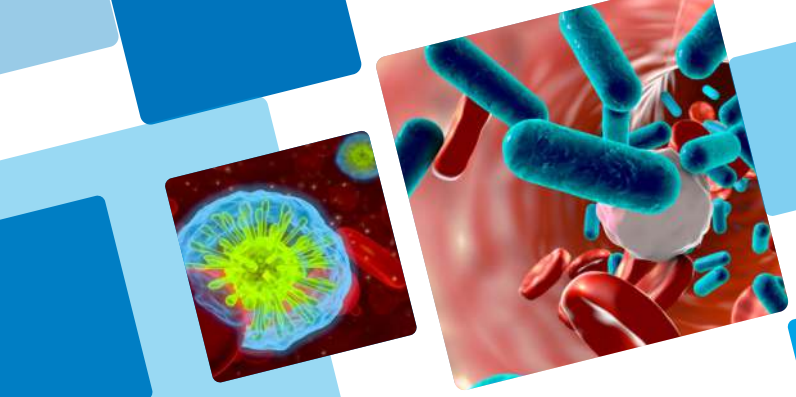


Sepsivac™

(Heat killed Mw)

Save More Lives

MONOGRAPH

Contents

1. Sepsis

1.1 Introduction

Sepsis and septic shock with resultant multi organ failure are one of the leading causes of mortality in intensive care units in adults.[1] Sepsis is the systemic response to severe infection.[2] It is a medical emergency which is explained by the host's immunological and inflammatory response to the infectious agent which may lead to multiple organ failure and ultimately death.[3]

1.2 Terminologies

When Systemic Inflammatory Response Syndrome (SIRS) is associated with infection it is known as sepsis.[4] In 1991, the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference outlined the definition of sepsis, i.e. systemic response to infection. This systemic response is manifested by two or more of the following conditions as a result of infection: temperature >38°C or <36°C; heart rate >90 beats per min; respiratory rate >20 breaths per min or PaCO2 <32 mm Hg; leukocyte count >12,000 cells per ml3 or <4,000 cells per ml3 or >10% immature (band) forms.[5]

If the sepsis is associated with concurrent one or multiple organ failures, it is considered as severe sepsis. A severe form of sepsis with associated cardiovascular dysfunction not responding to the fluid resuscitation is termed as septic shock.[6]

As per the Sepsis-3 definition, the different stages of severity of sepsis is simplified with the suppression of the 'severe sepsis' stage that becomes obsolete. So the new 'sepsis' is the old 'severe sepsis'. This will certainly facilitate communication about sepsis between healthcare personnel but also with regard to the public. This will improve the rapidity of diagnosis which is a key element of prognosis. Septic shock is now defined as a subset of sepsis.[7]

1.3 Prevalence

Sepsis continues to pose a challenge in critical care. The management of sepsis based on elimination of the causative infection by surgery, where ever possible, antibiotics, and supportive treatment (fluids, inotropes, vasopressors, replacement therapy of failing organ functions) has not sufficiently changed the mortality rate over the past decades.

Despite advances in the management of infectious disease, the inability to successfully treat sepsis remains an unsolved clinical problem. Each year, sepsis develops in more than 750,000 patients in the United States.[8]

Sepsis remains an important and life-threatening problem and the most common cause of death in the ICU with mortality between 20 to 50% for severe sepsis and 45 to 80% for septic shock.[9] Prevalence of severe sepsis in India is 28.3% out of which 20.5% are ICU acquired.[10]

1.4 Pathophysiology

Severe sepsis is associated with three integrated responses: activation of inflammation, activation of coagulation, and impairment of fibrinolysis. These three responses are due to a variety of proinflammatory mediators, procoagulant factors, and inhibitors of fibrinolysis. Sepsis syndrome seems to result from overwhelming systemic inflammation which is caused by excessive release of cytokines into the systemic circulation. Four cytokines, tumor necrosis factor-α (TNF-α), Interleukin 1 (IL-1), Interleukin-8 (IL-8) and Interleukin-6 (IL-6) have been most strongly associated with sepsis.[11] Figure 1 shows interrelationship among different aspects of severe sepsis

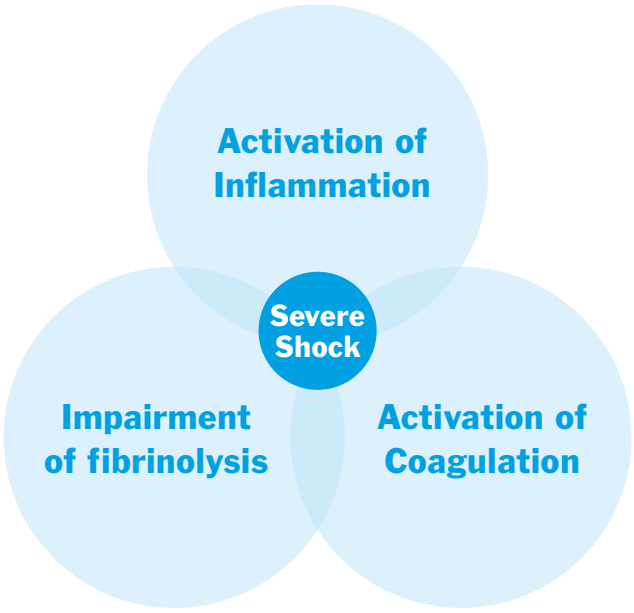


Figure 1: Severe Sepsis

1.4.1 Innate immunity and inflammatory mediators

A significant proportion of sepsis cases are caused by gram-negative bacilli.[12] The prime initiator of gram negative sepsis is endotoxin, the lipopolysaccharide (LPS) phospholipid protein complexes present in the bacterial outer membrane. It triggers the production of pro-inflammatory cytokines (e.g. TNF-α, Interleukin-1) which stimulate variety of inflammatory and pro-inflammatory mediator cascade that result in the systemic signs and organ dysfunction that characterize clinical sepsis. Tumor necrosis factor-α and Interleukin-1 are both endogenous pyrogens that contribute to the febrile response seen in sepsis.[12,13]

Recently it has been shown that binding of LPS with Toll Like Receptor (TLR) 4 activates two major intracellular pathways, MyD88 pathway and toll/interleukin-1 (IL-1) receptor domain containing adaptor protein inducing interferon-β (IFN-β) (TRIF) pathway. The former is involved with proinflammatory response while the latter leads to production of type 1 IFNs that stem the inflammatory response and cause a state of immuno-supression.[14,15,16]

