VASCULAR EFFECTS OF ADRENOMEDULLIN AND THE ANTI-ADRENOMEDULLIN ANTIBODY ADRECIZUMAB IN SEPSIS

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Received 19 Jul 2017; first review completed 7 Aug 2017; accepted in final form 4 Jan 2018

ABSTRACT—Sepsis remains a major scientific and medical challenge, for which, apart from significant refinements in supportive therapy, treatment has barely changed over the last few decades. During sepsis, both vascular tone and vascular integrity are compromised, and contribute to the development of shock. The free circulating peptide adrenomedullin (ADM) is involved in the regulation of the endothelial barrier function and tone of blood vessels. Several animal studies have shown that ADM administration improves outcome of sepsis. However, in higher dosages, ADM administration may cause hypotension, limiting its clinical applicability. Moreover, ADM has a very short half-life and easily adheres to surfaces, further hampering its clinical use. The non-neutralizing anti-ADM antibody Adrecizumab (HAM8101) which causes a long-lasting increase of plasma ADM has shown promising results in animal models of systemic inflammation and sepsis; it reduced inflammation, attenuated vascular leakage, and improved hemodynamics, kidney function, and survival. Combined with an excellent safety profile derived from animal and phase I human studies, Adrecizumab represents a promising candidate drug for the adjunctive treatment of sepsis. In this review, we first provide a brief overview of the currently available supportive therapy, treatment has barely changed over the last few decades. During sepsis, both vascular tone and vascular integrity are compromised, and contribute to the development of shock. The free circulating peptide adrenomedullin (ADM) is involved in the regulation of the endothelial barrier function and tone of blood vessels. Several animal studies have shown that ADM administration improves outcome of sepsis. However, in higher dosages, ADM administration may cause hypotension, limiting its clinical applicability. Moreover, ADM has a very short half-life and easily adheres to surfaces, further hampering its clinical use. The non-neutralizing anti-ADM antibody Adrecizumab (HAM8101) which causes a long-lasting increase of plasma ADM has shown promising results in animal models of systemic inflammation and sepsis; it reduced inflammation, attenuated vascular leakage, and improved hemodynamics, kidney function, and survival. Combined with an excellent safety profile derived from animal and phase I human studies, Adrecizumab represents a promising candidate drug for the adjunctive treatment of sepsis. In this review, we first provide a brief overview of the currently available data on the role of adrenomedullin in sepsis and describe its effects on endothelial barrier function and vasodilation. Furthermore, we propose a novel hypothesis concerning the mechanisms of action through which Adrecizumab may exert its beneficial effects in sepsis.

KEYWORDS—Antibody, endothelium, mechanism of action, shock, vascular integrity, vasodilation

INTRODUCTION

Sepsis is an inflammatory disorder, in which a dysregulated host response to an infection results in life-threatening organ dysfunction (1). Sepsis is a prevalent syndrome; approximately one third of all patients in intensive care units (ICU) present with sepsis on admission or develop sepsis during their ICU stay (2). Despite many advances in medical care, the incidence of sepsis is increasing and its mortality remains high (3). Sepsis is characterized by a complex and multilayered pathogenesis. In short, a host response is mounted by ligation of pathogen-associated molecular patterns (PAMPs) to pattern recognition receptors (PRRs) present on immune cells, in turn activating inflammatory and coagulation pathways, characterized by leukocyte and complement activation as well as release of cytokines, reactive oxygen species, and damage-associated molecular patterns (DAMPs). These events result in perpetuation of the inflammatory response and ultimately cause organ failure, which is a key determinant of survival (4). The vascular endothelium is a protective barrier involved in the maintenance of vessel integrity that controls diffusion of molecules and fluids between the intravascular and interstitial space. Endothelial function is often compromised during sepsis, leading to increased leukocyte adhesion, vascular wall permeability, and vasodilation (4–7). These changes result in, among others, extravascular fluid accumulation, causing tissue edema, a decrease in circulating volume, hypotension, and subsequent organ failure.

