

HOW CILENGITIDE REDUCES MORTALITY RATE IN SEPSIS THAN OTHER ANTIBIOTICS

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ABSTRACT

Sepsis is a complex condition characterised by the simultaneous activation of inflammation and coagulation in response to microbial entry. These events manifest as systemic inflammatory response syndrome or sepsis symptoms through the release of pro inflammatory cytokines, pro coagulants, and adhesion molecules from immune cells and damage endothelium. Today, sepsis is a severe multisystem disease with difficult treatments and high mortality rate. So, the drug cilengitide has developed to treat sepsis and to decrease the mortality rate because, all antibiotics that used in sepsis which involve in inhibiting the bacterial growth but they does not stop bacterial attachment to endothelial cells this cause bacteria to spread / reach to major organs (vital organs) i.e. accumulation of fluids in major organs may takes place and cause septic shock/ organ failure. Here, this review summarizes that cilengitide is an antagonist of the major endothelial cell integrin, alpha-v beta-3 & this integrin is an adhesion molecule that mediates the adhesion of cells to the extracellular matrix and work effectively in stabilizing the blood vessels so that they cannot leak bacteria and infect major organs.

KEYWORDS: Sepsis, pathogenesis, sepsis management, cilengitide, systemic inflammatory response syndrome.

INTRODUCTION

^[1]Sepsis is also known as septicaemia. Sepsis is a clinical syndrome caused by the body's immune and coagulation systems being switched on by an infection. ^[2]Sepsis is a life.

Threatening condition results from the presence of harmful micro-organisms in the blood or other tissues and body's response to their presence. In other words sepsis occurs when chemicals released in the blood stream to fight an infection trigger inflammation throughout the body. This can cause a cascade changes that damage multiple organ system, (major organs) leading to fail. Sepsis constitutes a medical emergency because, if person does not receive treatment, it can lead to death.



Fig. 1: Showing the presence of harmful bacteria in blood.

Target of Sepsis

^[3]The "vascular endothelium" is a major target of sepsis induced events and endothelial damage accounts for much of the pathology of septic shock. During sepsis the vascular endothelial barrier breaks down leaking fluid into the extra vascular space leading to life threatening oedema in the lungs, kidney and brain of septic patients which results in MULTI-ORGAN FAILURE. The inflammatory response also plays a key role in the sepsis phenotype and an excessive or sustained inflammatory response contributes to the tissue damage and death.

How Sepsis Will Spread To Major Organs

^[4]Even though, you are taking medications for sepsis small blood clots can form throughout your body. These clots block the flow of blood and oxygen to vital organs

and other parts of your body. It produces inflammatory responses throughout the body and damage vital organs & increases the risk of organ failure and tissue death (gangrene)

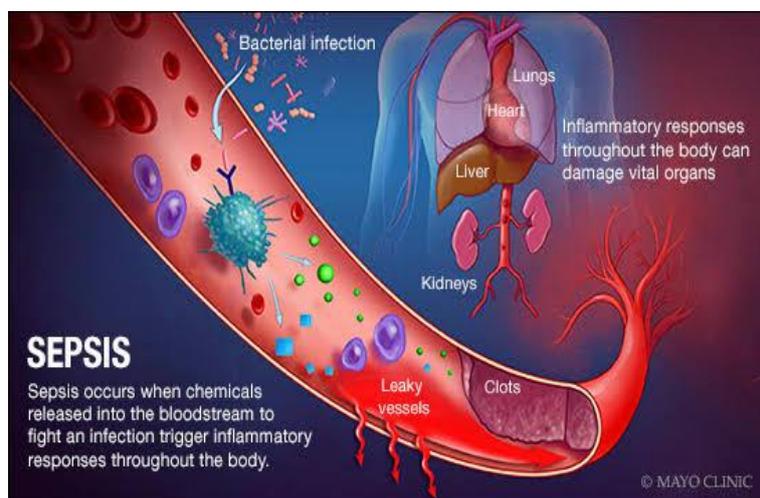


Fig. 2: Blood clots blocking the flow of blood and oxygen to major organs.

Etiology

^[5]Many types of microbes can cause sepsis, most commonly the infection is bacterial, but it may also be fungal, viral, or protozoan. Candida species are some of the most frequent fungi that cause sepsis. Mostly sepsis is caused by *Staphylococcus aureus* and *Escherichia coli*. Immune response triggered by an infection. Diet which is high in fat, sugar and low in fibre. It may also spread through pneumonia or genitourinary like urinary tract infection. There are many more examples of linking

terms to sepsis for example- tattoo, spider bite. It may also spread or attack to a person with weak immune system in “hospital environment”.