1.4.2 Dysregulation of hemostasis

In sepsis, there is an interaction between the inflammatory and hemostatic pathways, with the simultaneous activation of both the inflammatory and the coagulation cascades. The hypercoagulability of sepsis is thought to be driven by the release of tissue factor from disrupted endothelial cells. Tissue factor then causes the systemic activation of the coagulation cascade resulting in the production of thrombin, activation of platelets, and formation of platelet–fibrin clots. These microthrombi can cause local perfusion defects resulting in tissue hypoxia and organ dysfunction.[3] In addition to the hypercoagulability, a reduction of fibrinolysis is also observed as a result of sepsis.[17]

Because of the increased levels of TNF α and IL-1 β, tissue plasminogen activators are released which in turn results into blunting of the activation of plasmin. The ultimate result of this is diminished fibrinolysis and fibrin removal which contributes to the perpetuation of microvascular thrombosis.[3]

Microthrombi can cause local perfusion defects resulting in tissue hypoxia and organ dysfunction.[3]

1.4.3 Immunosuppression

The initial proinflammatory state of sepsis is often superseded by a prolonged state of immunosuppression. There is a decrease in the number of T cells (helper and cytotoxic) as a result of apoptosis and a decreased response to inflammatory cytokines.18 The immune system in a septic individual is unable to stage an effective immune response to secondary bacterial, viral, or fungal infections.[3]

1.4.4 Cellular, tissue, and organ dysfunction

In the patient of sepsis, there is an occurrence of hypo-perfusion due to the cardiovascular dysfunction that is seen in sepsis. This results in decreased delivery and utilization of oxygen by cells translating to tissue and organ dysfunction in sepsis. Circulating cytokines, such as TNF α and IL-1 β among others, which can cause depression of cardiac myocytes and an interference with their mitochondrial function.

This leads to septic cardiomyopathy in 18% to 60% of the sepsis patients. Secondly, in sepsis, both systolic and diastolic dysfunction with decreased stroke volumes and increased end-diastolic and end-systolic volumes in sepsis. Arterial and venous dilation (induced by inflammatory mediators) and consequent reduced venous return, a state of hypotension and distributive shock is produced by sepsis.[3] In the lungs, there is disruption of the alveolar–endothelial barrier with accumulation of protein-rich fluid in the interstitial lung spaces and alveoli, producing acute respiratory distress syndrome (ARDS) in extreme cases.

In the kidneys, reduced renal perfusion and acute tubular necrosis produce varying degrees of acute kidney injury. In the gastrointestinal tract, the increased permeability of the mucosal lining results in auto-digestion of the bowel by luminal enzymes. In the CNS, altered blood–brain barrier, causing the entry of toxins, inflammatory cells, and cytokines, results in changes of cerebral edema, neurotransmitter disruption, oxidative stress, and white matter.[3]

1.5 Current treatment options[20]

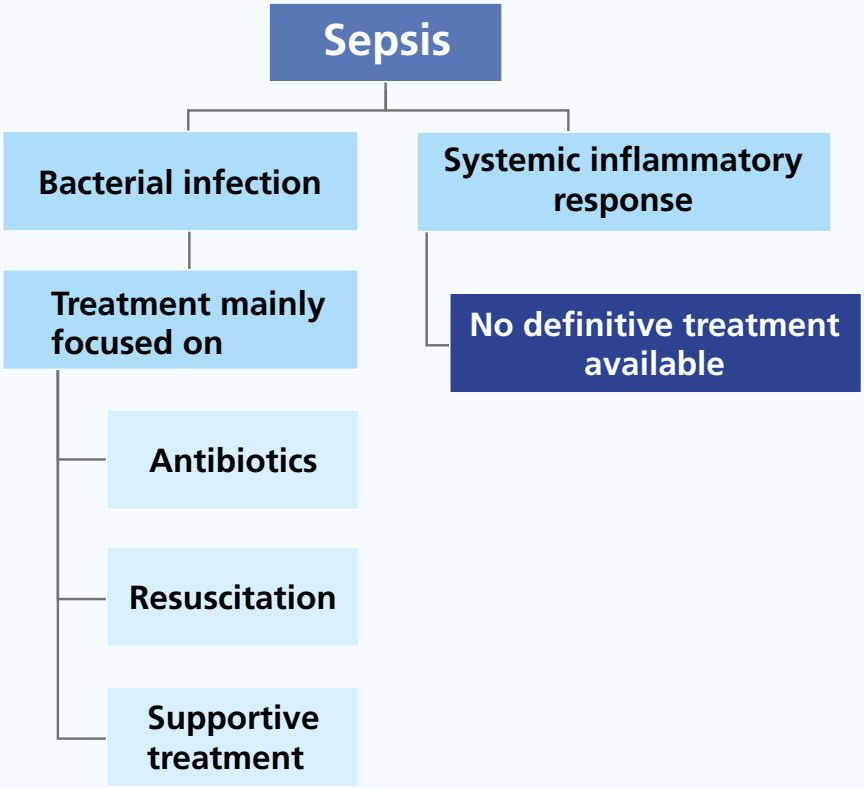
Treatment of sepsis largely vary from patient to patient. Depending upon the condition of the patient and the stage of sepsis, different treatments are advocated. Antibiotics have always been the mainstay of the treatment protocol. Below mentioned are the treatment options according to the "surviving sepsis" guidelines:

- **Resuscitation**
- **Antimicrobial Therapy**

  -Drug sensitivity testing
- **Source Control**
- **Hemodynamic Support and Adjunctive Therapy**

  - Fluid Therapy of Severe Sepsis
  - Vasopressors
  - Inotropic Therapy
  - Corticosteroids
- **Other Supportive Therapy of Severe Sepsis**
  - Blood Product Administration
  - Immunoglobulins
  - Mechanical Ventilation of Sepsis-Induced ARDS
  - Sedation, Analgesia, and Neuromuscular Blockade in Sepsis
  - Glucose Control
  - Renal Replacement Therapy
  - Bicarbonate Therapy
  - Deep Vein Thrombosis Prophylaxis
  - Stress Ulcer Prophylaxis
  - Nutrition

As it its evident here, all the treatment options deals with the infection component of the sepsis process. There is a potential gap in the treatment of sepsis to deal with the inflammatory response.



