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LESS IS MORE IN ICU

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^{R}.

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].

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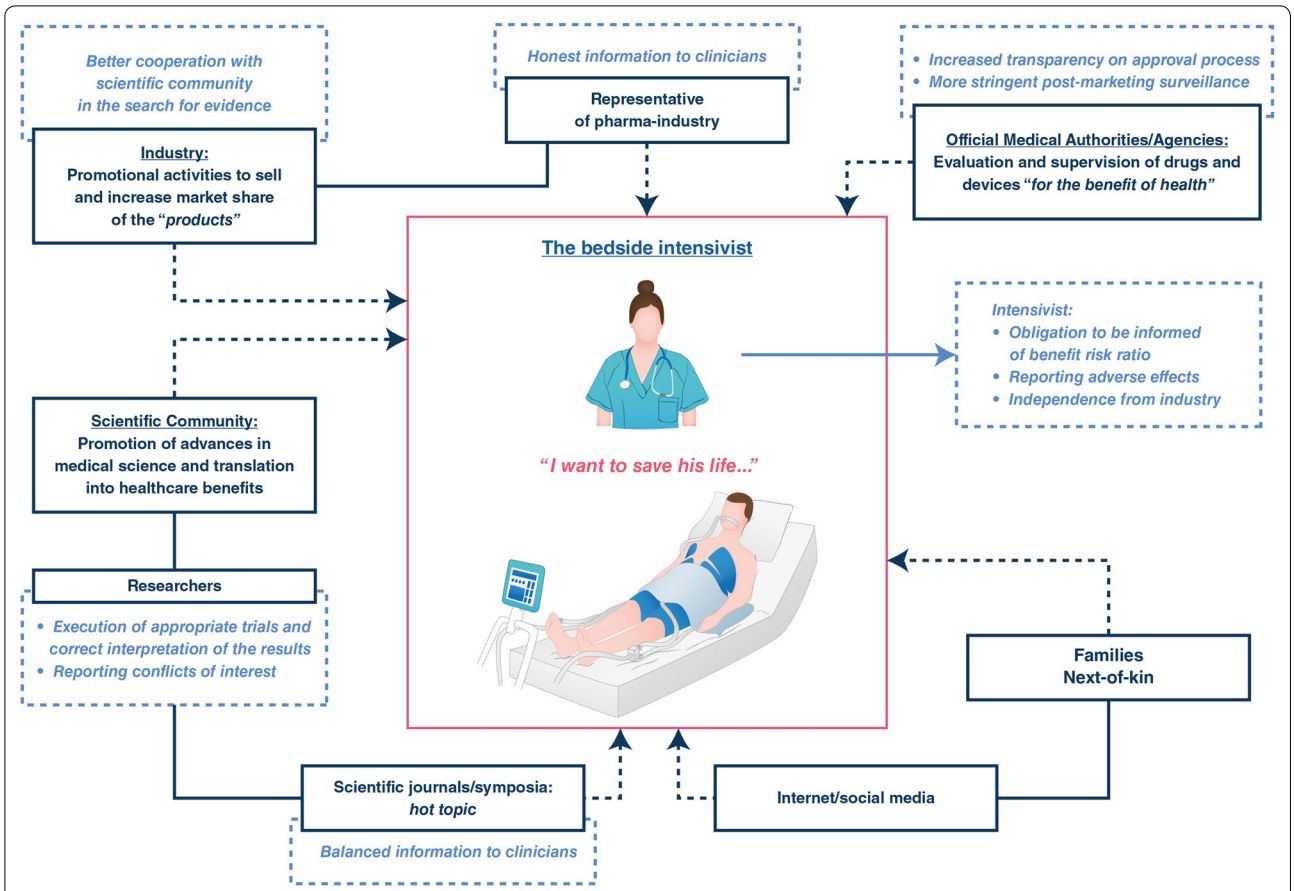

Fig. 1 Many stakeholders play a role in the process that leads to the delivery of safe and efficacious health care. Every stakeholder must be aware of his/her responsibility and contribute to this goal. The comments in blue denote potential pathways for improvement

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.

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Compliance with ethical standards

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

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