Cytosorb™ in a Patient with *Legionella*-Pneumonia Associated Rhabdomyolysis: A Case Report

Marion Wiegele and Claus G. Krenn

Acute renal failure after rhabdomyolysis is a well-known complication often requiring renal support. Severe rhabdomyolysis reported in the context of *Legionella* pneumonia particularly often necessitates prolonged extracorporeal renal hemodialysis sometimes with function never regained.[1,2]

Cytosorb™—a recently introduced detoxification system—was evaluated to reduce toxic levels of cytokines (in *e.g.*, systemic inflammatory response, sepsis, acute respiratory distress syndrome, trauma, and burn injury) leading to (multiple) organ failure and immunosuppression, thus cleaving fatal outcomes.[3] Cytokines (10–50 kDa) are adsorbed by polymer beads within a cartridge perfused via extracorporeal circulation.[3] The effectiveness of Cytosorb™ to remove myoglobin *in vitro* from saline solution and donated blood serum, respectively, has been demonstrated by Kuntsevich *et al*. in 2009, whereas *in vivo* data are missing so far.[4]

Case Report

A 44-year-old man presented with ongoing fever and impaired general condition for more than 5 days. Respiratory insufficiency finally led to hospitalization and rapid admission to an intensive care unit with consequent intubation and ventilatory support as leading symptom of the clinical deterioration toward multiple organ dysfunction syndrome. Collection of patient's history revealed a long lasting history of alcoholism reported by the patient's parents as only abnormality.

Results of x-ray investigation of the chest and computed tomography were consistent with the clinical diagnosis of acute respiratory distress syndrome. Thorough investigation of patient's specimen revealed infection with *Legionella pneumophila* by antigen detection in the patient's urine and proof of serology as causative for the patient's condition.

Despite administration of antibiotics, liver enzymes and parameters of renal function deteriorated in parallel within the following days, indicating a trend toward multiple organ failure. Continuous catecholamine support (noradrenalin) to maintain adequate hemodynamic condition ranged between 0.03 and 0.35 mcg/kg/min.

Although adequate fluid administration was started right from the beginning, creatine kinase and myoglobin sera levels increased in combination with reduced urine excretion (0.25 ml/kg/6 h). We started Cytosorb™ treatment by hemoperfusion-mode (multiFiltrate® by Fresenius; blood flow: 300 ml/min) on day 6 after admission. Vascular access was ensured by a two-lumen central venous catheter (ARROW® Multi-Lumen Indwelling Catheter, 12 French, 8″ [20 cm]). Given that there was no indication for citratedialysis in our patient, Cytosorb™ was used in its stand-alone application form (**Figure 1**). Within 8 hours, myoglobin levels decreased from 18,390 to 10,020 ng/ml. A second cycle was conducted on day 7 and myoglobin levels again declined from 13,400 to 8,359 ng/ml (**Figure 2**). Parameters of renal function and liver enzymes decreased within hours and subsequently during the next days. In parallel, the patient's urine output increased from <0.5 ml/kg/6 h to >1 ml/kg/h (day10). F1 F2

The patient's condition improved subsequently. Renal function completely recovered and hemodialysis was not necessary at any time of hospitalization. Finally, the patient was transferred to a normal ward on day 22.

Discussion

Positive serum myoglobin levels are related to muscle injury as it is released from damaged muscle cells. The protein`s half-life in plasma is in the range of 9 minutes because it is rapidly eliminated by the kidneys. Rhabdomyolysis can lead to acute renal failure in critically ill patients because of prerenal, renal, and postrenal factors.[5] Acute renal failure is thus associated with uremia, electrolyte and metabolic imbalance, volume overload, impairment of other organ systems (*e.g.*, liver, intestine), alterations within the blood coagulation system and increased mortality.[5] Furthermore, higher medical costs should be kept in mind.

