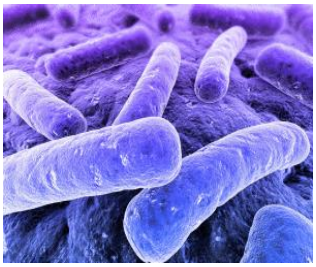
CytoSorbents™

Infection and Sepsis



INFECTION CAUSES SEPSIS. Superficial wounds and burns are susceptible to infection. Prolonged hospital stays with surgical intervention, mechanical ventilation, indwelling catheters, and an overuse of antibiotics often result in hospital-borne infections from highly resistant bacteria such as Acinetobacter baumannii, MRSA, VRE, Pseudomonas, Klebsiella, and others. Gastroenteritis, from ingesting contaminated water or food, is another common cause of infection. Sepsis is a massive inflammatory state that is the result of an overzealous immune response to a severe infection.

SEPSIS CAUSES ORGAN FAILURE. ORGAN FAILURE CAUSES DEATH. Normally, the body responds to an infection by producing cytokines – small proteins that help stimulate and regulate the immune system. In severe infection, however, the immune system often goes haywire, producing high concentrations of cytokines or "cytokine storm", which can result in sepsis, and a high risk of organ failure and new infections. Organ failure is the leading cause of death from sepsis, with no therapies available to either prevent or treat it.

- Excessive levels of pro-inflammatory cytokines can be toxic to cells and can cause direct cell death and organ injury through apoptosis, induction of shock and ischemia, capillary leak syndrome, hypercoagulability, and a cascade of other pathophysiologic effects. Left unchecked, pro-inflammatory cytokines can lead to a deadly systemic inflammatory response syndrome (SIRS), which in turn, can cause the failure of many organs such as the lungs, heart, kidneys, brain, and liver

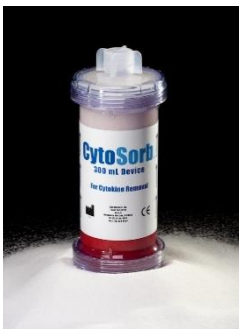
- A pro-inflammatory cytokine storm can also lead to organ damage via "immune cell confusion". Activated neutrophils play an important role in innate immunity and can kill pathogens through phagocytosis and the release of many toxic substances including reactive oxygen species and proteases. These cells normally hone in on an area of infection by binding to cell adhesion molecules overexpressed (due to cytokine stimulation) on the endothelium of capillaries in the infected area. A cytokine storm, however, makes the entire body appear infected, resulting in increased cell adhesion molecule expression throughout the body, resulting in activated neutrophils migrating to, and attacking otherwise healthy organs

- Pathogens also produce species specific toxins such as Staph. aureus alpha hemolysin, PDL toxin, and toxic shock syndrome toxin, fungal aflatoxin, and many others that can cause widespread tissue destruction and organ damage

- In late stage sepsis, the compensatory anti-inflammatory response syndrome (CARS) can yield excessive anti-inflammatory cytokines that can cause "immune paralysis", or the inability of the immune system to respond to infectious stimuli, leading to a much higher risk of infections such as ventilator-associated pneumonia and catheter-related infections

When cytokine storm leads to organ dysfunction, it is called severe sepsis. Despite the best standard of care therapy, which includes antibiotics, severe sepsis has a mortality of 25-35%. When severe sepsis is accompanied by hypotension that is unresponsive to fluids, it is called septic shock and kills nearly one in every two patients. More than 27 million people worldwide, and one million patients in the U.S. alone, are afflicted with severe sepsis or septic shock each year. There are currently no approved therapies on the market in the U.S. or Europe approved to treat sepsis.

CYTOSORB® – A NEXT GENERATION "ACTIVE" THERAPY FOR SEVERE SEPSIS AND SEPTIC SHOCK.



CytoSorb® is the only specifically approved extracorporeal cytokine adsorber in the European Union. Reductions in elevated cytokines and toxins represent a promising strategy to prevent or treat cytokine storm and SIRS in wounded soldiers with infection and sepsis. At the heart of the CytoSorb® technology is a biocompatible, highly porous polymer bead designed to capture appropriately sized cytokines, toxins, and inflammatory mediators in its pores, while letting larger or smaller substances pass around or through. Treatment is very similar to hemodialysis. As blood is pumped out of the body and through the CytoSorb® cartridge using standard hospital dialysis machines or small portable hemoperfusion pumps, cytokines and toxins are captured by the beads and removed from blood. The "purified" blood is then returned to the patient. In clinical trials, patients were treated for up to 24 hours a day (>70 total blood volumes each day), for seven days, each day with a new device.

