Fluid challenge in Intensive Care: a worldwide global inception cohort study.

The FENICE II study

Maurizio Cecconi[1,2], Elie Azoulay[3], Michelle Chew[4], Katia Donadello[5,6]; Ignacio Martin Loeches[7], Jan de Waele[8], Lennie Derde[9], Marlies Ostermann[10], Michael Darmon[11], Daniel De Backer[12], Xavier Monnet[13], Jean-Louis Teboul[14], Antonio Messina[1,2].

[1]IRCCS Humanitas Research Hospital – Rozzano (Milano), Italy
[2]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, MI, Italy
[3]Assistance Publique Hôpitaux de Paris, Service de Médecine Intensive et Réanimation, Hôpital Saint-Louis, Paris, France; ECSTRA Team, Biostatistics and Clinical Epidemiology, Center of Epidemiology and Biostatistics Sorbonne Paris Cité, Institut national de la santé et de la recherche médicale, Paris Diderot Sorbonne University, Paris, France.
[4]Department of Anaesthesia and Intensive Care, Biomedical and Clinical Sciences, Linköping University, Sweden
[5]Department of Surgery, Dentistry, Gynaecology and Paediatrics, University of Verona, 37129 Verona, Italy
[6]Anaesthesia and Intensiva Care B, AOUI-University Hospital Integrated Trust of Verona, 37134 Verona, Italy
[7]Department of Intensive Care Medicine, Multidisciplinary Intensive Care Research Organization (MICRO), St James Hospital, Dublin 8., Ireland.
[8]Department of Critical Care Medicine, Ghent University Hospital, Ghent, Belgium
[9]Department of Intensive Care Medicine, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands.
[10]Department of Critical Care & Nephrology, King's College London, Guy's & St Thomas' Hospital, London, SE1 7EH, UK.
[11]APHP, Service de médecine intensive et de réanimation, Hôpital Saint-Louis, 75010 Paris, France; Université de Paris, ECSTRA team, UMR 1153, Center of Epidemiology and Biostatistics, INSERM, Paris, France.
[12]Department of Intensive Care, CHIREC Hospitals, Université Libre de Bruxelles, Brussels, Belgium
[13]AP-HP, Service de médecine intensive-réanimation, Hôpital de Bicêtre, DMU 4 CORREVE, Inserm
[14]Paris-Saclay Medical School, Paris-Saclay University, Le Kremlin-Bicêtre, France

Summary

Title	Fluid challenge in Intensive Care: a worldwide global inception cohort study. The FENICE II study
Investigator sponsor	U.O. ANE1, IRCCS Istituto Clinico Humanitas – Rozzano (Milano) Italy. Principal Investigator: Prof. Maurizio Cecconi
Study coordinator	Dr. Antonio Messina
Protocol identifying number	FENICE II
Protocol version date	Version 1.0, 30/06/2023
Background and rationale	Fluids are the first line treatment of critically ill patients with shock, Unfortunately, the modality, the volumes and the target adopted to titrate fluid therapy are not standardised in current clinical practice
Aims	The primary aim of the FENICE II study is to globally describe the modality of fluid administration during the first days of intensive care unit (ICU) admission, and to assess if it may impact on in-hospital mortality. Secondary aims are to describe the modality of fluid challenge administration and to appraise the use of variables and functional hemodynamic tests to guide bolus infusion.
Population	All consecutive adult (≥18 years old) patients admitted to ICU and expected to stay at least 48h.
Study design and study duration	Prospective multicentre worldwide study

