FENICE trial

FLUID CHALLENGES IN INTENSIVE CARE
How do we administer fluids in the ICU?
One week in 2013
Multicentre observational study conducted by the ESICM Trials group.

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Scope: International Multicentre Observational Trial
Introduction

Fluid Administration in Critically Ill Patients.

Fluids are one of most common therapies used in critically ill patients. Fluids are the cornerstone of hemodynamic management. In overt bleeding, fluids are often given without guidance with specific haemodynamic monitoring. In other conditions when hypovolemia may be more subtle or when the response to fluids is more variable, fluids are often given in a more titrable way, monitoring their haemodynamic impact. This practice, called the fluid challenge technique has been proposed by Max Harry Weil more than 30 years ago [1].

Fluids have beneficial impact on outcome, especially in the context of hemodynamic optimization. Haemodynamic optimization has been shown to improve patient outcome when applied in the perioperative period and in the early phases of septic shock [2,3]. On the other hand, a positive fluid balance is associated with a poor outcome [4,5], but this may just reflect patient severity. In patients with respiratory failure, once hemodynamically stable, fluid restriction is associated with earlier separation from mechanical ventilation [4]. Altogether, it seems reasonable to give just the amount of fluids needed when the patient is hemodynamically unstable and to restrict fluids when the patient is stabilized. Such an approach seems associated with better outcomes [6].

The fluid challenge has been used in several papers and studies assessing the response of patients to fluids. The way this practice is performed varies in terms of:

- type of fluid
- volume of fluid
- rate of fluid administration
- clinical endpoints used

There is no data that describe how fluid challenges are administered in ICU’s across the world. Understanding this will provide valuable information regarding current practice and would be a basis for improving current practice and future research.
Fluids in guidelines

Current guidelines on fluid administration that cover how to give fluids in all critically ill patients do not exist. In the surviving sepsis guidelines fluids are recommended in the very early phase of hemodynamic resuscitation of patients with severe sepsis[7]. At this stage it is recommended to administer these according to CVP [7]. In france, the use of functional hemodynamic tests (see below) is recommended in this setting [8]. After the initial phase, these guidelines are evasive on the way fluids should be guided.

In the UK there guidelines covering the administration of fluids in the perioperative setting. In the perioperative setting in high risk surgical patients, guidelines recommend the use of fluids for stroke volume optimization {9}

Apart from these specific settings, fluids administration is not covered in current guidelines.
Prediction of fluid responsiveness using Functional haemodynamic tests

Heart and Lung Interaction in fully mechanically ventilated patients

During mechanical ventilation, increases in the intra-thoracic pressures induced by the inspiration, decrease the venous return to the right ventricle. If the right ventricle is ‘volume’ responsive, this results in a reduction in right ventricular stroke volume, which is subsequently translated through to a decreased left ventricular stroke volume, several beats later. This change in stroke volume (or stroke volume variation) can be detected by monitors that track real-time changes in stroke volume as a stroke volume variation.’

When the two ventricles are working on the ascending part of the stroke volume/ventricular preload curve, then mechanical ventilation will induce changes in stroke volume which will be reflected, depending on the monitor used, in changes in stroke volume (Stroke Volume Variation, SVV), pulse pressure (Pulse Pressure Variation PPV), and systolic pressure (Systolic Pressure Variation, SPV). These are also called dynamic indices of preload because, by detecting these changes, they provide information on the preload reserve of the ventricles (fluid responsiveness). Therefore they can predict which patients may benefit from fluid administration prior to give fluids.

This has been widely studied with several monitors and proved to be effective in predicting fluid responsiveness with high sensitivity and specificity [10].

These techniques do have some limitations. In order to be reliable the patients need to be fully sedated and mechanically ventilated, with no spontaneous breathing activity and no arrhythmias. Also, as reported by De Backer et al. these indices lose power to predict fluid responsiveness in patients ventilated at volumes lower than 8 ml/kg [11].

Heart and Lung Interaction in spontaneously breathing patients

Passive leg raising is a manoeuvre that produces an autologous fluid challenge by shifting venous blood from the legs to the intra-thoracic compartment. The response measured by a
Fluid challenges in Intensive Care (FENICE Trial)

A flow monitor is able to predict the response to a fluid challenge [12]. This has been studied with different monitors.

