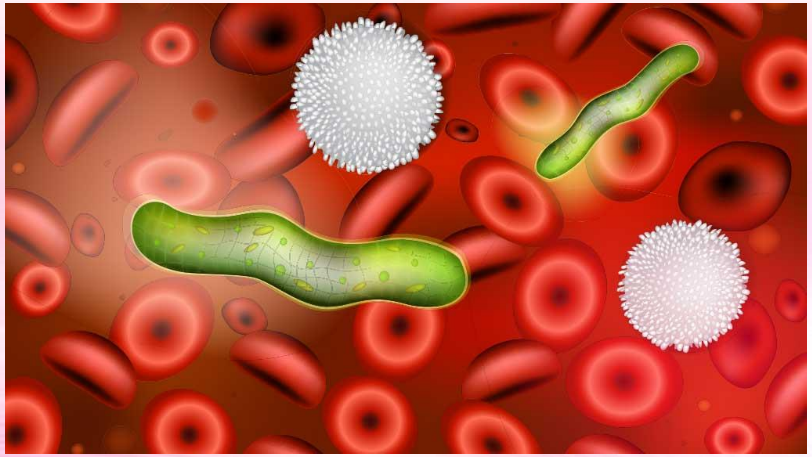
Fluid Therapy in Septic Shock



Shiva Seyrafian

M.D.-Nephrologist- IKRC- Isfahan University of Medical Sciences

23/5/2023- 1402/3/2

Introduction

Sepsis is characterized by

- Vasoplegia with loss of arterial tone,
- Venodilation with sequestration of blood in the unstressed blood compartment
- Reduced ventricular compliance and reduced preload responsiveness.

Recent evidence:

- Most septic patients poorly responsive to fluids.
- Almost all of the administered fluid is sequestered in the tissues, resulting in severe edema in vital organs.
- Increasing the risk of organ dysfunction.

Marik and Bellomo, British Journal of Anaesthesia, (2016)

Introduction…

- Less than 40% of hypotensive patients with **severe sepsis** or **septic shock** are fluid responders.
- In healthy volunteers, only 15% of a crystalloid bolus remained in the intravascular space at 3 h.
- In patients with sepsis less than 5% of a crystalloid bolus remains intravascular an hour after the end of the infusion.
- Damage to the glycocalyx profoundly increases endothelial permeability.

Marik and Bellomo, British Journal of Anaesthesia, (2016)

Introduction…

- Fluids are drugs, **effective** and also **deleterious effects**.
- Administered at the right dose and only to patients need them.

Personalize decisions:

1. The severity of the vasodilation, the importance of the fluid accumulation
2. Clinical history (the depth of the initial hypovolemia),
3. Physiological conditions (preload responsiveness)

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How to customize the initial fluid volume?

- Relative hypovolemia is linked to venous vasodilation, depending on shock severity
- Tolerance to fluid administration also depends on the cardiac function.
- Volume expansion should be individualized according to the degree of preload responsiveness, to avoid unnecessary fluid infusion

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We must personalize the fluid balance of patients in septic shock!

- Fluid accumulation during the ICU is harmful, influences mortality in ICU patients, particularly during septic shock and acute respiratory distress syndrome (ARDS).
- Some showed that the reduction in fluid balance, decreased the duration of mechanical ventilation and the ICU stay

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IV fluids

1. **Crystalloids**
    a) **Unbalanced (Normal saline)**
    b) **Balanced crystalloids**
        i. Lactated Ringer's (USA)
        ii. Hartmann's solution (Europe)
        iii. Plasma-lyte
    c) **Hypertonic saline**
2. **Colloids**
    a) **Albumin**
    b) **Hydroxyethyl starch**
3. Plasma
4. Blood
5. Bicarbonate

	Plasma	Crystalloid	Balanced solutions			
		Saline 0.9% Sodium chloride	Lactated Ringer's	Hartmann's solution	Isolyte S	Plasma-Lyte A/Normosol-R
Sodium	135–145	154	131	131	141	140
Potassium	3.5–5.0		4.0	5.4	5.0	5.0
Calcium	2.2–2.6		1.5	1.8		
Magnesium	0.8–1.0				3	3
Chloride	94–111	154	109	112	98	98
Acetate					27	27
Lactate	1–2		28	28		
Gluconate					23	23
Bicarbonate	23–27					
Octanoate						
Osmolarity	291	308	273	277	295	294