CYTOSORB® ATTACKS SEPSIS FROM MULTIPLE FRONTS unlike most previous unsuccessfully attempts to treat sepsis with drugs or biologics. Most have tried to remove or interfere with only a single cytokine or inflammatory mediator. In sepsis, however, there are too many cytokines and too much redundancy in the immune system for this strategy to work.

- CytoSorb® has repeatedly demonstrated hemodynamic stabilization and weaning of vasopressors when used early in septic patients. Improvements in lung function and faster weaning of mechanical ventilation and dialysis have also been observed
- CytoSorb® is clinically proven to reduce cytokine storm and key cytokines in the blood of septic patients
- CytoSorb® has removed greater than 90% of many different bacterial toxins *in vitro* from whole blood, including Staph. aureus alpha hemolysin, TSST-1 toxin, fungal aflatoxin & T2 toxin, E.coli shiga-like toxin (STX-1 & 2), and others
- CytoSorb® is capable of redirecting activated immune cells to the true site of infection and away from "innocent bystander" organs in rat models of sepsis, improving bacterial source control and reducing inadvertent organ injury.[1]

The multiple activities of CytoSorb® are all intended to try to prevent or treat organ failure and reduce infections – something that no other therapy has been capable of doing, attacking the key reasons patients die from sepsis today.

CYTOSORB® ADVANTAGES

- **Broad spectrum device** – Specifically designed to remove a broad range of cytokines, toxins, and other inflammatory mediators, making this the most logical strategy to treat cytokine storm in sepsis patients
- **Efficient cytokine removal** – Capable of removing up to 30-50% of key cytokines in septic shock patients with multi-organ failure
- **Removes many bacterial toxins** – Greater than 90% removal of important bacterial toxins *in vitro* from whole blood
- **Excellent safety profile** – No serious device related adverse events in more than 14,000 human treatments with good tolerability.
- **Positive human clinical data –** European Sepsis Trial showed the safe reduction of cytokines and demonstrated encouraging improvements in mortality and organ dysfunction in high risk patients
- **Easy to use** – Minimal learning curve, uncomplicated set up, and high ease of use
- **Works with existing hospital dialysis equipment or portable, small hemoperfusion pumps** – No new equipment needed
- **No extra fluids or dialysate needed** – Makes treatment logistically simple
- **Compatible with both heparin and regional citrate anti-coagulation** – No systemic anticoagulation is needed if contraindicated
- **ISO 10993 Biocompatible** – Biocompatible, hemocompatible, no genotoxicity or cytotoxicity, no acute sensitivity or complement activation
- **Massive capacity** – A single cartridge has more than seven football fields of surface area to bind cytokines
- **Long shelf life** – No biologic components such as antibodies or cells means excellent storage – three years at room temp
- **High Quality Manufacturing –** CytoSorbents manufactures CytoSorb® at its ISO 13485:2012 manufacturing facility in New Jersey

CYTOSORBENTS HAS POSITIVE *IN VIVO* AND HUMAN CLINICAL DATA IN SEPSIS

- In collaboration with Dr. John Kellum at University of Pittsburgh Medical Center Department of Critical Care, CytoSorb® treatment has significantly improved survival in animal models of sepsis and prevented shock. [1,2,3]
- CytoSorb® met its primary endpoint of safety and kinetic cytokine removal in its 43 patient, multi-center, randomized, controlled European Sepsis Trial comparing standard of care therapy (control) versus standard of care therapy plus CytoSorb® (6 hours of CytoSorb® treatment daily for up to seven days) in patients with sepsis and ARDS or ALI
- In a 22-patient single arm, prospective study in patients with multi-organ failure, high lactate and refractory shock, twice daily CytoSorb® usage led to a resolution of shock in 68% of patients, and 28-day survival of 41% (vs 0-10% historical)
- More clinical data can be found at www.cytosorb.com

DARPA IS SUPPORTING NEXT GENERATION CYTOSORB® DEVELOPMENT WITH $3.8M

CytoSorbents was awarded $3.8M in contracts from DARPA to develop novel porous polymers for DARPA's "Dialysis-Like Therapeutics" program to treat sepsis using blood purification, and collaborates with Battelle Labs, Harvard Wyss Institute, MIT, NxStage Medical, and others

SUMMARY. CytoSorbents has developed a hemocompatible, blood purification technology with the potential to protect and preserve American lives in the face of a number of growing health threats. CytoSorb®, the company's flagship product, is now approved in the European Union as a broad, extracorporeal cytokine filter, designed to help fight "cytokine storm" in critical-illnesses such as sepsis, trauma and burn injury. Case series and reports can be found at www.cytosorb.com.

CytoSorb® is approved in the European Union but is not yet FDA-approved.

CytoSorbents™
NASDAQ: CTSO

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