Introduction

Fluids are the first line treatment of critically ill patients with shock aiming to increase venous return, stroke volume (SV) and, consequently, cardiac output (CO) and tissue oxygen delivery (DO_2) [1-5]. Fluid administration is also one of the most disputed interventions in the treatment of critically ill patients [6, 7]. Even more debated is how to appraise and manage the response to fluid administration [1-6]. The optimal volume of fluids to be given in hypotensive patients with sepsis or in septic shock is still debated. The 2016 Surviving Sepsis Campaign (SSC) guidelines (SCC) strongly recommended giving at least 30 ml/kg of crystalloids for initial resuscitation of patients with sepsis-induced hypoperfusion [8]. This was downgraded to a weak recommendation in the 2021 update of the SSG due to a lack of prospective intervention studies comparing different volumes for initial resuscitation in sepsis or septic shock [9]. A recent randomized-controlled trial in patients with sepsis-induced hypoperfusion (averaged mortality of 14%) [10] and another in patients with septic shock (averaged mortality of 42%) [11], showed that a "restrictive" fluid strategy was non inferior to a "liberal" one.

From a physiological point of view, the goal of fluids is to increase SV and then CO and should only be given if the plateau of cardiac function is not reached in the individual patient (fluid responsiveness state). Fluid challenge (FC) is a diagnostic test consisting in the administration of a fixed volume of fluids with the purpose of identifying patients who will increase CO in response to fluid infusion [3, 12, 13]. Since several bedside clinical signs, systemic arterial pressure and static volumetric variables are poorly predictive of the effect of FC, the response to FC may be predicted at the bedside by using a functional hemodynamic test. This consists of a manoeuvre that affects cardiac function and/or heart-lung interactions, with a subsequent hemodynamic response, the extent of which varies between fluid responders and non-responders [14-16]. The combination of a functional hemodynamic test to assess fluid responsiveness and FCs to customize fluid infusion may be used to reduce the risk of fluid overload. Of note, at least 30% of the overall amount of fluid administered in septic patients may be related to the hidden and unintentional creep volume [17] (i.e. fluid administration not driven by a functional assessment of hemodynamics). In fact, a recent retrospective study on 14,654 patients during the cumulative 103,098 days showed that maintenance and replacement fluids accounted for 24.7% of the mean daily total fluid volume, thereby far exceeding

resuscitation fluids (6.5%) and were the most important sources of sodium and chloride. Fluid creep represented a striking 32.6% of the mean daily total fluid volume [median 645 mL (IQR 308-1039 mL)] [17].

Unfortunately, neither the FC nor the use of functional hemodynamic test are standardised in current clinical practice [18-21]. This was confirmed by the FENICE study, a large observational study on 2,213 patients conducted by the European Society of Intensive Medicine (ESICM) [19]. Since the first FENICE study publication, many activities have been by provided by the ESICM in an effort to improve education and implementation of evidence-based haemodynamic management in intensive care unit (ICU) patients. These programs have focused on physiology, haemodynamic monitoring and interpretation, and fluid therapy. These efforts may have improved the use of functional hemodynamic tests and FC at bedside, with an impact on haemodynamic management and fluid administration policy in the ICU.

Research question

What is the modality of fluid administration in ICU patients worldwide and what is the impact of fluid administration on clinical outcomes?

Aims

The primary aim of the FENICE II study is to describe the modality of fluid administration in the acute phase of resuscitation from hemodynamic instability in ICU patients.

As secondary aims, we'll appraise in-hospital, ICU and 30-day mortality and major organ dysfunction. Finally, we'll assess the use of variables (including clinical signs of hypovolemia, and indexes/images obtained from hemodynamic monitoring or echography) and functional hemodynamic tests to guide FC infusion in ICU patients, and the modality of FC administration (i.e. volume, rate, type of fluid), of evaluation of fluid responsiveness at the bedside.

Methods

Enrollment and study period

The phase of centers enrolment will be conducted over a time window of 12 months starting from 1st January 2024.

The phase of patients' enrolment will be conducted over a two-weeks period (14 days), chosen within a time window of 6 months starting from 1st January 2025.

The study period for data collection regarding the modality of fluid administration will consider the first 5 days from ICU admission (ICU days 1-5).

