Cytokine adsorption as a promising option for septic shock and multiple organ failure due to Candida infection and decompensated type 1 diabetes mellitus

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THOUGHTS AND PROGRESS

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INTRODUCTION

Candida is by far the most common fungal blood stream pathogen.1 Candidemia and invasive candidiasis are major causes of morbidity and mortality, and their incidence is increasing because of the growing complexity of critically ill patients.2 Recognition and treatment of this infection is frequently delayed with dramatic clinical deterioration.3

Apart from that, type 1 diabetes mellitus (T1DM) represents one of the most common chronic diseases in childhood. The disease is accompanied by high morbidity and mortality rates due to a metabolic dysregulation, its immunosuppressive effects and a predisposition of these patients to fungal infections, particularly candida yeast species.4,5

Therefore, the combination of both diseases (ie, Candida infection and T1DM) carries a high risk for the development of bloodstream infections and if left untreated, this can result in sepsis or its most severe form septic shock.

Both represent life-threatening syndromes induced by a dysregulated immune response to infections and are connected to high rates of morbidity and mortality especially among critically ill patients.6 High cytokine levels related to an overwhelming immune response of the organism as well as the refractory hypotension play a crucial role for the

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Abstract
Type 1 diabetes mellitus (T1DM) represents one of the most common chronic diseases in childhood. It is associated with high morbidity and mortality rates due to metabolic dysregulation, immunosuppressive effects, and a predisposition to fungal infections. Candidiasis is a severe infection and its prevalence has increased throughout the last decades. We report the case of a 19-year-old female patient admitted to our intensive care unit with T1DM and Candida infection associated with severe metabolic acidosis. In the absence of response to high dose catecholamine cardiovascular therapy and the presence of severe metabolic acidosis, a CytoSorb cartridge was implemented into the extracorporeal dialysis circuit resulting in a stabilization of hemodynamics accompanied by a tremendous decrease in vasopressor requirements, control of the hyperinflammatory response, as well as a resolution of metabolic acidosis and regeneration of renal function. Treatment with CytoSorb was safe and feasible without technical problems. Notably, this is the first case description reporting on the effects of CytoSorb in a patient with Candida infection as part of T1DM.

KEYWORDS
Candida, CytoSorb, hemoadsorption, multiple organ failure, type 1 diabetes mellitus
dysfunction of the cardiovascular system. The hemodynamic instability implies ischemic tissue damage as a result of hypoperfusion and inflammation. Extended vasopressor requirement is reported to correlate with vascular failure, metabolic dysregulation, and acute renal failure and is known to be associated with increase of mortality during sepsis.8

In this context, the reduction of cytokine blood levels by means of extracorporeal hemadsorption represents a novel strategy to control the overwhelming immune response in the early phase of septic shock with cardiovascular dysfunction. Owing to the improvement of vasopressor efficacy, the stabilization of hemodynamic conditions is reported to be beneficial for patients suffering from septic shock with multiple organ failure. CytoSorb has been applied in many patients suffering from various diseases and is reported to reduce high cytokine plasma levels effectively.9 ‒ 14 We herein report the case of a 19-year-old female patient with T1DM and Candida infection associated with severe metabolic acidosis admitted to our intensive care unit, who was successfully treated with CytoSorb hemoperfusion in combination with continuous renal replacement therapy (CRRT).

2 | CASE DESCRIPTION

A 19-year-old female patient with severe metabolic acidosis and coma (GCS 4) was admitted to the intensive care unit. Acid–base analysis revealed a severe metabolic acidosis with advanced electrolyte disturbances (pH < 6.7; pCO2 = 2.8 kPa; pO2 = 22 kPa; SpO2 = 98%; HCO3 = 3.7 mmol/L; BE = −32.6). Additionally, high infection parameters, hyperkalemia, elevated retention parameters as well as acute renal failure (AKIN III according to KDIGO) were observed. Sedation, protective intubation, and mechanical ventilation were performed and a Shaldon catheter was inserted.

In the state of septic shock, circulatory stabilization including high-dose catecholamine support, balanced volume therapy, hydrocortisone, and buffering with NaHCO3 and THAM was administered. Antibiotic therapy was initially performed by the administration of meronem (meropenem, Merck & Co., Kenilworth, NJ, USA). Since Candida dublinensis aerobic and Candida albicans could be detected in blood cultures, antibiotic therapy was completed with candidas (caspofungin, Merck & Co.).

Given that metabolic acidosis and increased retention parameters persisted, continuous renal replacement therapy (CRRT) was initiated within 24 hours of admission. Due to her advanced hemodynamic instability despite high-dose catecholamine therapy and due to significant elevated IL-6 levels (>1000 pg/mL), a CytoSorb 300 adsorber (CytoSorbents Europe, Berlin, Germany) was additionally implemented.

