Controversies in sepsis

Daniele Coen
Doctor 1
Doctor 2
How do we define sepsis and septic shock?
SIRS in the setting of an infection

1. T > 38.3 °C < 36°C
2. WBC <4.000 o >12000 o >10% bands
3. HR > 90/min
4. RR > 20/min
Yet...
Diagnostic criteria for sepsis

**Infection**
Documented or suspected *and* some of the following:

**General parameters**
- Fever (core temperature >38.3°C)
- Hypothermia (core temperature <36°C)
- Heart rate >90 bpm or >2 SD above the normal value for age
- Tachypnea: >30 bpm
- Altered mental status
- Significant edema or positive fluid balance (>20 ml/kg over 24 h)
- Hyperglycemia (plasma glucose >110 mg/dl or 7.7 mM/l) in the absence of diabetes

**Inflammatory parameters**
- Leukocytosis (white blood cell count >12,000/μl)
- Leukopenia (white blood cell count <4,000/μl)
- Normal white blood cell count with >10% immature forms
- Plasma C reactive protein >2 SD above the normal value
- Plasma procalcitonin >2 SD above the normal value

**Hemodynamic parameters**
- Arterial hypotension (systolic blood pressure <90 mmHg, mean arterial pressure <70, or a systolic blood pressure decrease >40 mmHg in adults or <2 SD below normal for age)
- Mixed venous oxygen saturation >70%
- Cardiac index >3.5 l/min^{-1} m^{-2}

**Organ dysfunction parameters**
- Arterial hypoxemia (PaO$_2$/FiO$_2$ <300)
- Acute oliguria (urine output <0.5 ml kg$^{-1}$ h$^{-1}$ or 45 ml/h for at least 2 h)
- Creatinine increase ≥0.5 mg/dl
- Coagulation abnormalities (international normalized ratio >1.5 or activated partial thromboplastin time >60 s)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count <100,000/μl)
- Hyperbilirubinemia (plasma total bilirubin >4 mg/dl or 70 mmol/l)

**Tissue perfusion parameters**
- Hyperlactatemia (>3 mmol/l)
- Decreased capillary refill or mottling
Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis

Kirsi-Maija Kaukonen, M.D., Ph.D., Michael Bailey, Ph.D., David Pilcher, F.C.I.C.M., D. Jamie Cooper, M.D., Ph.D., and Rinaldo Bellomo, M.D., Ph.D.

ABSTRACT
Severe sepsis

Infection   SIRS   Sepsis   Severe   Septic
                 sepsis

Infection + organ failure

**CV:** SBP<90mmHg or MAP<70 mmHg or SBP decrease > 40mmHg below normal

**Respiratory:** PaO2/Fio2<250 in the absence of pneumonia or <200 with pneumonia

**Renal:** diuresis<0.5ml/Kg/h for over 2 h, creatinina 0.5 mg/dl above usual values;

**Liver:** bilirubin >2mg/dl; ALT, AST > high normal x 2;

**CNS:** altered consciousness;

**Coagulation:** INR >1.5 or aPTT>60sec; PTL <100.000

**Metabolic:** lactates >2mmol/L

The organ failure must not be preexisting nor be in the organ which is source of the infection
Mortality in severe sepsis according to the number of organs involved

Mortality

One  Two  Three  Four (*)  Five

OD

SOFA: Vincent, CCM 1998. (*) Four and Five for SOFA
SBP<90 mmHg or
MAP<70 mmHg or
SBP decrease >40 mmHg below normal values

After an adequate volume resuscitation

or lactates >4 mmol/l ("cryptic" shock)
Yet...
<table>
<thead>
<tr>
<th>SHOCK</th>
<th>%</th>
<th>MORTALITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension and lactate &gt; 4</td>
<td>16,6</td>
<td>46,1</td>
</tr>
<tr>
<td>Hypotension and normal lactate</td>
<td>49,5</td>
<td>36,7</td>
</tr>
<tr>
<td>Lactate &gt; 4 and no hypotension</td>
<td>5,4</td>
<td>30</td>
</tr>
</tbody>
</table>

Levy et al, Crit Care Med 2010
Should we use CVP as an index of fluid responsiveness?