Referring to the updated panel conclusions of an international consensus article, recommendations on preventing renal failure in rhabdomyolysis suggest intensive hydration with isotonic crystalloids and maintenance of polyuria, alkalinization of urine (pH > 6.5–7.0), and prudent use of diuretics.[6] Close

From the Clinical Division of Anesthesiology and General Intensive Care Medicine Department of Anesthesia, General Intensive Care and Pain Control, Medical University of Vienna, Währinger Gürtel 18–20, 1090 Vienna

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Reprint Requests: Marion Wiegele, MD, Clinical Division of Anesthesiology and General Intensive Care Medicine Department of Anesthesia, General Intensive Care and Pain Control, Medical University of Vienna, Währinger Gürtel 18–20, 1090 Vienna . Email: marion.wiegele@meduniwien.ac.at.

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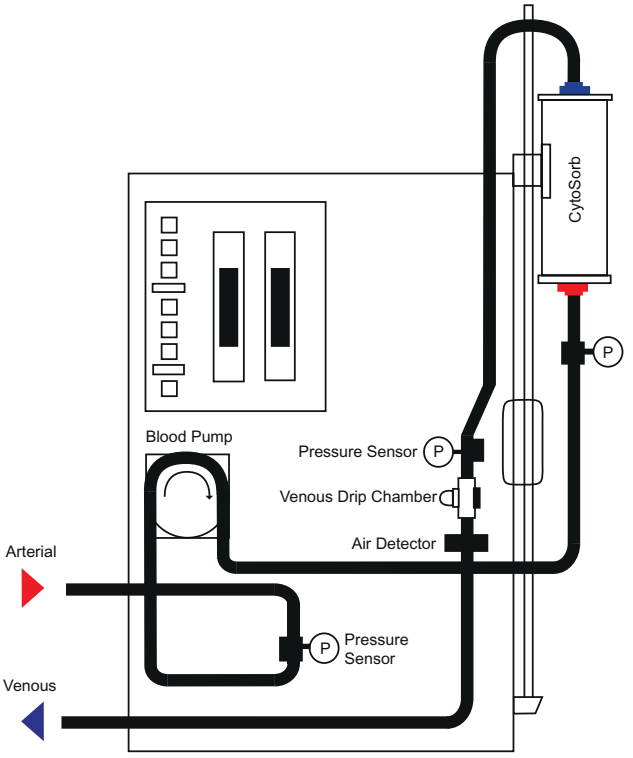

Figure 1. Cytosorb™ circuit (stand alone application).

monitoring of renal function is recommended because initial creatinine serum levels >150 µmol/l and creatine kinase >5,000 U/l are associated with increased risk of acute kidney injury or necessity of renal replacement therapy (RRT).[6] Nevertheless, these references only allow level C recommendation. Current therapy regimes implying use of high-flux hemodialysis membranes are sometimes not effective to reduce myoglobin levels in blood plasma in an adequate way and may cause undesirable side effects.[4,5]

In other words, elimination of myoglobin is crucial to preserve renal function but to date, there is lack of sufficient therapeutics.

In the European Union, Cytosorb™ system is specifically approved as an extracorporeal cytokine filter to prevent from cytokine storm and deterioration of organ function in septic

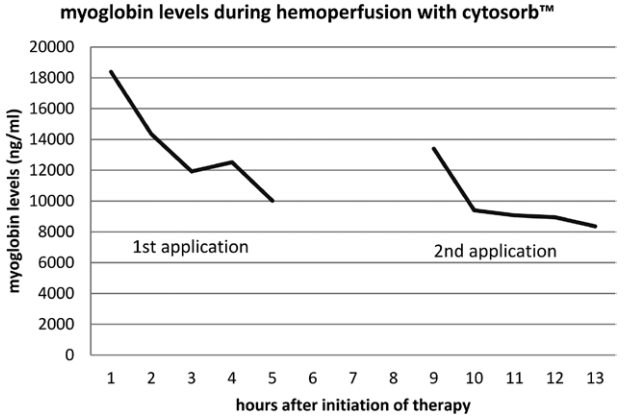

Figure 2. Decrease of myoglobin levels during Cytosorb™ application (1st run: 0–6hours; 2nd run: 9–14hours).