A considerable proportion of deaths are attributed to the early phase of sepsis, as a result of multi-organ failure despite supportive therapy. For decades, treatment of sepsis consists of antimicrobial therapy, source control, and supportive treatments such as fluid resuscitation, vasopressor use, and mechanical ventilation (6). Many trials have investigated possible adjuvant treatments, primarily focussing on anti-inflammatory therapies. Unfortunately, not a single intervention is currently in use because of lack of efficacy. This can partially be explained by methodological issues, such as heterogeneity of the study population and timing of the intervention, but also by the complexity of the immune response with multiple pathways contributing to injury (6,8). Thus, there is still a great unmet need for novel adjuvant therapies for sepsis. Interestingly, interventions aimed at improving endothelial barrier function have only sparsely been investigated, while this represents a highly relevant target (9).

ADRENOMEDULLIN

Adrenomedullin (ADM) is a free circulating 52 amino-acid peptide belonging to the calcitonin gene-related peptide family that was first discovered in human pheochromocytoma tissue...
more than two decades ago (10,11). Although ADM was initially thought to primarily possess vasodilatory properties (12), it was subsequently discovered that it exerts a multitude of biological effects, both in health and in disease, including anti-inflammatory effects, stabilization of endothelial barrier function, and regulation of vascular tone (13). These effects are attained through binding of ADM to heterodimeric receptor complexes consisting of the calcitonin receptor-like receptor and a specific receptor activity-modifying protein (RAMP), RAMP2 and RAMP3 (14). ADM is produced by many cells, including endothelial cells, vascular smooth muscle cells (VSMCs), monocytes, renal parenchymal cells, and macrophages (15–20). A wide variety of mediators involved in the pathophysiology of sepsis have been reported to enhance ADM production. For instance, in rat VSMCs, interleukin-1 (IL-1) alpha and beta, tumor necrosis factor (TNF) alpha & beta, epinephrine, substance P, endothelin-1, angiotensin II, fetal calf serum (FCS), and lipopolysaccharide (LPS) all increased ADM gene expression and synthesis (21,22). Conversely, other substances known to play a role in sepsis, such as thrombin, vasoactive intestinal polypeptide, and interferon-gamma (IFN-γ), were shown to decrease ADM production in VSMCs (22). Studies in rat endothelial cells revealed that ADM is not stored, but rather constitutively produced, and that endothelial cells secrete ADM at a higher rate than VSMCs (23). Similar to rat VSMCs, TNF, IL-1, LPS, and thyroid hormone increase ADM secretion by endothelial cells, whereas transforming growth factor β1, INF-γ, and FCS suppress ADM secretion. Other studies have demonstrated increased ADM production by renal parenchymal cells and endothelial cells under hypoxic conditions (19,24). The effects of endotoxin and hypoxia on ADM production were also confirmed in vivo in a rat model of LPS-induced inflammation, as well as in models of induced hypoxia with the inhalation of carbon monoxide and air with reduced concentrations of oxygen (25,26). ADM has a short circulating half-life (22 min) (27), and is removed from the circulation in two ways. First, the ADM receptors function as clearance receptors: upon ligation of ADM with its receptors, the ADM–receptor complex is internalized and subsequently degraded (28). The lung has been reported as a significant site of clearance via this mechanism (29,30). The second clearance mechanism is represented by proteolytic degradation of ADM (31–33).

**ADRENOMEDULLIN IN SEPSIS**

Increased levels of circulating ADM are found during sepsis which correlate with relaxation of vascular tone (34) as well as with disease severity and mortality in septic patients (35–38). Although these associations may suggest that ADM plays a detrimental role in sepsis, they should be interpreted with caution, as no causal relationships—detrimental or beneficial—can be directly deducted from these observational studies. In fact, many experimental studies, both in vitro (39) and in vivo (40–42), have demonstrated that ADM administration is beneficial during systemic inflammation and sepsis through favorable effects on endothelial barrier function. Another relevant peptide in this context is adrenomedullin-binding protein 1 (AMBP-1), also known as complement factor H (43). AMBP-1 binds to ADM, albeit with a lower overall affinity than ADM binding to its receptors (44). AMBP-1 is reported to protect ADM from proteolytic degradation (32), and modulates ADM activity: coincubation of fibroblasts with ADM and AMBP-1 resulted in a 2-fold increase of cyclic adenosine monophosphate (cAMP), compared with treatment with ADM alone (45). Furthermore, several studies have demonstrated that co-administration of ADM and AMBP-1 improves outcome in preclinical animal studies employing various models of systemic inflammation, organ injury, and septic shock (46–49).

