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When more could be industry-driven: the case of the extracorporeal treatment of sepsis

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The actual and complex situation

Sepsis, defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, continues to have a distressingly high morbidity and mortality. This is especially the case in septic shock, a subset of sepsis with profound circulatory, cellular, and metabolic abnormalities [1]. Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) and the resultant production of inflammatory cytokines play an important role in the pathogenesis. Currently, no drugs are approved for the treatment of sepsis, because none of the candidate modulators of the sepsis immune response could show a beneficial effect on patient outcomes in large randomized controlled trials, illustrating the urgent need for new treatment approaches.

The idea of extracorporeal removal of evil substances (blood “purification”), resulting in restoration of the immune balance, has already been raised in the 1980s and rapidly found strong proponents. This paper will focus on two devices that use adsorptive mechanisms for removal of bad mediators and reduce “the fuel of fire”: coupled plasma filtration and adsorption (CPFA) and Cytosorb®. Before describing the clinical results of these physiologically attractive but expensive devices, it is important to stress the differences that exist between the marketing approval of a drug and a device [2]. A drug can only receive market authorisation when a competent authority [e.g. the European Medicines Agency (EMA) or the Food and Drug Administration (FDA)], after scientific assessment based on adequately designed randomized trials, concludes that the drug has a beneficial effect on human health. Exceptions to this pathway may exist for, e.g. orphan diseases. The requirement for marketing authorisation of medical devices is less stringent. In the EU, manufacturers of devices must fulfil the requirements for conformity with the European directives [3], recently replaced by regulation 2017/745 [4]. This conformity results in a CE Mark that stands for safety (mainly related to product and production quality) and “label efficacy” or “performance as intended”, which in the case of the above-mentioned treatments means that they remove inflammatory mediators. More stringent requirements for clinical evaluation only exist for high-risk devices such as permanent implants. The conformity assessment, the content of which is not in the public domain, is performed by (supervised) notified bodies that are commercial organizations. In case of high-risk devices, the assistance of an expert panel is required. The CE mark is not an indication of efficacy regarding patient outcomes [4]. Vigilance and rigorous post-marketing surveillance of these devices thus become extremely important. CPFA, a combination of a plasma and a hemofilter, has been patented for the treatment of patients with multiple organ failure or sepsis. After promising experimental data, the first pilot clinical trial was performed in 2002 [5], followed by several case reports and case series, showing improvement of surrogate outcomes such as cytokine levels or vasopressor requirement. The treatment was widely used, mainly in Italy. A first RCT, aiming to evaluate the effect on mortality in 330 patients, was stopped early because of futility [6]. A second RCT, using a higher volume of treated plasma, was stopped because of an increased mortality in the treatment group and the company stopped marketing of the product in April 2018 [7].

Cytosorb uses biocompatible, highly porous polymer beads to remove toxic substances. In 2011, the device received EU regulatory approval in the moderate risk category (class IIb) for situations with excessive cytokine levels (amongst others sepsis and cardiopulmonary bypass) and it is the only CE-marked device with this indication. In the setting of septic shock, many case reports and case series [8, 9] show very hopeful results (safety, clinical improvement (mainly decrease in vasopressor requirement) and “saving” of severely ill patients) but have a high risk of publication bias and make it difficult to ascribe causality. A large patient registry [10] has been started, with potential for providing interesting data on responders and non-responders, but still suffering from the same shortcomings. Only a few small RCTs have been performed in sepsis. The pivotal phase 2 trial supporting the CE Mark randomized 100 patients with sepsis and ARDS to standard therapy with or without Cytosorb and showed IL-6 removal, however, without affecting cytokine levels compared with controls [11]. Another small ($n = 20$) RCT (registered as a case-control study) in septic shock found a significant reduction in vasopressor requirement [12]. Evidence for clear benefit to patient-centered outcomes is still lacking, as concluded in a recent review on the subject [13]. Besides the high cost of the treatment there is also potential for harm related to the extracorporeal circuit and the associated need for anticoagulation and to the adsorption of “beneficial” substances including antibiotics (that is not well quantified). Several studies are ongoing but mainly in the setting of complicated cardiac surgery. Ongoing trials in sepsis, registered at clinicaltrials.gov, include an RCT (NCT02588794, posted in October 2015), with estimated enrolment of 124 septic patients, a recent registration (NCT04013269 aiming to enrol 32 patients with refractory septic shock and a retrospective study in 500 patients (NCT03977688). In the light of the limited evidence, it is surprising to see on the company’s website that worldwide more than 60,000 treatments have been performed in humans with this device [14]. It is clear that this treatment may have potential “niches” where it benefits patients. These indications, however, remain to be established. In the meantime, clinicians should be aware of the absence of evidence for an effect on patient-centered outcomes and of potential harmful effects.

A plea for a moral responsibility of all stakeholders

A concert of stakeholders plays with different instruments the melody of promising new therapies. The leading voices are: the industry, regulatory agencies, the scientific community with researchers, congresses (presenting 'hot topics') and scientific journals, bedside physicians and, sometimes, the families of critically ill patients, who search information on the internet or other media (Fig. 1).

