

Can Acute Care Biomarkers Change Patient's Management in Sepsis?

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Abstract

Sepsis and septic shock have an enormous burden on healthcare systems, having more than 30 million people worldwide suffering from those diseases. As emergency providers we must be able to immediately recognize the presence of sepsis to improve the management of this disease and reduce its burden on patient's lives and on the emergency departments. Biomarkers can play an important role in this attempt. Laboratory tests could help both to identify the presence of sepsis at patients' arrival and to stratify the risk of progression to septic shock. A new biomarker in that regard is represented by Bioactive Adrenomedullin (BioADM), which mirrors vascular integrity, and is able to detect the physio pathological deterioration of the patients with sepsis that will progress into septic shock. Now, thanks to point-of-care testing devices, we are able to measure BioADM in whole blood in less than twenty minutes, which will help the physician making faster and more adequate therapeutic decisions beside patient's bed. The good news is that BioADM will also serve as a target for a monoclonal antibody that will counteract the vascular dysfunction in septic shock. In conclusion, coupling BioADM with other biomarkers already routinely used such as procalcitonin and lactate we can immediately change patient's management in Sepsis improving our decision making and patient outcome

Keywords: Acute care biomarkers, sepsis, emergency

Introduction

There are more than 30 million people worldwide suffering from sepsis (1), and its incidence is even greater than other acute diseases such as cardiovascular and cancer ones (2). The mortality rate in ICU for patients with septic shock is estimated to be around 35% (3) and this high mortality rate may increase of 8% with every delayed hour of treatment (4).

As consequence we need to improve our diagnostic accuracy of sepsis in the emergency room (ER) to improve its earliest management and reduce its mortality.

The importance of improving the approach to patients presenting with infection in ER is not only related to the possibility that these subjects could be already suffering from sepsis and could suddenly

deteriorate to septic shock, but it's also linked to the fact that, even when they survive from sepsis and are discharged from the hospital, these patients could experience severe consequences, such as: cognitive dysfunction, physical and psychological disabilities (5).

Following recent guidelines, emergency providers must then be able, starting from the triage, to immediately recognize the presence of sepsis in order to reduce the burden of the disease (6). Papers, also from our group (7,8) demonstrated that overcrowding of the emergency department is linked with high mortality rate and when compared with other several diseases, such as acute coronary syndrome or acute respiratory distress, sepsis showed the highest mortality rate in the emergency room.



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Received: 17.03.2022
Accepted: 23.05.2022

Cite this article as: Di Somma S, Crisanti L. Can Acute Care Biomarkers Change Patient's Management in Sepsis? Eurasian J Emerg Med. 2022;21(2):79-85.

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Eurasian Journal of Emergency Medicine published by Galenos Publishing House.

Indeed, recent guidelines of the Surviving Sepsis campaign recommend to organize a specific pathway in the emergency department to deal with sepsis (6).

Previous guidelines on sepsis of 2016 (9) recommended to immediately stratify the severity of sepsis using the quick sequential organ failure assessment (qSOFA) score, while the new guidelines (6) are suggesting that qSOFA score is not adequate anymore in this attempt; recommending to immediately test blood lactate to decide to use or not antibiotics.

Lactate measurement is not a diagnostic tool for sepsis since it is mirroring organ dysfunction in the presence of septic shock (10); therefore, we need something else, before lactate rises, to properly diagnose Sepsis in ER and to stratify the risk of the patient to develop septic shock.

Our group recently published a paper that clearly shows that the standard diagnostic tool for sepsis is the culture positive for bacteria detection (11). The problem is that we cannot have a cultural positive result in the emergency room because it will take at least 24 hours, or even more to be obtained.

Biomarkers for Early Diagnosis and Risk Stratification of Sepsis in ER

As already demonstrated by several studies, the only biomarker that is linked with the high possibility to properly detect the presence of sepsis is procalcitonin (12,13). On the contrary, white blood cell count and C-reactive protein (CRP) are very unspecific biomarkers for the detection of sepsis (14).

