacy (Beltran et al. 2009), with an architectural structure that favours the loss of privacy, and a doctor-patient relationship that is not different, provoking a painful, and complex situation to resist. We must find ways to distract the patient by installing musical threads, audio devices, and televisions or resources that allow the patient to connect with the outside without putting their health at risk.

■ ■ we must aim to integrate each ICU into the project of humanisation through multidisciplinary management ■ ■

Weakness

It favours the loss of autonomy of the patient and generates the feeling of entrapment, so early mobilisation should be sought, avoiding the prolonged use of muscle blockers; the guidelines suggest limiting their use to up to 72 hours (Jarrin et al. 2022). In addition, care must be taken to administer early and adequate nutritional therapy in order to avoid sarcopenia and weakness, which commonly appear early in critically ill patients.

Family Grief

We often exclude ourselves from family pain without considering that a principle of care is to maintain patience and the will

to provide emotional support to the family. The patient is in a critical situation, and their family requires bio-psychosocial monitoring. We must aim to integrate each ICU into the project of humanisation of intensive care units through multidisciplinary management and to place the patient and their family as the centre of all care with strategic lines such as open-door ICUs, with the participation and presence of family members involved in their care (Baeza et al. 2020).

Conclusion

Taking care of the invisible is important, since many patients feel that during their stay in the unit, they lose their dignity due to the loss of empathy from healthcare personnel, who do not recognise the importance of physical and psychological comfort. Efforts should be made to take care of the patient's privacy, safeguarding it and stimulating permanent family accompaniment to avoid the uncertainty that the patient may feel. It has been clearly established that the most stressful factors for the ICU patient are the lack of privacy, moaning, and disorientation. For this reason, humanisation strategies must be established, which promote communication between the staff and the patient and family members. Therefore it can be reinforced and improved through the use of electronic whiteboards and video calls. Assertive strategies have been described through active listening and empathy, such as a fluid dialogue. Furthermore, an attentive look generates a trusting relationship (Evangelista et al. 2016).

Conflict of Interest

None. ■

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COVER STORY: ORGAN SUPPORT

Multiple organ failure occurs in critically ill patients and is associated with high mortality. In this issue, our contributors discuss progress in management of multiorgan failure and different forms of organ support and treatment strategies for liver failure, acute kidney injury, respiratory failure and cardiac failure.



COVER STORY: GREENER ICU

Climate change is an important issue that needs to be addressed. The process of transitioning to a greener intensive care unit can be challenging. In this issue, our contributors discuss strategies on how critical care can reduce its environmental impact and aspects related to research, education and clinical practice and attaining environmentally-sustainable anaesthesia and critical care.

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