**ADRENOMEDULLIN STABILIZES THE ENDOTHELIAL BARRIER**

Studies in genetically modified mice deficient for crucial parts of the ADM receptor signalling pathway reported development of lethal hydrops fetalis, indicating impaired development of the endothelial barrier (50–52). In conditional murine knock-out models, in which either ADM or the RAMP2 part of the AM1 receptor was abolished in endothelial cells, increased vascular permeability and edema formation was observed (53,54). Furthermore, in vitro studies demonstrated that ADM stabilizes the endothelial barrier through regulation of the actin myosin cytoskeleton (55). ADM is thought to prevent formation of stress fibers that pull on cell–cell junctions (56), which is primarily mediated through the cAMP-PKA pathway involving Rap1 activation and RhoA/ROCK inhibition (57). This is accompanied by attenuated endothelial myosin light chain phosphorylation, actomyosin contractility, and ultimately attenuation of endothelial cell gap formation (39,56). In addition, ADM activates Rac1, which stimulates cortical actin formation (58). Moreover, completely blocking ADM has been shown to increase endothelial layer permeability by inhibiting cell–cell contacts predominantly through disruption of VE-cadherin/β-catenin and Akt signalling pathways (59). Figure 1 presents a schematic overview of the pathways through which ADM exerts endothelial stabilizing and vasodilatory effects. Beneficial effects of ADM administration on endothelial barrier function have been demonstrated in animals in vivo, using models of systemic inflammation and sepsis. For example, ADM administration in a murine model of lung injury resulted in attenuation of pulmonary hyperpermeability, lung injury, and systemic hyperinflammation (42). In rats, administration of ADM significantly reduced extravasation of albumin and plasma fluid, and ultimately improved survival in septic shock induced by S aureus alpha-toxin (40).

**ADRENOMEDULLIN EXERTS VASODILATORY EFFECTS, HAS A SHORT HALF-LIFE, AND IS DIFFICULT TO HANDLE**

As mentioned earlier, one of the initially discovered properties of ADM is that it lowers blood pressure. Several studies have demonstrated that ADM promotes vasodilation in isolated blood vessels (60,61). Furthermore, infusion of high dosages of
ADM was shown to decrease blood pressure and peripheral vascular resistance in rats, cats, sheep, and humans, thereby inducing a compensatory increased heart rate and cardiac output (27,41,62–65). The vasodilatory effects of ADM are mediated through binding to the ADM receptors present on vascular endothelial cells and vascular smooth muscle cells (VSMCs). Several signaling pathways, both endothelium-dependent and -independent, appear to account for ADM-mediated vasodilation (66). Binding of ADM to its receptors on VSMCs leads to increased cAMP (67,68) in an endothelium-independent fashion, which subsequently activates protein kinase A (PKA). PKA phosphorylates a large number of proteins which ultimately results in relaxation of smooth muscle cells. Endothelium-dependent pathways have in common that they act through stimulation of endothelial NO synthase (eNOS), which in turn stimulates the cyclic guanosyl monophosphate (cGMP) system in VSMCs, leading to the activation of PKA and protein kinase G (PKG). PKG acts downstream to reduce intracellular calcium levels and alters sensitivity of contractile proteins for calcium, thereby also inducing smooth muscle relaxation. These pathways include the inositol-1,4,5-triphosphate (IP₃) system and the phosphatidylinositol-4,5-bisphosphate 3-kinase-protein kinase B (IP3K/Akt) pathway (69,70). It remains unknown as to what extent endothelium-dependent or -independent pathways account for ADMs vasodilatory effects.

So, despite ADMs potent endothelial barrier-stabilizing effects, systemic administration in higher dosages exerts hemodynamic effects, mainly vasodilatory, that may be detrimental for sepsis patients and even more so for septic shock patients (71). Moreover, it has a very short half-life (several minutes) (27,29) and is cumbersome to handle being very adhesive (72) and thus arguably sticking to artificial surfaces used in the clinic. Taken together, these unfavorable pharmacological properties might seriously hamper its clinical applicability in sepsis, and modulating the endogenous ADM response may represent a more viable strategy. Although at first glance it may appear counterintuitive, a specific type of antibodies targeting ADM may represent such a strategy.

