

CytoSorb™

A powerful new weapon in
the fight against Cytokine Storm





Cytokine storm can lead to multiple organ failure, infection and death in sepsis and systemic inflammatory response syndrome

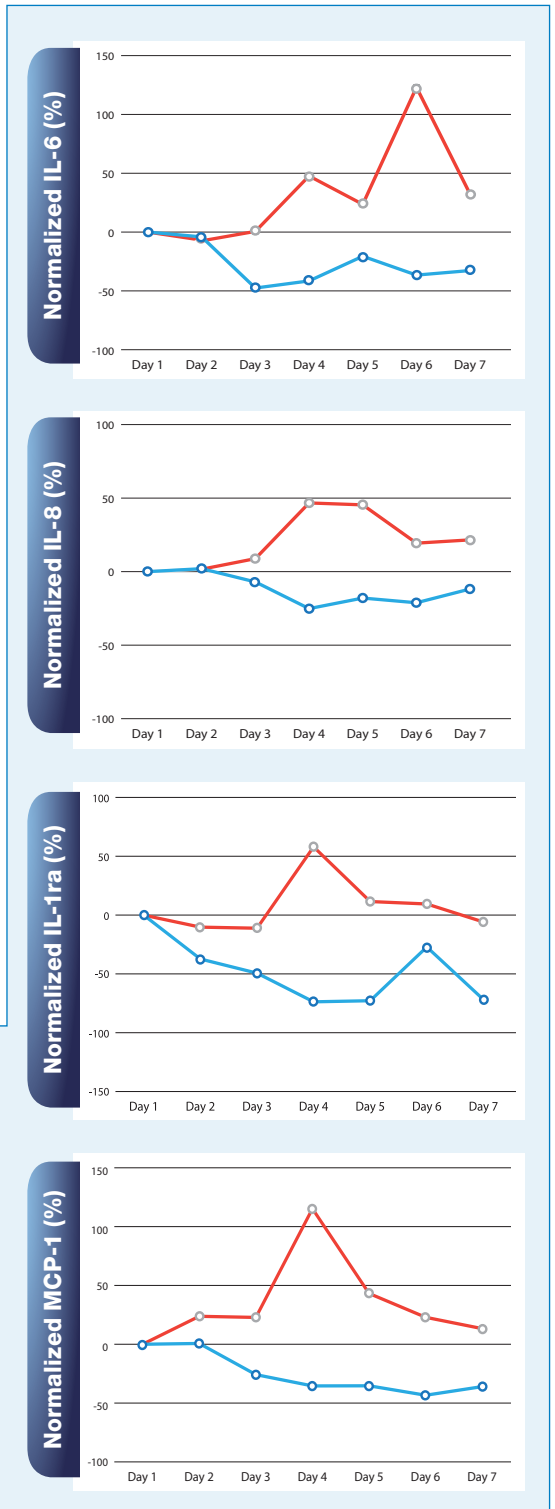
The overproduction of cytokines by the immune system, often called “cytokine storm”, is a hallmark of many life-threatening illnesses seen in the intensive care unit such as severe sepsis and septic shock, acute respiratory distress syndrome (ARDS), trauma, serious burn injury, post-surgical complications, influenza, and severe acute pancreatitis. Cytokine storm can be toxic, causing direct cell death, massive capillary leak, severe inflammation, and a cascade of events that can ultimately lead to shock and cardiovascular collapse, respiratory, renal and hepatic failure, immune system paralysis, and other problems. Multiple organ failure and secondary infections are two of the leading causes of death in the ICU. Current standard of care therapies are typically supportive care, with little to no “active” therapies to fight cytokine storm.