Common Infections Can Lead To Sepsis

The most common types of infections to cause sepsis in seniors are:

Respiratory like pneumonia
Genitourinary like urinary tract infection
Some other gut infections & skin infections.

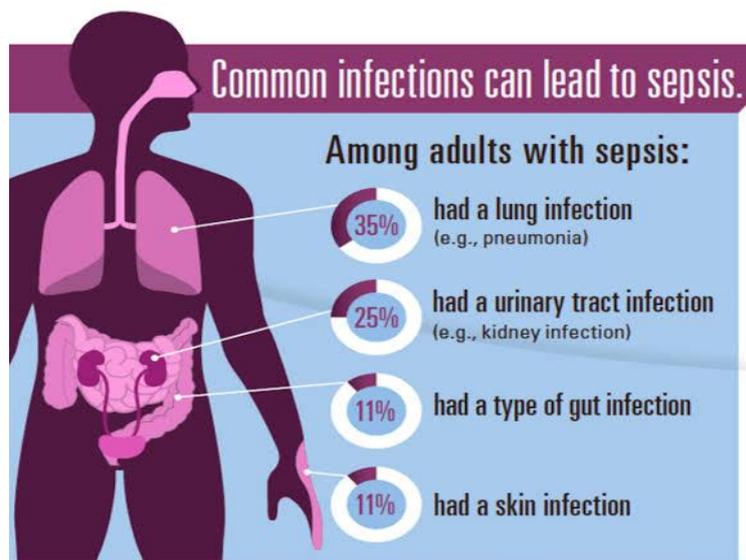


Fig. 3: Common infections that can cause or lead to sepsis.

Epidemiology

^[6]The global epidemiological burden of sepsis is difficult to ascertain. ^[7] It is estimated to affect more than 30million people worldwide every year, potentially leading to 6 million deaths. Only in Americans severe sepsis strikes more than a million every year, and 15 to

30 percent of those people die. The number of sepsis cases per year has been on the rise.

In the United States. It is estimated that 3 million newborns and 1.2 million children suffer from sepsis globally every year. Three out of every ten deaths due to

neonatal sepsis are thought to be caused by resistant pathogens. One in ten deaths associated with pregnancy and childbirth is due to maternal sepsis with over 95% of deaths. It affects all age groups (neonates, males and

females) but increased survival rates in females when compared with male patients. [Survival rate- 74% in women vs. 31% in men].

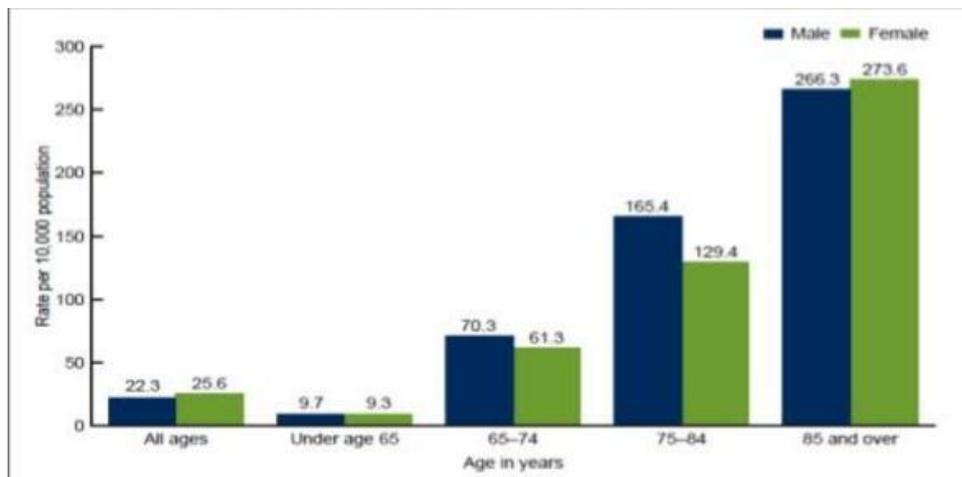


Fig. 4: Hospitalization rates of sepsis or septicemia were similar for males and females and increased with age.

STAGES

STAGE:1

Systemic inflammatory response syndrome (SIRS)

[8] Sepsis can be hard to identify, but is typically denoted by a very high or low body temperature, high heart rate, high respiratory rate, high or low white blood cell count and a known or suspected infection. The above mentioned signs are actually used to identify systemic inflammatory response syndrome, which only becomes sepsis when an infection is present. SIRS is, in some circles, a more commonly used term because sepsis only seen as a subcategory of SIRS signs, as well as an infection, need to be present.

