CytoSorbents Leads a New Era in Sepsis Treatment

In commemoration of World Sepsis Day 2025, CytoSorbents Corporation (NASDAQ: CTSO), a leader in the treatment of life-threatening conditions in the intensive care unit and cardiac surgery using blood purification, highlights the vital and evolving role of CytoSorb® therapy in the treatment of sepsis and septic shock – among the deadliest challenges in critical care medicine.

Specifically, we will discuss how:

- **CytoSorb® blood purification attacks sepsis and septic shock in a comprehensive and multi-faceted way**

- **CytoSorb helps to prevent or treat organ failure in septic shock by helping to achieve the following core treatment goals:**
    1) **Break the vicious cycle of massive, uncontrolled inflammation**
    2) **Stabilize the patient (e.g. reverse shock, improve oxygenation, support liver dysfunction, protect the kidneys, etc.)**
    3) **Promote the repair of capillary leak**
    4) **Enable the active removal of excessive fluid (that compromises organ function and perpetuates organ failure)**

- **Just like antibiotics, when CytoSorb is used in the "Right patient at the Right Time with the Right Dosage," new studies demonstrate that early and intensive use of CytoSorb therapy improves clinical outcomes for patients suffering from these conditions**

Dr. Phillip Chan, MD, PhD, Chief Executive Officer of CytoSorbents explains, "For more than a decade, CytoSorbents has partnered with clinicians and scientists to improve the treatment of sepsis and septic shock by supplementing traditional antibiotic therapy with the powerful, broad-spectrum blood purification capability of CytoSorb. While antibiotics target the source of infection, CytoSorb addresses the other major drivers of septic shock, including severe inflammation, shock, capillary leak, fluid overload, and organ failure.

Recent studies reinforce that, like antibiotics, CytoSorb therapy is most effective when initiated early, applied intensively, and continued for an appropriate duration. Backed by a strong safety record and many peer-reviewed publications, CytoSorbents and the global CytoSorb user community are helping to solve this critical problem that claims millions of lives around the world each year."

Sepsis and Septic Shock: A Life-Threatening Crisis Driven by Inflammation

Sepsis is a complex, life-threatening condition where the inflammatory response to a serious infection can spiral out of control, fueled by the excessive production of cytokines (cytokine storm), bacterial toxins, and other inflammatory agents. Left unchecked, this inflammation can lead to septic shock – an often fatal complication marked by circulatory collapse and a lethal drop in blood pressure, the failure of multiple vital organs, and fluid overload – essentially drowning the patient from within. Each year, sepsis and septic shock afflict an estimated 49 million people worldwide, killing 11 million, accounting for up to 20% of all global deaths.

Despite decades of effort, standard treatments of septic shock such as antibiotics, fluids, vasopressors, and organ support are often not enough, with mortality rates of 30-50% that can escalate rapidly with multiple organ failure. Survivors often face long-term disability and shorter life spans. The complexity of sepsis has led to the failure of hundreds of therapy candidates and over 100 Phase II and III clinical trials over many decades – underscoring the urgent need for more effective solutions.

CytoSorb: A Broad-Spectrum Solution with Real-World Impact

CytoSorb® is a first-in-class, extracorporeal blood purification therapy approved in the European Union with nearly 300,000 human treatments across more than 70 countries globally. It is not yet approved or cleared in the U.S. although was granted FDA Emergency Use Authorization to treat critically-ill COVID-19 patients with respiratory failure. CytoSorb uses advanced porous polymer beads to remove a wide array of toxic substances directly from the bloodstream, including, for example, inflammatory cytokines and mediators, bacterial toxins, activated complement, and other damaging molecules that contribute to inflammation, shock, blood vessel damage, fluid overload, and organ injury.

However, what sets CytoSorb apart from other approaches that often simply focus on a single target or pathway, is a comprehensive, multi-faceted approach to the core problems

of sepsis and septic shock. Based on a substantial body of published, peer-reviewed literature, CytoSorb can (click on hyperlinks for references):

CytoSorb Mechanisms of Action:

- **Control inflammation by reducing cytokine storm** and a **wide array of other inflammatory mediators such as activated complement**
- **Remove circulating bacterial toxins** produced by the active infection that can cause widespread inflammation and tissue damage
- **Redirect activated immune cells to sites of infection** and away from healthy tissues thereby reducing collateral damage
- **Reverse shock and restore natural blood pressure**, reducing the need for vasopressors and restoring oxygenated blood flow to vital organs
- **Improve microcirculation** among small blood vessels, improving oxygen delivery to tissues and organs like the kidney and **reducing lactic acidosis** – an independent risk factor of mortality
- **Protect blood vessels and promote reversal of capillary leak (leaky blood vessels)** by binding and removing numerous toxic substances in the blood that disruot endothelial tight junctions and damage or kill the endothelial cells lining the blood vessel wall
- **Remove excessive fluid and improve fluid balance** once capillary leak is resolved
- **Improve lung function and reduce time on mechanical support** such as mechanical ventilation and extracorporeal membrane oxygenation (ECMO)
- **Prevent and treat sepsis-associated acute kidney injury,** key to maintaining the ability to remove excessive fluid, maintain proper acid base balance, and eliminate toxic metabolic wastes
- **Remove liver toxins and support liver dysfunction** that is common in sepsis

As our understanding of how CytoSorb helps to treat sepsis and septic shock continues to evolve, we view CytoSorb not just as an adjunctive therapy, but rather as a fundamental part, just like antibiotics, of an end-to-end strategy to manage the septic patient.