CytoSorb™ reduces cytokine storm in critical care illnesses

CytoSorb™ is the first-in-class therapy specifically approved as an extracorporeal cytokine filter in the European Union. Its use is broadly indicated where cytokines are elevated. At the heart of the CytoSorb™ technology is a biocompatible, highly porous polymer bead designed to capture and adsorb cytokines in the ~10-50 kDa “cytokine sweet spot” where most cytokines reside. The goal is to reduce toxic cytokine levels to prevent or mitigate organ failure and immune suppression, thereby improving clinical outcome. CytoSorb™ was evaluated in the company’s European Sepsis Trial – a randomized, controlled, multi-center study in Germany in 43 patients with septic shock and respiratory failure (predominantly ARDS). CytoSorb™ plus standard of care (SOC) therapy achieved the primary endpoint of the trial, demonstrating the statistically significant reduction of many key cytokines 30-50% compared to standard of care therapy alone (Figure 1). These findings are consistent with *ex vivo* serum perfusion experiments where CytoSorb™ also reduced a broad spectrum of cytokines in this ~10-50 kDa range (Figure 2).

Relative Reduction in IL-6, IL-8, IL-1ra and MCP-1 (Treatment versus Control)

○—○ CytoSorb™ + SOC ○—○ SOC Only



CytoSorb™ removes a broad spectrum of cytokines in the ~10-50 kDa range.

Cytokine	Molecular weight	% removal
IL-8	8 kDa	100%
IL-1ra	17 kDa	100%
IL-1 α	17 kDa	100%
IL-10	18 kDa	85%
IL-6	26 kDa	87%
HMGB1	30 kDa	80%
TNF- α trimer	51 kDa	55%

(Fig. 2) 8 mL of horse serum spiked with 1000-5000 pg/mL of individual cytokines was recirculated through a 1 mL CytoSorb™ cartridge for 4 hours at ~1mL/min.

CytoSorb™ reduced blood cytokine levels by an average of 30-50% versus controls in patients with septic shock and respiratory failure.

Cytokine	% reduction	p-value
IL-6	49.1%	0.01
IL-8	30.2%	0.002
IL-1ra	36.5%	0.001
MCP-1	49.5%	0.002

(Fig. 1) Patients were treated with a standard CytoSorb™ device for 6 hours a day for 7 consecutive days (each day with a new device) at flow rates of ~200-300 mL/min. Percent reduction of plasma cytokine levels taken from whole blood were compared across the 7-day period to cytokine levels upon enrollment. SOC = standard of care therapy.

A powerful new weapon in the fight against Cytokine Storm **CytoSorb™**

CytoSorb™ treatment results in positive clinical benefits in high-risk patients

Data from the European Sepsis Trial suggest that CytoSorb™ treatment has a protective benefit, particularly in those at highest risk for death in sepsis. As expected, there is a correlation between CytoSorb™ cytokine reduction in patients with highly elevated levels of IL-6 ($\geq 1,000$ pg/mL) or IL-1ra ($\geq 16,000$ pg/mL), which are both independent predictors of mortality in sepsis.^{1,2} In these patients, CytoSorb™ treatment showed:

- Statistically significant absolute reduction in 28-day all-cause mortality (0.0% vs 62.5% control, $p=0.03$, $n=14$)
- Trends to benefit in 60-day mortality (16.7% vs 62.5% control, $p=0.14$, $n=14$), fewer patients on mechanical ventilation at 28 days (33% vs 88% control, $p=0.09$), and fewer days in the ICU (23.8 vs 27.5 days control)

In patients greater than 65 years of age, who account for two-thirds of all hospitalized sepsis patients and who historically have a 13-fold relative risk of death compared to younger patients³, CytoSorb™ treatment resulted in:

- Statistically significant absolute improvement in 14-day mortality (0% vs 36% control, $p=0.04$, $n=21$)
- Trends to benefit in 28-day mortality (40% vs 45% control), improvement in the Multiple Organ Dysfunction Score (MODS; -28% vs -9% control) after 7 days of treatment, fewer ventilated patients at 28 days (60% vs 73% control), and a reduced respiratory failure relapse rate requiring reintubation (0.0% vs 36.4%, $p=0.09$)

These data suggest that CytoSorb™ reduces mortality in patients with high cytokine levels and is protective for up to 14 days in patients 65 years of age and older. In this elderly population, longer treatment with CytoSorb™, beyond the 7-day treatment limitation of the trial, could yield even greater clinical benefit. Additional studies are being planned to further explore the use of CytoSorb™ in these high-risk patients.