In the setting of spontaneously breathing patients Monge Garcia et al. have demonstrated that changes in pressure during a Valsalva manoeuvre predict fluid responsiveness (The Valsalva manoeuvre is a forced expiration against a closed glottis) [13].
Summary of evidence
A summary of the evidence relating to use of fluids in the context of haemodynamic resuscitation suggests that:

1. During the perioperative period and in the early phases of septic shock, the administration of targeted fluids to optimize pre-load provides an improvement in patient outcome.
2. There is no evidence that protocols aimed at optimizing cardiac output are beneficial for the patient if not applied “early” or when oxygen debt has established.
3. Observational studies have shown that a positive fluid balance is associated with an increased 60 day mortality.
4. Despite this, patients who remain unstable after initial fluid resuscitation often receive fluids in an attempt to reverse their shock.
5. Functional Haemodynamic tests have been developed to help the clinician in predicting the response to fluid administration.
6. How the decisions of giving or not giving these fluids are made in different diseases, in different ICU’s and in different countries is not known.
7. How often functional haemodynamic tests are used is not known either.
8. How the effects of fluids are monitored is not known either.

This study should give answers to points 6, 7 and 8.

The way fluids are administered vary widely. Indications for fluids and monitoring of the effects are not standardized and may thus lead to heterogeneity in practice. The purpose of this study is to evaluate how fluids are administered
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What does this study involve?
1. All patients enrolled in the study will receive standard clinical care
2. Data will be collected in order to study how fluid challenges are performed in ICU’s
3. No extra tests will be performed for this study
4. Only measurements and data available as part of clinical practice will be collected

Methods

This is a one week observational trial (either APRIL 17-23 or May 23-29, to be selected by investigators according to what fits best with local organization) in which we will collect information on the factors that indicated fluid challenge, the way fluids was administered and information on the effectiveness and safety of fluid administration. We will collect information on one fluid challenge per patient (ideally the first).

Definition of a fluid challenge

For the purpose of this study a fluid challenge is defined as administration of any bolus of fluid (crystalloid or colloid) in less than two hours. Administration of red blood cell transfusions or fresh frozen plasma is not considered as a fluid challenge.
Unit selection: Any Intensive Care Unit around the world

PATIENTS Inclusion Criteria
All consecutive adult (18 years old and above) patients, up to a maximum of 20, in whom a fluid challenge is performed during a one week period will be included.

Exclusion Criteria
The exclusion criteria are: 1/ Patient already included in the trial; 2 Overt bleeding Patients younger than 18 year

Ethical issues
This is a pure observational trial on current practice. According to local legislation in each country, consent from patient or relative to record data will be obtained or may be waived. Local Investigators will have to make sure that the study is compliant with local and national requirements. A list of national coordinators will be available on the website.
Data will be anonymously be collected. All information allowing patient identification will not be collected.

Data anonymisation

Each unit will be identified with a unique number. Coordination of units registration and number allocation will be performed at ESICM office by the research team. Each patient enrolled in the study will be identified with the unit number and a number between 1 and 20. Local Investigator will keep in a locked office the list of hospital numbers and study numbers for 12 months after the end of the data collection. It will then be destroyed. This information could be used during the cleaning of the database, however no patient identifiable information will be sent out of the each individual unit.

The following data will be collected: (See appendix 2 for details, and appendix 1 (paperCRF))

- Date of ICU admission
- Date of performance of fluid challenge
- Basic demographic data (main diagnosis, age, gender, outcome, height, weight, SOFA score, ICU outcome)
- Nature of hemodynamic monitoring
- Arterial pressure (S/D), heart rate, CVP, PAOP, GEDV, EVLWI, CO,PaO2 (+FiO2), ScvO2, lactate before and after fluid challenge
- Vasoactive agents before/after fluid challenge
- Ventilatory settings
- Type and amount of fluids
- Results of the FC (according to physician opinion Positive/Negative/ indeterminate) (data to support this assessment will be reported)
- Maintenance Fluid (type and rate)
- Fluid administered in the previous 6 hours
Fluid challenge conduction:

- Amount of fluid
- Type of Fluid
- Rate of Administration (measure time in minutes)
- Response definition by the clinician (SV increase, MAP...)
- Actual response measured (SV, HR, MAP, etc)
- Safety limit used? (ie if CVP has been used as a safety limit see below)
  - Baseline CVP
  - Maximum CVP during the fluid challenge
  - (CVP at the end of the fluid challenge?)
  - Fluid challenge stopped because of safety limit during the administration?

-Hemodynamic criteria used to indicate FC (selection+ value):
  CVP / PAOP / GEDV / LVEDA / CO / DeltaPP / SVV / PLR / end exp trial / IVC

-Reasons for not using functional HD (items to select:)
  - Data to evaluate whether functional HD was contra-indicated:
    (tidal volume) / arrhythmia / respiratory movements / abdominal pressure
STATISTICAL ANALYSIS

Variables classified as categorical will be described as proportions and will be compared using chi-square or Fisher’s exact test.