Seitz et al., Nutr. Clin. Pract. 2022;37:990–1003

IV fluids - Crystalloids

Normal saline

- The most commonly fluid therapy for sepsis in the united states
- A dutch physiologist, incorrectly concluded the physiologic concentration of sodium chloride in blood to be 0.9% based on red blood cell lysis studies in the 1880s,
- Hyperchloremic metabolic acidosis and increased inflammatory markers.
- The hyperchloremia alter renal blood flow and thereby renal function.
- Increased mortality in ICU patients with hyperchloremia.

Shock. Ronald Chang., TX ; available in PMC 2017 July 01

IV fluids – Crystalloids..

2- Balanced crystalloids

a) Lactated Ringer's (USA) : chloride similar to plasma, Ca^{++}

b) Hartmann's solution (Europe): chloride similar to plasma, Ca^{++}

c) Plasma-lyte: chloride similar to plasma, Mg^{++}

Plasma-lyte to be given concurrently with blood products, but ringer’s and Hartmann's theoretical risk of causing a blood clot in the transfusion line.

Shock. Ronald Chang., Houston, TX ; available in PMC 2017 July 01

IV fluids - **Colloids**

1. Albumin

Hypoalbuminemia: poor outcome in severe sepsis.

The **Surviving Sepsis Campaign guidelines** recommend use of albumin in those received a significant volume of crystalloid.

Correction of hypoalbuminemia does not appear to improve outcome.

Shock. Author manuscript; available in PMC 2017 July 01

IV fluids – **Colloids…**

2. Plasma: Currently no definitive data in human subjects that plasma mitigates endothelial injury in trauma or in sepsis.
3. Blood: The available evidence supports red blood cell transfusion to maintain a hemoglobin target of ≥7 g/dl.

Seitz et al., Nutr. Clin. Pract. 2022;37:990–1003

How to customize the choice of fluid type?

- The 2021 Surviving Sepsis Campaign (SSC) guidelines suggested to prefer balanced crystalloids in all septic shock patients

Normal saline: hyperchloremia

- If in a 70-kg patient, 12 litres must be infused for the blood bicarbonate level to drop by 10 mmol/L.
- Balanced crystalloids should be logically reserved for patients requiring large fluid volumes.

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INITIAL RESUSCITATIVE THERAPY

Tissue perfusion:

- Intravenous fluids: 30 mL/kg (actual body weight), started by one hour and completed within the first **three** hours following presentation.

Targets to measure the response:

- Central venous oxyhemoglobin saturation (ScvO2) ≥70 percent, central venous pressure (CVP) 8 to 12 mmHg, mean arterial pressure (MAP) ≥65 mmHg, and urine output ≥0.5 mL/kg/hour.

Uptodate®,Mar 06, 2023

How to customize the initial fluid volume?

- The latest SSC guidelines state that septic patients with hypotension or an elevated blood lactate should receive ≥30 ml/kg of crystalloid within 3 hours of presentation.
- To compensate Relative and absolute hypovolemia during initial septic shock.

(downgraded from a strong to a weak recommendation with low-quality of evidence)

- An arbitrary volume of 30 ml/kg inevitably leads to under-resuscitation in some patients and fluid overload in others.

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Targets for fluid administration

- The chest radiograph
- CVP
- Central venous oxygen saturation (ScvO2)
- Ultrasonography, including the vena-caval collapsibility index
- Have **limited value** in guiding fluid management and **should not be used** for this purpose.

Marik and Bellomo, British Journal of Anaesthesia, (2016)

- Aggressive fluid resuscitation to achieve a CVP> 8 mmHg has been the standard of care.
- Recent Cl. Tr.: that this approach does not improve the outcome of patients with severe sepsis and septic shock.

SEITZ ET AL., Nutr. Clin. Pract. 2022;37:990–1003;

Targets for fluid administration

Physical examination:

- **Cannot predict** fluid responsiveness
- **Unreliable** for estimating intravascular volume status.