STAGE:2-severe sepsis

The second stage, called severe sepsis, is diagnosed when acute organ dysfunction begins. Severe sepsis can also be diagnosed when sepsis present along with hypotension (low blood pressure) or hypoperfusion (decreased blood flow through an organ). Organ

dysfunction is characterised by symptoms such as decreased urine output, sudden changes mental state, decreased blood platelet count, difficulty breathing, abnormal heart pumping function and abdominal pain. Partly because of this, urine output is one of the factors measured in the SSC sepsis 6 bundle (sepsis resuscitation bundle) { Is a combination of evidence based objectives that must be completed with in 6 hours for patients presenting with severe sepsis, septic shock, & / or lactate > 4mmol/L (36mg/dl)} immediately after diagnosis of sepsis to track progression.

STAGE:3- septic shock

Septic shock is the most severe stage of sepsis. It is defined as presence of hypotension, induced by sepsis, despite fluid resuscitation. In addition, perfusion abnormalities such as elevated lactate levels. Septic shock has the highest chance of mortality, with estimates ranging from 32% to 50%.

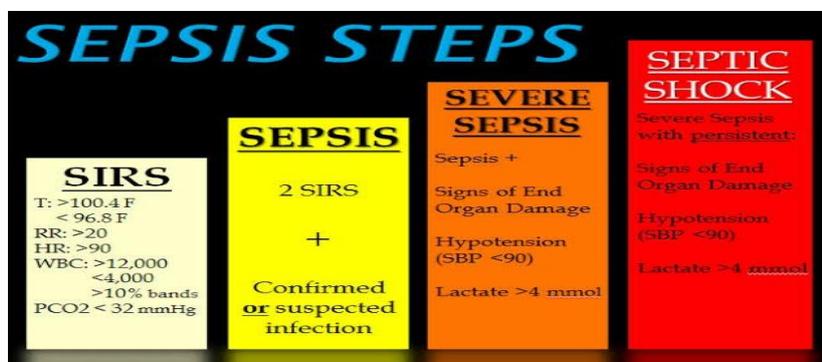


Fig. 5: Steps involved in sepsis along with investigated values.

Types of Sepsis

Neonatal sepsis[9] neonatal sepsis is a type of neonatal infection and specifically refers to the presence in a new

born baby of a bacterial blood stream infection (BSI) such as meningitis, pneumonia, pyelonephritis, or gastroenteritis in the setting of fever. Criteria with regards

to hemodynamic compromise or respiratory failure are not useful clinically because these symptoms often do not arise in neonates until death is imminent and unpreventable. Neonatal sepsis is divided into two categories: Early-onset (EOS) : it refers to sepsis presenting in the first 7 days of life i.e 72 hours. Late-onset (LOS): it refers to presentation of sepsis after 7 days. This helps the doctor decide what kind of treatment to administer. Low birth weight and premature babies are more susceptible to late onset sepsis because their immune systems are immature, while symptoms can be subtle and non.

Severe sepsis- is sepsis causing poor organ function or insufficient blood flow. Insufficient blood flow may be evident by low blood pressure, high lactate, or low urine output.

Abdominal sepsis^[10] Abdominal sepsis represents the host's systemic inflammatory response to bacterial or yeast peritonitis, gram negative, gram positive, as well as anaerobic bacteria, including common gut flora. (peritonitis is an inflammation of the peritoneum). They enter the peritoneal cavity and lead to release of proinflammatory cytokines., it increases the capillary leakage by damaging the endothelial lining (tissue that lines the inner wall of the abdomen) This can rapidly spread into blood and cause organ failure.

Puerperal sepsis- ^[11] was defined as infection of the genital tract occurring at any time between the onset of rupture of membrane or labour, and the 42nd day postpartum in which two or more of the following are present:

Fever (oral temperature 38.5^oC/101.3^oF)

Pelvic pain

Abnormal vaginal discharge e.g: Presence of pus.

Puerperal sepsis is preventable with provision of adequate antenatal care, referral and timely treatment of complications of pregnancy, promoting institutional delivery and postnatal care.

Lactate sepsis – Elevated lactate is typically present in patients with severe sepsis or septic shock and has clinical and statistical significance in predicting mortality in patients with infections. Measurement of lactate in all septic patients is a simple strategy that may assist clinicians to more effectively manage the care of septic patients and improve outcomes. Lactate and cryptic shock – cryptic shock is defined as a serum lactate greater than 4 mmol/L with a systolic blood pressure of at least 90 mmHg. Severe sepsis with cryptic shock has a mortality rate similar to that of patients with overt septic shock.

