Adrenomedullin and MR-proADM:
The key mediator in sepsis

Plays a central role in the hyperdynamic and immunosuppressive phases of sepsis • Increased levels in accordance with severity of disease • Rapid rise in response to a bacterial infection • Highlights the risk of developing nosocomial infections and the need for vasopressor treatment • Accurately predicts mortality risk and organ failure in both adults and pediatrics
Sepsis, severe sepsis, and septic shock are the increasingly severe stages of an uncontrolled, systemic inflammatory host response to a bloodstream infection, whilst the standard host response to a non-infectious insult is commonly known as SIRS (systemic inflammatory response syndrome)\(^1,2\). The increasing severity and progression to septic shock is not thought to be a linear development\(^2\); on the contrary, sepsis can be viewed as a pathophysiological process rather than a specific syndrome\(^3\), where approximately 9\% of patients with sepsis progress to severe sepsis, and 3\% progress to septic shock\(^4\).

Studies have shown the most common sites of infection to include the lungs (68\%), abdomen (22\%), blood (20\%) and urinary tract (14\%)\(^5\), with organs such as the lungs (18\%), kidneys (15\%) and the cardiovascular system (7\%)\(^6\) contributing towards multiple organ dysfunction and failure, and ultimately death, in over 65\% of cases\(^5,6\).

However, despite significant improvements in diagnosis, treatment, care, and preventative measures, the incidence of sepsis continues to increase by as much as 8.7\% per year\(^6\). During the early stages of infection, proper triage, management, and disposition of patients are associated with improved outcomes\(^7\), and the early identification of patients at a high risk of cardiovascular and organ dysfunction can lead to a reduction in the number of clinical complications and overall mortality\(^8\).

It is therefore of extreme importance to accurately diagnose and determine the risk of septic progression at the earliest opportunity, and in this respect, the blood biomarker, adrenomedullin, plays a key role.

### Adrenomedullin: a key mediator

- Up-regulated by LPS and pro-inflammatory cytokines (including TNF-\(\alpha\) and IL-1\(\beta\))\(^9,12\)
- Potent anti-microbial actions, through membrane channel formation and lysis, and anti-apoptotic properties\(^13,16\)
- Enhanced or modified activity via interaction with complement factor H\(^17,20\)
- Significant role in cellular growth, development, chemotaxis and migration\(^21,26\)
Adrenomedullin plays a central role in initiating the inflammatory response observed in the early stages of septic onset, as well as in its progression from sepsis to septic shock. Accordingly, levels of its more stable precursor, MR-proADM, have been shown to be rapidly elevated in response to bacterial infection, and to strongly correlate with increasing disease severity.

However, its main strength lies in its ability to accurately and rapidly assess the immediate risk of the septic infection to a patient’s health, by highlighting any additional complications caused by the original infection, and by providing an accurate short- to mid-term mortality risk in both adults and pediatrics. To that end, specific cut-off values for sepsis, severe sepsis and septic shock (figure 1) have been established in order to make risk assessment more accurate and faster to determine.

Figure 1: Established MR-proADM cut-offs in adults for different septic severity levels.
The early pro-inflammatory, hyperdynamic response

The early phase of sepsis results from either a severe infection and/or large-scale tissue damage, resulting in an excessive activation of the host immune system. Thus, responses that are normally beneficial for fighting infections are turned into a multitude of excessive, damaging pro-inflammatory stimuli.

It has been proposed that increased adrenomedullin production plays a pivotal role in initiating the pro-inflammatory, hyperdynamic response in sepsis\(^{12, 27, 28}\), where key inflammatory cytokines such as TNF-\(\alpha\) and IL-1\(\beta\), in addition to bacterial endotoxin, strongly stimulate its synthesis and secretion\(^{11, 29, 30}\); predominantly from endothelial\(^{31}\) and vascular smooth muscle cells\(^{29}\), but also from the small intestine, which has been shown to be a major source of production during polymicrobial sepsis\(^{32}\).

The vasodilatory properties of adrenomedullin are of significant importance during the pathophysiology of sepsis, and can be initiated by either a direct effect on vascular smooth muscle cells to increase cyclic AMP production\(^{33}\), or an indirect effect on vascular endothelial cell nitric oxide production\(^{34}\). Consequently, increased adrenomedullin levels can lead to decreased vascular resistance and significantly increased microvascular blood flow in the liver, small intestine, kidney and spleen\(^{12}\), which can be crucial in maintaining blood flow to individual organs in need. Indeed, studies have shown specific adrenomedullin binding sites on many organs, including the intestine, heart, lungs, spleen and liver\(^{35}\), and increased circulatory adrenomedullin levels have been shown to increase heart rate, cardiac output and stroke volume, similar to characteristics of the hyperdyanamic stage of sepsis itself.