INPUT - Fluid data collection – definitions
Fluid Challenge/Fluid bolus (FC in test)

The FC is defined as the administration of any bolus of fluid (crystalloid or colloid) which is expected to affect pressure/flow/perfusion variables. The FC is expected to be completed within 30 min. Whenever possible, the exact time of fluid infusion will be collected. Considering the observational nature of the study, the indication for FC will be triggered by the decision of the attending ICU physician at the bedside (according to clinical practice of the ICU).

Continuous IV fluid administration (fluid maintenance or any other type of fluids given)

Any form of fluid infusion given for the purpose of optimizing overall fluid balance or to manage electrolytes (i.e. continuous infusion of any type of crystalloids). *(ml)*

Other IV fluids

Any form of fluid infusion received by the patients in the context of the therapy adopted (i.e. drugs solutions, glucose control, parenteral nutrition etc). *(ml)*

Blood products

Administration of red blood cells or fresh frozen plasma. *(ml)*

Other non IV intake

Any other form of non-IV intake received by the patients in the context of the therapy adopted (i.e. nutrion, solutions given for oral therapy).

OUTPUT

- *Urine output (ml)*
- *Blood loss (ml)*
- *Drainages (thorax, abdomen) (ml)*
- *Leak from other sites (estimation) (ml)*

Daily fluid balance

- *24 h fluid balance of the first 5 days (ml)*

Inclusion / Exclusion criteria

Inclusion Criteria:

- All consecutive adult (≥18 years old) patients admitted to ICU and expected to stay at least 48h.

Exclusion criteria:

- Planned admission after surgery for overnight ICU stay.
- Refusal of consent
- Moribund patients (i.e. expected survival < 24h)

Endpoints

Primary aim: the primary aim is to describe the modality of fluid administration during the first 5 days of ICU stay considering 1) the overall fluid balance; 2) the characteristics of the fluids given; 3) the modality of fluid administration (i.e. FC and not FC).

Secondary aims:

- The secondary aim is to explore any association between fluid administration characteristics and clinical outcomes (see further)
- To evaluate factors potentially associated with the respective proportion of the different modalities of fluid administration
- To characterize FC administration modality in a large cohort of ICU patients.

Secondary clinical outcomes

- In-hospital mortality
- ICU mortality
- 30-days mortality
- Alive without any organ support (the number of calendar days between inclusion and 28 days that the patient is alive and with no requirement of cardiovascular, respiratory and renal support. Patients who die during ICU stay will have zero days counted for this variable, irrespective of vital support status)
- Organ dysfunction:
  - Lung
    - Time to cessation of mechanical ventilation during ICU stay [The number of calendar days between intubation / start of mechanical ventilation and extubation / liberation from mechanical ventilation, including non-invasive mechanical ventilation (maintained for at least 48 hours)].
    - Mechanical ventilation support-free days free days from day 1 to day 28. Cessation of mechanical ventilation support implies its complete interruption for at least 24 consecutive hours)

- Ventilation Associated Pneumonia (VAP) cumulative incidence (number of VAP per patient) and rate (number of VAP per 1000 days of MV) [22].

- Heart
  - Time to cessation of vasopressor support during ICU stay (The number of hours between enrollment and complete stopping of vasopressor support (defined as its complete interruption for at least 24 consecutive hours).
  - Vasopressor support-free days during ICU stay from day 1 to day 28. Cessation of vasopressor support implies its complete interruption for at least 24 consecutive hours)
  - Inotropes-support free days
- Kidney
  - Time to cessation of Renal Replacement during ICU stay [The number of calendar days between start of renal replacement therapy and complete liberation from renal replacement therapy (at least 48 hours for continuous replacement modalities and 5 days for intermittent ones).
  - Renal Replacement support-free days during ICU stay from day 1 to day 28. Cessation of Renal Replacement support implies its complete interruption at least 48 hours for continuous replacement modalities and 5 days for intermittent ones)
  - Variation of creatinine-based KDIGO stage (Time Frame: 7 days after ICU admission). Renal function assessed according to KDIGO staging system from randomization through day 7 to assess for "de novo" or "worsening" acute kidney injury. Patients under chronic renal replacement therapy will not meet this end-point

