

oXirisNet Registry: A Prospective, National Registry on the oXiris Membrane

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Abstract

Worldwide, the widespread use of extracorporeal blood purification therapies (EBPTs) is progressively increasing in everyday clinical practice, particularly in critical care settings. The efficacy of EBPTs on removal of inflammatory mediators is already well established in the literature. Nonetheless, clinical research is particularly cumbersome in this setting, and many clinical trials aiming at exploring the effect of EBPTs on outcomes have failed in demonstrating consistent results regarding 28-day- or hospital-mortality rates. In recent years, data emerging from large registries have been increasingly used to provide real-world evidence on the effectiveness, quality, and safety of EBPTs. The philosophy behind this Italian Registry is a renewal of the concept of “clinical research” in the field of EBPTs applied to critically ill, septic patients with or without acute kidney injury. The platform used for the registry – specifically designed for research purposes and fed by clinical data prospectively observed – promotes good practice with a positive and active interaction with the

physician/researcher. This interaction has favorable real-time effects for the specific patient, providing “*bed-side clinical feedbacks*,” similarly to the decision support system. Examples of these issues are bundles reminders, suggestions for drug adjustment according to the extracorporeal clearance, clinical calculator for body mass index, or mechanical ventilation setting. The platform-physician interaction has additional useful effects on the single utilizing center, providing “*mid-term, center-specific clinical feedbacks*.” These generally consist of clusters of data taken over a certain period, for example, regarding patients’ outcome, microbiological data, or use of disposable for EBPTs.

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Extracorporeal Blood Purification Therapies: the Need for “Precision”

Worldwide, the use of extracorporeal blood purification therapies (EBPTs) is progressively increasing in everyday clinical practice, particularly in critical care settings [1]. The efficacy of these therapies in terms of extracorporeal clearing of inflammatory mediators (via enhanced

transmembrane clearance and/or selective/unselective adsorption of bacterial toxins and/or cytokines) has been already well established in the literature for most of these treatments [2]. The so-called “immunomodulation” is the main rationale for the use of EBPTs, and it might explain the clinical effects of these treatments on multiorgan dysfunction in critically ill patients [2]. In particular, an improvement in patients’ hemodynamics has been consistently observed across different studies available in the literature [2–4]. On the other hand, there still are several doubts that removal of bacterial toxins and cytokines is invariably associated to clinical efficacy. Many clinical trials aiming to explore the effect of EBPTs on patients’ long-term outcomes have failed in demonstrating any improvement in the 28 day- or hospital-mortality rates [3, 5, 6].

Interestingly, several studies agree that clinically relevant, positive effects of EBPTs can be observed only in specific subpopulations of patients, that is, applying these therapies only in relation to a specific immune or inflammatory status [6–8]. As an example, a post hoc analysis from the Euphrates trial suggests that a specific range of baseline endotoxin activity assay might correlate with a favorable long-term outcome in patients treated with Toraymyxin cartridges [8]. Similarly, a post hoc analysis from Abdomix trial suggests that in a specific subpopulation of patients with abdominal sepsis and high baseline values of interleukine-6, endotoxin removal through EBPTs was particularly effective in improving long-term survival [7].

Nowadays, this “personalized” approach to extracorporeal therapies has been advocated as the main strategy to maximize the clinical effectiveness of EBPTs and their impact on patient outcomes (i.e., precision medicine) [9, 10].

The implementation of large databases encompassing multidisciplinary and multiparametric characteristics (e.g., clinical, biochemical, immunological) of patients undergoing EBPTs is thus widely encouraged to identify clusters of patients with specific features who would benefit the most from these treatments [3, 10].

