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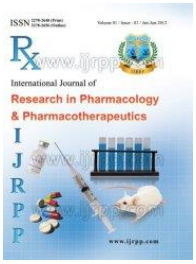

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# Cilengitide- A novel therapy in sepsis to prevent antimicrobial resistance

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## ABSTRACT

Sepsis is a fast progressing disease, triggered by the host response to infection. If untreated, sepsis can rapidly evolve to multi-organ dysfunction and septic shock. Despite numerous advances in palliative intensive care and antibiotic treatment, sepsis remains a major cause of morbidity and mortality. The vascular endothelium is a major target of sepsis-induced events. Upon entry to the bloodstream, bacteria attach to the endothelium within 15s. Attachment triggers dysregulated signals that result in endothelial cell (EC) death and loss of barrier integrity, which give rise to increased capillary permeability clinically associated with hypotension, subcutaneous and body-cavity edema and impaired tissue oxygenation. Early and adequate antimicrobial therapy is the cornerstone of the therapy in sepsis. Broad empirical antimicrobial therapy should be administered as soon as possible after at least two sets of blood cultures have been obtained. This has lead to high load of antimicrobial use and in turn resulted to an emergent problem that is antimicrobial resistance. Cilengitide, the most advanced integrin inhibitor in clinical development, is a cyclized pentapeptide peptidomimetic designed to compete for the arginine–glycine–aspartic acid (RGD) peptide sequence that regulates integrin-ligand binding. Specifically, cilengitide selectively and potently blocks the ligation of the αvβ3 and αvβ5 integrins to provisional matrix proteins such as vitronectin, fibronectin, fibrinogen, von Willebrand factor. Cilengitide is capable of competitively antagonizing bacterial binding to ECs and as a result removes the signal that perpetuates vascular EC involvement in sepsis and thus presents as a potential as new complementary strategy for the treatment of established sepsis and as prophylaxis in high risk patients. This indeed can result in lowering of the antimicrobials used and will reduce resistance.

**Keywords:** Septic shock, Vascular endothelium, Cilengitide, Integrins, Antimicrobial resistance

## BACKGROUND

Sepsis is a fast progressing disease, triggered by the [1] host response to infection. If untreated,sepsis can rapidly evolve to multi-organ dysfunction and septic shock . Despite numerous advances in palliative intensive care and antibiotic treatment,

sepsis remains a major cause of morbidity and mortality [2].To combat against sepsis antibiotics have been a blessing for human civilization but resistance to antibiotics develops in no time and hence is a bigger matter of concern [3] [4].Antimicrobial resistance has posed increasing challenge to public health[5]. The vascular endothelium is a major target of sepsis-induced events [6, 7]. Upon entry to the bloodstream, bacteria attach to the endothelium within 15 s [8].During sepsis the vascular endothelial barrier breaks down leaking fluid into the extravascular space leading to life threatening edema in the lungs, kidney and brain of septic patients which results in multi-organ failure. Bacterial binding to the major EC integrin αVβ3 as a novel host-pathogen interaction that occurs early in sepsis [8, 9]. By this mechanism, both Staphylococcus aureus and Escherichia coli induce loss of junction protein VE-cadherin, which weakens the EC barrier and increases permeability. cilengitide is capable of competitively antagonizing bacterial binding to ECs and as a result removes the signal that perpetuates vascular EC involvement in sepsis, and thus presents as a potential as new complementary strategy for the treatment of established sepsis and as prophylaxis in high risk patients.

## SEPSIS

Sepsis is responsible for tremendous morbidity, mortality and health care expenditure worldwide. Sepsis is a fast progressing disease, triggered by the host response to infection. If untreated, sepsis can rapidly evolve to multi-organ dysfunction and septic shock [10]. Despite numerous advances in palliative intensive care and antibiotic treatment, sepsis remains a major cause of morbidity and mortality. Empirical antibiotic use is needed to eradicate the microbe that causes sepsis. Empirical antibiotic therapy must also consider the site of infection, the common pathogen that caused sepsis and antibiotic sensitivity based on local patterns of antibiotic resistance [11]

## INVOLVEMENT OF INTEGRINS IN SEPSIS

Integrins are heterodimeric receptors that are important for cell-cell and cell-extracellular matrix (ECM) interactions and are composed of one (Alpha) and one (Beta)-subunit [12,13].In the case of sepsis the incoming bacteria is responsible for binding to the endothelial cell integrin (EC) αVβ3 a novel host-pathogen interaction that occurs early in sepsis[14.15] due to this binding mostly staphylococcus aureus and E.coli is responsible for inducing loss of VE cadherin junction this results in weakening of EC barrier this results in increasing of the permeability .These cell adhesion molecules act as transmembrane linkers between their extracellular ligands and the cytoskeleton, and modulate various signaling path-ways essential in the biological functions of most cells. Integrins play crucial role in processes such as cell migration, differentiation and survival during embryogenesis, angiogenesis, wound healing, immune and non-immune defense mechanisms, hemostasis and oncogenic transformation[16].many integrins are also linked with pathological conditions has converted them into very promising therapeutic targets [17]

## PATHOGENESIS OF SEPSIS

The pathogenesis of sepsis is complex [18,19].The host cytokine tumor necrosis factor (TNF, also known as cachectin) could reproduce many of the pathological and clinical features of sepsis[20]. The host response to infection plays an important role in the pathogenesis of the condition.