Lactic acid:

A metabolic byproduct in hypoperfusion and organ dysfunction.

- In severe sepsis: Increased activity of Na+ K+ ATPase leads to increased lactate production under well-oxygenated conditions
- Results do not support the use of a lactate-guided strategy.

SEITZ ET AL., Nutr. Clin. Pract. 2022;37:990–1003.

A hemodynamically-guided conservative fluid resuscitation strategy

The septic patient with an intra-abdominal catastrophe:

- Urgent surgical intervention,
- Aggressive fluid resuscitation,
- Intra-abdominal hypertension,
- High risk of complications and death.

Continuous stroke volume (SV) monitoring is essential.

1. Ongoing fluid: guided by trend in the SV and response to mini-fluid bolus.
2. Perioperative intra-abdominal pressure monitoring is required.

Marik and Bellomo, British Journal of Anaesthesia, (2016)

Choice of test or index of preload responsiveness

- The **passive leg raise maneuver:** assessment of fluid responsiveness when continuous cardiac output monitoring is available.
- Maneuver: patient's upper body is laid flat and legs are raised to 45° for 30–90 s, which causes ~300 ml of venous blood to return from the legs to the heart.
- An increase in cardiac output of 10%–15% or more suggests an increase in cardiac output with IV fluid bolus

SEITZ ET AL., Nutr. Clin. Pract. 2022;37:990–1003.

Passive leg raise(PLR) test

- Ease of use
- Simplicity
- High diagnostic accuracy
- Safety
- Short procedure time (less than 5 min to perform)

Marik and Bellomo, British Journal of Anaesthesia, (2016)

Passive leg raise -5 steps

1. First, PLR should start from the semi-recumbent and not the supine position
2. Second, the PLR effects must be assessed by a direct measurement of cardiac output and not by the simple measurement of blood pressure.
3. Third, the technique must be able to detect short-term and transient changes of CO since the PLR effects may vanish after 1 minute (arterial pulse contour analysis, echocardiography, esophageal Doppler)