Although only clinical trials can formally assess the effects of the EBPTs on a specific clinical outcome, their restricted inclusion and exclusion criteria, their application to a specific setting, endpoints, study population, and results generated by inferential methods do not allow a complete vision of the real clinical practice. Furthermore, trials are practically limited by several drawbacks in the critical care setting. In most European centers, the local Internal Review Boards do not allow the enrollment and randomization of incompetent patients, as critically ill patients formally are due to ethical issues [11]. Furthermore,

clinical trials are often very expensive and rarely feasible and sustainable for treatments infrequently applied in the intensive care unit (ICU; e.g., EBPTs for immunomodulation in septic patients) and thus characterized by prolonged expected enrollment periods. For example, COMPACT [6] and COMPACT 2 (<http://www.giviti.marionegri.it/Compact2.asp>) trials failed to demonstrate a significant effect of coupled plasma-filtration adsorption on mortality of critically ill septic patients, with the notable exception of specific subpopulations (i.e., those where an adequate volume of plasma was filtered and adsorbed). This conclusion emerged from post hoc analyses performed on a subgroup of an already limited sample size derived from 2 highly costly multicenter randomized clinical trials, prematurely halted due to ethical issues.

In recent years, data emerging from large registries have been increasingly used to provide real-world evidence on the effectiveness, quality, and safety of EBPTs. This approach usually allows to prospectively observe a multicenter, large, and widely broadened population undergoing the same EBPTs according to its regulatory approval. Moreover, with a negligible impact on ethical issues, limited costs, and easy management, registries might recognize clusters of patients associated with specific short- and long-term positive outcomes. For this reason, patient registries offer a *unique feature* that may be particularly useful for patient-centered outcomes research, realistically showing drawbacks and accurately refining indications of specific treatments.

EBPTs and Database Registries

Several web-based registries have been developed to monitor the use of EBPTs in the daily clinical practice. Through an ethically regulated tool, networks of researchers can thus easily upload and share clinical data of patients undergoing EBPTs, in accordance with regulatory authorities and routine clinical practice of every single center. These observation-based registries are inexpensive and effective tools able to identify specific clusters of patients within a considerable sample size with widely heterogeneous clinical characteristics.

For instance, the web-based EUPHAS 2 registry has been already implemented to describe the clinical effects of polymyxin-B (PMX)-based cartridges (Toraymyxin, Toray Medical Co., Ltd., Tokyo, Japan) for endotoxin removal [12]. This registry contains clinical data from 357 septic patients (297 in Europe and 60 in Asia) with a proved or suspected infection related to Gram-negative

bacteria and undergoing at least one cycle of extracorporeal endotoxin removal by PMX hemoperfusion (PMX-HP). Data were retrospectively collected in 57 centers between January 2010 and December 2014. The significant number of patients observed allowed a reliable statistical analysis of PMX-HP feasibility in a real clinical context, despite the retrospective nature of EUPHAS 2 and the lack of a control group. Interestingly, in 142 patients (42%) of the EUPHAS 2 registry with a clinical diagnosis of severe sepsis or septic shock, the results of microbiological cultures were not reported, indicating poor compliance to the bundles recommendations [12].

Regarding the effects of Toraymyxin, patients showing a significantly cardiovascular improvement after PMX-HP had a 28 survival rate of 75% in comparison to the 39% of patients who did not ($p < 0.001$). Cox regression analysis found the variation of cardiovascular, respiratory, and coagulation SOFA to be independent covariates for 28-day survival [12]. An interesting point of the EUPHAS 2 registry was that PMX-HP is often used by physicians to treat nonabdominal infections. Indeed, the respiratory source was the second most frequent clinical condition observed in the study. Data recorded in the EUPHAS 2 registry demonstrate that the efficacy of the PMX-HP seemed less efficient in these “extra-abdominal indications.” ICU and hospital survival were quite similar between patients with abdominal and respiratory sepsis, but patients with respiratory infections showed a trend toward a higher 28-day mortality rate. In conclusion, EUPHAS 2 is an effective example showing that a multicenter registry might be useful in categorizing the clinical use of a specific EBPT in the real clinical context and in identifying clusters of patients in which the treatment may be more effective [12].