Who is at risk ?

Although some people have a higher risk of infection, anyone can get sepsis. People who are at risk include:

Neonates, young children, women, men and old age people.

People with weaker immune systems, such as those with HIV or those in chemotherapy treatment for cancer, liver cirrhosis, kidney disease etc.

People being treated in an intensive care unit (ICU), People exposed to invasive devices, such as intravenous catheters or breathing tubes.

Principles About Icu Transfer

Many patients with sepsis and some subsets of severe sepsis may be managed safely on the general care floor. However, ICU transfer should be strongly considered for all patients with cardiopulmonary dysfunction. The indications for ICU transfer depends on the patient's comorbidities, magnitude and trajectory of the cardiopulmonary dysfunction, and goals of care. However, consensus guidelines recommend that all patients with septic shock, and those with cryptic shock on presentation (lactate 4.0 mM/L or greater), to be triaged to the ICU. In addition, ICU transfer should also be considered for most patients with moderate to severe respiratory failure and central nervous system depression.

Is Sepsis Contagious

^[12] Sepsis is not contagious. Sepsis can't be transmitted from person to person, including between children, after death or through sexual contact. Sepsis spreads within a person's body from the original source of infection to other organs through the blood stream. Many strains of these bacteria have become drug-resistant, which may be why some believe sepsis is contagious.

Pathogenesis

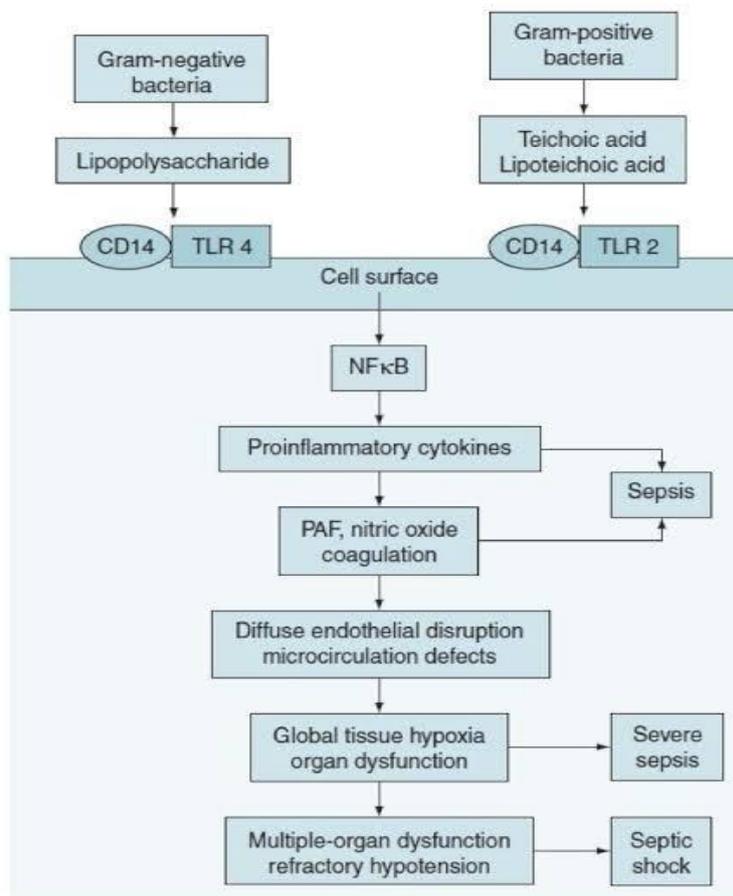


Fig. 6: Pathogenesis from the entry of bacteria into blood to multiple-organ dysfunction.

In sepsis condition gram negative bacteria like staphylococcus aureus, streptococcus pyogenes, Klebsiella Escherichia coli and pseudomonas aeruginosa; these bacteria produce sepsis and septic shock via the release of cell wall component known as endotoxin (lipopolysaccharide).^[13] The gram positive bacteria like cocci, streptococcus pneumoniae this bacterial cell wall contain teichoic acids and lipoteichoic acids appear to extend to the surface of the peptidoglycan layer. Lipopolysaccharide endotoxins are biologically important PAMPs. (Pathogen-associated molecular patterns). Endotoxins, which are an integral part of the gram negative cell wall, are released on the death of the bacterium and react with CD14 and TLR-4 receptors on the macrophage surface. It was found that TLR4 and complement system are involved in the initiation of the inflammatory response in sepsis. Intracellular signalling induces the synthesis and release of pro-inflammatory cytokines and NF-KB (Nuclear Factor Kappa Beta) is a central mediator of pro-inflammatory gene induction and function in both innate and adaptive immune cells.^[14] NF-KB is also involved in regulating the transcription of many of the immune modulatory mediators involved in the development of sepsis-induced organ failure. Increased activation of NF-Kappa B occurs with sepsis and^[15] greater levels of nuclear accumulation of NF-