patients. Application of the cartridge is feasible via commonly used standard continuous RRT devices (*e.g.*, multiFiltrate, Fresenius Medical Care). A drawing of the circuit is given in **Figure 1**. The single use cartridge may be used 6 hours per day up to 7 consecutive days. Given that optimal blood flow rates of 250–400 ml/min are recommended by the manufacturer, we adapted blood flow rates to 300 ml/h. Because there was no indication for citrate dialysis in our patient, Cytosorb™ was used in its stand-alone application form.

Cytosorb™ therapy was implemented to prevent from cytokine storm and further deterioration of systemic inflammatory response seen in this patient. Myoglobin levels initially have been monitored in addition but independently from usage of Cytosorb™. Hence, we did not calculate myoglobin levels so far, but the interesting finding of coincidental decrease of myoglobin draw our interest and—from our point of view—needs further investigation especially because Cytosorb™ has already been demonstrated to effectively reduce myoglobin levels in an experimental setting *in vitro*.[4] To our knowledge, this is the first time that a decrease of myoglobin levels after application of Cytosorb™ cartridge could be demonstrated *in vivo*.

No side effects of therapy have been observed in this patient. In general, application of Cytosorb™ is stated to be performed safely in more than 650 human treatments to date. Nevertheless, using this device, physicians have to be aware of patient's hypersensitivity to component parts of the cartridge and platelet count (because Cytosorb™ may cause a decrease in platelet count comparable to other extracorporeal devices). Moreover, application of Cytosorb™ in patients with heparin-induced thrombocytopenia is restricted to availability of citrate dialysis. In this patient, enoxaparin was administered subcutaneously to prevent from thromboembolic events according to current ACCP Guidelines but no additional anticoagulant had to be added to the extracorporeal system.[7] AQ1

Measured myoglobin levels were not extremely high in our patient but comparable to those mentioned in the few existing relevant case reports.[2,8] Creatine kinase and myoglobin levels deteriorated continuously and renal function was worsening in parallel. According to RIFLE criteria (urine output < 0.5 ml/kg/6 h) and recommendations of above-mentioned international consensus article (initial CK > 5,000 U/l), our patient was at risk for acute kidney injury potentially necessitating RRT.

After finalizing two treatment sequences, the patient's clinical condition started to improve. It remains speculative whether this is an effect of the Cytosorb™ treatment or an epiphenomenon. Eventually, the removal of myoglobin was an additional effect to the described removal of cytokines triggering an inflammatory state which is also observed in the development of acute renal failure. Furthermore, it could be speculated, that alcohol abuse mitigated the immune response in our patient thus abetting infection and development of organ dysfunction.

To date, little is known about drug elimination via Cytosorb™. Following the manufacturer's instructions for use, Cytosorb™ "may be capable of removing drugs (*e.g.*, antibiotics, vasopressor agents)" which could be of important relevance in the setting of critically ill patients. Current literature referring to drug binding in RRT recommends to higher dosing regimens of antibiotics (piperacillin, meropenem, and vancomycin) in critically ill patients in the presence of high effluent flow rates or the presence of poorly susceptible pathogens.[9] Furthermore,

AQ2

Table 1. Course of Standard Laboratory Parameters and Myoglobin Levels During Intensive Care Unit Stay