Similarly, the CytoSorb registry was designed to explore the use of CytoSorb (Cytosorbents Corp., NJ, USA) cartridge in critically ill patients under real-life conditions (<https://www.cytosorb-registry.org/>). This web-based registry aims to record all relevant information (e.g., diagnosis, comorbidities, treatment/concomitant medication, clinical laboratory parameters, outcome) during treatments with CytoSorb (ClinicalTrials.gov Identifier: NCT02312024) [13]. The primary endpoint of this prospective, multicenter registry involving more than 130 centers from 22 countries was to compare the in-hospital mortality with that predicted according to APACHE II and SAPS II score. Interestingly, the observed population is not limited to septic patients but instead it expanded to patients with cardiac surgery and cardiopulmonary bypass, those preemptively treated with CytoSorb in the operating room or postoperatively

in the ICU or those with liver failure, acute pancreatitis, trauma, burns, or acute respiratory distress syndrome. Preliminary data are available from the first 198 patients [13]. This project aims to design and nationally promote a web-based registry specifically designed for oXiris membrane (Baxter, Meyzieu, France).

The Italian oXiris Registry

The philosophy behind this Italian Registry is a new concept of “clinical research” in the field of EBPTs in critically ill, septic patients, with or without acute kidney injury (AKI). The web-based platform used for the registry – specifically designed for research purposes and fed by clinical data prospectively observed – promotes good clinical practice with a positive and active interaction between the physician and the researcher. This interaction has favorable real-time effects for the specific patient, providing “*bed-side clinical feedbacks*,” acting as a decision support system (DSS). Examples of these issues are bundles reminders, suggestions for drug adjustment according to the extracorporeal clearance, clinical calculator for body mass index, or mechanical ventilation setting. The platform–physician interaction may provide reports to the single utilizing center, such as “*mid-term center-specific clinical feedbacks*.” These generally consist of aggregate of data collected over a definite time-lag, for example, about patients’ outcome, microbiological data, or use of disposables for EBPTs, and so on.

Research Purpose

The research aim of this multicenter registry is to verify the presence of clusters of patients that mostly benefit from EBPTs with oXiris membrane among all critically ill patients treated in the ICU with this filter (ClinicalTrials.gov Identifier: NCT03807414). This peculiar subpopulation will be described using the baseline variables statistically associated through multivariable regression analyses with positive long-term patient’s outcomes (survival at hospital discharge). The overtime variation of clinical variables will be described during the first 24 h of EBPT with oXiris, and the specific trends of variables associated with positive outcomes will be identified as potential early predictors of treatment responsiveness in clinical practice. All these indicators might be employed to guide indications for EBPT with oXiris, to personalize treatments and to improve patients’ long-term outcomes.

All patients undergoing EBPT with oXiris membrane in the enrolling centers will be prospectively observed.

Patients candidate to be included in the registry will be all the critically ill patients for whom the attending physicians indicated continuous renal replacement therapy with oXiris membrane, according to widely accepted guidelines and local clinical practice. As oXiris membrane has received CE mark and regulatory approval for immunomodulation independently from kidney function, AKI will be mostly present among the enrolled population, but it might not be strictly required as an inclusion criterion. Similarly, although sepsis will be frequently observed, the systemic inflammatory state leading to multiorgan dysfunction and supported by extracorporeal treatment might have several different etiologies, such as ischemia-reperfusion, severe acute pancreatitis, and intoxication (i.e., “sepsis-like syndromes”).

Data will be prospectively recorded in 5 thematic sections, temporarily ordered: (1) a baseline section, describing the patient’s comorbidities and anagraphic/physiologic features; (2) an enrollment section, describing the patient’s clinical status at the time of initiation of continuous renal replacement therapy with oXiris membrane and its relative setting parameters; (3) a monitoring section, describing the overtime variation of clinical variables during EBPT; (4) a withdrawal section, describing the patient’s clinical features when the EBPT is withdrawn (for any cause, from patient recovery to patient death or filter clotting); (5) a follow-up section, describing the ICU-/in-hospital- mortality rate and organ functional recovery. Patients’ survival at hospital discharge will be considered as a primary outcome for the statistical analysis.

