EDITORIAL

# Adrenomedullin in Sepsis: Finally, a Friend or an Enemy?

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## Abstract

Adrenomedullin (ADM) is a 52 amino acid containing free circulating vasoactive peptide hormone found to be active in various pathophysiological states including sepsis. High ADM levels at admission have been correlated with vasopressor requirements, organ dysfunction, and mortality in sepsis patients. ADM stimulation results in vasodilation and loss of vascular resistance in humans resulting in hypotension with the potential for negative impact in septic shock. However, *in vitro* human and animal experiments have shown that ADM decreases hyperpermeability and capillary leak, thus having an endothelial barrier stabilizing effect during septic shock. Adrenomedullin thus appears to be a double-edged weapon. This editorial critically reviews the article by Daga et al. who evaluated serum ADM as a prognostic marker to review the gender-related difference in mortality pattern, and also the correlation of ADM level to APACHE II and SOFA scores. The role of adrenomedullin in sepsis and the potential developments in the future have been discussed concisely.

**Keywords:** Adrenomedullin, Lipopolysaccharides, Sepsis.

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Adrenomedullin (ADM) is a 52 amino acid containing free circulating multifunctional vasoactive peptide hormone found to be active in various pathophysiological states including sepsis. It is derived from a bigger precursor peptide (Pro-ADM) and possesses a half-life of about 20 minutes. The human ADM gene is encoded on chromosome 11p15.4 and contains three introns and four exons. Adrenomedullin is synthesized and released by most mammalian tissues including adrenal medulla, cells of vascular smooth muscle and endothelium, myocardium, lung, liver, kidney, and central nervous system under conditions of hypoxia, inflammation, and oxidative stress. Infectious processes resulting in exposure to lipopolysaccharides (LPS), cytokine release, and hypoxia stimulate ADM secretion. Angiotensin II and endothelin-1 also promote ADM release. ADM stimulation results in vasodilation and loss of vascular resistance in humans resulting in hypotension.[1–4] Vasodilation, which is one of the key properties of this peptide is contributed by the accumulation of cAMP and could have a negative impact in septic shock. However, *in vitro* human and animal experiments have shown that ADM decreases hyperpermeability and capillary leak, thus having an endothelial barrier stabilizing effect during septic shock.[5–9] Adrenomedullin has also got anti-bacterial and anti-inflammatory properties, and ADM levels are noted to be 20–30 folds higher in septic shock. It is to be noted that endogenous ADM levels will also increase in a variety of other conditions including overhydration, hypertension, ischemia, endocrine, and metabolic disorders.[10] Elevated concentrations of ADM at admission in sepsis patients are correlated to high vasopressor requirements, worsening organ failure, and increased mortality.[1,11,12] A double-monoclonal antibody sandwich assay has been introduced to measure the C-terminal amidated biologically active ADM. A cut-off value of >70 pg/mL of biologically active ADM (bio-ADM) at admission has been found to predict mortality in sepsis, and the same has been validated by various major independent multicenter studies.[11–14] In 2016, a prospective observational study by Helmy et al. found that a cut-off value of ADM (measured by ELISA technique) above 40 pg/mL at admission could predict sepsis mortality with sensitivity and specificity of 91.3 and 87.0%, respectively.[15]

In this issue of IJCCM, Daga et al. have published a noteworthy paper on serum ADM as a prognostic marker to review the gender-related difference in mortality pattern, and also the correlation of ADM level to APACHE II and SOFA scores.[16] They concluded that ADM is a protective neurohormone of the stress response and the serum levels in sepsis are elevated more in females than males which might be the rationale for the reduced mortality in sepsis within the former. Critically analyzing, we need to be extremely cautious of the intricacies and pitfalls before attempting to interpret the results of this study. As mentioned in the article, it was a prospective observational study quite underpowered because of the small sample size. The average ADM levels on day 1 were high among non-survivors vs survivors and the difference was statistically significant (*p* value of 0.006). The ADM levels on day 5 were still high in non-survivors when compared with survivors however the difference was statistically nonsignificant (*p* value of 0.088). The average day 1 ADM levels between males vs females were also statistically nonsignificant (*p* value of 0.306). The 28-day mortality rate including the first-week mortality between males and females was again not statistically significant (*p* values >0.05). Interestingly, the ADM levels observed during this study appear significantly higher than the mean ADM values reported in 2016 by Tamer et al. who also had utilized the ELISA technique for ADM measurement.[15] Females were in bit of mortality advantage in the Daga et al. study group. The male patients during this study had higher average APACHE II and SOFA scores which could subject them to higher predicted mortality than females though the observed mortality difference was not statistically significant. Urosepsis is known to have reduced mortality in comparison with