### The four important process involved in sepsis are

1. **Endothelial dysfunction**: Generalized endothelial activation increases the expression of a number of leucocyte adhesins, with increased leucocyte transmigration into tissues. The permeability of the endothelium is also increased, in the lung leading to interstitial pulmonary edema and in the gut increasing bacterial translocation, potentially exacerbating the inflammatory cascades already initiated by microbial products.
2. **Coagulopathy**: Altered coagulation is extremely common in sepsis. Endothelial damage removes the protective function of the natural anticoagulation protein C pathway and converts the endothelium into a prothrombotic surface. In addition, bacterial products and inflammatory cytokines activate tissue factor, the main initiator of the extrinsic pathway of blood coagulation. This prothrombotic state may lead to blockage of the microvasculature, as well as giving rise to a

consumption coagulopathy (disseminated intravascular coagulation). Gram-positive products can also directly activate the contact clotting system.

3. **Cellular dysfunction**: The molecular basis of this is still not clear, although a generalized reduction in energy expenditure by cells suggests some kind of hibernation like process. Concomitant with this alteration in cellular function are numerous metabolic changes, notably increased catabolism, insulin resistance and hyperglycemia.
4. **Cardiovascular dysfunction**: Patients with sepsis have a decreased systemic vascular resistance (SVR) with a normal or increased cardiac output, the so-called 'hyperdynamic' state of sepsis. Cardiac output is maintained at the expense of left ventricular dilation, with reduced ejection fraction and a reduced left ventricular stroke work index in response to left ventricular end diastolic volume increase. These changes can lead to the hypotension characterizing septic shock.

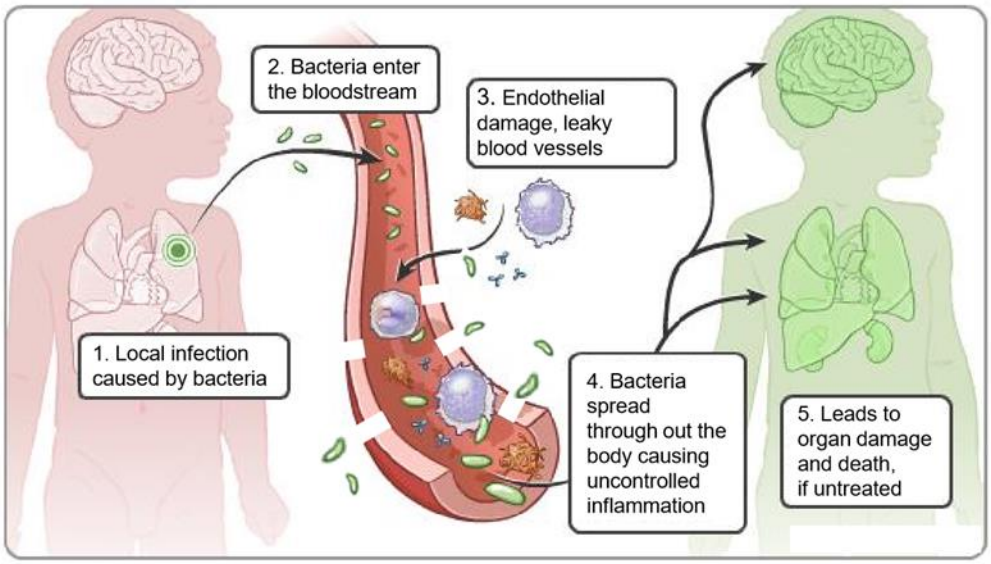


**Figure 1-Pathogenesis of sepsis**

## Anti-infectious management

Early and adequate antimicrobial therapy is the cornerstone of the anti-infective therapy in sepsis. Broad empirical antimicrobial therapy should be administered as soon as possible after at least two sets of blood cultures have been obtained. Timing is crucial for this patient population as mortality increases when antimicrobial therapy is delayed [21,22].Broad spectrum coverage is also necessary since inappropriate antimicrobial therapy is associated with a significant increase in mortality [23]. In general, broad-spectrum carbapenems (i.e., meropenem, imipenem/cilastatin or doripenem) or extended-range penicillin/β-lactamase inhibitor combination (i.e., piperacillin/tazobactam or ticarcillin/clavulanate) can be recommended as first choice drugs. Third- or higher-generation cephalosporins may also be considered [24].Patients with a very high risk of mortality such as septic shock should receive a multidrug therapy to broaden the antimicrobial spectrum. However, combination therapy should be avoided in no-shock sepsis [25,26]Empiric antimicrobial therapy should be narrowed as soon as the underlying pathogen and its resistance pattern is identified. De-escalation strategies are safe [27] and are independently associated with a decrease in mortality [28]