Although every effort will be made to obtain informed consent from the enrolled patients, the Institutional Review Board has waived the patient’s consent for data analysis considering that most of them will likely be acutely incompetent (According to the Italian Data Protection Authority, Prov. no. 497, December 13, 2018).

A sample size calculation for primary endpoint has not been carried out, considering the pilot characteristic of this first prospective registry on oXiris. The expected enrollment rate is 4–5 patients/year/ICU. As the total number of the enrolled patients likely increases directly with the number of ICUs involved, nationwide dissemination of this registry represents a specific work package of this project. In this context, a formal endorsement for this registry is currently under evaluation from the major national societies of Intensive care (Italian Society of Analgesia, Anesthesia, Reanimation and Intensive Care-SIAARTI, and the Italian Society of Intensive Care-SITI). Although it cannot be a priori guaranteed, the observation of about 270 patients is cumulatively expected over the entire 3-year study period.

Bedside Clinical Feedback

Beyond the research purpose, the bedside use of this registry in the daily routine clinical practice will have direct effects on patients’ outcomes. Several characteristics of the website platform promote this proactive interaction; in particular, it is designed (1) to be customized to each enrolling center; (2) to continuously manipulate recorded data, providing clinical tools in terms of calculated fields; and (3) to provide the physician with specific suggestions, depending on the current clinical situations and/or EBPT treatment characteristics.

Although a formal and rigid structure is strictly required to guarantee consistency of type and quality of research data recorded among different centers, customization of the electronic case report form (eCRF) for clinical purposes still remains a key feature of this registry. In particular, once a superstructure of fields required for the research purposes has been fixed (e.g., hemodynamic monitoring), the specific items used within (e.g., mean arterial pressure assessed by an intra-arterial catheter, or by Pressure Recording Analytical Method, Pulse Index Continuous Cardiac Output or Vigileo systems) are independently chosen by each specific center. In this context, every single center is able to perform an overtime monitoring of patients treated with EBPT taking advantages from its local practice or expertise (e.g., the use of a specific hemodynamic monitoring system). Nonetheless, clinical data required for research purpose (e.g., mean arterial pressure or vasoactive-inotropic score) still remain comparable or agreeable among different centers. Theoretically, the need for customization seems to be against the idea of a multicenter registry, where a single eCRF should fit with all the centers involved. To resolve this issue, the eCRFs are prepared to consequently explode specific items “on request.” In particular, this solution gives the opportunity for each center to independently choose the preferred option (e.g., the Pressure Recording Analytical Method monitoring, instead of Pulse Index Continuous Cardiac Output system) but without increasing complexity and length of the eCRF (Fig. 1).

The web-based platform is able to manipulate in real time the recorded data through specific calculated fields. For instance, providing the patient’s height and weight, the platform automatically provides body mass index or tidal volume that should be set for protective mechanical ventilation. Every parameter potentially helpful for clinical purposes, requiring mathematical calculations to be assessed, can be easily added to the platform to support and facilitate the physician decision (i.e., DSS).

As a DSS, the web-based platform can also provide physician-specific suggestions based on the current clini-

Fig. 1. eCRF are prepared with a modular approach. Minimal and condensed when fields are unused (**a**), expanded and detailed “on request” if desired by the physician (**b**, **c**). As example, if in panel **a** is indicated that the patient is treated with vasoactive drugs, the panel **b** appears for details. **b** Further shows an example of automatic calculated field: once dose of vasoactive are recorded, the

platform automatically provides vasoactive-inotropic score (VIS). Similar automatic calculated fields are available in this platform for most of scoring systems (e.g., SOFA, SAPS II, APACHE II). If in panel **a** hemodynamic monitoring is declared, panel **c** appears. Interestingly, the physician chooses the specific type of hemodynamic monitoring in accordance with his preference and local practice.