In particular, this broad-spectrum approach helps to support four essential treatment goals of CytoSorb in septic shock to prevent or treat organ failure:

1) **Break the vicious cycle of massive, uncontrolled inflammation**

2) **Stabilize the patient (e.g. reverse shock, improve oxygenation, support liver dysfunction, protect the kidneys, etc.)**

3) **Promote the repair of capillary leak**

4) **Enable the active removal of excessive fluid (that compromises organ function and perpetuates organ failure)**

Importantly, capillary leak and exudative fluid underlie the pathophysiology of severe ARDS. Capillary leak also results in intravascular hypovolemia that contributes to shock. Interstitial edema in the kidneys can lead to congestive nephropathy due to the non-expandable fibrous renal capsule, causing increased intrarenal pressure that not just reduces renal blood flow, but importantly collapses nephrons, resulting in anuric renal failure.

Treatment with CytoSorb can promote the repair of capillary leak by removing the toxins that cause endothelial tight junction disruption, as well as the inhibition and killing of endothelial cells. In turn, blood vessels can now heal naturally, leading to a reversal of capillary leak that then enables the removal of excessive fluid. In many cases of CytoSorb treatment, this has led to rapid improvements in lung function and oxygenation, reversal of shock, as well as a rapid return of urine production and improvement in renal function. Interestingly, the latter is consistent with the histopathology of sepsis-associated acute kidney injury (AKI), where in the majority of cases, there is no structural injury to the kidney, just interstitial edema and cellular infiltration. **This concept of reversal of capillary leak is key to driving improved outcomes with CytoSorb therapy in sepsis and septic shock and other critical illnesses.** CytoSorb gives the "gift of fluid removal," but this should be done AFTER capillary leak has primarily reversed, which starts with CytoSorb therapy but can take several days after CytoSorb is stopped. Overagressive attempts to remove fluid while on CytoSorb therapy and when capillary leak has not yet reversed, particularly with CRRT that removes fluid directly from the intravascular space, can exacerbate hemodynamic instability and make it harder to wean patients off of vasopressors. Patience is key.

Like antibiotics, CytoSorb works best when used early, intensively, and at the right dose and duration – the foundation of the Company's "Right patient, Right Timing, Right Dosing" educational campaign.

Positive Clinical Results Backing Early and Intensive CytoSorb Use

CytoSorbents' clinical impact is supported by hundreds of peer-reviewed publications in many different clinical applications such as sepsis, including data from the COVID-19 pandemic, where CytoSorb was granted U.S. FDA Emergency Use Authorization in critically ill COVID-19 patients with respiratory failure.

Importantly, in sepsis, antibiotics to treat the infection is the best analogy to guide the treatment of deadly inflammation with CytoSorb. In serious infection and sepsis, it is critical to administer antibiotics as soon as possible, to increase the dose and give the antibiotics intravenously, and to keep using the antibiotics until the infection is resolved. These principles are the same for CytoSorb and inflammation, where hyper-inflamed patients should be treated early (once organ dysfunction has occurred), intensively (with more frequent device changes and higher flow rates to achieve more total blood volumes treated), and for the right duration (e.g. need to treat long enough to completely or near completely reverse shock and wean vasopressors, or other instability caused by inflammation).

In the 100-patient, multi-center registry of U.S. COVID-19 patients on CytoSorb and ECMO, published in the journal Critical Care (2023), where all had refractory respiratory failure and sepsis with 76% in septic shock, Hayanga and colleagues reported 74% 90-day survival, that rose to 82% in those treated early. This significantly outperformed published U.S. survival benchmarks of approximately 50% when CytoSorb was not used. In addition, those treated earlier had significantly shorter times on ECMO, mechanical ventilation, and ICU stay.

A separate, retrospective study of 175 septic shock patients recently published by Berlot and team in the Journal of Intensive Care Medicine (2025) demonstrated that early and intensive CytoSorb use (≥3 cartridges within 2–3 days) nearly doubled survival rates (70% observed vs. 37% predicted), with strong correlations between clinical benefit and treatment intensity. The study also corroborated the findings of another 75 septic shock patient retrospective study published by Schultz, et al. (2021) in the Journal of Critical Care that correlated survival with higher volumes of blood treated, highlighting that duration of treatment is critically important.