CytoSorb™ therapy is safe and well-tolerated

Aside from a slight reduction of platelets as seen with all extracorporeal therapies, standard hematology and chemistry panels were unaffected.

CytoSorb™ therapy is similar to, yet easier than, hemodialysis

CytoSorb™ therapy is gentle, well-tolerated, and has been used in more than 650 human treatments without serious device-related adverse events.

CytoSorb™ therapy uses standard hemodialysis machines found in all major hospitals to pump blood out of the body via a temporary dialysis catheter and directly through the



CytoSorb™ beads, with a surface area equivalent to more than 5 European football fields in a single cartridge, remove cytokines efficiently from blood.

CytoSorb™ cartridge. Beads with a surface area equivalent to more than 5 European football fields in a single cartridge remove cytokines and the “purified” blood is then pumped back into the patient’s body. Blood is continuously circulated through the device at flow rates of 200-400 mL/min, treating a patient’s entire blood volume 20-30 times over a 6-hour period. CytoSorb™ is compatible with both systemic heparin and regional citrate anti-coagulation. Drugs are dosed after treatment, as is customary in dialysis. Standard hemodialysis and hemofiltration cannot remove significant quantities of cytokines. Unlike newer high molecular weight cutoff filters, CytoSorb™ can be used in the absence of acute kidney injury, does not clinically impact critically balanced blood chemistries, and does not need dialysate or replacement fluid.

CytoSorb™ Advantages

- **First in class therapy to obtain E.U. approval specifically as an extracorporeal cytokine filter** – CE Mark approval meets safety and efficacy label claims as dictated by the European Union Medical Devices Directive.
- **Broad spectrum device** – Removes a broad range of cytokines making this the most logical strategy to treat cytokine storm.
- **Proven, efficient cytokine removal** – Robust and broad cytokine removal demonstrated in critically ill humans and animals.
- **Strong animal data and promising human data** – Statistically significant improved short and long-term survival, hemodynamic stability, and cytokine removal in septic animals^{4,5} and promising human data.
- **No new infrastructure is needed** – Works with standard hospital dialysis equipment and does not need dialysate or replacement fluid.
- **Easy to use** – Minimal learning curve, uncomplicated set up, and high ease of use.
- **Hemocompatible** – Polymer beads can directly contact blood without material negative effects.
- **Massive capacity** – A single cartridge has more than 5 European football fields of surface area to bind cytokines.
- **Long shelf life** – No biologic components (e.g. antibodies or cells) means excellent storage at room temperature.
- **Extensive testing and safety history** – Passed extensive animal safety with ISO 10993 biocompatibility testing. No serious device-related adverse events in more than 650 human treatments with good tolerability and safety.
- **High-quality manufacturing** – CytoSorbents manufactures and packages its own polymer bead cartridges under ISO 13485:2003 Full Quality Systems certification.
- **Reimbursement friendly** – A clear path exists for immediate reimbursement.



CytoSorbents™

Working to save lives through blood purification

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CYTOSORBENTS CORPORATION (OTCBB: CTSO) is a critical-care focused therapeutic device company using blood purification to treat life-threatening diseases. Its purification technology is based on biocompatible, highly porous polymer beads that can actively remove toxic substances from blood and other bodily fluids by pore capture and adsorption.

References

¹ Spittler A., et al., Clin Infect Dis, 2000 Dec; 31(6):1338-1342
² Pablo R, et al., J Intensive Care Med, 2011; 26(2):124-132
³ Martin, GS, Crit Care Med 2006, 34(1):15-21

⁴ Kellum, JA, et al., Crit Care Med, 2004; 32(2): 801-805
⁵ Peng, ZY, Carter, MJ, Kellum, JA., Crit Care Med, 2008; 36(5): 1573-1577