We performed one treatment session with CytoSorb for 20 hours. The CytoSorb 300 adsorber was installed post-hemofilter into the CRRT circuit (Prismaflex, Baxter Deutschland, Unterschleißheim, Germany). Treatment was carried out in CVVHD mode with citrate as anticoagulation at a blood flow rate of 100‒150 mL/min.

The combined application of both therapeutic procedures was associated with a resolution of metabolic acidosis. Hemodynamics stabilized and vasopressor support could be reduced and finally stopped during the treatment interval. Hyperinflammation could be rapidly controlled and all inflammatory parameters were reduced during the course of treatment (Table 1). Additionally, treatment resulted in a reduction of retention parameters and an overall regeneration of renal function as evidence by a return of spontaneous diuresis to normal levels. Initial i.v. insulin therapy was changed to a subcutaneous regimen due to moderate blood sugar levels (8–12 mmol/L).

The patient was transferred to the internal ward 9 days after admission. Due to appropriate handling, the treatment with CytoSorb was safe and feasible without technical problems.

3 | DISCUSSION

Several studies have reported the impact of cytokine adsorption by extracorporeal CytoSorb therapy on an improvement in hemodynamics and metabolic variables among critically ill patients.15 ‒ 18 CytoSorb treatment was reported to be highly effective if started within 24 hours of sepsis diagnosis.17

The aforementioned patient suffered from a severe metabolic acidosis due to Candida infection as part of T1DM, which resulted in septic shock and multiple organ failure. The combination of CytoSorb hemoadsorption and CRRT was started within 24 hours from sepsis diagnosis and resulted in improved renal function, significantly improved hemodynamics including reduction of catecholamine therapy, and a resolution of severe ketoacidosis (Table 1). In addition, therapy led to a general improvement in the patient’s clinical condition. Therefore, no follow-up IL-6 measurement was performed.

Weingold et al suggested IL-6 to be necessary for the induction of the CRP gene. Our findings are in concordance with their assumption inasmuch as an increase of IL-6 was associated with an increase of CRP.18

Simoni recently discussed the role of CytoSorb for sepsis and septic shock.19 Inter alia, he mentioned Malard et al who described this device as “unable to remove endotoxins.”20 Feri already discussed the limitations of these in vitro experiments.21 Whereas the CytoSorb adsorber has been originally marketed for the removal of excess cytokine blood levels, its effects seem to reach far beyond this and there is growing evidence that the adsorption properties also enable the removal of pathogen-associated molecular pattern molecules.
(PAMPs), such as bacterial exotoxins, as well as damage-associated molecular pattern molecules (DAMPs).\textsuperscript{22} In this regard, CytoSorb might have also helped to lower the pathogenetic burden by the removal of bacterial exotoxins as well as mycotoxins in addition to other inflammatory relevant parameters resulting in an attenuation of the inflammatory response in our patient.

Little data is available regarding the removal of anti-infective drugs during treatment with CytoSorb. Besides a recently published in vitro attempt by König et al who quantified the adsorptive capacity of various commonly used antibiotic and antifungal drugs, also Reiter et al investigated this important topic.\textsuperscript{23,24} To our knowledge, nothing is known about the clearance of further drugs particularly like cancidas (caspofungin). Moreover, the use of CytoSorb in vivo regarding the adaptation of drug administration should be considered in further investigations. Of note, this is the first case description reporting on the effects of CytoSorb in a patient with Candida infection as part of T1DM.

The attenuation of the overwhelming inflammatory response in systemic inflammatory diseases can effectively be controlled by the application of CytoSorb resulting in improved clinical outcomes. As Simoni recently mentioned, CytoSorb among other devices “showed a limited ability to significantly improve the outcomes, their positive role in the treatment of septic shock patients remains undisputed.”\textsuperscript{19}

With regard to our results, there is a need to perform prospective randomized controlled studies to appropriately assess the diverse effects as well as to optimize the therapeutic procedures of this tool beyond the context of sepsis or septic shock. Various peculiarities of other diseases for example, cardiogenic shock\textsuperscript{25} or focal segmental glomerulosclerosis (FSGS)\textsuperscript{26} etc., have to be taken into consideration as well.

CONFLICTS OF INTEREST
The authors declare that they have no conflicts of interest with the contents of this article.

AUTHOR CONTRIBUTIONS
Concept, Data collection, Data interpretation, Drafting article, Critical revision of article: GK
Critical revision of article, Approval of article: MBS
Data interpretation, Critical revision of article: AM

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REFERENCES

How to cite this article: Klinkmann G, Stope MB, Meyer A. Cytokine adsorption as a promising option for septic shock and multiple organ failure due to Candida infection and decompensated type 1 diabetes mellitus. Artif Organs. 2020;44:522–525. https://doi.org/10.1111/aor.13606