Pros
### Table 1. Clinical and biological factors suggesting that a patient may require fluid administration

<table>
<thead>
<tr>
<th>Static evaluation</th>
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<tbody>
<tr>
<td>Signs of dehydration</td>
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<tr>
<td>Diminished skin turgor</td>
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<tr>
<td>Thirst</td>
</tr>
<tr>
<td>Dry mouth</td>
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<tr>
<td>Dry axillae</td>
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<tr>
<td>Hypernatremia, hyperproteinemia, elevated hemoglobin/hematocrit</td>
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<tr>
<td>Circulatory signs of hypovolemia</td>
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<tr>
<td>Tachycardia</td>
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<tr>
<td>Arterial hypotension (severe cases)</td>
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<tr>
<td>Increased serum lactate (severe cases)</td>
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<tr>
<td>Decreased toe temperature</td>
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<tr>
<td>Decreased renal perfusion</td>
</tr>
<tr>
<td>Concentrated urine (low urine sodium concentration, high urine osmolarity)</td>
</tr>
<tr>
<td>Increased blood urea nitrogen relative to creatinine concentration</td>
</tr>
<tr>
<td>Persistent metabolic alkalosis</td>
</tr>
<tr>
<td>Dynamic evaluation</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Respiratory variations in arterial pressure or stroke volume (during mechanical ventilation, in the absence of ventilatory dyssynchrony or arrhythmias)</td>
</tr>
<tr>
<td>Passive leg raising</td>
</tr>
<tr>
<td>Positive response to fluid challenge</td>
</tr>
</tbody>
</table>
Physiology as a guide

1. CVP is determined by:
   • Transmural pressure in the right heart
   • Vis a tergo : vascular tone + intravascular volume

2. CVP is a good proxy for right atrial pressure and end diastolic right ventricular pressure

3. In the absence of a known cardiac or pulmonary disease (see) CVP may be considered as a good indicator for intravascular volume
FACTORS THAT INCREASE CVP INCLUDE:
Hypervolemia
Forced exhalation
Tension pneumothorax
Heart failure
Pleural effusion
Decreased cardiac output
Cardiac tamponade
Mechanical ventilation
Pulmonary hypertension
Pulmonary embolism

FACTORS THAT DECREASE CVP INCLUDE:
Hypovolemia
Deep inhalation
Distributive shock
During the first 6 hrs of resuscitation, the goals of initial resuscitation of sepsis-induced hypoperfusion should include all of the following as a part of a treatment protocol (grade 1C):

a) CVP 8–12 mm Hg
b) MAP ≥ 65 mm Hg
c) Urine output ≥ 0.5 mL · kg · hr
d) Superior vena cava oxygen saturation (Scvo2) or mixed venous oxygen saturation (Svo2) 70% or 65%, respectively.
The consensus panel judged use of CVP and Svo2 targets to be recommended physiologic targets for resuscitation. Although there are limitations to CVP as a marker of intravascular volume status and response to fluids, a low CVP generally can be relied upon as supporting positive response to fluid loading.
Updated Bundles in Response to New Evidence

DOCUMENT REASSESSMENT OF VOLUME STATUS AND TISSUE PERFUSION WITH:

EITHER

• Repeat focused exam (after initial fluid resuscitation) by licensed independent practitioner including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings.

OR TWO OF THE FOLLOWING:

• Measure CVP
• Measure ScvO₂
• Bedside cardiovascular ultrasound
• Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge
Should we use CVP as an index of fluid responsiveness?

**PROS**

- It has a sound physiological base
- It is part of a bundle of interventions which proved effective in EGDT trials
- It has been used for over 50 years and is still endorsed by the Surviving Sepsis Campaign Guidelines
Should we use CVP as an index of fluid responsiveness?