Kappa B are associated with higher rates of mortality and worse clinical outcome. These inflammatory responses are tightly interwoven with different physiologic processes within the human host such as coagulation, metabolism and neuroendocrine activation. This cause inflammation –induced dysregulation of nitric oxide coagulation & PAF^[16] (platelet activation factor) signalling cascade in sepsis which involves in activation of myeloid leucocytes, platelets, & endothelial cells micro vascular injury & thrombosis, damage (or) global tissue hypoxia organ dysfunction which cause severe sepsis and multiple-organ dysfunction refractory hypotension which cause septic shock.^[17] Subsequent studies identified a variety of damage associated molecular pattern (DAMP)

How Do You Identify Sepsis: (Signs & Symptoms)

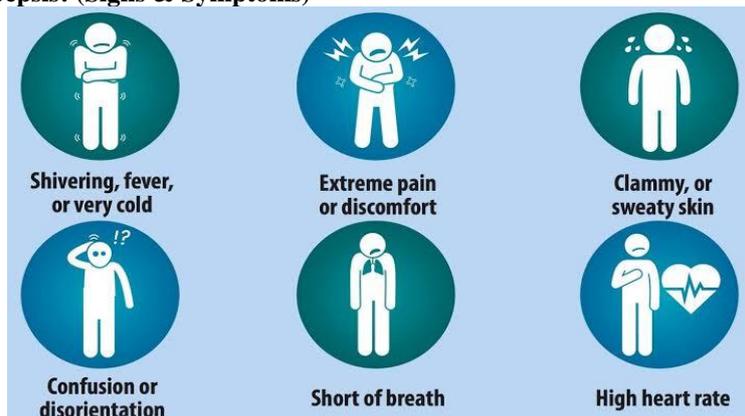


Fig. 7: Showing the signs and symptoms of sepsis.

How sepsis rash look like?

^[18]People with sepsis often develop a haemorrhagic rash. This may be a reddish discolouration or a cluster of tiny blood spots that look like Pink pricks in the skin. If

untreated, these dark dots gradually get bigger and begin to look like fresh bruises.



Fig. 8: Skin discoloration in sepsis effected person.

They join together to form larger areas of purple discoloration. If you or someone you know has a rash that you're worried could be a sign of sepsis, try pressing it down. A sepsis rash won't fade with pressure.

How to diagnose sepsis/ how do doctor's know if patient had sepsis

If you have symptoms of sepsis, your doctor will order tests to make a diagnosis and determine the severity of your infection. One of the first tests is a blood test. Your blood is checked for complications like:

Infection (presence of bacteria in blood), Clotting problems, Abnormal prothrombin time/partial thromboplastin time (PT/PTT) Abnormal liver or kidney function, increased creatinine (>2.0 or increased by 50%) or oliguria. Hyperbilirubinemia (>2.0) or liver function tests (LFTs) greater than twice the upper limit of normal. Decreased amount of oxygen an imbalance in minerals called electrolytes that affect the amount of water in your body as well as acidity of your blood. Depending on your symptoms and the results of your blood test, your doctor may other tests, including: a urine test (to check for bacteria in your urine) a wound secretion test (to check an open wound for an infection) a mucus secretion test (to identify germs responsible for an infection).

Confirmatory Diagnosis

Procalcitonin test:^[19] Procalcitonin (PCT) is a biomarker it contain 116 amino acids, i.e... Peptide precursor of the hormone calcitonin, a hormone that is synthesized by the parafollicular C cells of the thyroid and involved in calcium homeostasis. Procalcitonin in the blood can increase significantly. Normally procalcitonin levels are very low in the blood. [Normal range of procalcitonin: 0.10 to 0.49ng/ml]. The reference value of PCT in adults and children older than 72 hours is 0.15ng/ml or less. However, production can be stimulated in almost every organ by inflammatory cytokines and especially bacterial Endotoxins, causing high amounts of procalcitonin to be released in the blood. In this test a health care professional will take blood sample from a vein in your arm, using small needle and the sample will be collected into a test tube or vial. It reveals procalcitonin level range in patient body. This indicates the need for sensitive biomarkers for infection and organ dysfunction to support the early detection & treatment of sepsis. [Elevated level of PCT > 2ng/ml or > 10ng/ml] Is a sign of alarm indicating a high risk of organ dysfunction.