Monnet and Teboul, Critical Care (2015) 19:18

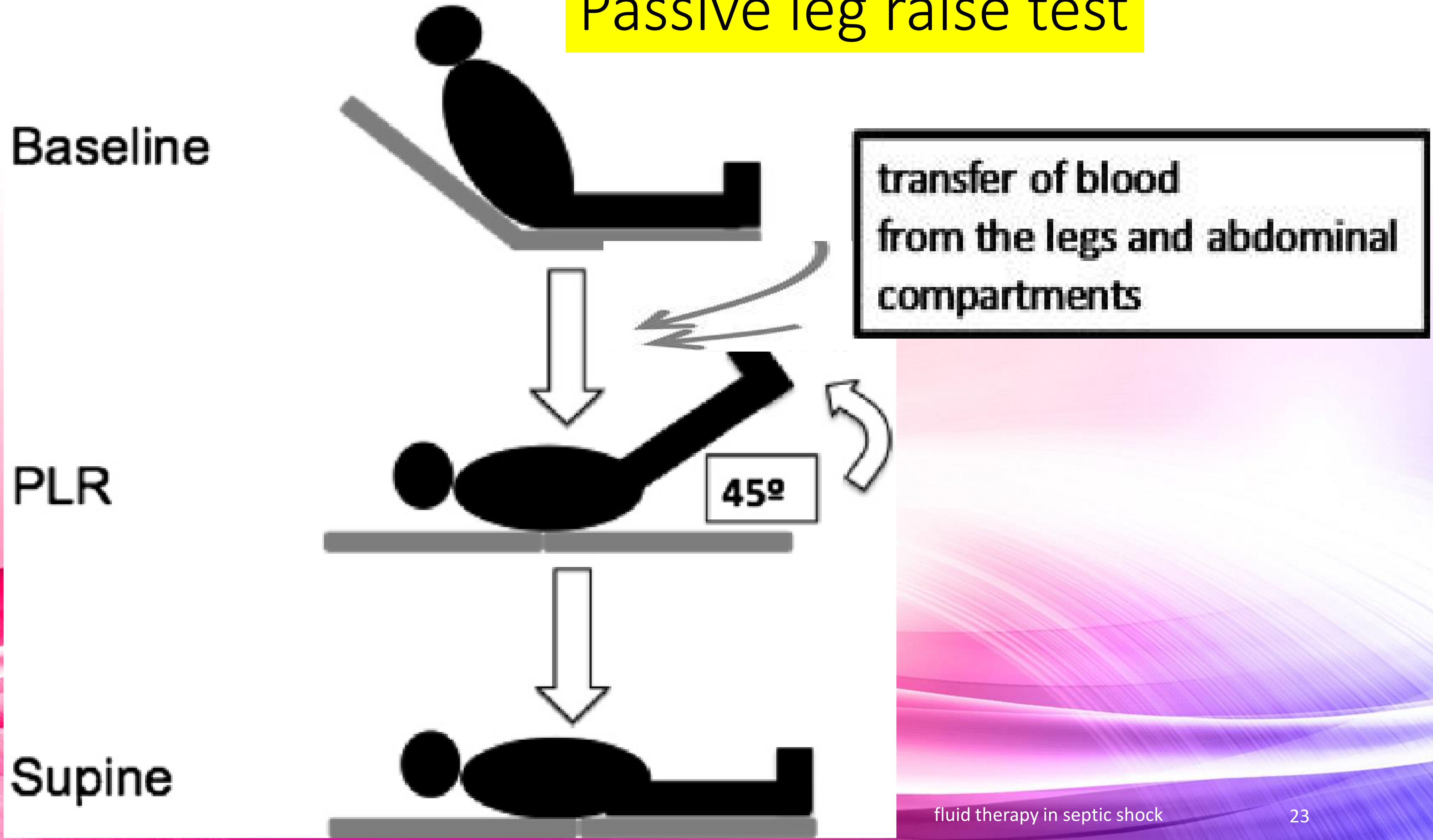
Passive leg raise -5 steps..

4. Fourth, **cardiac output** must be measured **before, during** and **after** PLR, in order to check that it returns to its baseline.
5. Fifth, **pain, cough, discomfort, and awakening** could provoke adrenergic stimulation, resulting in mistaken interpretation of cardiac output changes.

- Some simple precautions to avoid these confounding factors.
- PLR by **adjusting the bed** and **not by manually** raising the patient’s legs.

Monnet and Teboul, Critical Care (2015) 19:18

Passive leg raise test



Passive leg raise -5 steps…

The main drawback of the fluid challenge:

- If negative, fluid irreversibly administered to the patient.
- Repeated fluid challenges therefore can lead to fluid overload.

Detection of preload responsiveness by a positive PLR test should not routinely lead to fluid administration.

Monnet and Teboul, Critical Care (2015) 19:18

Passive leg raise …

Administer fluid always on the presence of the three situations:

1. Hemodynamic instability or signs of circulatory shock (or both),
2. Preload responsiveness (positive PLR test), and
3. Limited risks of fluid overload.