In (Figure 1A) ROC curve for diagnosis of sepsis: white blood cell (WBC) area under the curve (AUC): 0.533, p=0.780; procalcitonin

(PCT) AUC: 0.798, p<0.0001; CRP AUC: 0.720, p=0.001. In (Figure 1B) receiver operating characteristics (ROC) curve for outcome (in-hospital death) in total population: WBC AUC: 0.635, p=0.180; PCT AUC: 0.723, p<0.0001; CRP AUC: 0.538, p=0.239. T0, time of arrival in ED (14).

Consequently, many subjects could suddenly develop septic shock even though at ED arrival the clinical signs and laboratory testing were not able to detect it.

Could we be able to immediately detect the presence of sepsis upon the patient's arrival? This is what we are trying to achieve in the future, to help physicians to identify the presence of infection, sepsis and septic shock so that we could be able to stop the progression of the disease.

From physio pathological point of view, the mechanism that mirrors the transition from systemic infection to septic shock is due to an acute vascular dysfunction with loss of vascular integrity (15).

So, we need to have biomarkers that are able to detect the presence of ongoing severe vascular dysfunction as soon as possible in septic patient.

BioAdrenomedullin: A Biomarker of Vascular and Endothelial function and Utility in Sepsis

Bioactive adrenomedullin (BioADM) was discovered in 1993 by Kitamura et al. (16), it is a peptide that is present into the circulatory vessel and it is responsible for vascular integrity inside and outside the vessel and plays also a role in vasodilatation.

This was firstly demonstrated in animal models (17,18) and then confirmed in humans (19-21).

Table 1. Characteristics at baseline of patients with sepsis divided into Culture-negative and Culture-positive				
Characteristics	CnS (n=449)	CpS (n=324)	Un p	Un OR
Patients untreated with antibacterials during their stay in ED*, n (%)	26 (6)	6 (2)	0.009	3.257 (1.325-8.009)
Median body temperature (°C), (IQR)	37.5 (36.6-38.2)	37.8 (36.7-38.2)	0.331	
Median mean arterial pressure (mmHg), (IQR)	86 (76-95)	85 (75-93)	<0.001	1.019 (1.009-1.029)
Median heart rate (beats/min), (IQR)	100 (90-110)	104 (78-120)	0.912	
Median respiratory rate (breaths/min), (IQR)	24 (20-28)	24 (21-32)	0.361	
Median Glasgow Coma Scale (IQR)	15 (15-15)	15 (15-15)	0.183	
Median white blood cell count x 1000/mm ³ (IQR)	12.5 (9.0-16.4)	13.4 (9.8-18.5)	0.025	0.806 (0.629-1.001)*
Biomarkers				
Median C-reactive protein (mg/L) (IQR)	81 (31-170)	127 (53-215)	<0.001	0.769 (0.678-0.872)
Median lactate (mg/dL) (IQR)	14 (9-19)	14 (10-21)	0.103	
Median procalcitonin (ng/mL) (IQR)	0.51 (0.16-2.43)	1.12 (0.29-9.51)	<0.001	0.698 (0.619-0.787)
*Log scale transformed. CnS: culture negative sepsis, CpS: Culture positive sepsis, Un: Unstandardised, OR: Odds ratio, IQR: Interquartile, ED: Emergency department (Adjusted from Di Somma et al.)				