- Variation in Sequential Organ Failure Assessment (SOFA) score (Time Frame: 7 days) Sequential Organ Failure Assessment (SOFA) score calculated upon the maximum values observed on the day of enrollment and then, at days 2, 3, 4, 5 and 7 (or until patient discharge or death, if this happened before day-7), using clinically available data. If an individual organ dysfunction value is not available (i.e., cardiovascular, respiratory, renal, etc.), it will be assumed to be zero unless previous value was abnormal (in which case it would be considered the same organ score). Neurological score under sedation/invasive mechanical ventilation will be computed as that observed just before sedation/intubation.

Secondary functional outcomes

- Volume of resuscitation fluids (Time Frame: up to day 5). The volume of fluids administered with resuscitative intention up to 5 days from inclusion
    - Type of fluids
    - Modality of fluid administration
- Net fluid balance (Time Frame: up to day 5).
- Evolution of Capillary Refill Time (CRT) (Time Frame: up to day 5 - worst value)
- Evolution of Lactate levels (Time Frame: up to day 5 - worst value)
- Evolvement of central venous pressure (Time Frame: up to day 5 - highest and lowest value)
- Evolvement of central venous oxygen saturation (Time Frame: up to day 5 - worst value)
- Evolvement of central venous to arterial carbon dioxide difference (Time Frame: up to day 5 - worst value)

Statistical analysis

Data will be described as median and interquartile range (IQR) or number and percentage. Categorical variables were compared using Fisher's exact test and continuous variables using the nonparametric Wilcoxon test, Mann-Whitney test, or Kruskal-Wallis test.

In way to assess volume of fluid received, group-based trajectory modeling (GBTM) will be used to identify clusters of patients with similar patterns of fluid administration profile. GBTM is a semiparametric technique used to identify distinct subgroups of individuals following a similar pattern of changes over time for a given variable [23]. To do so, we will use the R-software "kml" package that implements the k-means algorithm in context of longitudinal data [24]. Briefly, longitudinal change in fluid received each day from day 1 to day 3 will be assessed. In way to avoid misinterpretation of findings due to time dependent competing events such death or ICU discharge, this analysis will be performed on patients alive and still in the ICU at day 3. The optimal number of clusters was evaluated using Calinski & Harabasz criterion [25].

In way to assess impact of fluid administration strategy, factors associated with in-hospital mortality, including identified cluster of fluid administration, will be assessed using mixed logistic regression where in-hospital mortality will be event of interest. Variables of interest will be selected according to their relevance and statistical significance in univariate analysis. We will use conditional stepwise regression with 0.2 as the critical P-value for entry into the model, and 0.1 as the P-value for removal. It will be planned a priori to force identified clusters and relevant variable related to hemodynamic instability in the model. Last, the center effect will be included as a random effect against the interecept. Should a center effect be identified, a secondary analysis in line with centers characteristics will be performed. Interactions and correlations between the explanatory variables will be checked. Continuous variables for which log-linearity will not confirmed, will be transformed into categorical variables according to median or IQR.

For secondary outcomes, and in particular for day-30 mortality, number of days alive without vasopressors, mechanical ventilation or renal replacement therapy, will be assessed using survival analysis.

All tests will be two-sided, and P-value less than 0.05 will be considered statistically significant. Analyses will be performed using R software version 3.4.4 (https://www.r-project.org), including 'kml', 'caret', 'lme4', and 'lmerTest' packages.

Sample size

Considering the results of the FENICE study, we plan to enrol 10,000 patients and 15,000 FCs [30 patients / centre (max) and > 300 centres (min)]. The planned number of patients to be enrolled is in line with previous similar large observational trials regarding the use of fluids in ICU patients with the purpose of assessing current clinical practice and potential impact on clinical outcomes.