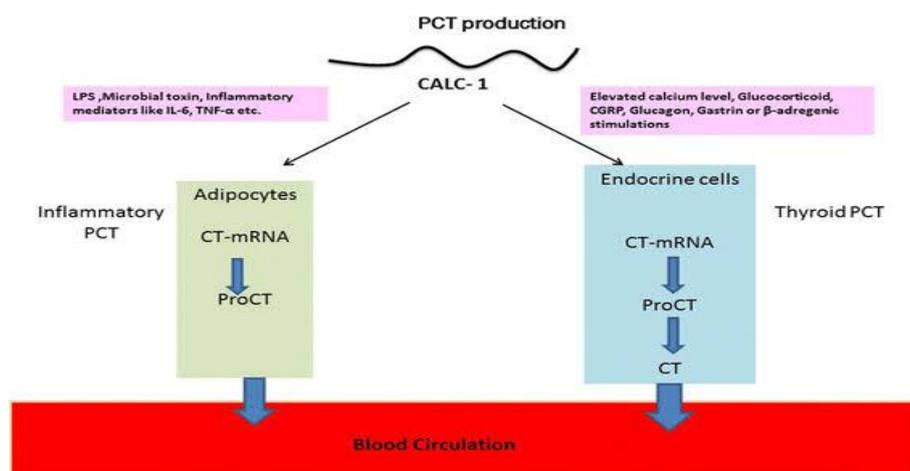


Fig. 9: Inflammatory cytokines causing procalcitonin to be released into blood.

Treatment for Sepsis

A number of medications are used in treating sepsis and septic shock. They include:

Antibiotics – Ceftriaxone Meropenem Ceftazidime Cefotaxime Cefepime Piperacillin & tazobactam Ampicillin & sulbactam. Ceftazidime

You may receive a prescription for antibiotics to take at home. But if your condition progresses to severe sepsis, you will receive antibiotics intravenously in the hospital.

Vasopressors: Nor-epinephrine Epinephrine Vasopressin Phenylephrine Dopamine.

These are the most commonly used vasopressors for septic shock.

Corticosteroids: Hydrocortisone Methylprednisolone Dexamethasone.

Researchers discover a drug that has the potential to stop sepsis before the condition reaches major organs and

becomes fatal So, In order to avoid (or) stop sepsis to major organs the new drug CILENGITIDE is used.

New Research Cilengitide Introduction

New research brings much – needed hope for treatment of sepsis. Researchers at the royal college of surgeons in Ireland [RCSI] which is located in Dublin have tested a compound called CILENGITIDE in a pre-clinical trial. Steve Kerrigan, PhD, an associate professor in pharmacology at the RCSI, invented the drug and led the trial. Sinead Hurley, a post doctoral fellow at royal college of surgeons and Irish centre for vascular biology, presented the findings at the RCSI research day 2019.

The drug CILENGITIDE goes by the Brand name – INNOVOSEP

Molecular formula: $C_{27}H_{40}N_8O_7$

Molecular weight: 588.7/mol

Dose: 500 – 2000 mg

Molecular^[20] structure of Cilengitide:

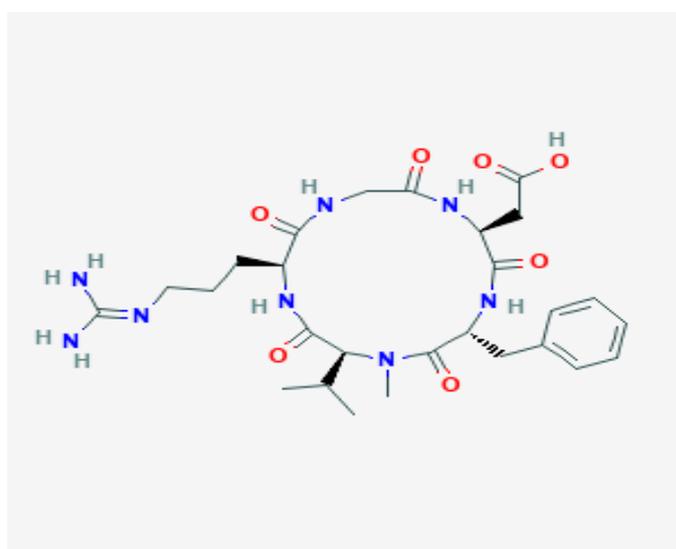


Fig. 10: Molecular structure of Cilengitide.