cal situations and/or EBPT treatment characteristics. As an example, Surviving Sepsis Campaign bundles [14] are provided to the physician once sepsis is diagnosed or suspected. Similarly, the kidney disease improvement global outcome [15] checklist is proposed when AKI occurs in the clinical scenario recorded by the physician. Notably, poor compliance to the microbiological bundles suggested by the Surviving Sepsis Campaign occurred in at least 42% of patients observed in the EUPHAS 2 registry. Deviations from microbiological bundles might affect patient’s outcomes behind and beyond the use of EBPT itself, acting as a significant confounding factor [12].

Probably the antibiotic drug adjustment during EBPT represents the most interesting example of this real-time platform/physician interaction. Several concerns usually

exist on drug adjustment during renal replacement therapy in daily clinical practice. This is particularly true for EBPT performed in septic patients for immunomodulation via extracorporeal treatments that greatly increase the transmembrane and/or adsorption clearance. Once the administered antibiotic has been indicated, the platform automatically informs the physician on the requirement to optimize posology and/or type of administration (continuous vs. intermittent) during renal replacement therapy. All these characteristics may improve short- and long-term outcomes of patients enrolled in this prospective study.

Mid-Term Center-Specific Clinical Feedback

Clinical feedbacks provided by the web-based platform of this national registry include analysis of medium-