Cons
The central venous pressure in a normal person in the upright posture is usually less than zero (atmospheric pressure) with a normal volume and normal cardiac function. However, a low central venous pressure also can indicate hypovolemia or can be present in someone who is hypervolemic (i.e., with increased return function) but has a very dynamic heart. On the other hand, a high central venous pressure can be present in someone with a high volume and normal cardiac function as well as in someone with normal volume and decreased cardiac function.

Magden S, Crit Care Med 2006
Think in terms of stroke volume

Fundamentally, the only reason to give any patient a fluid challenge is to increase their stroke volume
DO2 = CO \times CaO2
A meta-analysis

43 clinical trials were included that reported the correlation coefficient or area under the receiver operating characteristic curve (AUC) between the central venous pressure and change in cardiac performance following an intervention that altered cardiac preload.

Overall 57% ± 13% of patients were fluid responders. The summary AUC was 0.56 (95% CI, 0.54–0.58) with no heterogeneity between studies. The summary correlation coefficient between the baseline central venous pressure and change in stroke volume index/cardiac index was 0.18 (95% CI, 0.1–0.25), being 0.28 (95% CI, 0.16–0.40) in the ICU patients, and 0.11 (95% CI, 0.02–0.21) in the operating room patients.

It has been well established that there is no relationship between the CVP and intravascular volume and no relationship between the CVP and fluid responsiveness. Consequently, I believe that the CVP should not be used to guide fluid therapy.

Marik PE, Chest 2014
Calibrated pulse contour analysis, bioreactance, the ultrasonic cardiac output monitor (USCOM), carotid Doppler flow, Doppler echocardiography, or esophageal Doppler techniques can be used to dynamically follow the cardiac output in real time. Bioreactance, USCOM, and carotid Doppler flow are truly noninvasive and are suitable for guiding fluid resuscitation in the ED

Marik PE, Chest 2014
Should we use CVP as an index of fluid responsiveness?

CONS

• It has NOT a sound physiological base
• It does not correlate with CO
• Its baseline value has no direct relationship with positive response to a fluid challenge
• It has been used for over 50 years DESPITE evidence to the contrary
Should we give a large amount of fluids in the resuscitative phase of severe sepsis?

Pros
Pathophysiologic changes in sepsis

1. Vasoplegia (distributive shock)
2. Myocardial depression
3. Altered microvascular flow
4. Disrupted endothelium

Fluids may counteract the effects of all of these
### TABLE 6. Recommendations: Hemodynamic Support and Adjunctive Therapy

#### G. Fluid Therapy of Severe Sepsis

1. Crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B).

2. Against the use of hydroxyethyl starches for fluid resuscitation of severe sepsis and septic shock (grade 1B).

3. Albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (grade 2C).

4. Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients (grade 1C).

5. Fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (e.g., change in pulse pressure, stroke volume variation) or static (e.g., arterial pressure, heart rate) variables (UG).
The Importance of Early Goal-Directed therapy

Treatment administered (6 hrs)

Rivers E, et Al. NEJM 2001
Fluids administered in the first 6 hrs 
(Usual care arm)

<table>
<thead>
<tr>
<th>CLINICAL TRIAL</th>
<th>PRE RANDOMIZATION FLUIDS (L)</th>
<th>POST RANDOMIZATION FLUIDS (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIVERS’ EGDT TRIAL</td>
<td>?</td>
<td>3.5 ± 2.4</td>
</tr>
<tr>
<td>PROCESS</td>
<td>2.1 ± 1.4</td>
<td>2.3 ± 1.9</td>
</tr>
<tr>
<td>ARISE</td>
<td>2.6 ± 1.3</td>
<td>1.7 ± 1.4</td>
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<tr>
<td>PROMISE</td>
<td>2.0 ± 1.1</td>
<td>2.0 ± 1.3</td>
</tr>
</tbody>
</table>
Should we give a large amount of fluids in the resuscitative phase of sepsis?

PROS

• Septic patients are hypovolemic because of vasoplegia and endothelial disruption
• Intravascular volume is a basic determinant of CO
• Patients in sepsis studies have all received an average of 4L fluids during the first 6 hrs (and often more) with low mortality rates
Should we give a large amount of fluids in the resuscitative phase of severe sepsis?