Data imputation

No data imputation will be performed on main outcome variables. Patients discharge alive from hospital, not admitted in rehabilitation unit or palliative care unit and/or lost of sight will be considered alive and free from organ support until day 30. Missing daily fluid volume will be imputed only if available every other day in which case it will be averaged.

Sensitivity analyses

In way to assess impact of fluid administration strategies, fluid volume considering only high chloride concentration fluids and impact of hypotonic fluids, three dedicated analyses using same methods than main analysis will be performed.

Ethical considerations and personal data protection

Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki or the laws and regulations of the country. The protocol has been written, and the study will be conducted according to Guideline for Good Clinical Practice. The protocol and its annexes are subject to review and approval by the competent Independent Ethics Committee(s) ("IEC").

Subject identification

All records identifying the subject must be kept confidential and, to the extent permitted by the applicable laws and/or regulations, not be made publicly available. The name of the patient will not be asked for nor recorded at the Data Center. A sequential identification number will be automatically attributed to each patient registered in the study. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, patient initials and date of birth will also be reported on the case report forms.

Any and all patient information or documentation pertaining to a clinical study, to the extent permitting, through a "key" kept anywhere, regardless of whether such key is supplied along with the information or documentation or not, must be considered as containing sensitive personal data of the patient, and is therefore subjected to the provisions of applicable data protection ("privacy") regulations. Breach of such regulations may result in administrative or even criminal sanctions.

Particularly, an information sheet prepared according to such regulations and a form to evidence the consent of patients to the processing of such data must therefore accompany the informed consent administered to the patient. Such information must (i) identify the roles of the holder ("titolare") and processor ("responsabile", appointed by the holder) of the patient personal data (also if not directly identifying the patient), as well as the purposes of the personal data collection and processing (medical treatment and related/unrelated scientific research), (ii) adequately describe the flows of communication involving them, particularly if third parties should become involved, and (iii) seek the patient's prior and specific consent to such processing.

Patient information or documentation may be considered “anonymous”, and as such not subject to privacy regulations, only when no key whatsoever, permitting the identification of the patient, is any longer available.

Particular attention should therefore be paid (and information/consent materials adapted accordingly) whenever patient data are supplied to third parties and may be autonomously processed, or biological samples/materials are taken and kept for future research purposes, associated or not with the pathology considered in the study.

Informed consent

All patients will be informed of the aims of the study. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for study purposes by authorized individuals other than their treating physician.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient’s subsequent care. Documented informed consent must be obtained for all patients included in the study, except for those unable to give his/her consent since the retrospective nature of the study. This must be done in accordance with the national and local regulatory requirements.

For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that “the written informed consent form should be signed and personally dated by the patient or by the patient’s legally acceptable representative”.

Conflict of Interest

Any investigator and/or research staff member who has a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) must fully disclose the nature of the conflict of interest.

Data ownership and management

According to the ICH Guidelines on Good Clinical Practice the sponsor of a study (the Institution, the investigator or study coordinator act as sponsor in the performance of her/his institutional duties under the employment or collaboration agreement with Humanitas) is the owner of the data resulting therefrom. All centres and investigators participating in the study should be made aware of such circumstance and invited not to disseminate information or data without the Institution's prior express consent.

Forms and procedures for collecting data and data managing

Data collection serves a scientific purpose. The data will be generated in the participating centres and recorded via a web application on servers of ICH using the study management software RedCap (Research Electronic Data Capture) [26, 27]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; 4) procedures for data integration and interoperability with external sources. Data will be recorded in the e-CRF only using coding procedures described in a separate document to comply with data protection applicable laws, including EU GDPR. A coding key reporting patient's name, surname, and date of birth will be filed only in local site files together with a subject screening and enrolment log. In cases where a medical institution is interested in participating, for each authorized user an account is created in the RedCap platform.