2. Sepsivac

Sepsivac™ (Heat killed Mw)
Save More Lives

2.1 Summary product information

Route of administration	Dosage form / strength
Intradermal	0.3 ml is given in three divided dose of 0.1 ml on three different sites daily for three days.

2.2 Description

2.2.1 Name of the medicinal product

Sepsivac

Heat killed mycobacterium W

2.2.2 Qualitative and Quantitative Composition

Sepsivac is a heat killed suspension of Mycobacterium W (Mw), a nonpathogenic, cultivable atypical mycobacterium with biochemical properties and growth characteristics resembling those belonging to Runyans group IV class of mycobacteria.

Each dose of 0.1ml Contains	
Mycobacterium w	0.5 x 10^9 bacilli (Heat Killed)
Sodium Chloride IP	0.9% W/v
Thiomersol IP	0.01% W/v
Water for injection	q.s.

2.2.3 Pharmaceutical Form

0.6 ml vial for Intradermal Injection

2.3 Therapeutic Indications

Sepsivac has been found useful in various clinical conditions apparently unrelated to each other. However, underlying immune mechanism explains its role in various diseases.

- Sepsis due to Gram Negative Infection
- Leprosy – in Lepromin negative patients

2.4 Posology and method of administration

The recommended site for giving the Sepsivac is at the insertion of the deltoid muscle near the middle of the left upper arm. Sites higher on the arm are more likely to lead to keloid formation, the tip of the shoulder particularly. For cosmetic reasons, a scar on the upper and lateral surface of the thigh may be preferred and this is an alternative site.

The upper arm must be approximately 45 degrees to the body. This can be achieved if the hand is placed on the hip with the arm abducted from the body. The skin should be swabbed with spirit and allowed to dry. The operator stretches the skin between the thumb and forefinger of one hand and with the other slowly inserts the needle, with the bevel upwards, till bevel is fully in the demises and not visible out. The needle can usually be seen through the epidermis. A correctly given intradermal injection results in a tense blanched raised bleb (peau d'orange) and considerable resistance is felt when the fluid is being injected.

A bleb typically of 7mm diameter follows a 0.1ml injection. If little resistance is felt when injecting and a diffuse swelling occurs as opposed to a tense blanched bleb, the needle is too deep. The subject must always be advised of the normal reaction to the injection.

2.5 Immunization reaction and care of the immunization site

Following intradermal administration of Sepsivac, normally a local reaction develops at the immunization site within two to six weeks, beginning as a small papule which increases in size for a few weeks widening into a circular area with scaling, crusting and occasional bruising. Occasionally a shallow ulcer develops. It is not necessary to protect the site from becoming wet during washing and bathing, but should any oozing occur, a temporary dry dressing may be used until a scab forms. It is essential that air be not excluded.

If absolutely essential an impervious dressing may be applied but only for a short period (for example, to permit swimming) as it may delay healing and cause a larger scar. The lesion slowly subsides over several months and eventually heals leaving only a small, flat scar.

A correctly given intradermal injection results in a tense blanched raised bleb (peau d'orange) and considerable resistance is felt when the fluid is being injected.

2.6 Contraindications

Individuals with generalized septic skin condition (if eczema exists, a site should be chosen that is free from skin lesions).

2.7 Pregnancy and lactation

Pregnancy Category C: Animal reproduction studies have not been conducted with Sepsivac. It is also not known whether Sepsivac can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Sepsivac should be given to a pregnant woman only if clearly needed.

It is not known whether Sepsivac is excreted in human milk. As many drugs are excreted in human milk, caution should be exercised when Sepsivac is administered to a nursing woman.

2.8 Undesirable effects

Severe injection site reactions, large ulcers and abscesses are most commonly caused by faulty injection technique where part or the entire dose is administered too deeply (subcutaneous instead of intradermally).
Keloid formation at the injection site is an uncommon and largely avoidable complication of Sepsivac.

There was twenty seven (27) AEs observed during the study. Out of these, eight (08) AEs were observed in Test treatment arm and nineteen (19) AEs were observed in Control arm.

The delayed mortality was observed in Test group compared to the Control group during the study which shows effectiveness of Test drug and lesser mortality in Test group shows the safety of Test formulation over control group. Hence, the study drug Sepsivac is found to be safe and well tolerated, without any major safety concerns in patients with severe sepsis.

2.9 Interaction with other medicinal products and other forms of interactions

Data evaluating the concomitant administration of Sepsivac with other vaccines are not available.

2.10 Overdose

No data are available on the overdose with Sepsivac.

2.11 Storage and Stability

- Store between 2-8 °C
- Do not freeze. Discard if vaccine has been frozen
- Protect from light

2.12 Special precautions for disposal

Any unused medicinal product or waste material should be disposed off in accordance with the local requirements.

3. Sepsivac in sepsis

3.1 Mechanism of action

Mycobacterium w is a nonpathogenic, cultivable atypical mycobacterium which is a known immunomodulator. It is a potent TLR2 agonist[21, 22] as well as a poly TLR antagonist (4, 5, 7, 9).[23] Sepsivac as an antagonist of TLR 4 receptor would inhibit the downstream cytokine production pathway and decrease production of various cytokines (Figure 3, 4, 5, 7). Apart from that, Sepsivac also inhibits P38 and MyD88/TRIF pathway which further decrease cytokine production mainly TNF- α and IL1β. Sepsivac also reduces the production of increased level of other cytokines like IL2, 4, 5, 6, 8, 10 and 12. (Figure 9) In a gene expression study, Sepsivac was shown to down regulate the gene which were upregulated by the disease process and establish immune homeostasis. Some of the important genes are IL 1β, IL 6r, IL 10 and STAT 3. (Table 1)

TLR2 agonistic properties of Mw results in the stimulation of strong Th1 response.[24-30] Sepsivac given intradermally would result in increased number of stimulated macrophages (M1 response).[31] Stimulated macrophages are responsible for the intracellular pathogen clearance.[32] (Figure 8) Mycobacterium w is known to induce potent activation of the dendritic cells by its TLR2 agonistic property, which further helps in curbing the bacterial infection.[33]