Variables classified as continuous will be described as mean and standard deviation if normally distributed or median and inter-quartile range if not normally distributed. Comparisons of continuous variables will be performed using one-way ANOVA or Mann-Whitney test as appropriate.

SAMPLE SIZE CALCULATION

For this observational trial we expect that at least 2000 patients would be included. As we allow inclusion of maximum 20 patients per centre, at least 100 centres should enroll (min)

PRIMARY OUTCOMES

Primary endpoints/aims:
- evaluate how physicians conduct fluid challenge.
- variable used to trigger/indicate fluid challenge

SECONDARY OUTCOMES

Secondary endpoints/aims: evaluation in a large cohort the proportion of patients responding to fluids, incidence of factors contra-indicating use of functional hemodynamic variables/tests, evaluation of “grey zone” of DPP, tolerance to fluid loading, impact of timing,
Organisation
Enrolment of an ICU in the study will happen via the ESICM Brussels Office. The email research@esicm.org will be used for communication between units and the FENICE study group.

National co-ordinators
A list of national coordinators is available on the FENICE webpage.

National co-ordinators are appointed by the steering committee. Their role is to lead the project within individual nations. They:

- make sure necessary regulatory approvals (i.e., national ethics approval if needed) are in place prior to the start of the study
- Identify local co-ordinators in participating units
- Assist with translation of study paperwork as required
- Distribute of research protocol, eCRF and other materials

Local co-ordinators will register and be responsible for individual units. They:

- make sure the unit questionnaire has been sent to research@esicm.org to register their unit and to receive the unique unit number
- make sure all relevant regulatory approvals are in place for their unit/institution
- make sure there has been adequate training of all relevant staff prior to data collection
- Supervise data collection and assist with problem solving
- Act as guarantor for the integrity and quality of data collected
- Ensure timely completion of the electronic CRF (xls file or eCRF if available)
- Communicate with the relevant national coordinator and research@esicm.org
Data management and ownership

On behalf of the steering committee, ESICM will act as custodian of the data. The Steering committee will retain the right to use all pooled data for scientific and other purposes. Members of the FENICE steering group will be able to access the data for research purposes provided the research proposal has been reviewed and deemed satisfactory by the Steering committee. The primary consideration for such decisions will be the quality and validity of any proposed analysis.
REFERENCES:


APPENDIX 1: CRF

Fluid challenges in Intensive Care (FENICE Trial)
Case Record Form

1. Centre number: __________  2. Patient number: __________

3. Fluid challenge: hour (24:00) & date: __________ 2013
4. ICU admission: hour (24:00) & date: __________ 2013

5. Age: _______  6. Gender: □ M □ F
7. Height: cm _______  8. Weight: kg _______

9. Principal diagnosis:
   □ Sepsis □ Cardiac □ Respiratory □ Trauma □ Neurologic □ Intoxication
   □ Other; please specify: __________________________

10. Surgical/Medical:
    □ Medical □ Scheduled surgical □ Emergency surgical

11. Shock:
    □ No □ Septic □ Cardiogenic □ Hypovolemic □ Anaphylactic □ Other

12. SOFA score at inclusion:
   SOFA CV: □ 0 □ 1 □ 2 □ 3 □ 4
   SOFA Respiration: □ 0 □ 1 □ 2 □ 3 □ 4
   SOFA Circulation: □ 0 □ 1 □ 2 □ 3 □ 4
   SOFA Liver: □ 0 □ 1 □ 2 □ 3 □ 4
   SOFA Neurology: □ 0 □ 1 □ 2 □ 3 □ 4
   SOFA Urinary: □ 0 □ 1 □ 2 □ 3 □ 4

13. ICU Outcome:
    □ ICU Discharge □ ICU death

14. Mechanical ventilation:
    □ Yes □ No; if yes: fully sedated: □ Yes □ No; Spontaneous resp. movements: □ Yes □ No

Please indicate mode: __________________________

FIO2
Respiratory rate R/min
Tidal volume ml
Plateau pressure cmH2O
PEEP cmH2O

FENICE patient ID ____________________________

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### 15. Renal support:
- [ ] No
- [ ] HD
- [ ] CVVH

### 16. Fluid balance (24h):
- In ml: [ ]
- Out ml: [ ]

### 17. Lab:
- Creatinine mg/dl or umol/l: [ ]
- Sodium mEq/l: [ ]
- Potassium mEq/l: [ ]
- Chloride mEq/l: [ ]

### 18. What was the main indication for fluid administration?
- [ ] Hypotension
- [ ] Weaning vasopressor
- [ ] Cardiac output
- [ ] Oliguria
- [ ] Skin mottling
- [ ] Hyperlactatemia
- [ ] SvO₂
- [ ] SVV/PPV
- [ ] CVP/PAOP
- [ ] Other; please specify: [ ]