Data will be uploaded using an encrypted data connection (HTTPS) throw a web browser or mobile app and stored in an encrypted database. To ensure pseudonymized data analysis, each patient will be assigned a unique Subject ID (Patient Identification Number). RedCap is a secure web application for building and managing online databases. By using a hierarchical, role-based access concept, unauthorized access to the data will be prevented. Access to RedCap will be granted only to data collecting staff of participating centres, in accordance with the procedures outlined in the present protocol. These persons are bound to secrecy. Principal Investigator and monitoring team will maintain adequate and accurate the clinical report forms.

A copy of the electronic databank will be kept in ICH databases and preserved for 5 years for subsequent use by the Steering Committee. Data will remain property of Principal Investigator and Humanitas Research Hospital.

Other considerations

Status

The study is supposed to be started on 1th January 2025 and patients' enrollment is expected to be completed within 6 months.

Financial compensation for participants

There will be no financial compensation for participants.

Publication Policy

The FENICE II study will be registered at www.clinicaltrials.gov and, after the completion, will be submitted to a peer-reviewed medical journal irrespective of the direction of the results. We will adhere to the CONSORT statement including the accountability of all patients screened. The Steering Committee will grant authorship depending on personal involvement according to the Vancouver definitions. The listing of authors will be as follows: M Cecconi (principal investigator) will be responsible for the conduct of the study and data processing. In agreement with ICH-GCP, the Principal Investigator agrees to produce a yearly report on the study and publish all data generated from this study irrespective of results. The Principal Investigator will ensure that data are properly reported, and research findings are disseminated responsibly. The Principal Investigator is responsible Data dissemination and communication through scientific publications and/or presentations at congresses and conferences, as well as participation in multicentre studies, will follow statistical analysis of anonymized data. Publication of the data takes place in an aggregated form only. Information about individual patients will not be published or shared. M Cecconi will appear as first author. A Messina and M Cecconi will be responsible for the writing of the manuscript and will coordinate the enrollment of the centers. A Messina will be the last author, and the next authors will be the other members of the Steering Committee. Centers coordinators and site investigators will

appear either in the front page or in the group authorship ("FENICE II Study Group"), according to the number of included patients per study site, overall commitments and centers' recruitment.

Bibliography

1. Myburgh JA, Mythen MG: **Resuscitation fluids**. *The New England journal of medicine* 2013, **369**(13):1243-1251.
2. Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, Jaeschke R, Mebazaa A, Pinsky MR, Teboul JL *et al*: **Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine**. *Intensive care medicine* 2014, **40**(12):1795-1815.
3. Cecconi M, Parsons AK, Rhodes A: **What is a fluid challenge?** *Current opinion in critical care* 2011, **17**(3):290-295.
4. Magder S: **Fluid status and fluid responsiveness**. *Current opinion in critical care* 2010, **16**(4):289-296.
5. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R *et al*: **Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012**. *Intensive care medicine* 2013, **39**(2):165-228.
6. Messina A, Bakker J, Chew M, De Backer D, Hamzaoui O, Hernandez G, Myatra SN, Monnet X, Ostermann M, Pinsky M *et al*: **Pathophysiology of fluid administration in critically ill patients**. *Intensive Care Med Exp* 2022, **10**(1):46.
7. De Backer D, Cecconi M, Chew MS, Hajjar L, Monnet X, Ospina-Tascon GA, Ostermann M, Pinsky MR, Vincent JL: **A plea for personalization of the hemodynamic management of septic shock**. *Critical care* 2022, **26**(1):372.
8. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME *et al*: **Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016**. *Intensive care medicine* 2017, **43**(3):304-377.
9. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, McIntyre L, Ostermann M, Prescott HC *et al*: **Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021**. *Intensive care medicine* 2021, **47**(11):1181-1247.
10. National Heart L, Blood Institute P, Early Treatment of Acute Lung Injury Clinical Trials N, Shapiro NI, Douglas IS, Brower RG, Brown SM, Exline MC, Ginde AA, Gong MN *et al*: **Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension**. *The New England journal of medicine* 2023.
11. Meyhoff TS, Hjortrup PB, Wetterslev J, Sivapalan P, Laake JH, Cronhjort M, Jakob SM, Cecconi M, Nalos M, Ostermann M *et al*: **Restriction of Intravenous Fluid in ICU Patients with Septic Shock**. *The New England journal of medicine* 2022, **386**(26):2459-2470.
12. Marik PE, Monnet X, Teboul JL: **Hemodynamic parameters to guide fluid therapy**. *Annals of intensive care* 2011, **1**(1):1.
13. Monnet X, Marik PE, Teboul JL: **Prediction of fluid responsiveness: an update**. *Annals of intensive care* 2016, **6**(1):111.
14. Hadian M, Pinsky MR: **Functional hemodynamic monitoring**. *Current opinion in critical care* 2007, **13**(3):318-323.
15. Pinsky MR: **Functional hemodynamic monitoring**. *Crit Care Clin* 2015, **31**(1):89-111.