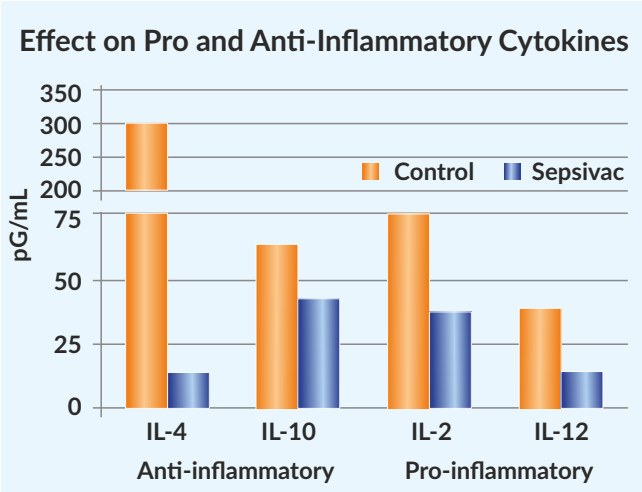


Figure 3: Effect of Sepsivac on pro and anti-inflammatory cytokines

Moreover, Mw is known to clear intracellular pathogens like viruses, mycobacterium Tuberculosis etc. on its own or when added to approved therapies.[34 - 54]

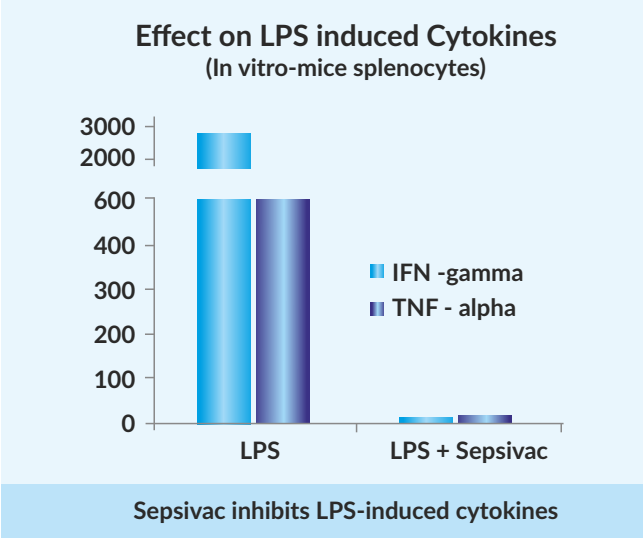


Figure 4: Sepsivac reduces LPS induced cytokines (Interferon gamma, Tumour necrosis factor alpha)

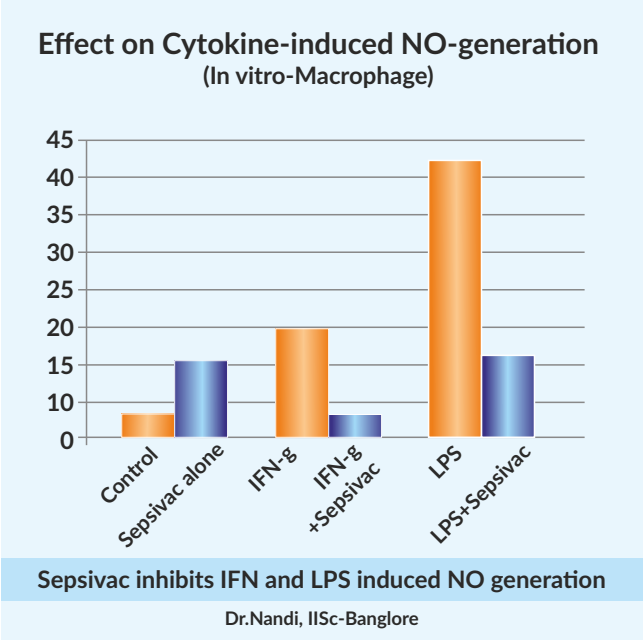


Figure 5: Sepsivac decreases cytokine induced NO generation

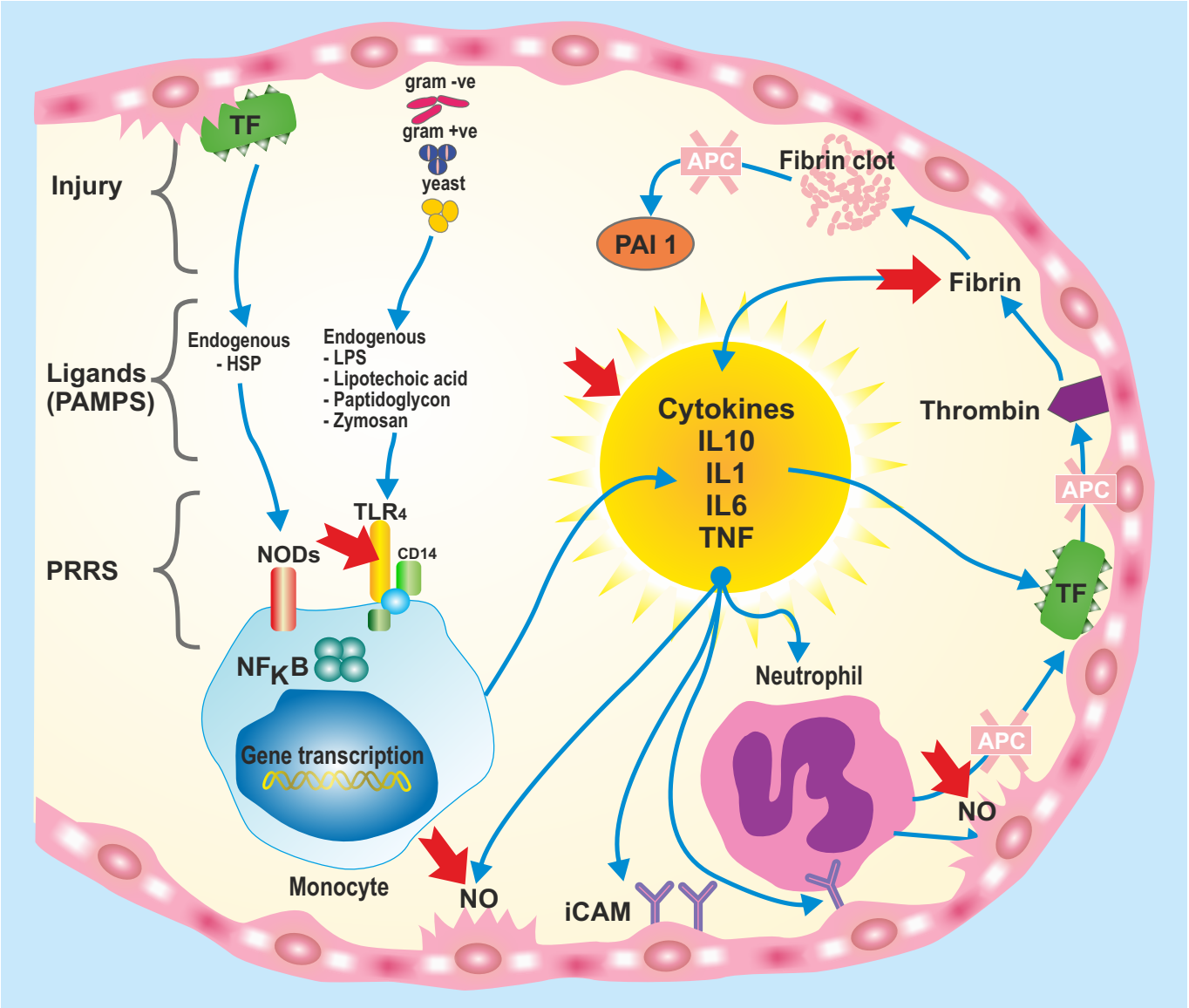
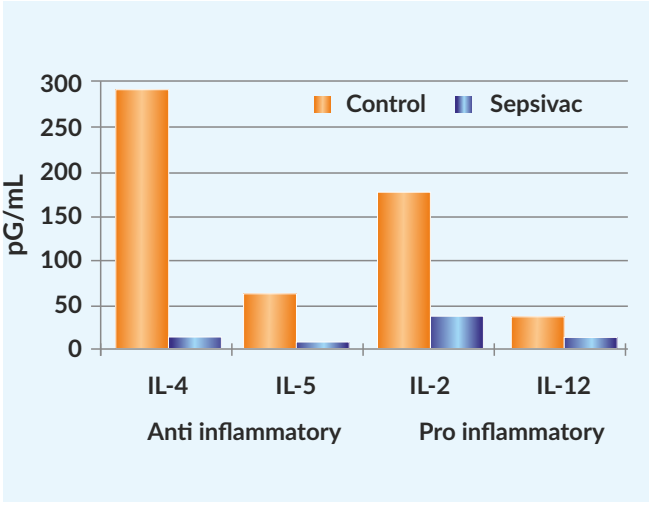