Chemical structure

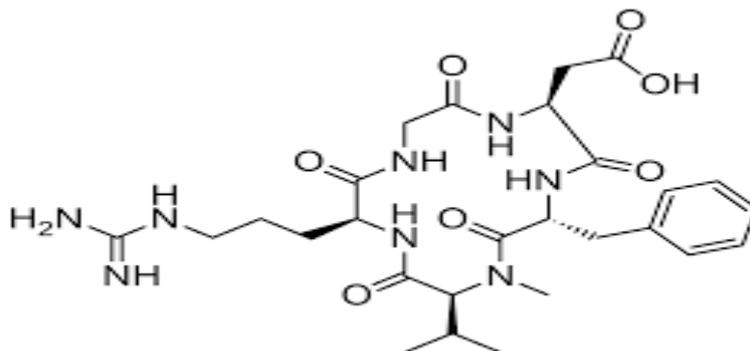


Fig. 11: Chemical structure of Cilengitide.

Cilengitide is a cyclic Arg-Gly-Asp peptide

Cilengitide Working Related To Cancer

^[21]Integrin's are heterodimeric receptors that are important for cell-cell and cell extracellular matrix (ECM) interactions and are composed of one α and one β subunit. These cell adhesion molecules act as transmembrane linkers between their extracellular ligands and the cytoskeleton, and modulate various signalling pathways essential in the biological functions of most cells. Integrin's play a crucial role in processes such as cell migration, differentiation, and survival during embryogenesis, angiogenesis, wound healing, immune and non-immune defense mechanisms, haemostasis and oncogenic transformation.

In particular, integrin's $\alpha v \beta 3$, $\alpha v \beta 5$ and $\alpha v \beta 1$ are involved in angiogenesis and metastasis of solid tumours, being excellent candidates for cancer therapy. Here, the $\alpha v \beta 3$ / $\alpha v \beta 5$ are blocked by the cilengitide disables the osteoclast-like differentiation of malignant plasma cells in multiple myeloma. The main effect of cilengitide is on the inhibition of adhesion without affecting proliferation, as shown by exploring the $\alpha v \beta 3$ -dependent and $\alpha v \beta 5$ -dependent intracellular signalling.

How Cilengitide Works In Sepsis

We have recently reported bacterial binding to major EC integrin (endothelial cell) $\alpha v \beta 3$ as a novel host- pathogen

interaction that occurs early in sepsis. By this mechanism, both staphylococcus aureus and Escherichia coli (primary triggers of sepsis) induce loss of junction protein VE-cadherin, which weakens the EC barrier and increases permeability. We identified that the compound cilengitide is an antagonist of the major endothelial cell integrin; alpha v beta 3. This integrin is an adhesion molecule that mediates the adhesion of cells to the extracellular matrix. Innovosep stopped the infection from advancing septic shock and organ failure by preventing damage to endothelial cells.

How Innovosep Work In Time Dependent Manner

^[22]To ascertain if cilengitide would be useful post-bacterial attachment we perfused clinical strains of S.aureus or E.Coli over human ECs for 360s using real time ex vivo model of sepsis. Cilengitide ($0.05 \mu\text{M}$) was either co-administered with the bacteria from $t=0$ s (pre-emptive effect) or introduced to the suspension at $t=15$, 30 and 180 s (therapeutic effect). Our data demonstrate that S.aureus and E.Coli binding to ECs increases steadily over time (FIG.1) when applied at $t=0$, cilengitide ($0.05 \mu\text{M}$) completely abolished S.aureus and E.Coli attachment to ECs. Following bacterial attachment to ECs (at $t=15$, 30 and 180 s), cilengitide significantly displaced bound bacteria in a time-dependent manner, rapidly reducing bacterial load back to background levels.

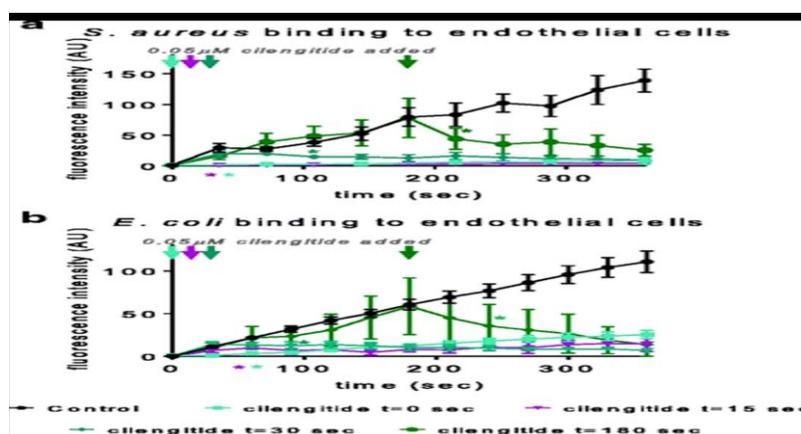


Fig. 12: Graph showing Cilengitide abolishing the bacterial attachment to endothelial cells.