Adrenomedullin: vasodilation is key

- Key mediator of vascular tone regulation resulting in an intense, prolonged vasorelaxation and hypotension\(^{37, 38-40}\).
- Widespread production helps maintain blood supply to individual organs\(^{31, 38, 41}\).
- Localized cellular production and release to meet specific perfusion requirements of individual organs\(^{19, 42}\).
- Significant role in hemorrhagic and endotoxic shock\(^{43-45}\), pulmonary hypertension\(^{46}\), hypertrophy\(^{47, 48}\), hypoxia\(^{49-54}\), oxidative stress\(^{55}\), ischaemic myocardial injury\(^{56-58}\) and ischaemic injury and organ failure\(^{60, 61}\).
The late immunosuppressive response

The failure of numerous anti-inflammatory therapies raises the question of whether mortality in sepsis actually derives from the uncontrolled, pro-inflammatory response. Indeed, while some patients die during this phase, many succumb at later time points that are associated with a prolonged immunosuppressive state.

Whilst adrenomedullin levels remain elevated during the late immunosuppressive stage\textsuperscript{62}, potentially due to diminished clearance by the lungs\textsuperscript{63}, studies have indicated that vascular endothelial cell function, which is responsible for a significant proportion of adrenomedullin production, is depressed\textsuperscript{64}, can undergo apoptosis due to increased pro-inflammatory mediator levels, and may be partially detached from the base membrane\textsuperscript{65}, thus playing an important role in any subsequent development of multiple organ failure\textsuperscript{66, 67}.

However, the defining characteristic of the immunosuppressive stage is a reduced vascular responsiveness and immune paralysis, and thus, adrenomedullin is thought to play a significant role in the transition between the early, hyperdynamic phase, and the late, immunosuppressive phase\textsuperscript{12}.

Indeed, vascular responsiveness to adrenomedullin is decreased at both the macro- and microcirculatory levels during the immunosuppressive stage, despite up-regulated adrenomedullin levels, and this reduction can lead to a deterioration in haemodynamics and provide the stimulus for the transition between the hyperdynamic and immunosuppressive stages\textsuperscript{68}. It is also thought that alterations and disruptions in membrane bound adrenomedullin receptors, signal transduction, adenylate cyclase sensitization\textsuperscript{69}, the down-regulation of adrenomedullin binding sites, the internalization of adrenomedullin receptors or in a decrease in adrenomedullin binding proteins may play a role in altering adrenomedullin activity at this stage\textsuperscript{70}.

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Adrenomedullin: key role in organ protection

- Use as a marker for the early prediction of organ dysfunction and outcome\textsuperscript{71}
- Protects against endothelial permeability and consequent organ damage\textsuperscript{72-74}
- Protective effects in organs in response to bacterial induced shock\textsuperscript{75, 76}
- Stabilization of microcirculation in inflammation - a hallmark of organ failure\textsuperscript{77}
- Restoration of endothelial stability in infected organs due to prevention of undesired inflammatory decompartmentalization\textsuperscript{78}
MR-proADM: A rapid response to bacterial infection and disease severity

Extremely rapid response to LPS stimulation

In order to start prompt and appropriate treatment, it is crucial to make an accurate diagnosis and risk assessment as quickly as possible\textsuperscript{79}. MR-proADM levels have been shown to be rapidly elevated immediately after the administration of LPS, reaching significantly increased levels after only 2 hours\textsuperscript{30, 80} (figure 2a) and almost doubling in concentration\textsuperscript{80}. Concentrations were found to subsequently peak at 4 hours\textsuperscript{30, 80} before decreasing. No increases in PCT, on the other hand, can be found up to 2 hours after LPS stimulation, with the earliest increases becoming apparent at 4 hours\textsuperscript{80, 81} (figure 2b). In contrast to MR-proADM, peak PCT concentrations were subsequently observed at 24 hours\textsuperscript{80, 81}.

Thus, the differing time courses for MR-proADM and PCT production may be of significant clinical interest, especially in post operative ICU patients, in order to determine the onset of infection at the earliest possible opportunity using MR-proADM, and subsequently guide antibiotic administration using PCT.