Figure 6: Innate immune response to infection and tissue injury involving the inflammatory cytokines and the coagulation cascade[19]

Sepsivac blocks TLR4, production of various cytokines, NO as well as fibrin.

(TLR4: Toll Like Receptor 4, NO: Nitric Oxide, IL: Interleukin, APC: Activated Protein C, TNF: Tumour Necrosis Factor)



The multipronged approach of sepsivac balances back the disturbed equilibrium of the immune system of the body in sepsis and establishes immune homeostasis.

Figure 7: Effect of Sepsivac on various interleukins

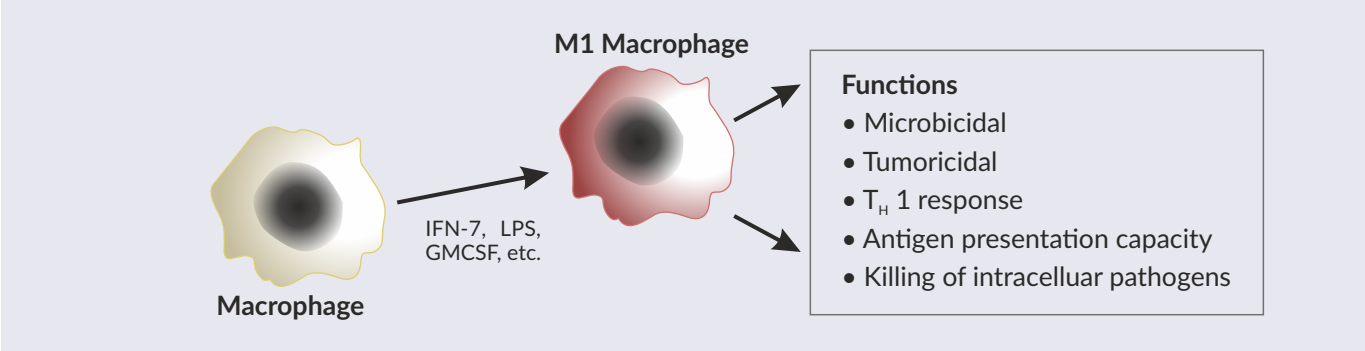


Fig 8: M1 response of macrophage due to TLR 2 agonistic activity of Sepsivac

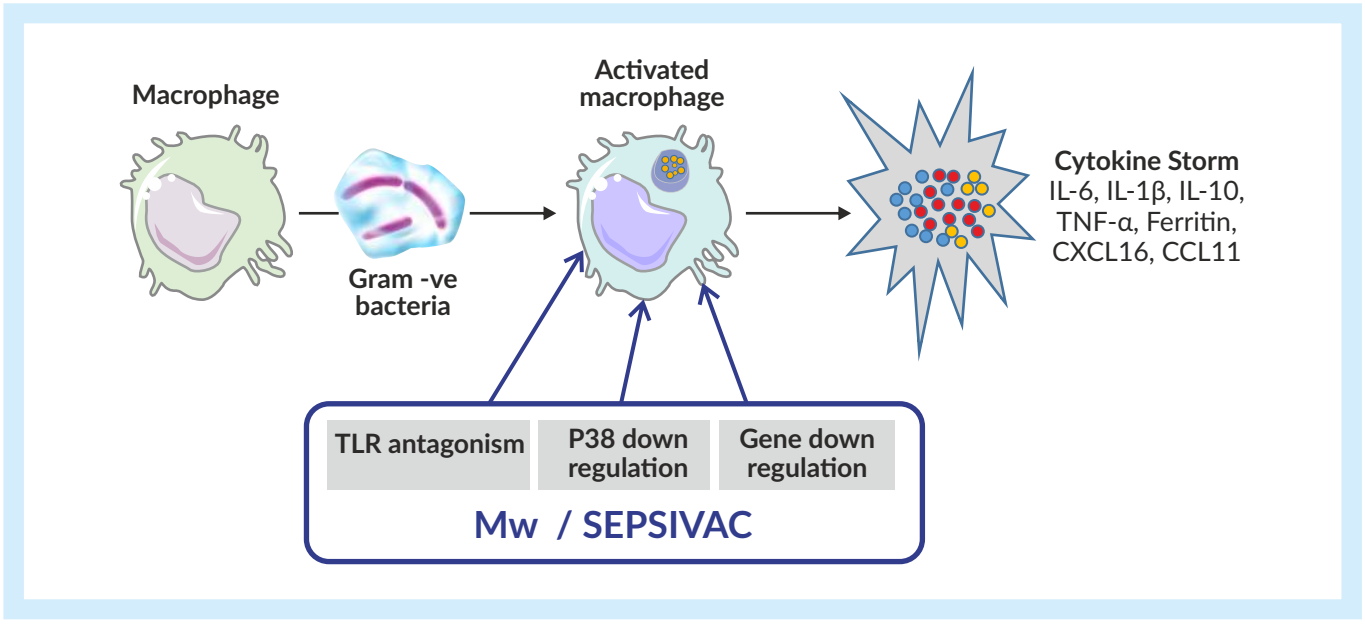


Fig 9: Mechanism of Sepsivac

Table -1: In a gene expression study, it was found that the genes that are modulated in sepsis get REVERSE modulated by Sepsivac stimulation.

Gene	Sepsivac	Sepsis	Remark
IL-1b	↓	↑	
IL-6r	↓	↑	Inflammatory
STAT3	↓	↑	Downstream components of the IL-6 signaling pathway in response to sepsis; primed for activation by IL-6.
Lymphotoxin beta	↓	↑	TNF super family, member 3
TNFRSF1A-associated via death domain	↓	↑	
TNF-alpha induced protein 6	↓	↑	Increased levels in non survivors
TNF-alpha induced protein	↓	↑	
HMGB-1 and 2	↓	↑	Mediator of lethal sepsis
TNFRSF1A-associated via death domain	↓	↑	
IL-11 receptor, alpha	↓	↑	
IL-7 receptor	↓	↑	
IL-10	↓	↑	
IL-1b	↓	↑	
IFN-related developmental regulator 1	↓	↑	
TNFRSF14	↓	↑	Cytokine/chemokine mediated immunity
TNFRSF6B	↑	↑	DNA repair
VEGF-d	↑	↓	Promotes homeostasis during sepsis
Complement component 4 binding protein, beta	↑	↓	A serine protease that inactivates C3b and C4b
Tyrosine kinase 2	↓	↑	Gemcitabin also works by lowering TrK2
Phospholipase D	↑	↓	
PF4	↑	↑	Platelet factor 4 (chemokine (C-X-C motif)
S-Adenosyl homocysteine hydrolase	↑	↓	Purine metabolism
Latent transforming growth factor beta binding protein 1	↑	↓	Cell communication
IL8R	↑	↓	
TIMP-1	↓	↑	Metallo-protease –tissue damage
a-2 macroglobulin	↓	↑	Tissue damage
PBEF1 (pre-B-cell colony enhancing factor 1)	↓	↑	Inhibits neutrophil apoptosis in inflammation and clinical sepsis
S100 calcium binding protein A8 (calgranulin A & C)	↓	↑	Macrophage-mediated immunity
CD69 antigen (p60, early T-cell activation antigen)	↓	↓	T cell activation
Ribosomal protein S9	↓	↑	Protein biosynthesis
Phospholipase A2, group 1 B	↓	↑	
Peroxisome proliferative activated receptor, gamma	↑	↑	
FLJ45224 protein;prostaglandin D2 synthase 21kDa (brain)	↑	↓	Increased prostaglandin restores homeostasis
TGFB1-induced anti-apoptotic factor	↓	↑	
Caspase 5	↓	↓	Apoptosis

3.2 Clinical trials

3.2.1 Dose finding study

A phase IIa dose escalation study of Sepsivac in sepsis was conducted. It was found that

- Patients receiving 0.3ml Sepsivac dose had significant early recovery of organ function including renal and respiratory, multisystem organ failure, fever, and there was an early improvement of SOFA (Sequential Organ Failure Assessment) score.