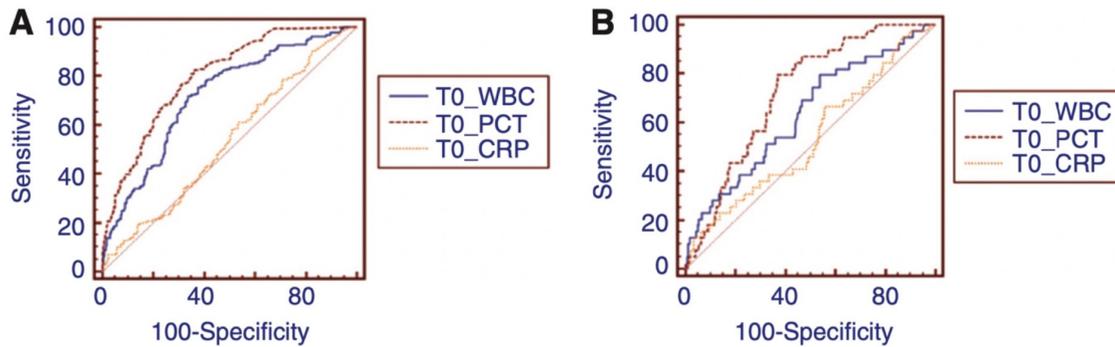


Figure 1. ROC curve for (A) diagnosis of sepsis and (B) prognosis of in-hospital death

ROC: Receiver operating characteristics, WBC: White blood cell, PCT: Procalcitonin, CRP: C-reactive protein

Role of bioactive adrenomedullin in the regulation of vascular function was shown in Figure 2 (22).

Using a new technology with immune sandwich assay (23) we are able to measure, *in vivo*, circulating levels of BioADM and its dynamic changes, mirroring the vascular dysfunction occurring in sepsis and we can really detect the physio pathological deterioration in septic patients and predict the progression to septic shock.

Scheme for biogenesis and measurement of bio-ADM was shown in Figure 3 (23).

First in the maturation process, the signal sequence is clipped off. The resulting pro-ADM is then proteolytically cleaved in four fragments (PAMP, proadrenomedullin NH2-terminal 20 peptide; MR-proADM, midregional proadrenomedullin; Adrenomedullin-Gly, C-terminally glycine-extended adrenomedullin; CT-proADM, C-terminal proadrenomedullin, also known as adrenotensin). The resulting C-terminally glycinated ADM is biologically inactive and is subsequently (but only partially) converted into the biologically active C-terminally amidated ADM (BioADM). Using

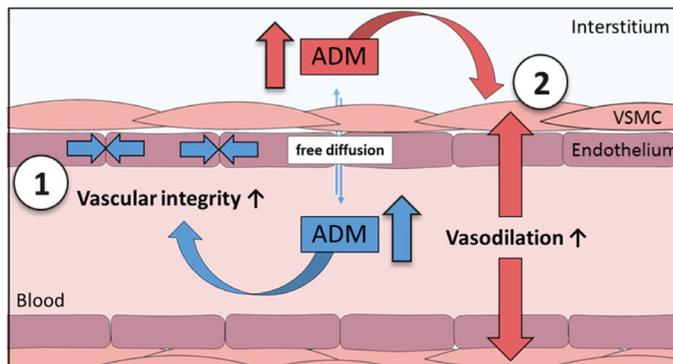


Figure 2. Role of bioactive adrenomedullin in the regulation of vascular function (22)

ADM: Adrenomedullin, VSMC: Vascular smooth muscle cells

highly specific monoclonal antibodies directed against the middle portion of ADM and the amidated C-terminus, BioADM can be detected with an immunometric assay (23).

This hypothesis has already been confirmed by our group (24) and by Chen and Li (25). Through the measurement of BioADM blood level in patients with the suspicion of sepsis at ED arrival. We were able to demonstrate that a value of bioADM greater than 70 pg/mL correlated with the severity of sepsis, the need for vasopressors and finally the progression to septic shock and death (24). After that study, multicentric studies, with other cohorts in other countries, have shown the same results (26-28). Therefore, the cut off of 70 pg/mL of bioADM should be considered as a marker for the severity of sepsis, predictor of septic shock and the need for vasopressors use.

Lately, in a small cohort, high circulating levels of BioADM were also correlated with organ failure and 30-days mortality in septic patients (29).

Bio-ADM cut-off of 70 pg/mL correlates with the severity of sepsis, the use of vasopressors and the septic shock as the cause of death (Figure 4) (24).