Cons
Physiology is not so simple

• Because of the endothelial injury, capillary leak, and increased hydrostatic pressures, 5% of infused crystalloid remains intravascular within 3 h after infusion, resulting in an increase in EVLW and further tissue edema.

• Increased EVLW has been demonstrated to be a strong independent predictor of death. In patients with pneumonia, large-volume fluid resuscitation may result in severe pulmonary edema. Myocardial edema due to excess fluid administration compounds the myocardial dysfunction.

Marik PE. Chest 2014
Clinical studies do not support positive fluid balance

- Many clinical studies have demonstrated an independent association between an increasingly positive fluid balance and increased mortality in patients with sepsis.

Boyd JH et Al. Crit Care Med 2011
Maitland K et Al. NEJM 2011
Micek ST, et Al. Crit Care 2013
After correcting for age and Acute Physiology and Chronic Health Evaluation II score, a more positive fluid balance at both at 12 hrs and day 4 correlated significantly with increased mortality. Central venous pressure was correlated with fluid balance at 12 hrs, whereas on days 1–4, there was no significant correlation. At 12 hrs, patients with central venous pressure <8 mm Hg had the lowest mortality rate followed by those with central venous pressure 8–12 mm Hg. The highest mortality rate was observed in those with central venous pressure >12 mm Hg. Contrary to the overall effect, patients whose central venous pressure was <8 mm Hg had improved survival with a more positive fluid balance.

Boyd et al. Crit Care Med 2011
**Measurements and Main Results:** Fluids and vasoactive agents had strong, interacting associations with mortality ($p < 0.0001$). Mortality was lowest when vasoactive agents were begun 1–6 hours after onset, with more than 1L of fluids in the initial hour after shock onset, more than 2.4L from hours 1–6, and 1.6–3.5L from 6 to 24 hours. The lowest mortality rates were associated with starting vasoactive agents 1–6 hours after onset.

**Conclusions:** The focus during the first hour of resuscitation for septic shock should be aggressive fluid administration, only thereafter starting vasoactive agents, while continuing aggressive fluid administration. Starting vasoactive agents in the initial hour may be detrimental, and not all of that association is due to less fluids being given with such early initiation of vasoactive agents. (Crit Care Med 2014; 42:2158–2168)
Should we give a large amount of fluids in the resuscitative phase of sepsis?

CONS

• Septic pts are hypovolemic, but giving them too much fluid may be detrimental for their disfunctioning heart

• Most of the fluids you give will very quickly move to the interstitium (also in the lungs)

• Clinical trials show that a positive fluid balance correlates with higher mortality in critical care patients
SO WHAT ?
PATOPHYSIOLOGY AND DEFINITIONS

GUIDELINES AND MAJOR CLINICAL TRIALS


ANTIMICROBIALS


CENTRAL VENOUS PRESSURE


FLUID RESUSCITATION


CONTROVERSIES

So what?

• Beware of protocols, especially those with pre-defined physiological endpoints
• Adopt a multi-parametric approach when making a potentially critical decision.
So what? 2

• Use dynamic measures (leg raising, inspiratory variation, fluid challenge) to evaluate fluid responsiveness

• CVP might be dear to you, but you should nevertheless get acquainted with the newer non invasive ways to measure stroke volume.
Figure 1. Key interventions in septic shock: Interactions and timing between fluids, vasoactive drugs, antibiotics, and source control.
Box 1 Time-dependent considerations

- Resuscitation: administration of fluid for immediate management of life-threatening conditions associated with impaired tissue perfusion
- Titration: adjustment of fluid type, rate and amount based upon context to achieve optimization of tissue perfusion
- De-escalation: minimization of fluid administration; mobilization of extra fluid to optimize fluid balance
Various **dynamic techniques** have been proposed in an effort to unmask hypovolemia or relative hypovolemia.