**THE ANTI-ADRENOMEDULLIN ANTIBODY ADRECIZUMAB IMPROVES OUTCOME IN EXPERIMENTAL SEPSIS**

ADM interacts with its receptor via the C-terminal moiety (73), and the N-terminal part of ADM is not required for its agonist function (74). Previously, several high-affinity mouse monoclonal anti-ADM antibodies were investigated, targeting different epitopes of ADM (75). Complete functional inhibition of ADM (by blocking the C-terminus) did not improve survival in cecal ligation and puncture (CLP) induced murine sepsis. However, pretreatment with high-affinity antibodies targeting the N-terminus of ADM, which only partially inhibits ADM signaling, even when applied in large molar excess over ADM, showed profound beneficial effects on mortality (75). A later
study, investigating the effects of this antibody in a resuscitated CLP-induced murine sepsis, reported decreased catecholamine infusion rates, prevention of kidney dysfunction, reduction of iNOS but not eNOS expression, and ultimately improved survival (76). Following these initial preclinical experiments HAM1101 was humanized to HAM8101 for further preclinical and clinical studies and named Adrecizumab. Adrecizumab was shown to reduce renal interstitial edema in endotoxemic rats and decreased renal VEGF expression (a potent inducer of vascular permeability) in CLP-induced murine sepsis, whereas expression of the protective peptide angiopoietin-1 was augmented (77,78). Furthermore, it reduced mortality in CLP-induced murine sepsis to a similar extent as the parent antibody HAM1101. An overview of these preclinical antibody studies is provided in Table 1.

### PROPOSED MECHANISM OF ACTION OF ADRECIZUMAB

The mechanisms by which Adrecizumab exerts its beneficial effects remain to be fully elucidated. However, there are indications that it involves modulation of the ADM equilibrium between the blood compartment and interstitium. The endothelium is a single cell monolayer, separating the blood compartment from the interstitial space. As ADM is a small peptide (6 kDa), it freely diffuses between the blood vessels and the interstitial space. In this homeostatic “normal” situation, ADM regulates the endothelial barrier function through ligation of receptors on endothelial cells, and regulates vascular tone through binding to receptors on endothelial cells (indirect effect) and vascular smooth muscle cells (direct effect (Fig. 2A)). During septic shock, circulating ADM levels are profoundly increased (35,38,79). Although there is no data on ADM concentrations in the interstitial compartment, it is plausible to assume that ADM concentrations are in equilibrium with the circulation, because ADM is able to diffuse freely between the two compartments (29). The previously described preclinical studies suggest that ADM present in the circulation counteracts—albeit insufficiently—sepsis-induced vascular leakage through its effects on endothelial cells, while excess circulating and interstitial ADM may lead to vasodilation and septic shock through indirect effects on endothelial and direct effects on VSMCs (Fig. 2B). Interestingly, in both the preclinical studies in healthy animals and animals with LPS-induced inflammation and CLP-induced sepsis, and the recently performed phase I study in humans (unpublished, discussed in the next section), an immediate (< 5 min) dose-dependent increase of plasma ADM concentrations was observed after Adrecizumab administration (80). This effect has been observed across all species investigated (mice, rats, beagle dogs, cynomolgus monkeys, and humans). The measured elevated plasma ADM concentrations in fact mainly represent complexes of ADM bound to Adrecizumab, as Adrecizumab is administered in several orders of magnitude molar excess over endogenous ADM, and the assay used to measure plasma ADM (sphingotest bio-ADM, Sphingotec GmbH, Hennigsdorf, Germany) detects both free ADM and ADM complexed with Adrecizumab (81). Given the small volume of distribution of Adrecizumab (100 mL/kg; unpublished data from phase I study in human volunteers), it can be concluded that Adrecizumab does not freely diffuse from the circulation into the interstitial space, which is not surprising it being a large IgG antibody of 160 kDa. Because plasma concentrations of MR-proADM, a non-functional peptide stemming from the same precursor peptide as ADM, do not increase upon administration of Adrecizumab (80), it can be concluded that the antibody does not induce