Furthermore, blood levels of BioADM are not affected by any previous antibiotic treatment, making it a very reliable biomarker.

In the same paper we also demonstrated, by monitoring BioADM levels from arrival for 7 days, that if there was a reduction of BioADM from high to low level, those patients showed a better prognosis (24), confirming that there is the possibility to reverse the negative outcome in these subjects.

This includes the concept that we can use this biomarker to monitor and evaluate the treatment efficacy.

Again, this was confirmed both by our preliminary study and through other multicentric studies (26,27).

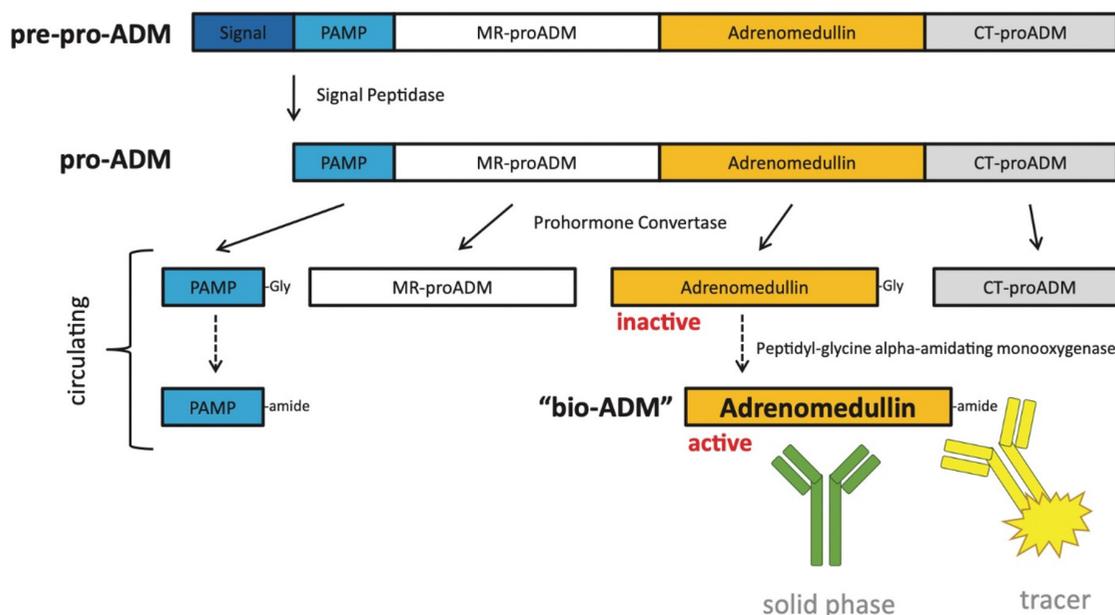


Figure 3. Scheme for biogenesis and measurement of BioADM (23)

