Submitted June 2015; Accepted February 2016

CASE REPORT

# First case of toxic shock treated with haemoadsorption by CytoSorb® in the Netherlands

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Keywords - septic shock, Haemoadsorption, CytoSorb®

## Abstract

Septic shock is one of the greatest challenges in intensive care medicine. Despite the development of several new therapies, morbidity and mortality remain high. The so-called holy grail has yet to be found. High-volume continuous renal replacement therapy has been subject to research for some time, with limited success. One of the novel therapies on septic shock is haemoadsorption with a CytoSorb® adsorber. We present the case of an adolescent with *Staphylococcus aureus* toxic shock syndrome treated with the CytoSorb® adsorber, who made a remarkable recovery afterwards. To the best of our knowledge, this was the first application of the CytoSorb® adsorber in the Netherlands. The effects of haemoadsorption with CytoSorb® have been investigated mainly in animal experimental studies; to date, there is very limited data on the use in human septic shock.

## Introduction

For a long time, septic shock has shown to have a high mortality and morbidity in the ICU.[1-3] Because of the high mortality and morbidity, the Society of Critical Care Medicine (SCCM) has set up the 'Surviving Sepsis Campaign' with treatment guidelines and regular updates; the last update was in 2012.[4]

One of the promising developments in intensive care medicine is the use of continuous renal replacement therapy (CRRT) during septic shock to decrease the amount of cytokines causing the septic shock.[5] Experimental studies in animals show promising results.[6,7] Multiple approaches have been considered; especially different kinds of adsorbers and adsorber speed have been subject to research.[8] One of the adsorbers being investigated is the CytoSorb® adsorber. Although no large-scale randomised controlled trials have been performed yet, some clinical use has already been reported.[9] In a German study, the device seemed to be safe.[10] Recently, the CytoSorb® adsorber was approved for clinical use in the Netherlands.

*Staphylococcus aureus* bacteraemia is known to be a disease with a high morbidity and mortality. Another important clinical feature is its ability to produce the state of *Staphylococcus* toxic shock syndrome. The overall case-fatality ratio for toxic shock syndrome was 4.1% (3% for menstrual cases, 5% for non-menstrual cases) and was significantly higher in cases not associated with menstruation ($p < 0.005$).[11]

## Case report

A 17-year-old male reported to the paediatrician at a local rural hospital with complaints of pretibial pain in his right leg, after he accidentally cut his leg while in the fields a few days earlier. Besides obesity (weight 110 kg, 1.90 m; BMI 30.5), his medical history was unremarkable. The surgeon diagnosed a phlegmon with an abscess; blood cultures were obtained before starting intravenous antibiotics. Because the referring hospital assumed he had an allergy to B lactam antibiotics because of his rash, antibiotic therapy consisting of clindamycin and ceftriaxone was initiated. The surgeon performed a debridement with wound nettoyage. No clinical signs of subcutaneous emphysema or necrotising fasciitis were present. A deep abscess in the pretibial region was successfully drained and wound cultures were taken. The first hours after surgery were uneventful; however some hours later the patient's condition deteriorated. After admission to the ICU in the referring hospital, he developed erythema, spreading from the right lower leg to the right upper leg, abdominal wall and the left leg, consistent with toxic shock syndrome. His vital signs were as follows: sinus tachycardia (135 beats/min), fever (40.2 °C), blood pressure 122/60 mmHg, tachypnoea (40 breaths/min). He was transferred to our level 3 ICU after the paediatric intensive care physician agreed to admission to the adult ICU. Blood cultures revealed *S. aureus* bacteraemia, which was penicillin resistant and ceftriaxone sensitive. *Table 1* shows the lab values.

According to the sepsis criteria of the SCCM, he was in septic shock.[4] When the erythema reached the abdominal wall, he

**Table 1.** Lab values on admission and 24 hours after cessation of CytoSorb®

| Lab value | At admission | 24 hours after CytoSorb® |
|---|---|---|
| C-reactive protein (mg/l) | 316 | 156 |
| Haemoglobin (mmol/l) | 7.5 | 6.0 |
| Haematocrit (l/l) | 0.33 | 0.29 |
| MCV (fl) | 86 | 92 |
| Thrombocytes (10*9 /l) | 94 | 107 |
| Leucocytes (10*9 /l) | 9.1 | 12.1 |
| INR | 1.2 | 1.1 |
| APTT (sec) | 29 | 27 |
| Urea (mmol/l) | 5.2 | |
| Creatinine (µmol/l) | 83 | 81 |
| Phosphate (mmol/l) | 0.31 | 0.94 |
| Magnesium (mmol/l) | 0.93 | 0.96 |
| Total bilirubin (µmol/l) | 32 | 12 |
| Direct bilirubin (mol/l) | 20 | |
| Gamma GT (U/l) | 63 | 75 |
| Alkaline phosphatase (U/l) | 74 | |
| ALAT (U/l) | 64 | 80 |
| ASAT (U/l) | 151 | |
| LDH (U/l) | 383 | |
| Creatine kinase (U/l) | 4185 | 1574 |
| Albumin (g/l) | 22 | 23 |
| Lactate (mmol/l | 2.3 | 2.4 |
| pH | 7.47 | |
| pCO2 (mmHg) | 31 | |
| pO2 (mmHg) | 93 (6 litres O2) | |
| HCO3- (mmol/l) | 23 | |
| Base excess | -1 | |
| Saturation | 98% | |
| SvO2 | 70% | |
| PaO2:FiO2 ratio | 233 | |