- Patients receiving 0.2ml Sepsivac dose also had statistically significant improvement in early recovery in hepatic, respiratory, cardiovascular, multisystem organ failure and fever.
- Patients receiving 0.1ml Sepsivac dose had marginal early recovery as compared to the standard treatment group although it was not statistically significant except in case of fever.
- Significant early clinical and microbiological resolution was seen in both 0.2ml and 0.3ml groups (p=0.01).
- SOFA scoring clearly showed that patients receiving 0.3ml Sepsivac had earliest decrease in scores with 83% of the patients recovering on day 15 and 100% on day 22 as compared to other groups receiving lesser doses as well as the standard treatment group.
- Serious adverse events were not seen in any patient receiving the drug. Mild local reactions were seen in 2 patients in 0.1ml group, 3 patients in 0.2ml group and 2 patients in 0.3 ml group. Other adverse events like biochemical, hematological and clinical seemed unrelated to the drug.
- Cytokine levels were significantly elevated at presentation in all the groups. However, statistically significant fall was noted in:

  -TNF α - 0.3 ml Sepsivac > 0.1 ml Sepsivac > standard 2 group.

  - IL 1 – 0.3 ml Sepsivac > 0.1 ml Sepsivac > standard 3 group.

  - Hs-CRP – In all the 6 groups.

To conclude, 0.3 ml Sepsivac dose seems to be efficacious in early organ function recovery and microbiological resolution among all the groups studied. Serious adverse events with the drug doses were not seen.

3.2.2 Pilot study

A pilot study was conducted in PGIMER, Chandigarh to evaluate the efficacy of Sepsivac, an immunomodulator in severe sepsis. A total of 50 patients of severe sepsis were randomized within 48 hours of first organ dysfunction to receive either intradermal Sepsivac or saline.[21]

The primary end point was 28-day mortality, whereas the secondary end points were ventilator days, intensive care unit (ICU) and hospital length of stay, and delta Sequential Organ Failure Assessment (SOFA) score.[21]

There were 7 and 8 deaths in the treatment and control groups, respectively (p = 0.51). The days on mechanical ventilator were significantly lesser in the treatment group compared with control (median, 6 vs 9; p=0.025). The median ICU and hospital length of stay was significantly less in the treatment arm (7 vs 12 days [p=0.006] and 10 vs 16 [p=0.007], respectively). The delta SOFA score was significantly higher in the control arm (p=0.027). There was a higher incidence of secondary bacterial infections in the control group (p=0.009).[21] (Table 2)

To conclude, 0.3 ml Sepsivac dose seems to be efficacious in early organ function recovery and microbiological resolution among all the groups studied. Serious adverse events with the drug doses were not seen.