## ANTIMICROBIAL RESISTANCE IN SEPSIS

The emergence of antimicrobial resistance is increasing at an alarming rate worldwide[29]and is becoming a serious threat to public health.[30,31]The challenge to clinicians treating patients with sepsis is to determine which microorganisms should be covered with the initial antibiotic regimen. Traditionally, this has been accomplished with knowledge of the pathogens causing infections at the local hospital level, along with their antimicrobial susceptibilities and the assessment of specific patient types likely to benefit from empirical broad-spectrum antibiotics [32,33]. Unfortunately, the use of specific risk factors for analysis has been shown to result in limited overall accuracy in determining the need for broad-spectrum antibiotic therapy and can result in unnecessary use of such agents [34].Empirical antibiotic use is needed to eradicate the microbe that causes sepsis. Empirical antibiotic therapy must also consider the site of infection, the common pathogen that caused sepsis and antibiotic sensitivity based on local patterns of antibiotic resistance.[35]Failed to define the source of infection will potentially lead to wrong pathogen identified, and will also lead to inappropriate antibiotic selection.[36]The global escalation in both community- and hospital-acquired antimicrobial-resistant bacteria is increasingly compromising effective antimicrobial therapy, particularly when it comes to empiric antimicrobial selection.[37].The appropriate use of an empirical antibiotic is critical to decrease the mortality rate of sepsis[38] ,Escherichia coli, Enterococcus faecalis, and Staphylococcus aureus are commonly isolated causes of sepsis in the United States [39,40], and E. coli and S. aureus have also been found to be common causes of bacteraemia in Thailand [41]. The emergence of multidrug resistance (MDR) especially in gram negative microbes like *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*has left clinicians with fewer treatment options, contributed to more healthcare resources and worst clinical outcomes.[42,43]

## CILENGITIDE IN SEPSIS

**Targetting Integrins**

| Antibodies | Small Molecule | Peptidomimetics/peptide |
|---|---|---|
| Volociximab<br>CNTO95<br>IMGN 388<br>MEDIMMUNE 522 | 1. E7820 | Cilengitide<br>ATN 161 |

**Targetting integrins:** classess of antagonists Cilengitide, the most advanced integrin inhibitor in clinical development, is a cyclized pentapeptide peptidomimetic designed to compete for the arginine–glycine–aspartic acid (RGD) peptide sequence that regulates integrin-ligand binding. Specifically, cilengitide selectively and potently blocks the ligation of the αvβ3 and αvβ5 integrins to provisional matrix proteins such as vitronectin, fibronectin, fibrinogen, von Willebrand factor, osteopontin, and others.[44,45,46]

The vascular endothelium is a major target of sepsis-induced events [47, 48]. Upon entry to the bloodstream, bacteria attach to the endothelium within 15 s . Attachment triggers dysregulated signals that result in endothelial cell (EC) death and loss of barrier integrity, which give rise to increased capillary permeability clinically associated with hypotension, subcutaneous and body-cavity oedema and impaired tissue oxygenation, key events leading to multi-organ failure.

cilengitide is capable of competitively antagonizing bacterial binding to ECs and as a result removes the signal that perpetuates vascular EC involvement in sepsis, and thus presents as a potential as new complementary strategy for the treatment of established sepsis and as prophylaxis in high risk patients.

cilengitide, inhibits bacterial binding to the endothelium both in vitro and in vivo. By preventing bacteria from binding to the endothelium, downstream injurious effects such as thrombus formation, coagulation activation, inflammation and loss of barrier integrity are significantly reduced. These effects are the key events driving organ failure and mortality during severe infection.

Basically, this medication prevents bacteria from binding to the cells that line the blood vessels. It is felt that, when these cells are damaged, the intense inflammation that follows is what causes the organ damage. If the damage to these cells can be prevented altogether, then the organ failure from infection may never happen in Sepsis.

## CONCLUSION

There is only a short window of opportunity for treatment of sepsis with the early administration of antibiotics and fluid. However, in many cases antibiotics are not effective due to drug resistance or delays in identifying the type of bacteria that has caused the infection. Therefore, there is a need for a non-antibiotic therapy that can be used at all stages of infection against all bacterial causes of sepsis.

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