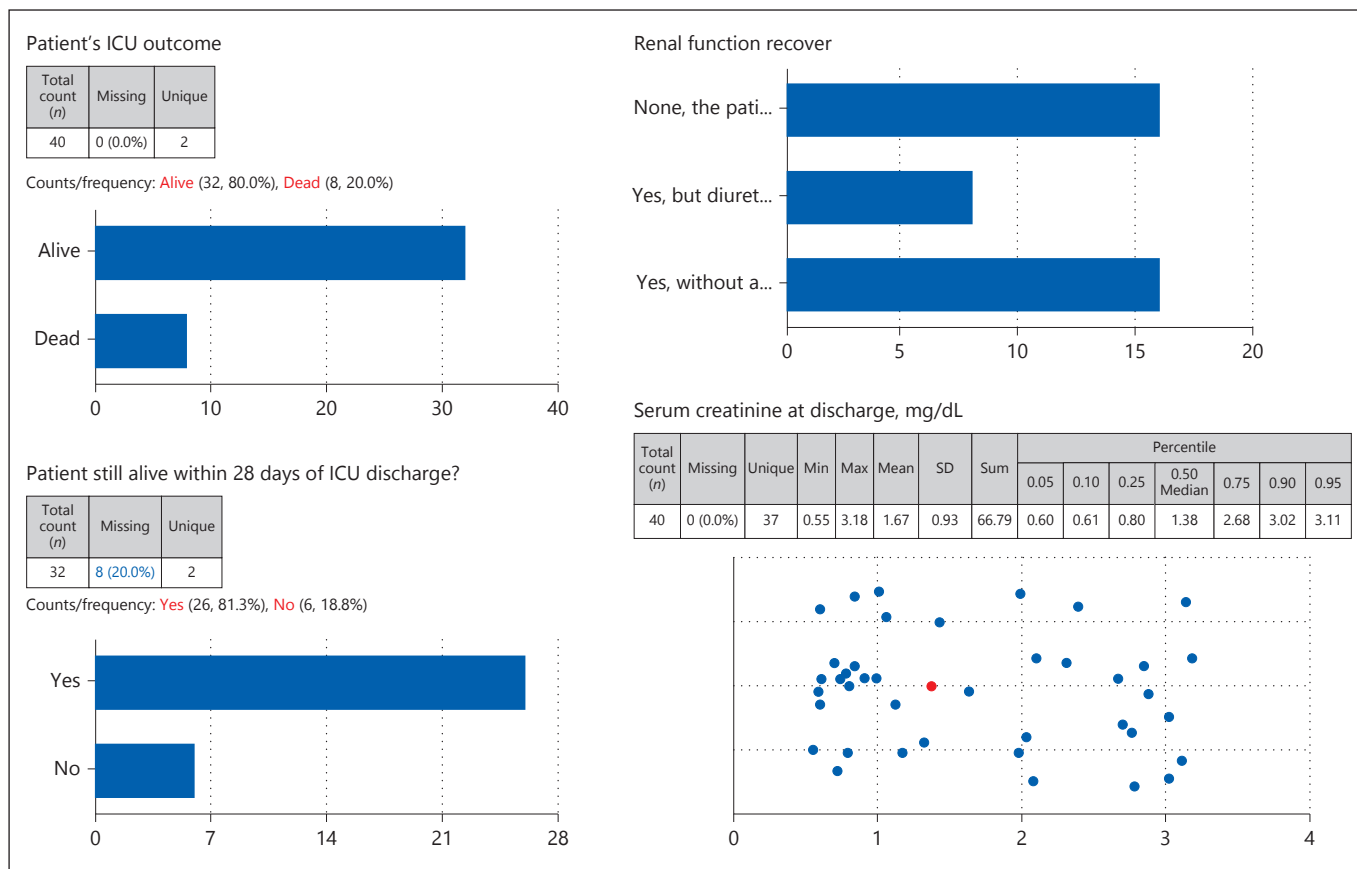


Fig. 2. Specific outcomes are automatically reported real-time by the website platform. The figure reports examples of qualitative data (e.g., ICU and 28-day mortality rate or renal recovery) and quantitative data (e.g., serum creatinine at ICU discharge). The

former detailed graphically with bar chart and Count/Frequency of occurrence, the latter via dot-plot and parametric/nonparametric details (mean, SD, median, IQR).

and/or long-term center-specific outcomes such as, but not limited to, mortality rates, rates of organ function recovery, infection of eradication instead of maintenance of colonization.

Regarding treatments applied less frequently in the ICU, the overall evaluation of specific outcomes might be particularly cumbersome. Indeed, the efficacy of usual treatments performed in the ICU (such as mechanical ventilation) is easily perceived by the physician and local coordinators. On the other hand, for treatments with restricted indications (as EBPT for immunomodulation in critically ill septic patients), clinical efficacy is based on the results of few treatments performed over a broad period of time. An objective recording process of specific outcomes and patients/treatments characteristics allow the physician to go over a subjective perception of efficacy. Stratification for other confounding factors recorded in this registry (e.g., disease etiology and/or clinical

scoring system for organ dysfunction) may further increase the reliability of the overall treatment effectiveness, thus evaluated *ceteris paribus*.

Since the critical care of septic patients is a rapidly evolving area as much as the extracorporeal treatments themselves, the chance of frequently monitoring their application, costs, and patients' outcomes in the ICU is particularly important. Interestingly, these feedbacks should be dynamic as much as the evolution of technologies applied. The physician should be autonomous in this process, not only for the intervention and/or the outcome chosen for evaluation but also the frequency of analysis in his center. The website platform of this registry allows the physician to decide outcomes autonomously and confounding factors to be evaluated in association with EBPT with oXiris.

Interestingly, the outcomes are independent of unspecific and often inaccurate diagnosis-related group- or international classification of disease-based information.

Analyses are automatically performed by the same website platform using data recorded in the oXiris registry. Furthermore, packages of analyses can be customized and saved in the platform along with the registry to be periodically applied (Fig. 2).

Conclusion

The rationale behind the oXirisNet Registry is a new concept of “clinical research” in the field of EBPTs in critically ill and it recognizes two different approaches: the real-life observation of the routine applications of the oXiris membrane and the prospective support for their customization in each specific patient. The former is based on the implementation of a large multidisciplinary and multiparametric database aimed at identifying clusters of patients with specific features who would benefit the most from oXiris membrane. The latter, based on the concept of precision medicine, provides real-time clinical feedbacks to the physician, acting as a Decision Support System and/or as a monitor for medium-long term patients’ outcomes.