<table>
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<tr>
<th>Authors (year)</th>
<th>Intervention</th>
<th>Model</th>
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<tr>
<td>Struck (2013)</td>
<td>Pretreatment with murine antibody against N-terminus ADM (HAM1101, 2 mg/kg)</td>
<td>Cecal ligation and puncture (CLP) induced murine sepsis</td>
<td>↑ survival</td>
</tr>
<tr>
<td>Wagner (2013)</td>
<td>Pretreatment with murine antibody against N-terminus ADM (HAM1101, 2 mg/kg), administered immediately after CLP surgery</td>
<td>Resuscitated CLP-induced murine sepsis</td>
<td>↑ norepinephrine infusion, ↓ urine production &amp; creatinine clearance, ↓ neutrophil gelatinase-associated lipocalin (NGAL), ↓ iNOS expression &amp; peroxynitrite formation in kidney &amp; aorta, ↓ Systemic inflammation, ↓ Tissue apoptosis in kidney, ↓ renal albumin extravasation</td>
</tr>
<tr>
<td>Geven (2018)</td>
<td>Pretreatment with humanized antibody against N-terminus ADM (Adrecizumab, 0.02, 0.1, 0.5, or 2.5 mg/kg)</td>
<td>Lipopolysaccharide (LPS) induced systemic inflammation in rats</td>
<td>↓ renal albumin extravasation, ↓ renal vascular endothelial growth factor (VEGF), ↑ renal angiopoietin-1</td>
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<tr>
<td>Geven (2018)</td>
<td>Pretreatment Adrecizumab (0.1, 2.0, or 20 mg/kg)</td>
<td>CLP-induced murine sepsis</td>
<td>↑ Survival</td>
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<tr>
<td>Geven (2018)</td>
<td>Pretreatment single dose Adrecizumab (2 mg/kg) and repeated dose Adrecizumab (pretreatment with 4 mg/kg followed by 2 mg/kg after 24 and 48 h)</td>
<td>CLP-induced murine sepsis</td>
<td>↑ Survival</td>
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**Table 1.** Overview of studies that have investigated the murine and humanized version (Adrecizumab) of the highly specific N-terminus antibody.
increased expression of ADM. Therefore, we hypothesize that Adrecizumab induces a shift of ADM from another compartment (most likely the interstitium) into the circulation (Fig. 2C). Whether bio-ADM concentrations after Adrecizumab administration also increase in patients with septic shock remains to be investigated, although based upon preclinical available data, this is to be expected.

Another effect of Adrecizumab is the prolongation of the half-life of endogenous ADM: Spiking of Adrecizumab to ADM-containing serum samples in vitro strongly increased the half-life of ADM in a dose-dependent manner (Fig. 3, based on unpublished data). A plausible mechanistic explanation for this observation is that binding of Adrecizumab to the N-terminus of ADM reduces accessibility for proteolytic decay, which is known to occur at the N-terminus of ADM (31).

Because Adrecizumab is only a weak inhibitor of ADM signaling, the net effect of Adrecizumab administration is that ADM activity on endothelial cells is not reduced, but rather increased. This allows for ADM levels in the circulation to exert the aforementioned beneficial effects on the endothelium (reduction of capillary leakage), whereas ADMs detrimental effects in the interstitium (vasodilation of VSMCs) may concurrently be reduced. Overall, we hypothesize that as a result of the weak inhibitory effects of the antibody, the net effects of ADM on endothelial cells are augmented by Adrecizumab, resulting in the stabilization of vascular integrity (Fig. 2C). This proposed mechanism of action also explains why the antibody directed against the C-terminus, which resulted in complete inhibition of ADM activity, did not improve sepsis outcome in preclinical studies (75).

Adrecizumab may have additional benefits over ADM for the treatment of sepsis. As alluded to before, ADM has a short half-life; therefore, it needs to be infused continuously. Adrecizumab has a half-life of approximately 15 days, allowing administration of a single dose. Moreover, Adrecizumab does
not have the adhesive properties that ADM has. Naturally, as our proposed mechanism of action is hypothetical, future experimental studies should focus on downstream signaling targets of ADM pathways and measuring tissue and/or interstitial ADM concentrations.

SAFETY OF ADRECIZUMAB

The safety and tolerability of Adrecizumab were extensively investigated in preclinical animal studies. Toxicology and safety was studied in three different animal species. In short, Adrecizumab was well tolerated and safe up to the highest dosages tested (400 mg/kg), which are about hundredfold over the preclinically efficacious and intended clinical therapeutic dose (unpublished data). Moreover, application of up to 50 mg/kg Adrecizumab did not influence the blood pressure in telemetry beagle dogs (unpublished data). Recently, a human phase I study was successfully completed (ClinicalTrials.gov identifier NCT02991508), and excellent safety results were observed (80).