Further strengthening the evidence base, the first meta-analysis of 744 patients with septic shock by Steindl and colleagues from Charité Berlin Hospital was recently reported in the Journal of Clinical Medicine (2025) comparing 449 patients treated with CytoSorb and standard of care versus 295 control patients receiving standard of care alone. The study

demonstrated statistically significant improvements in hemodynamics, vasopressor requirements, and survival compared to control patients, where CytoSorb:

- **Reduced in-hospital mortality** (OR 0.64 [0.42–0.97], p=0.036, n=462)
- **Halved 28–30 day mortality** (OR 0.46 [0.28–0.78], p=0.003, n=250)

Meanwhile, results from the first 150 patients enrolled into the international, prospective COSMOS (**C**yt**OS**orb treat**M**ent **O**f critically ill patient**S**) critical care registry by Ferrer and collaborators was recently published in the Journal of Intensive Medicine (2025), where 58% of patients had septic shock, highlighting improved mortality compared with risk-based predictions and significant improvements in oxygenation, shock reversal, fluid balance, and lactate levels before and after use of CytoSorb.

Overall, these results highlight CytoSorb's ability to intervene across the pathophysiology of septic shock, setting it apart from previous drug and device-based approaches that failed to show consistent benefit.

Dr. Chan concluded, "Septic shock remains one of the most devastating and complex challenges in critical care. Despite decades of research, outcomes remain poor with limited treatment options. CytoSorb, guided by the experience and insight of clinicians and scientists around the world, is helping that change that. With an ever-expanding body of published clinical evidence - including hundreds of peer-reviewed studies such as those mentioned above, real-world data, and impactful success stories, CytoSorb continues to evolve as a powerful therapy to treat critical illnesses such as septic shock, particularly when used early, intensively, and of the right duration – just like antibiotics. In treating the sickest patients in the hospital, we are proud of our mission of working to save lives…together."

For more detailed information, we invite you to watch a replay of our World Sepsis Day Global Webinar, entitled "Turning the Tide in Sepsis and Septic Shock: Real World Insights with CytoSorb," held on September 10, 2025, where we explore best practices in the treatment of septic shock with CytoSorb with some of the pioneering clinicians who are fighting this battle daily on the front lines, including Dr. med. Tobias Hübner, Priv.-Doz. Dr. med. Kevin Pilarczyk, and Prof. Dr. Zsolt Molnár, found here. Also, please follow our new septic shock blog series where we delve into greater detail on these points, found here. Meanwhile, watch videos from healthcare providers from around the world who detail their first-hand experiences with CytoSorb in the treatment of septic shock and other critical illnesses in our "Voices Around the World" segment, found here.

Disclaimer: CytoSorb is CE-mark approved in the E.U. as an extracorporeal cytokine adsorber and for the removal of bilirubin, myoglobin, and certain antithrombotic drugs. CytoSorb is not yet approved or cleared in the U.S.

About CytoSorbents Corporation (NASDAQ: CTSO)

CytoSorbents Corporation is a leader in the treatment of life-threatening conditions in the intensive care unit and cardiac surgery through blood purification. CytoSorbents' proprietary blood purification technologies are based on biocompatible, highly porous polymer beads that can actively remove toxic substances from blood and other bodily fluids by pore capture and surface adsorption. Cartridges filled with these beads can be used with standard blood pumps already found in hospitals (e.g. dialysis, continuous renal replacement therapy or CRRT, extracorporeal membrane oxygenation or ECMO, and heart-lung machines), where blood is repeatedly recirculated outside the body, through our cartridges where toxic substances are removed, and then back into the body. CytoSorbents' technologies are used in a number of broad applications. Specifically, two important applications are 1) the removal of inflammatory agents and toxins in common critical illnesses that can lead to massive inflammation, organ failure, and patient death, and 2) the removal of blood thinners during and after cardiothoracic surgery to reduce the risk of severe bleeding. The breadth of these critical illnesses includes, for example, sepsis, burn injury, trauma, lung injury, liver failure, cytokine release syndrome, and pancreatitis, as well as the removal of liver toxins that accumulate in acute liver dysfunction or failure, and the removal of myoglobin in severe rhabdomyolysis that can otherwise lead to renal failure. In these diseases, the risk of death can be extremely high, and there are few, if any, effective treatments.

CytoSorbents' lead product, CytoSorb®, is approved in the European Union and distributed in over 70 countries worldwide, with nearly 300,000 devices used cumulatively to date. CytoSorb was originally launched in the European Union under CE mark as the first cytokine adsorber. Additional CE mark extensions were granted for bilirubin and myoglobin removal in clinical conditions such as liver disease and trauma, respectively, and for ticagrelor and rivaroxaban removal in cardiothoracic surgery procedures. CytoSorb has also received FDA Emergency Use Authorization in the United States for use in adult critically ill COVID-19 patients with impending or confirmed respiratory failure. CytoSorb is not yet approved or cleared in the United States.

The Company has numerous marketed products and products under development based upon this unique blood purification technology protected by many issued U.S. and

international patents and registered trademarks, and multiple patent applications pending, including ECOS-300CY®, CytoSorb-XL™, HemoDefend-RBC™, HemoDefend-BGA™, VetResQ®, K+ontrol™, DrugSorb™, ContrastSorb, and others.

For more information, please visit the Company's website at www.cytosorbents.com or follow us on Facebook and X.