	Sepsivac	Control	Total	P-value
Primary Outcome				
Mortality, no (%)	7 (28)	8 (32)	15 (30)	0.505
Secondary Outcomes				
Days on ventilator	6 (3-7)	9 (5-14)	7 (4-10)	0.025
Days on vasopressor drugs	2 (2-3)	3 (2-4)	3 (2-4)	0.075
Delta SOFA	0 (0-4)	4 (0.5-4.5)	-	0.027
ICU length of stay, d	7 (5-10)	12 (9-17)	9 (5-14)	0.006
Hospital length of stay, d	10 (7-12)	16 (10-20)	12 (8-18)	0.007
Secondary infection, no. (%)	5 (20)	14 (56)	19 (38)	0.009
VAP, no. (%)	5(20)	12 (48)	25 (50)	0.037
CRBSI, no. (%)	2 (8)	6 (24)	8 (16)	0.123

SOFA: Sequential Organ Failure Assessment, VAP: Ventilator associated Pneumonia, CRBSI: Catheter-related blood stream infection
Table 2: Primary and secondary outcomes of the pilot study

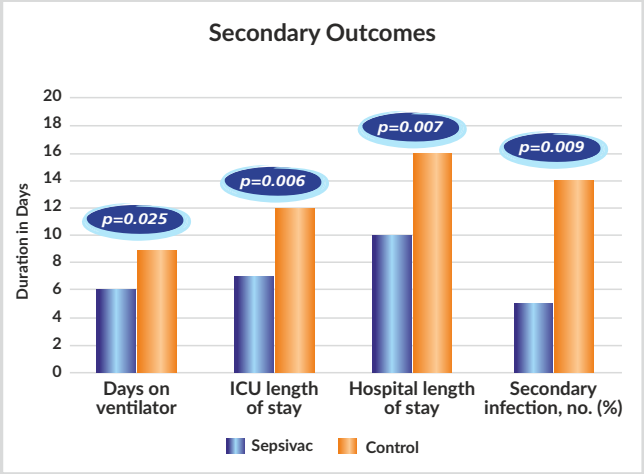


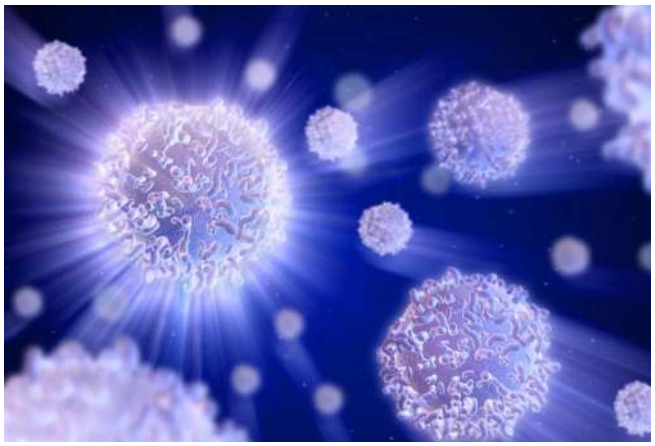
Figure 10: Secondary outcomes of the pilot sutdy

It was concluded in the pilot study that, Sepsivac may have a beneficial role in severe sepsis.

3.2.3 Pivotal study

This randomized, double blind, two arm, comparative controlled, prospective clinical trial was conducted at multiple sites across India to study the safety and efficacy of Sepsivac in combination with standard therapy versus standard therapy alone in sepsis due to gram negative infection.

A total of 202 patients were randomized in 1:1 ratio to receive either test drug or its placebo along with the standard of care. Primary end point for the study was 28-day mortality in treatment arm compared to standard therapy alone. Patients in both the groups were comparable. (Table 3)



Parameters	Treatment Arm (N=101)	Control Arm (N=101)	p - value
Sex (Male/Female)	49 / 52	45 / 56	--
Mean Age (Years)	39.9	40.6	0.9896
Mean Height (cm)	159.2	159.1	0.39
Mean Weight (kg)	57.7	58.7	0.412
Mean SOFA Score	6.9	7.1	0.3416
Patients in ICU	101	101	--
Patients on Ventilator	78 (77.23%)	78 (77.23%)	1
Patients on Vasopressor	46 (45.54%)	50 (49.50%)	0.573
Patients with abnormal SGPT	42 (41.58%)	46 (45.54%)	0.5703
Patients with abnormal SGOT	49 (48.51%)	51 (50.50%)	0.7784
Patients with abnormal S. Creatinine	38 (37.62%)	30 (29.70%)	0.2336

Table 3: Base line characteristics

Inclusion Criteria

- 18 – 65 years of age
- Patient of severe sepsis or septic shock
- Presumed or documented gm –ve infection
- One or more organ dysfunction
- Female of child bearing age with –ve pregnancy test

Exclusion criteria

- Pregnancy
- Gram +ve culture
- Fungal infection as source of infection
- Received CPR
- On immunosuppressive therapy
- Unwilling to provide consent

Primary outcome

- 28-day all-cause mortality

Secondary outcome

- Delta SOFA scores
- Ventilator-free days
- Time-to-vasopressor withdrawal
- To assess safety/tolerability
- To assess emergent and recurrent infection rate

Out of 202 patients, total 27 (26.73%) deaths have been reported [8 deaths (7.92%) - treatment arm, 19deaths (18.81%)-control arm]. Thus, there was 10.89% absolute reduction and 55.56% relative reduction in mortality in Treatment Arm. This difference was clinically relevant and statistically significant (p = 0.0229). (Figure: 11)

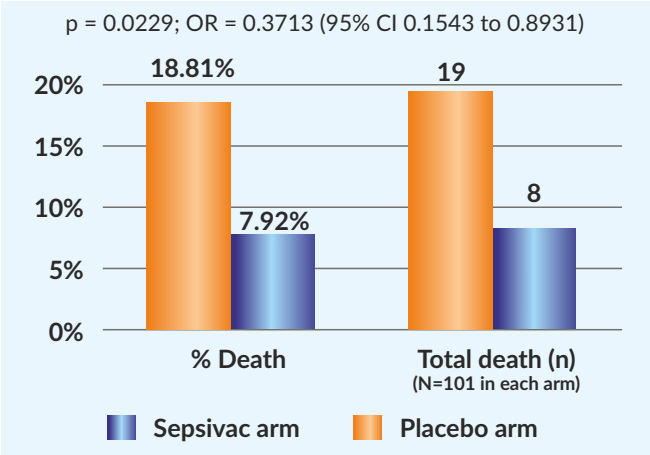


Figure 11: 28 days mortality

The mortality is also affected by baseline SOFA score, higher the SOFA score, higher the expected mortality. To evaluate the effect of investigational product on mortality based on SOFA score, additional subgroup analysis has been performed and mentioned in table 4.