POSSIBLE LIMITATIONS

In the preclinical studies discussed before, Adrecizumab was administered prior to, or immediately after endotoxin administration or the cecal ligation and puncture procedure. This approach is common for proof of principle studies, but represents a relevant limitation, as pretreatment of septic patients is unattainable in clinical practice. Moreover, previous work has convincingly shown that Adrecizumab administration results in a rapid and potent increase of circulating ADM, both in healthy animals and humans as well as in inflamed and/or septic animals (77,78,80). Because ADMs vasodilatory effects are mediated not only through direct effects on VSMCs (which are presumably reduced by Adrecizumab (Fig. 2C), but also through indirect effects on endothelial cells, the increase in ADM levels could theoretically also cause unwanted vasodilation and subsequent aggravation of hypotension in septic shock patients. However, the relative importance of the indirect endothelial cell pathway compared with the direct effects on VSMCs in the vasodilatory effects of ADM remains to be determined. Nevertheless, no hypotensive effects were observed after Adrecizumab administration in telemetered healthy beagle dogs (unpublished data) and healthy human volunteers (80). Furthermore, in the aforementioned preclinical study in CLP-induced sepsis in mice (76), lower norepinephrine infusion rates were observed in the treatment group, which strongly suggests that Adrecizumab did not exert vasodilatory effects. Finally, it is unclear whether the long half-life of Adrecizumab is a benefit or a limitation of the compound. While it enables single dosing treatment, increasing the feasibility of the therapy, this also may represent a limitation if unwanted effects of the drug may occur. Taken together, although there are currently no indications of hypotensive effects of Adrecizumab, the compound has not been investigated in septic patients yet, so no definitive conclusions can be drawn on the safety profile in patients. Moreover, it is imperative that future research also encompasses administration of Adrecizumab after the inflammatory and/or infectious insult to increase clinical relevance.

OTHER ENDOTHELIAL BARRIER STABILIZING AGENTS

Current guidelines do not recommend any adjunctive treatment for sepsis, except for hydrocortisone in patients with septic shock who respond poorly to fluid resuscitation and vasopressor therapy (82). Although several adjunctive interventions (mainly anti-inflammatory agents) have been investigated in septic patients, up to now no clinical trials have been performed that have investigated endothelial barrier-stabilizing agents. This is slowly changing. Currently, the short-acting selective vasopressor 1a receptor agonist selepressin is under investigation in a study aiming to include 1,800 patients with septic shock (ClinicalTrials.gov identifier NCT02508649). Preclinical data suggest that this selective V1-agonist (83) can improve vascular leakage by ligation of V1a receptors. In two studies employing ovine models of septic shock induced by smoke inhalation combined with Pseudomonas aeruginosa pneumonia or CLP, selepressin decreased fluid accumulation compared with vasopressin and norepinephrine, indicating decreased vascular leakage (84,85). Also, in a recent phase IIa study, selepressin was an effective substitute for norepinephrine, and in one dosage group an improved fluid balance was observed (86). Another important regulator and potential target for endothelial barrier-stabilizing therapy is the angiopoietin-Tie-2 receptor pathway (87,88). Several studies have demonstrated that Tie-2 agonists such as angiopoietin-1 (ang1) and modifications/alterations of ang1 which increase the half-life and binding efficacy, can prevent capillary leakage in animal models of septic shock (89–91), whereas targeted angiopoietin-2 inhibition also appears to hold potential (92). Another potential treatment target with respect to endothelial barrier function is vascular endothelial growth factor (VEGF) (93), a potent inducer of endothelial barrier hyperpermeability (94), although the body of evidence is small and negative studies have also been reported (95). It remains to be determined whether these strategies are truly effective in septic patients and whether one agent holds advantage over another.

CONCLUSION

ADM freely diffuses over the endothelial cell layer. In the blood compartment ADM improves endothelial barrier function, while in the interstitium it causes vascular smooth muscle relaxation. During sepsis, higher ADM concentrations are found which may aggravate vasodilation. As the non-neutralizing antienomedullin antibody Adrecizumab does not cross the endothelium, we hypothesize that ADM distribution is shifted toward the circulation where it is still functional after binding to Adrecizumab. Adrecizumab was shown to enhance endothelial barrier function in experimental models of systemic inflammation and sepsis, in the absence of untoward (vasodilatory) effects. Furthermore, administration of the antibody improved clinical outcomes, while safety and tolerability studies so far showed no
side effects. These results pave the way for further clinical studies with Adrecizumab, which will have to reveal whether these effects are also present in patients with sepsis.

REFERENCES