16. Pinsky MR, Payen D: **Functional hemodynamic monitoring**. *Critical care* 2005, **9**(6):566-572.
17. Van Regenmortel N, Verbrugghe W, Roelant E, Van den Wyngaert T, Jorens PG: **Maintenance fluid therapy and fluid creep impose more significant fluid, sodium, and chloride burdens than resuscitation fluids in critically ill patients: a retrospective study in a tertiary mixed ICU population**. *Intensive care medicine* 2018, **44**(4):409-417.
18. Finfer S, Liu B, Taylor C, Bellomo R, Billot L, Cook D, Du B, McArthur C, Myburgh J, Investigators ST: **Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units**. *Critical care* 2010, **14**(5):R185.
19. Cecconi M, Hofer C, Teboul JL, Pettila V, Wilkman E, Molnar Z, Della Rocca G, Aldecoa C, Artigas A, Jog S *et al*: **Fluid challenges in intensive care: the FENICE study: A global inception cohort study**. *Intensive care medicine* 2015, **41**(9):1529-1537.
20. Messina A, Longhini F, Coppo C, Pagni A, Lungu R, Ronco C, Cattaneo MA, Dore S, Sotgiu G, Navalesi P: **Use of the Fluid Challenge in Critically Ill Adult Patients: A Systematic Review**. *Anesthesia and analgesia* 2017.
21. Messina A, Dell'Anna A, Baggiani M, Torrini F, Maresca GM, Bennett V, Saderi L, Sotgiu G, Antonelli M, Cecconi M: **Functional hemodynamic tests: a systematic review and a metanalysis on the reliability of the end-expiratory occlusion test and of the mini-fluid challenge in predicting fluid responsiveness**. *Critical care* 2019, **23**(1):264.
22. Papazian L, Klompas M, Luyt CE: **Ventilator-associated pneumonia in adults: a narrative review**. *Intensive care medicine* 2020, **46**(5):888-906.
23. Nagin DS, Odgers CL: **Group-based trajectory modeling in clinical research**. *Annu Rev Clin Psychol* 2010, **6**:109-138.
24. Elsensohn MH, Klich A, Ecochard R, Bastard M, Genolini C, Etard JF, Gustin MP: **A graphical method to assess distribution assumption in group-based trajectory models**. *Stat Methods Med Res* 2016, **25**(2):968-982.
25. Genolini C, Pingault JB, Driss T, Cote S, Tremblay RE, Vitaro F, Arnaud C, Falissard B: **KmL3D: a non-parametric algorithm for clustering joint trajectories**. *Comput Methods Programs Biomed* 2013, **109**(1):104-111.
26. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG: **Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support**. *J Biomed Inform* 2009, **42**(2):377-381.
27. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, McLeod L, Delacqua G, Delacqua F, Kirby J *et al*: **The REDCap consortium: Building an international community of software platform partners**. *J Biomed Inform* 2019, **95**:103208.