...**Increased variations in arterial pressure with breathing** reflect changes in the stroke volume contingent on the respiratory cycle and may help to predict the response to fluid repletion

...**Passive leg raising** may also be used to assess the response to a volume load.

...The technique we propose herein is a provocative test in which a **fluid challenge** is administered over defined intervals and the effect on right-sided filling pressures is quantitated.
Calibrated pulse contour analysis, bioreactance, the ultrasonic cardiac output monitor (USCOM), carotid Doppler flow, Doppler echocardiography, or esophageal Doppler techniques can be used to dynamically follow the cardiac output in real time. Bioreactance, USCOM, and carotid Doppler flow are truly noninvasive and are suitable for guiding fluid resuscitation in the ED

Marik PE, Chest 2014
Fig 2 Patients’ volume status at different stages of resuscitation. Reproduced with permission from ADQI (www.ADQI.org).
<table>
<thead>
<tr>
<th>Minimum monitoring requirement</th>
<th>Rescue</th>
<th>Optimization</th>
<th>Stabilization</th>
<th>De-escalation</th>
</tr>
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<tbody>
<tr>
<td>Blood pressure</td>
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<td>Heart rate</td>
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<tr>
<td>Lactate/arterial</td>
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<td>Blood gases</td>
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<td>Capillary refill/</td>
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<tr>
<td>Pulse volume</td>
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<tr>
<td>Altered mental status</td>
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<tr>
<td>Urine output</td>
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<tr>
<td>Fluid balance</td>
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<tr>
<td></td>
<td>Rescue</td>
<td>Optimization</td>
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<td>De-escalation</td>
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<tr>
<td><strong>Echo/Doppler</strong></td>
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<tr>
<td><strong>CVP monitoring</strong></td>
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<tr>
<td><strong>ScvO₂</strong></td>
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<td><strong>Cardiac output</strong></td>
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<tr>
<td><strong>Signs of fluid responsiveness</strong></td>
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<tr>
<td><strong>Fluid challenge</strong></td>
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</table>

Hoste EA, et Al. BJA 2014
<table>
<thead>
<tr>
<th><strong>Rescue</strong></th>
<th><strong>Optimization</strong></th>
<th><strong>Stabilization</strong></th>
<th><strong>De-escalation</strong></th>
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<tr>
<td>Principles</td>
<td>Lifesaving</td>
<td>Organ rescue</td>
<td>Organ recovery</td>
</tr>
<tr>
<td>Goals</td>
<td>Correct shock</td>
<td>Organ support</td>
<td>Mobilize fluid accumulated</td>
</tr>
<tr>
<td>Time (usual)</td>
<td>Minutes</td>
<td>Optimize and maintain tissue perfusion</td>
<td>Aim for zero or negative fluid balance</td>
</tr>
<tr>
<td>Phenotype</td>
<td>Severe shock</td>
<td>Stable</td>
<td>Days</td>
</tr>
<tr>
<td>Fluid therapy</td>
<td>Rapid boluses</td>
<td>Stable</td>
<td>Days to weeks</td>
</tr>
<tr>
<td>Typical clinical scenario</td>
<td>- Septic shock</td>
<td>Minimal maintenance infusion only if oral intake inadequate</td>
<td>Recovering</td>
</tr>
<tr>
<td></td>
<td>- Major trauma</td>
<td>- NPO postoperative patient</td>
<td>Oral intake if possible</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 'Drip and suck' management of pancreatitis</td>
<td>Avoid unnecessary i.v. fluids</td>
</tr>
<tr>
<td>Amount</td>
<td>Guidelines, for example, SSC, pre-hospital resuscitation, trauma, burns, etc.</td>
<td>Patient on full enteral feed in recovery phase of critical illness</td>
<td>Recovering ATN</td>
</tr>
</tbody>
</table>

Table 1 Characteristics of different stages of resuscitation: ‘Fit for purpose fluid therapy’. GDT, goal directed therapy; DKA, diabetic keto acidosis; NPO, nil per os; ATN, acute tubular necrosis; SSC, surviving sepsis campaign.