		Cytosorb™ 1st application			Cytosorb™ 2nd application						
Length of ICU Stay	Days	1	5	6	7	8	8	8	8	15	22
	Time				20:39:59	04:37:53	07:07:13	12:44:11	21:10:11		
Creatinine	mg/dl	1.25	1.21	1.07	1.56	1.09	1.06	1.04	1.15	0.45	0.34
Blood urea nitrogen	mg/dl	15	54.2	51	74.6	71.2	70.4	72.7	78.1	18.8	9.8
Bilirubin	mg/dl	4.98	1.94	1.52	1.57	1.44	1.4	1.4	0.94	0.73	0.66
Overall protein	g/l	51.2	51.7	57.6	57.7	56.7	57.5	58.4	53.7	53.3	52.8
Albumin	g/l	19.9	25.1	24.1	25.5	24.2	25.7	25.2	23.9	27.5	30.3
ASAT (GOT)	U/l	149	106	161	440	462	456	395	285	113	20
ALAT (GPT)	U/l	71	40	38	120	138	141	137	121	163	57
Gamma - GT	U/l	44	124	244	764	873	897	864	853	738	343
Myoglobin	ng/ml			7066	18390	10020	9173	13400	8359	387	
LDH	U/l	413	342	429	629	712	620	529	430	315	214
Urine output	ml/kg/6 h				0.25				2.44		
Noradrenalin	mcg/kg/min	0.309	0.02	0.103	0.144	0.137	0.103	0.12	0.10		

Reiter *et al*. investigated removal of glycopeptide antibiotics, digoxin, theophylline, phenobarbital, phenytoin, carbamazepine, and valproic acid within the setting of BetaSorb™, another cytosorbent. Although this was about an *in vitro* experiment, it showed potent absorptive capacity concerning these therapeutic drugs.[10] Thus, it can be speculated that Cytosorb™ has an effect on drug elimination in critically ill patients too. Further investigation is needed.

Whether application of Cytosorb™ prevents acute renal failure necessitating hemodialysis in patients with rhabdomyolysis in any case remains to be investigated in randomized controlled trials.

References

1. Andre E, Thurm C, Bhawal J, *et al: Legionella pneumophila* pneumonia presenting with severe rhabdomyolysis and acute kidney failure *Chest* 142(4_MeetingAbstracts): 174A. doi:10.1378/chest.1389344, 2012.
2. Shimura C, Saraya T, Takata S, *et al*: Pathological evidence of rhabdomyolysis-induced acute tubulointerstitial nephritis accompanying *Legionella pneumophila pneumonia J Clin Pathol* 61:1062–63, 2008.
3. Honore PM, Jacobs R, Joannes-Boyau O, *et al*: Newly designed CRRT membranes for sepsis and SIRS—a pragmatic approach for bedside intensivists summarizing the more recent advances: a systematic structured review. *ASAIO J* 59: 99–106, 2013.
4. Kuntsevich VI, Feinfeld DA, Audia PF, *et al*: In-vitro myoglobin clearance by a novel sorbent system. *Artif Cells Blood Substit Immobil Biotechnol* 37: 45–47, 2009.
5. Bellomo R, Kellum JA, Ronco C: Acute kidney injury. *Lancet* 380: 756–766, 2012.
6. Brochard L, Abroug F, Brenner M, *et al*: ATS/ERS/ESICM/SCCM/SRLF Ad Hoc Committee on Acute Renal Failure: An Official ATS/ERS/ESICM/SCCM/SRLF Statement: Prevention and Management of Acute Renal Failure in the ICU Patient: an international consensus conference in intensive care medicine. *Am J Respir Crit Care Med* 181: 1128–1155, 2010.
7. Kahn S., Lim W., Dunn A.S, *et al:* Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines *Chest* 141 (Suppl): e195S–e226S, 2012.
8. Abe M, Kaizu K, Matsumoto K: Clinical evaluation of pneumonia-associated rhabdomyolysis with acute renal failure. *Ther Apher Dial* 12: 171–175, 2008.
9. Jamal JA, Udy AA, Lipman J, Roberts JA: The impact of variation in renal replacement therapy settings on piperacillin, meropenem, and vancomycin drug clearance in the critically ill: an analysis of published literature and dosing regimens. *Crit Care Med* 42: 1640–1650, 2014.
10. Reiter K, Bordoni V, Dall`Olio G, *et al*: In vitro removal of therapeutic drugs with a novel adsorbent system. *Blood Purif* 20:380–388, 2002.

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