Figure 2a and 2b: Significant increases in MR-proADM levels can be observed 2 hours after a single LPS injection (4 ng/kg IV), as opposed to 4 hours in the case of PCT (adapted from de Kruif et al. 2008)\textsuperscript{80}.
Increasing MR-proADM levels correlate to disease severity

In critically ill patients on admission, studies have shown there to be a stepwise increase in MR-proADM levels, from patients without infection (SIRS) to patients with sepsis, severe sepsis and septic shock (figure 3a). Furthermore, a clear separation can be observed between SIRS and septic patients (figure 3b).

Figure 3a and 3b: Levels of MR-proADM in critically ill patients on ICU admission, grouped according to the severity of disease. Squares donate median values and whiskers indicate 25th and 75th percentiles. Non-infectious SIRS and sepsis are clearly distinguishable with significantly different MR-proADM levels.
MR-proADM and Pediatrics: Mortality risk scores and organ failure

Enhanced sensitivity and specificity

The availability of accurate tools to rapidly assess the risk of critically ill children on admission, or during the first 24 hours, to the Pediatric Intensive Care Unit (PICU) is of critical importance. Commonly used tools include the Pediatric Risk of Mortality (PRISM III), the Pediatric Index of Mortality (PIM 2)$^{84-88}$ and the Pediatric Logistic Organ Dysfunction (PELOD) scores, however, whilst these tools can be useful in predicting the evolution of a wide group of patients, their utility with regards to individual patients appears to be limited, complex to determine, and more suited to an audit and research environment rather than in clinical decision making.$^{85, 87, 88}$

The availability of a rapid and accurate biomarker test, therefore, to provide similar or improved risk assessment values, can greatly aid clinical decision making and earlier treatment intervention. A study by Rey et al. (2013)$^{83}$ separated 254 pediatric admissions into mortality risk and organ failure groups, and found that CRP, PCT and MR-proADM values were increased in patients with a higher mortality risk, and in those with more than one organ failure. However, MR-proADM clearly had greater sensitivity and specificity for both mortality risk and organ failure (table 1).

Table 1: Sensitivity and specificity values of MR-proADM, PCT and CRP in PICU mortality risk and organ failure groups.
Enhanced mortality and organ failure predictions

An analysis of AUC values for mortality risk scores and organ failure (table 2) show extremely high values for MR-proADM (overall AUCs of 0.866 and 0.922 respectively). This is also the case for mortality risk scores in the presence of an infection (AUC of 0.869), and organ failure scores in both the presence and absence of an infection (AUCs of 0.943 and 0.901 respectively).

Accordingly, this highlights the strength of MR-proADM in both predicting the risk of developing organ failure and mortality in pediatrics.

Table 2: AUC values for MR-proADM, PCT and CRP for mortality risk groups (total sample and with an infection) and organ failure groups (total sample, with and without an infection).
Adrenomedullin: More accurate prediction of adverse effects and nosocomial infections

Vasopressors are a powerful class of drugs that induce vasoconstriction, and thereby elevate mean arterial pressure (MAP). These drugs are particularly useful in patients suffering from septic shock, who exhibit a sepsis-induced hypotension which is not reversed with adequate fluid resuscitation\(^9\). Vasopressors, therefore, help to maintain adequate blood flow and tissue perfusion\(^9\). Patients who require vasopressor treatment upon admission have significantly higher ADM concentrations than those who do not require vasopressor infusion\(^9\) (figure 4), with MR-proADM levels in some cases nearly three times higher, and a corresponding AUC of 0.76 for patients in need of blood pressure support\(^8\).

Furthermore, MR-proADM can provide predictive information on NI development in septic shock patients\(^8\). Over a period of 7 days, MR-proADM levels are consistently higher in patients that suffer from NIs (n = 20), as opposed to those that do not (n = 78; figure 5; \(p < 0.05\)). It is known that ADM, which can be secreted by several leukocyte subpopulations, possesses anti-inflammatory properties\(^9\), and can therefore participate in the delayed process of sepsis-induced immunosuppression, which is believed to be closely associated with and increased risk of NIs\(^9\).

**Figure 4:** Association of ADM with vasopressor treatment. ADM concentrations are shown for patients who received (yes) or did not receive (no) vasopressor treatment on admission.

**Figure 5:** Differential MR-proADM concentrations in septic patients based on the occurrence of NIs.
References


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Accurately predicts mortality risk and organ failure in both adults and paediatrics

Increased levels in accordance with severity of disease

Help maintains blood supply to individual organs

Rapid rise in response to a bacterial infection

Localized cellular production to meet perfusion requirements of individual organs

Highlights the risk of developing nosocomial infections and the need for vasopressor treatment

Accurately predicts mortality risk and organ failure in both adults and paediatrics

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