The bedside physician may find himself captured in a complex net of 'appeals' from these different stakeholders, but he/she has only a 'simple' but burning and vital question: "How can I make this patient survive?" The intensivist is thrown back and forth between a trial of individual healing and a lack of evidence-based treatments for sepsis. From an ethical point of view, neither industrial sponsors nor clinical scientists must leave the intensivist on the cold front. The moral duty of the industry is to collaborate with scientists to create well-designed prospective randomised studies—irrespective of an expected market benefit—and to provide the clinical community with solid results, allowing the physician to perform 'personalised medicine' while balancing harm and benefit of these devices. Manufacturers should avoid spectacular public campaigns for their products

(putting published case reports into glittering wallets for congress attendants is no solution) and maintain transparent and honest relationships with the physician. Frequent 'visits' by a representative of the manufacturer could influence the intensivist's behaviour, although the era of gifts from the industry should be over. It has indeed been shown that physicians are prone for medical overuse by contact with trained and clever representatives [15], and a special training for physicians is needed on how to handle merchandising by the industry. Regulatory agencies may play an important role by increasing the transparency of the approval process and by more stringent post-marketing surveillance. The scientific community is responsible for the performance and correct reporting of high-quality clinical trials. The moral task of the physician at the front is a continuous awareness for new scientific results—even when they are sometimes contradictory, reporting adverse events and maintaining independence from the industry. Only a reputable discourse between all the stakeholders will result in the development/implementation of efficient innovative treatments which are urgently needed to improve survival in sepsis and septic shock.

Compliance with ethical standards

Conflicts of interest

MS and TB declare having no conflict of interest related to this manuscript.

References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, Hotchkiss RS, Levy MM, Marshall JC, Martin GS, Opal SM, Rubenfeld GD, van der Poll T, Vincent JL, Angus DC (2016) The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 315:801–810
2. Van Norman GA (2016) Drugs and devices: comparison of European and U.S. approval processes. *JACC Basic Transl Sci* 1:399–412
3. https://ec.europa.eu/growth/singl e-marke t.../medic al-devic es_en. Accessed 19 June 2019
4. https://ec.europa.eu/growth/secto rs/medic al-devic es/regul atory -frame work_en. Accessed 11 June
5. Ronco C, Brendolan A, Lonnemann G, Bellomo R, Piccinni P, Digito A, Dan M, Irone M, La Greca G, Inguaggiato P, Maggiore U, De Nitti C, Wratten ML, Ricci Z, Tetta C (2002) A pilot study of coupled plasma filtration with adsorption in septic shock. *Crit Care Med* 30:1250–1255
6. Livigni S, Bertolini G, Rossi C, Ferrari F, Giardino M, Pozzato M, Remuzzi G, GiViTI (2014) Efficacy of coupled plasma filtration adsorption (CPFA) in patients with septic shock: a multicenter randomised controlled clinical trial. *BMJ Open* 4:e003536
7. http://www.hsa.gov.sg/conte nt/dam/HSA/HPRG/Medic al_Devic es/Updat e_and_Safet y_repor ting/Filed_Safet y_Corre ctive Actio n/FSN/2018/April %20218 HSA%20600 4-046-18-04_46%FSN_Redac ted.pdf. Accessed 11 June 2019
8. Träger K, Skrabal C, Fischer G, Datzmann T, Schroeder J, Fritzler D, Hartmann J, Liebold A, Reinelt H (2017) Hemoadsorption treatment of patients with acute infective endocarditis during surgery with cardiopulmonary bypass—a case series. *Int J Artif Organs* 40:240–249
9. Friessecke S, Stecher SS, Gross S, Felix SB, Nierhaus A (2017) Extracorporeal cytokine elimination as rescue therapy in refractory septic shock: a prospective single-center study. *J Artif Organs* 20(3):252–259
10. Friessecke S, Träger K, Schitteck GA, Molnar Z, Bach F, Kogelmann K, Bogdanski R, Weyland A, Nierhaus A, Nestler F, Olboeter D, Tomescu D, Jacob D, Haake H, Grigoryev E, Nitsch M, Baumann A, Quintel M, Schott M, Kielstein JT, Meier-Hellmann A, Born F, Schumacher U, Singer M, Kellum J, Brunkhorst FM (2017) International registry on the use of the CytoSorb® adsorber in ICU patients: study protocol and preliminary results. *Med Klin Intensivmed Notfmed*. 2017 Sept 4. <https://doi.org/10.1007/s0006 3-017-0342-5>. (Epub ahead of print)
11. Schädler D, Pausch C, Heise D, Meier-Hellmann A, Brederlau J, Weiler N, Marx G, Putensen C, Spies C, Jörres A, Quintel M, Engel C, Kellum JA, Kuhlmann MK (2017) The effect of a novel extracorporeal cytokine hemoadsorption device on IL-6 elimination in septic patients: a randomized controlled trial. *PLoS ONE* 12:e0187015 Hawchar F, Laslo I, Öveges N, Trasy D, Ondrik Z, Molnar Z (2019) Extracorporeal cytokine adsorption in septic shock: a proof of concept randomized, controlled pilot study. *J Crit Care* 49:172–178
13. Poli EC, Rimmelé T, Schneider AG (2019) Hemoadsorption with CytoSorb®. *Intensive Care Med* 45:236–239
14. <https://cytos orb-thera py.com/the-thera py>. Accessed 19 June 2019
15. Korenstein D (2019) Medical overuse as a physician cognitive error: looking under the hood. *JAMA Intern Med* 179:26–27