developed respiratory failure, necessitating intubation and artificial ventilation. His blood pressure dropped to 76/50 mmHg, requiring vasopressors. Norepinephrine was initiated with a maximum dosage of 0.12 µg/kg/min. Hydrocortisone 100 mg x3/day was also started; this is standard care in our hospital after the initiation of vasopressors in septic shock. Wound cultures, which were obtained at the local hospital during surgery, revealed the presence of an invasive *S. aureus* infection. Antibiotic therapy consisting of ceftriaxone and clindamycin was continued. Due to the severity of the disease in a healthy young adult, CRRT (citrate anticoagulation, blood flow 240 ml/min, in series to the CRRT filter; Baxter HF 19 Aquamax) was initiated with a CytoSorb® adsorber. There were no signs of an acute kidney injury and there was no need for renal replacement therapy. During this septic phase, the only goal was to remove the cytokines with the CytoSorb® adsorber. Informed consent was obtained through his father. Within six hours after the start, the erythema progression stopped and after 12 hours the need for vasopressors diminished.

After 24 hours, the CytoSorb® adsorber had to be replaced. His vital signs were as follows: sinus tachycardia (112 beats/min), blood pressure 117/49 mmHg without vasopressors. The erythema diminished after a few hours and had disappeared after 24 hours. He was still on the ventilator. He no longer had any fever, possibly due to the CRRT. Because of the clinical improvement, CRRT with CytoSorb® was discontinued. Twenty-four hours after discontinuing CRRT with CytoSorb®, his vital signs were unchanged. *Table 1* shows his lab values.

We concluded that the patient was no longer septic and diuretics were started because of fluid overload. His respiration improved, the ventilator support was diminished and he was extubated on day 5 after admission, within 72 hours of cessation of CRRT. On day 6, he was transferred back to the local hospital for further revalidation.

## Discussion

The CytoSorb® adsorber

A main shortcoming of most blood purification techniques is their limited capacity to remove cytokines from the blood compartment, resulting in the inability to significantly lower cytokine levels.[9] The CytoSorb® adsorber, which was mainly developed for this purpose, might be useful in septic shock patients. Unfortunately, no interleukin levels were measured due to logistic issues. The CytoSorb® adsorber contains beads made up of polystyrene-divinylbenzene porous particles (450 µm average particle diameter, 0.8-5 nm pore diameter, 114 850 $m^2$ $g^{-1}$ surface area) with a biocompatible polyvinyl-pyrrolidone coating).[12] CytoSorb® is an adsorber technology, which selectively binds substances physico-chemically (hydrophobic molecules with a molecular weight of up to approximately 55 kD). The adsorber is placed in series to our usual CRRT filter. The large surface area provides a high level of cytokine adsorption; plasma tumour necrosis factor (TNF)-α, interleukin (IL)-6, CXCL-1, and CCL2 were significantly reduced in haemoadsorption versus sham [12]. After 24 hours, the adsorbing abilities of the beads decrease and therefore the filter needs to be replaced.

*Side effects*

It is as yet unsure to what extent medication is removed as well. An earlier publication reports a decrease in antibiotic peak concentrations.[13] In our experience, a decrease of antibiotic concentrations is a serious issue.[14] We decided to adjust the dosage of ceftriaxone to 2 grams twice daily in order to minimise this effect. To the best of our knowledge, no other side effects have been reported, although there has been no research on the activity of or damage to platelets. It would be reasonable to consider the possibility of platelet dysfunction; in our experience, we have not yet had to discontinue the treatment because of thrombocytopenia (<50 $x10^9$).

*Effect on our patient*

The presented patient suffered from mild septic shock. The progression of the erythema, together with that of the respiratory and circulatory failure, seemed to stop after six hours of CytoSorb® therapy. We would not go as far as to state that the complete recovery was only due to the CytoSorb®; antibiotics and source control also played a major role. The reduction in the erythema after the start of CytoSorb® was, however, remarkable and the need for vasopressors stabilised and decreased within six hours after initiation. In our opinion, the patient would have survived without the CytoSorb®, but we feel that his stay in our ICU might have been shortened by the CytoSorb® adsorber.

To the best of our knowledge, no large-scale randomised controlled trials have been conducted yet on this topic. Randomised controlled trials will have to be performed to find out whether the theoretical beneficial effects of the CytoSorb® adsorber are clinically relevant, as well as the possibilities of unwanted side effects. Although the clinical value still has to be established, the first experiences with the CytoSorb® adsorber are promising and justify further investigation.

## Acknowledgment

We would like to thank Eric Willemsen for his assistance and for sharing his knowledge on the use of the CytoSorb® adsorber.

## Disclosures

All authors declare no conflict of interest. No funding or financial support was received.

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