A powerful new weapon in the fight against Cytokine Storm
Cytokine storm can lead to multiple organ failure, infection and death in sepsis and the 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 leakage, 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® therapy is gentle, well-tolerated, and has been used in more than 650 human treatments without serious device-related adverse events. Aside from a slight reduction of platelets as seen with all extracorporeal therapies, standard hematology and chemistry panels were unaffected.

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).

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Molecular weight</th>
<th>% removal</th>
<th>Cytokine</th>
<th>% reduction</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-8</td>
<td>8 kDa</td>
<td>100%</td>
<td>IL-6</td>
<td>49.1%</td>
<td>0.01</td>
</tr>
<tr>
<td>IL-1ra</td>
<td>17 kDa</td>
<td>100%</td>
<td>IL-8</td>
<td>30.2%</td>
<td>0.002</td>
</tr>
<tr>
<td>IL-1α</td>
<td>17 kDa</td>
<td>100%</td>
<td>IL-1ra</td>
<td>36.5%</td>
<td>0.001</td>
</tr>
<tr>
<td>IL-10</td>
<td>18 kDa</td>
<td>85%</td>
<td>MCP-1</td>
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<td>87%</td>
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<tr>
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<td>30 kDa</td>
<td>80%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF-α trimer</td>
<td>51 kDa</td>
<td>55%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(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.
Data from the European Sepsis Trial suggest that Cytosorb® treatment has a protective benefit, particularly in patients with high cytokine levels. As expected, there is a correlation between clinical outcome and highly elevated levels of IL-6 (≥1,000 pg/mL) or IL-1ra (≥16,000 pg/mL), which are both known independent predictors of mortality in sepsis.1,2 In these patients, Cytosorb® cytokine reduction showed:

- Improvement in respiratory function with fewer patients on mechanical ventilation at 28 days (Figure 3: 33% vs 88% control, p=0.09), and fewer days in the ICU (24 vs 28 days control)
- Statistically significant absolute reduction in 28-day all-cause mortality (Figure 4: 0% vs 63% mortality control, p=0.03, n=14), and a trend to benefit in 60-day mortality (17% vs 63% control, p=0.14, n=14)

These promising data obtained in a post-hoc analysis suggest that Cytosorb® can potentially reverse lung injury and improve survival in patients with high cytokine levels. Additional data also suggest a protective effect in patients 65 years of age and older that have a historical 13-fold relative risk of death compared to younger patients, and account for the majority of patients hospitalized with sepsis.3 Additional prospective studies will further explore the use of Cytosorb® in these high-risk patients.

### Cytosorb®

**First-in-Class Treatment For Cytokine Storm**

- **First-in-class extracorporeal cytokine filter with CE Mark regulatory approval** indicated for use in any clinical situation where cytokines are elevated. Can be used in patients with or without renal failure.
- **Clinically proven cytokine removal** – Robust and broad cytokine removal demonstrated in critically-ill human patients.
- **Safe to use** – No serious device related adverse events in more than 650 human treatments, including more than 300 in patients with primarily septic shock and respiratory failure, with good tolerability and safety. Passed extensive animal safety with ISO 10993 biocompatibility testing. Does not impact delicately balanced blood chemistries.
- **Strong animal and promising human clinical efficacy data** – Statistically significant improved short and long-term survival, hemodynamic stability, and cytokine removal in septic animals4,5 and promising human survival data and improved organ function in high risk patients.
- **Currently reimbursed in Germany** in addition to the standard DRG
- **Works with standard hospital dialysis equipment** – No additional expensive equipment is required or needed to be purchased.
- **Easy to use** – Minimal learning curve, uncomplicated set up, blood goes in and blood comes out. Easier to use than hemodialysis or hemofiltration. Does not require dialysate or replacement fluid. Works with heparin and regional citrate anti-coagulation. Drugs are dosed after treatment, like hemodialysis.
- **Difficult to overtreat** – Device performance is concentration dependent so at low cytokine concentrations, device efficacy is automatically reduced, preventing excessive cytokine removal with no need to monitor cytokine levels.
- **Massive capacity** – A single cartridge has more than 5 European football fields of surface area to bind cytokines.
- **Ability to treat large amounts of blood** – Cytosorb® is a high flow, low resistance cartridge, capable of flow rates of 200-400 mL/min, necessary to neutralize ongoing cytokine production.
- **Long shelf life** – No biologic components (e.g. antibodies or cells) means excellent storage at room temperature.
- **High-quality manufacturing** – CytoSorbents manufactures its own polymer bead cartridges under ISO 13485:2003 Full Quality Systems certification.

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

**Cytosorb® treatment results in positive clinical benefits in high-risk patients**

- Improvement in respiratory function with fewer patients on mechanical ventilation at 28 days (Figure 3: 33% vs 88% control, p=0.09), and fewer days in the ICU (24 vs 28 days control)
- Statistically significant absolute reduction in 28-day all-cause mortality (Figure 4: 0% vs 63% mortality control, p=0.03, n=14), and a trend to benefit in 60-day mortality (17% vs 63% control, p=0.14, n=14)
CYTOSORBENTS CORPORATION (OTCBB: CTSO) is a critical-care focused therapeutic device company using blood purification to modulate the immune system and fight multiple organ failure to treat life-threatening illnesses. 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. www.cytosorbents.com

CytoSorb® is a registered trademark of CytoSorbents Corporation.

References