References

- 1 Ankawi G, Neri M, Zhang J, Breglia A, Ricci Z, Ronco C. Extracorporeal techniques for the treatment of critically ill patients with sepsis beyond conventional blood purification therapy: the promises and the pitfalls. *Crit Care*. 2018 Oct;22(1):262.
- 2 Rimmelé T, Kellum JA. Clinical review: blood purification for sepsis. *Crit Care*. 2011;15(1):205.
- 3 Villa G, Chelazzi C, Morettini E, Zamidei L, Valente S, Caldini AL, et al. Organ dysfunction during Continuous venovenous high cut-off hemodialysis in patients with septic acute kidney injury: A prospective observational study. *PLoS One*. 2017 Feb 16; 12(2):e0172039.
- 4 Cruz DN, Antonelli M, Fumagalli R, Foltran F, Brienza N, Donati A, et al. Early use of polymyxin B hemoperfusion in abdominal septic shock: the EUPHAS randomized controlled trial. *JAMA*. 2009 Jun;301(23):2445–52.
- 5 Payen DM, Guilhot J, Launey Y, Lukaszewicz AC, Kaaki M, Veber B, et al.; ABDOMIX Group. Early use of polymyxin B hemoperfusion in patients with septic shock due to peritonitis: a multicenter randomized control trial. *Intensive Care Med*. 2015 Jun;41(6):975–84.
- 6 Livigni S, Bertolini G, Rossi C, Ferrari F, Giardino M, Pozzato M, et al.; GiViTI: Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva (Italian Group for the Evaluation of Interventions in Intensive Care Medicine) is an independent collaboration network of Italian Intensive Care units. Efficacy of coupled plasma filtration adsorption (CPFA) in patients with septic shock: a multicenter randomised controlled clinical trial. *BMJ Open*. 2014 Jan;4(1):e003536.
- 7 Coudroy R, Payen D, Launey Y, Lukaszewicz AC, Kaaki M, Veber B, et al.; ABDOMIX group. Modulation by Polymyxin-B Hemoperfusion of Inflammatory Response Related to Severe Peritonitis. *Shock*. 2017 Jan;47(1):93–9.
- 8 Iba T, Fowler L. Is polymyxin B-immobilized fiber column ineffective for septic shock? A discussion on the press release for EUPHRA-TES trial. *J Intensive Care*. 2017 Jul;5(1):40.
- 9 Cerdá J, Villa G, Neri M, Ronco C. Technology in Medicine: Moving Towards Precision Management of Acute Kidney Injury. *Contrib Nephrol*. 2018;193:89–99.
- 10 Cerdá J, Baldwin I, Honore PM, Villa G, Kellum JA, Ronco C; ADQI Consensus Group. Role of Technology for the Management of AKI in Critically Ill Patients: From Adoptive Technology to Precision Continuous Renal Replacement Therapy. *Blood Purif*. 2016; 42(3):248–65.
- 11 Zamperetti N, Piccinni M, Bellomo R, Citerio G, Mistraretti G, Gristina G, et al. How to protect incompetent clinical research subjects involved in critical care or emergency settings. *Minerva Anestesiol*. 2016 Apr;82(4):479–85.
- 12 Cutuli SL, Artigas A, Fumagalli R, Monti G, Ranieri VM, Ronco C, et al.; EUPHAS 2 Collaborative Group. Polymyxin-B hemoperfusion in septic patients: analysis of a multicenter registry. *Ann Intensive Care*. 2016 Dec; 6(1):77.
- 13 Friesecke S, Träger K, Schittek GA, Molnar Z, Bach F, Kogelmann K, et al. International registry on the use of the CytoSorb® adsorber in ICU patients: study protocol and preliminary results. *Med Klin Intensivmed Notf Med*. 2017.
- 14 Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med*. 2017 Mar;43(3):304–377.
- 15 Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL, et al. KDI-GO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl*. 2012;2:1–138.

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