These results suggest that cilengitide is capable of competitively antagonizing bacterial binding to EC involvement in sepsis, and thus presents as a potential as new complementary strategy for the treatment of established sepsis and prophylaxis in high risk patients. These observations warrant the initiation of preclinical and human clinical trials to validate the use of cilengitide as a pharmacological tool to reduce risk and / or increase the time window for the decision- making in sepsis patients.

Reason for Developing Cilengitide

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. Most of the antibiotics are used to inhibit the bacterial cell wall synthesis but unable to protect endothelial cell lining (ECL); which can cause severe endothelial dysfunction leading to dysregulation of haemostasis and vascular reactivity, as well as tissue oedema. This failure of ECL is considered central to the progression to organ failure during sepsis. But cilengitide successfully inhibit *S.aureus* and *E.Coli* from binding to human endothelial cells, both in vivo and invitro.

Because endothelium forms the essential vascular barrier for solute transport and osmotic balance. In simpler terms, "the drug appears to act by preventing the bacteria from getting into the blood stream from the site of infection by stabilizing the blood vessels. So that they cannot leak bacteria and infect the major organs.

In which stage of sepsis cilengitide can be used?

In order to prevent sepsis effectively either in early stage or in severe stage cilengitide a non-antibiotic therapy that can be used at all stages of infection against all bacterial causes of sepsis.

Can we use cilengitide with other antibiotics?

Patient suffering with sepsis can take cilengitide with other antibiotics because antibiotics work by inhibiting bacterial growth and cilengitide protects endothelial cells. So, cilengitide can be used with other antibiotics to prevent organ failure and death.

Pharmacokinetics of Cilengitide: (In Vivo Studies)

Absorption

It is administered in IV route. [23] At 0.1 hour after IV dosing, mean plasma concentrations of cilengitide, that is, unchanged drug, were 1240ng/ml in males and 2493ng/ml in females respectively. The plasma $t_{1/2}$ was short in both males and females. Clearance of cilengitide was high in males and females & indicating significant contribution of hepatic clearance to the total clearance of drug present in the body.

Distribution

Following IV administration, cilengitide was rapidly distributed. The highest concentrations are distributed into liver. In males and females, mean concentration at

0.1 h after dosing in the adrenals, heart, and brain were 765,627 and 272 ng/g. At this time, levels in ovaries and uterus were 2 times higher compared to testes but up to 3.5 times lower than those in plasma, indicating limited distribution into these tissues.

Metabolism

The major component circulating in plasma was unchanged drug. In males and females 7.5 to 31% of the radioactive dose was recovered in urine within 24 h of dosing & more than 79% of sample radioactivity in faeces.

Excretion

Most of the radioactive dose (iv) in males and females was excreted in the faeces within 24 h of dosing, via biliary secretion. The drug and its metabolites are rapidly eliminated from the body.

Cilengitide First Aid Measures In Toxic Conditions

In case of inhalation: Remove to fresh air. If not breathing, give respiration or oxygen by trained personnel. Get immediate medical attention.

In case of skin contact: immediately wash skin with soap and plenty of water for at least 15minutes. Remove contaminated clothing. Get medical attention if symptoms occur. Wash clothing before reuse.

In case of eye contact: hold eyelids apart and flush eyes with plenty of water for at least 15 min. Have eyes examined and tested by medical personnel.

In case of ingestion: wash out mouth with water provide person is conscious. Never give anything by mouth to an unconscious person. Get medical attention. Do not induce vomiting unless directed to do so by medical personnel.

Uses / Advantages Of Cilengitide

Cilengitide can prevent sepsis spreading to major organs. It protects endothelial cell lining (ECL).

It is also used to treat several cancers

It induces^[24] cellular detachment and apoptosis in endothelial and glioma cells.

Cilengitide in^[25] combination with radiation could be benefit for breast cancer.

Contraindications

1. Recurrent high grade glioma – hypersensitivity; inadequate bone marrow reserve.
2. Methylated MGMT (Methyl guanine- DNA-methyl transferase) + cilengitide = poor cardiac and respiratory risk.

CONCLUSION

Sepsis remains a significant burden on health systems worldwide. However, the clinical trials made on cilengitide gave successful result in preventing bacterial spread to major organs, fluid retention. Even in severe

stage of sepsis this drug will work effectively with very mild adverse reactions. Therefore, cilengitide is very helpful in decreasing mortality rate.

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