### 19. Hemodynamic variable considered to predict a positive response to a fluid challenge:
- [ ] No variable used
- [ ] PAOP mmHg
- [ ] CVP mmHg
- [ ] SVV %
- [ ] PPV %
- [ ] GEDV ml
- [ ] Passive leg raising (PLR):
  - [ ] Arterial pressure increase during PLR %
  - [ ] CO /SV increase during PLR %
- [ ] Other test; please specify: [ ]

### 20. Type of fluid:
- [ ] NaCl 0.9%
- [ ] RL Hartmann
- [ ] Starch
- [ ] Albumin 4.5%
- [ ] Gelatine
- [ ] Dextrane
- [ ] Other; please specify: [ ]

### 21. Amount fluids given as fluid challenge: [ ] ml

### 22. Rate of fluid administration: [ ] ml/min

### 23. Specific comments of the investigators:

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**FENICE patient ID** [ ] [ ] [ ] [ ] [ ] **FENICE Case record form V1.3 / Page 2 of 4**
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**24. Evolution of variables during fluid challenge:**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>End of Fluids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time elapsed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td>°C</td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>bpm</td>
<td></td>
</tr>
<tr>
<td>Arterial pressure systolic</td>
<td>mmHg</td>
<td></td>
</tr>
<tr>
<td>Arterial pressure diastolic</td>
<td>mmHg</td>
<td></td>
</tr>
<tr>
<td>Arterial pressure mean</td>
<td>mmHg</td>
<td></td>
</tr>
<tr>
<td>PAP systolic</td>
<td>mmHg</td>
<td></td>
</tr>
<tr>
<td>PAP diastolic</td>
<td>mmHg</td>
<td></td>
</tr>
<tr>
<td>PAP mean</td>
<td>mmHg</td>
<td></td>
</tr>
<tr>
<td>PAOP</td>
<td>mmHg</td>
<td></td>
</tr>
<tr>
<td>CVP</td>
<td>mmHg</td>
<td></td>
</tr>
<tr>
<td>CO</td>
<td>L/min</td>
<td></td>
</tr>
<tr>
<td>SV</td>
<td>L/min</td>
<td></td>
</tr>
<tr>
<td>SVV</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>PPV</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>GEDV</td>
<td>ml</td>
<td></td>
</tr>
<tr>
<td>EVLW</td>
<td>ml/kg</td>
<td></td>
</tr>
<tr>
<td>Urine output</td>
<td>ml/h</td>
<td></td>
</tr>
</tbody>
</table>

**25. Blood gas analysis during fluid challenge:**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>End of Fluids</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH arterial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaCO₂</td>
<td>mmHg</td>
<td></td>
</tr>
<tr>
<td>PaO₂</td>
<td>mmHg</td>
<td></td>
</tr>
<tr>
<td>SaO₂</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>ScvO₂</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>SvO₂</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Lactate</td>
<td>mmol/l</td>
<td></td>
</tr>
</tbody>
</table>
26. Vasoactive drugs during fluid challenge:

<table>
<thead>
<tr>
<th>Drug</th>
<th>mcg/kg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td></td>
</tr>
<tr>
<td>Norepinephrine</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td></td>
</tr>
<tr>
<td>Vasopressin</td>
<td>U/min</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>mcg/kg/min</td>
</tr>
</tbody>
</table>

27. Response to fluids:
- No response
- Positive response
- Do not know/uncertain

28. Positive response to fluids based on:
- Change in arterial pressure
- Change in heart rate
- Change in urine output
- Change in skin perfusion
- Change in SVV/PPV
- Other; please specify:

29. Did you consider further fluids?
- No
- Yes

30. Was a variable used as safety limit?
- No variable used
- PAOP mmHg
- SVV %
- EVLV ml/kg
- CO l/min
- CVP mmHg
- GEDV ml
- SpO2/SaO2 %
- Other; please specify:

31. Was the fluid challenge stopped for safety reasons?
- No
- Yes: Stopped due to:
  - Low arterial pressure
  - High arterial pressure
  - Low CO
  - High CO
  - Pulmonary edema
  - High CVP/PAOP
  - Futility

32. Why didn’t you use the following parameters?
- CVP
- PAOP
- GEDV
- SVV
- PPV
- PLR

PLR: Passive leg raising

FENICE patient ID

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