Arm	All Patients		SOFA Score ≥7	
	Died/Total Patients	%Died	Died/Total Patients	%Died
Treatment Arm	8/101	7.92	6/54	11.11
Control Arm	19/101	18.81	15/54	28.30
Total	27/202	13.37	21/108	19.63
P value	0.023		0.029	

Table 4: Death as per SOFA Score

SOFA score was recorded at baseline and during subsequent visits. Mean SOFA score was calculated for all the patients during each visits and change in mean SOFA score between the treatment and control arm is shown in figure 12.

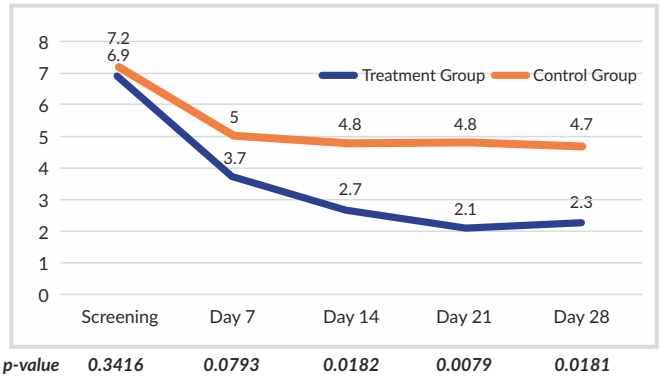


Figure 12: Mean SOFA Score Over Time

Mean SOFA score was comparable at baseline. The result showed that SOFA score reduced from baseline to day 28 in both arm, but the reduction in SOFA score was significantly more in treatment arm at day 14 (p=0.0182), at day 21 (p=0.0079) and at day 28 (p=0.0181) compare to control arm.

The survival data of all patients shown significant difference between two arms for the days of discharge. Time to discharge was also shorter in treatment arm for alive patients. [p-value: 0.0001, Hazard Ratio: 0.964 (95% CI: 0.948-0.981)]

A statistical significant difference was also observed between two arms in the vasopressor withdrawal. The requirement of vasopressor administration was found to be statistically less in the treatment arm as compared to control arm. In other word, vasopressor withdrawal was also early in treatment arm compared to control arm. (Figure 13)

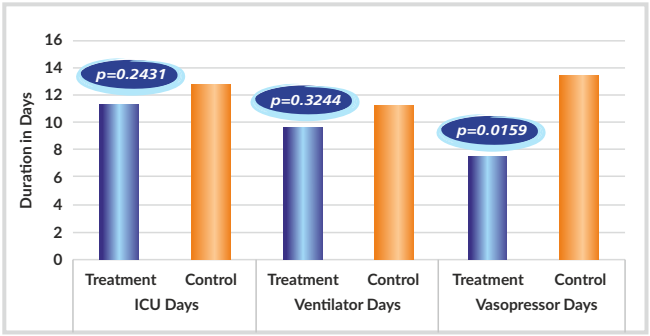


Figure 13: Duration of ICU stay, ventilator and vasopressor Treatment

The laboratory parameter of each patients were evaluated at screening, day 7, day 14, day 21 and day 28. In the present study 202 patients were randomized, out of these SGPT in 98 patients and SGOT in 114 patients were abnormal. During the study period, improvement in abnormal LFTs was observed in both the study arms, and the difference between the treatment and control arm was significant. Also it was observed that in treatment arm, improvement started earlier as compared to control arm. (Table 5 & 6)

Day	SGPT				SGOT			
	T	%	C	%	T	%	C	%
Normal	47	50.54	43	45.26	36	39.56	35	37.23
Abnormal	46	49.46	52	54.74	55	60.44	59	62.77
Abnormal Mean	553.21	-	254.22	-	585.60	-	313.53	-

Table 5: Baseline characteristics lab parameters (LFT)

Day	SGPT				SGOT			
	T	%	C	%	T	%	C	%
Screening	46	100	52	100	55	100	59	100
Normal Day 7*	10	21.74	01	1.92	08	14.55	01	1.69
Normal Day 14*	16	34.78	01	1.92	12	21.82	01	1.69
Normal Day 21*	20	43.48	01	1.92	14	25.45	01	1.69
Normal Day 28*	23	50.00	01	1.92	16	29.09	01	1.69
p=value	***0.0002***				***0.0001***			

Table 6: No. of patients having abnormal baseline values change to normal (at different time point)

*T=Treatment Arm, C=Control Arm, *Cumulative*

It was shown in the trials that Sepsivac addresses the potential therapy gap present in the treatment of sepsis and improves the mortality outcomes, reduces SOFA scores, time to discharge from ICU and ventilator and secondary infection.

4. Conclusion

Sepsis is a life threatening disease involving a high mortality rate. Current guidelines for the treatment focus on the elimination of the infection and treatment of the symptoms rather than treating the root cause – systemic inflammation. There exists a gap in the current therapy of sepsis to deal with the inflammatory component of sepsis. Sepsivac is an immunomodulator which has shown to reverse the inflammatory changes induced by sepsis. The clinical trials showed definite benefit of 11% reduction in mortality. Sepsivac also reduces the need of vasopressor and ventilator support. Hospital and ICU stay have also been reduced with the use of Sepsivac. Rapid reduction in SOFA score again proves faster recovery associated with the use of Sepsivac. Thus, Sepsivac fills in the gap that currently exists in the treatment of sepsis and can be a new potential entry as an adjuvant to the standard of care treatment.

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