Hoste EA, et Al. BJA 2014
Recognize severe sepsis, maintain airway and establish IV access

- 500 ml boluses of LR Max. of 20-30 ml/kg.
- Early broad spectrum antimicrobial therapy
- Blood cultures, lactate and PCT

If MAP < 65 mmHg after fluid bolus

- Start norepinephrine @ 0.01ug/kg/min and titrate up to 0.1 - 0.2 ug/kg/min
- Establish central venous access
  - Assess fluids status with ECHO/ultrasound/PLR
  - Additional 500 cc bolus x2 If signs of volume depletion

Marik PE. Chest 2014
I suggest limiting the initial fluid resuscitation to approximately 20 to 30 mL/kg. Furthermore, I recommend this fluid be given as 500-mL fluid challenges. It is important to emphasize that this conservative approach to fluid management in patients with sepsis is based on indirect evidence and not on a randomized controlled trial specifically designed to answer this question.

Marik PE. Chest 2014
The optimal time to start a vasopressor agent in patients with sepsis has not been well studied. However, after receiving 20 to 30 mL/kg of crystalloid, it seems unlikely that additional fluid boluses will increase the mean arterial pressure (MAP) in patients who remain hypotensive. I would, therefore, recommend the initiation of a vasopressor agent (norepinephrine) in patients who remain hypotensive (MAP < 65 mm Hg) after receiving 20 to 30 mL/kg of crystalloid solution. Additional fluid boluses (500 mL) may be given once the “target” norepinephrine dose is achieved (about 0.1-0.2 mg/kg/min), and this should be based on a dynamic assessment of volume responsiveness and ventricular function.
Several decades ago, Weil and Hennin(7) proposed the fluid challenge technique, based on the 2–5 rule using central venous pressure and the 3–7 rule for the pulmonary artery occlusion pressure. According to this scheme, the corresponding filling pressure was measured at 10-min intervals. If the change in pulmonary artery occlusion pressure was 3 mm Hg (2 mm Hg for central venous pressure), the infusion was continued, if it was in the 3–7 mm Hg range (2–5 mm Hg for central venous pressure), the infusion was interrupted and reevaluated after a 10-min wait. If the change was an increase of _7 mm Hg (5 mm Hg for central venous pressure), the infusion was stopped.
Box 2 Terminology

- Fluid bolus: a rapid infusion to correct hypotensive shock. It typically includes the infusion of at least 500 ml over a maximum of 15 min.
- Fluid challenge: 100–200 ml over 5–10 min with re-assessment to optimize tissue perfusion
- Fluid infusion: continuous delivery of i.v. fluids to maintain homeostasis, replace losses, or prevent organ injury (e.g. prehydration before operation or for contrast nephropathy)
- Maintenance: fluid administration for the provision of fluids for patients who cannot meet their needs by oral route. This should be titrated to patient need and context and should include replacement of ongoing losses. In a patient without ongoing losses, this should probably be no more than 1–2 ml kg\(^{-1}\) h\(^{-1}\)
- Daily fluid balance: daily sum of all intakes and outputs
- Cumulative fluid balance: sum total of fluid accumulation over a set period of time
- Fluid overload: cumulative fluid balance expressed as a proportion of baseline body weight. A value of 10% is associated with adverse outcomes
When blood volume is increased very rapidly even in areflexic preparations, the immediate change in mean systemic pressure (the pressure in the venous system when the heart is not pumping) begins to wane almost immediately. The effect is the result of stress relaxation of the walls of the large capacitance vessels, although fluid transudation out of the vascular space into the interstitium undoubtedly contributes gradually to the phenomenon as well. In one study, Guyton and associates rapidly infused 35% of the blood volume of a dog and then followed mean systemic pressure over the following minutes. Mean systemic pressure reached its maximum (24 mm Hg) at the conclusion of the 1-minute infusion and then began immediately to decline asymptotically toward a steady-state value somewhat above the initial level with an estimated half-time of 2–4 min.

Young DB. 2010