BioADM: Bioactive adrenomedullin

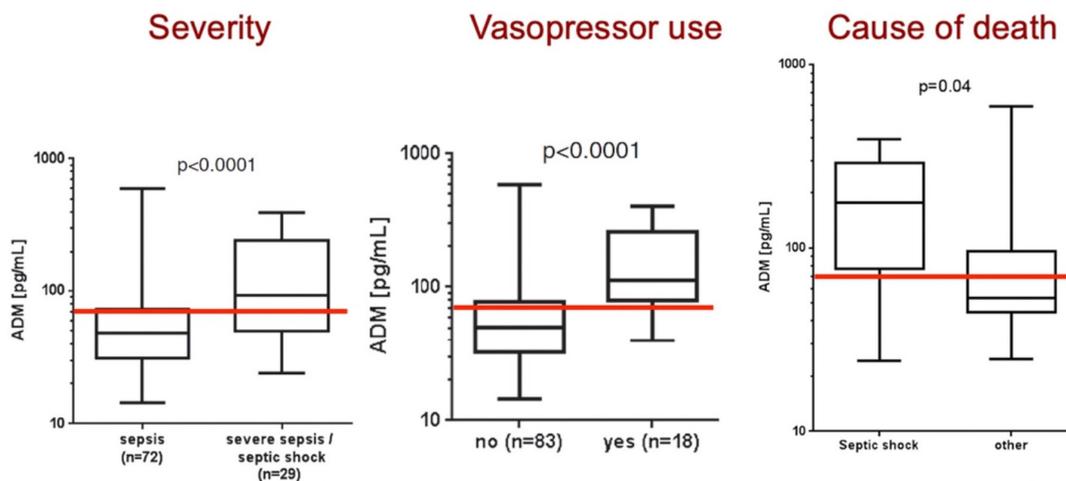


Figure 4. BioADM cut-off of 70 pg/mL correlates with the severity of sepsis, the use of vasopressors and the septic shock as the cause of death (24)

BioADM: Bioactive Adrenomedullin

BioADM medical utility in sepsis: prediction, diagnosis and monitoring of acute vascular dysfunction resulting in septic shock (Figure 5).

Utility of POCT Device for BioADM Evaluation

In the future we will use, as much as possible, the ultrasound point of care systems in the emergency room and point of care biomarkers devices in order to make a more appropriate and rapid decision making (30). This would be of great utility

also in patients presenting with sepsis in order to start the best treatments as soon as possible.

Thanks to the POCT IB10 (Nexus Dx Inc., San Diego, CA, USA) device it's possible to measure BioADM levels in whole blood in less than 20 minutes, allowing ED physicians to make faster therapeutical decision in patients with sepsis and improve their outcome (Figure 6).

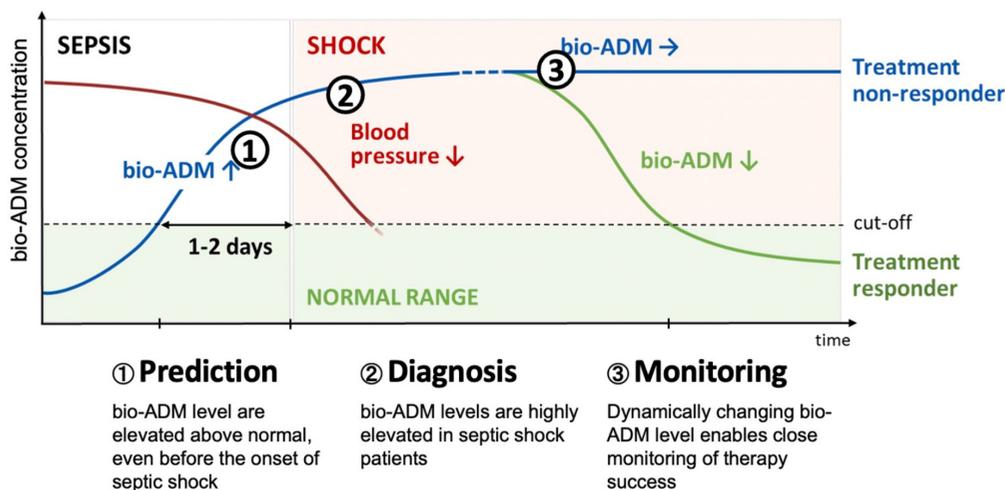


Figure 5. BioADM medical utility in sepsis: prediction, diagnosis and monitoring of acute vascular dysfunction resulting in septic shock
BioADM: Bioactive adrenomedullin

Since the value of IB 10 could be obtained 20 minutes after the arrival of patients in the emergency room, if the obtained result is greater than 70 pg/mL, the ED physician could have immediately important information on the patient's severity and make a specific decision in terms of therapeutical options and final disposition.

So, we would suggest that patients arriving to the ED with fever and risk factors, such as: hypertension, diabetes, kidney failure, they could be good candidates for BioADM testing, since they're at high risk for progression to septic shock.