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the source of sepsis in other organs or tissues.[17] A significant number of female patients in this study had urosepsis (47.72%) which again has got the potential to reduce mortality in the female group. All prognostic parameters on day 1 including the ADM levels, the APACHE II and SOFA scores were statistically significant between survivors vs non-survivors. Calculation of mean SOFA scores between non-survivors vs survivors on the 28th day is expected to show lower values in survivors since the survivors are likely to have lower scores and longer duration of stay when compared with non-survivors who are likely to have higher SOFA score and shorter duration of stay. This method of mean SOFA calculation is hence inappropriate. The finding of three subgroups of patients based on ADM levels and the correlation with mortality is interesting. There was an increasing trend in mortality starting from an ADM level of >320 pg/mL, and it peaked between 480 pg/mL and 520 pg/mL. Subsequently, it was showing a downward trend till it reached a value of 640 pg/mL. Beyond the level of 640 pg/mL, the mortality touched the highest peak in this study. This trend could probably be explained by the complex variations in the vasodilatory vs vasoprotective (prevention of hyperpermeability and capillary leak) actions of ADM at different concentrations. However, interpretation of this observation during this study needs to be cautious due to the small sample size. In short, this study failed to show any statistically significant differences in ADM levels or mortality between male vs female patients with sepsis. There were statistically significant differences in day 1 ADM levels, APACHE II and SOFA scores between survivors vs non-survivors. Though this small study did not attain any major positive conclusions, this could still be utilized as a resource for hypothesis generation in future studies.

The uncertainty about the clinical effects of ADM in sepsis has been compounded further by conflicting studies in animals. Temmesfeld-Wollbrück et al. in 2007 reported that exogenous ADM administration improved the outcome in rat models.[7] However, two further studies published in 2013 reported beneficial effects of administration of anti-ADM antibodies in murine cecal ligation and puncture (CLP) models.[18,19] While the former study by Struck et al. showed reduced mortality in septic murine models after administration of antibodies against different epitopes of ADM, the latter study by Wagner et al. showed that administration of an antibody against the N-terminal part of ADM (HAM1101) reduced systemic inflammation, enhanced vasoactive responsiveness to catecholamines, and improved renal function.

Finally, human clinical trials on anti-ADM antibodies have been conducted in two studies; AdrenOSS-1 and AdrenOSS2.[14,20] The former showed that bio-ADM levels at admission could predict short-term outcome in sepsis and septic shock. The latter was a randomized double blinded, biomarker-guided, proof of concept and dose-finding phase II trial comparing adrecizumab (an ADM-binding non-neutralizing antibody) with placebo in patients with septic shock having bio-ADM concentration >70 pg/mL at admission. The trial has been completed and results are awaited. Adrenomed AG has presented data pertaining to the above trial at the e-ISICEM September conference claiming a relative reduction of mortality by 45% mortality with adrecizumab (8101) on day 14.[21]

Before concluding, based on the current body of evidence, the bio-ADM levels at admission effectively predict short-term outcomes in sepsis patients including vasopressor requirements, worsening organ dysfunction, and mortality. However, interpretation of clinical effects of ADM in sepsis and septic shock (friend, enemy, both, or none?) appears extremely complex with varying studies in humans and animals giving conflicting results. In short, high endogenous ADM levels at admission are strongly correlated with high sepsis mortality in humans. However, the administration of exogenous ADM has been found to improve survival in a rat model with septic shock though two subsequent murine studies showed that anti-ADM antibodies provided clinical benefits. Before we try to make a judgment on the nature of ADM as whether it is our friend or enemy in sepsis, we need to consider the following points. Animal experiments or human *in vitro* studies need not reflect the clinical effects of ADM in humans, and consistency and reproducibility of results are a must before scientific acceptance. Adrenomedullin is a vasodilatory stress response hormone and high ADM levels could be having the potential for harming the patients by aggravating septic shock *via* vasodilatation. Adrenomedullin could also be exerting opposing actions in the same sepsis patient with the net clinical impact trending toward the predominant mode of action at a particular concentration. Thus, ADM could promote endothelial barrier stabilization as shown in certain studies (thus having a protective effect in septic shock), as well as profound vasodilation, thereby worsening septic shock and increasing mortality. The net clinical effects hence depend on the concentration, timing, and duration of action of ADM, and its complex interactions with other cytokines released in the sepsis cascade. Being a multifunctional hormone, its action in other tissues could also affect the net clinical effects of septic shock. Finally, serum ADM levels and its net clinical effects may also depend upon the genotypic–phenotypic expression of the complex sepsis cascade in an individual patient. The mere presence of high ADM levels and the occurrence of high mortality in such sepsis patients is insufficient to attribute the entire sepsis-related morbidity and mortality to this hormone at this stage. How much of its vasodilatory action contributes to septic shock, and sepsis-related morbidity and mortality is yet to be ascertained. While we are eagerly awaiting the complete results of the AdrenOSS-2 trial, we need to plan further large well-designed studies to delineate the action of ADM at different concentrations in various settings to elucidate the clinical effects in a much more precise manner. Yes; ADM appears to be a friend as well as a potential enemy at this juncture.

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