From the recent guidelines (6), it is mandatory in patients with suspicion of sepsis to measure lactate, since patients with

a lactate value greater than 2 mmol/L are at increased risk to develop septic shock. A recent paper shows that, when testing for BioADM and lactate (31), if both are elevated the mortality of patients with sepsis rises up to around 50%.

This supports the fact that we can use both biomarkers together to better understanding of the severity of our patient.

Adrecizumab: A Novel Monoclonal Antibody for BioADM

The good news is that soon we will have a new drug option that could be taken into account during our therapeutical decisions. It has been developed a new monoclonal, Adrecizumab, that is able to restore the physiological function of BioADM on vessels.

The efficacy of anti-adrenomedullin antibodies in reducing mortality had already been demonstrated in 2013 through murine models (32).

Its mode of action is described in Figure 7, basically it manages to rise ADM concentration inside the vessels by translocating pre-existing ADM from the interstitial compartment. Furthermore, Adrecizumab seems to prevent ADM from being degraded and to prolong its half-life. In fact, a recent paper demonstrated that Adrecizumab is able to counteract the vascular dysfunction in septic shock (22).

Confirming this, Laterre et al. (33) recently showed how this drug improved the survival of patients with sepsis and a BioADM level greater than 70 pg/mL.

Therefore, in the future, it will be possible to use this monoclonal antibody in those patients that present in the emergency room with sepsis and a BioADM value greater than 70 pg/mL. This will improve their outcome by counteracting the vasculature damage before the patients goes to deteriorate into septic shock.



Figure 6. Nexus Dx Inc. IB10 device for poct BioADM testing (<https://www.nexus-dx.com/nexus-ib10/>)

BioADM: Bioactive adrenomedullin

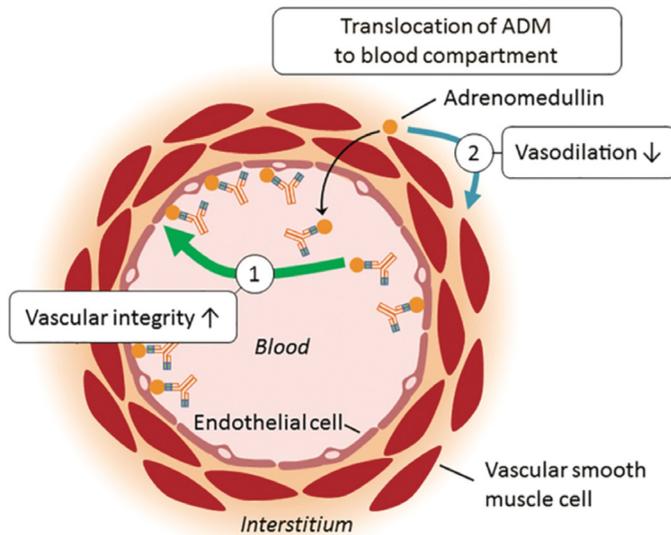


Figure 7. Mechanism of action of adrecizumab (19)

ADM: Adrenomedullin

Anyway, while we wait for the possibility of routinely using Adrecizumab, when we have a patient that seems to be stable, but his circulating BioADM is greater than 70 pg/mL, we could anticipate the start of vasopressors treatment in order to reduce the possibility of the patient to develop septic shock. Moreover, it would be possible to monitor BioADM for the following 7 days in order to verify the effect of the vasopressors early treatment.

Conclusion

Since every hour of delay in diagnosing of sepsis and septic shock in the emergency room is going to be linked with high mortality rates, we need new biomarkers for early detection of sepsis, beyond lactate. BioADM, that could also be measured by POCT devices on whole blood in 20 minutes, seems to be a very good new biomarker now available to reduce the burden of septic shock in the emergency room.

Finally, we would recommend using biomarkers in the emergency room really with care, since we do not need to treat the number, we need to treat the patients.

Ethics

Peer-review: Externally peer-reviewed.

Financial Disclosure: The authors declared that this study received no financial support.

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