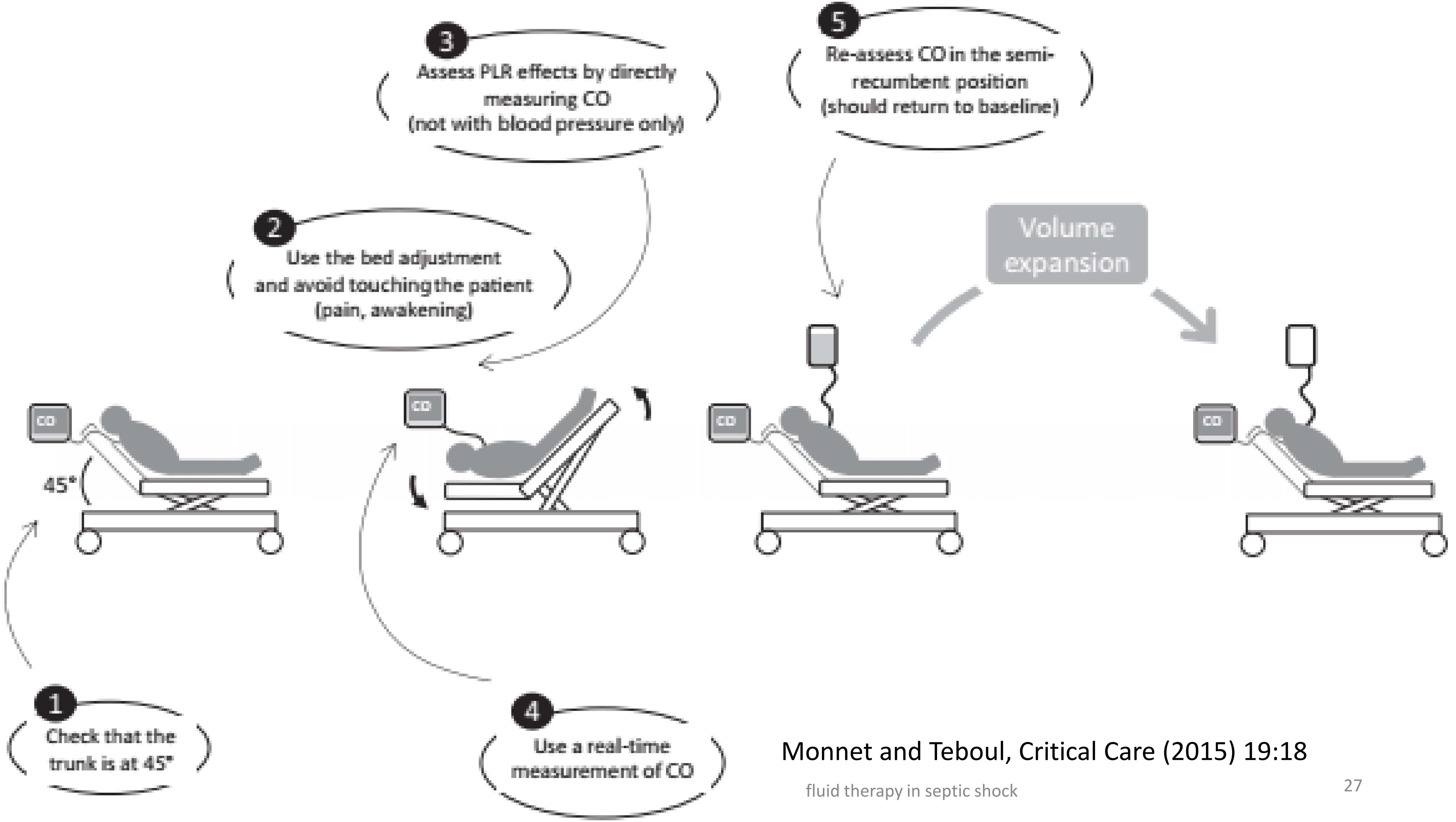
Monnet and Teboul, Critical Care (2015) 19:18

Passive leg raise…

A negative PLR test:

- Should stop or discontinue fluid infusion, in order to avoid fluid overload,
- Suggesting that hemodynamic instability should be corrected by means other than fluid administration.

Monnet and Teboul, Critical Care (2015) 19:18



Monnet and Teboul, Critical Care (2015) 19:18

How to personalize the decision to add a vasopressor to fluid?

Vasopressors may have synergistic effects with fluids

Norepinephrine:

- Once fluid boluses no longer exert any benefit.
- Induces vasoconstriction which increases the part of stressed blood volume.
- Increases mean systemic pressure, exerting a fluid like effect.
- Its venous effects synergistic with the administration of fluid, reduce the quantity of fluid administered for resuscitation.

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How to personalize the decision to add a vasopressor to fluid?

Norepinephrine:

In hypotensive (MAP < 65 mm Hg)

- Increases arterial vascular tone, BP and organ blood flow.
- Mobilize blood from the unstressed reservoirs in the splanchnic circulation and skin,
- Thereby increasing venous return and cardiac output.
- The effect on venous return is enduring, no tissue edema.

Should not be used in hypovolemic shock.

Marik and Bellomo, British Journal of Anaesthesia, (2016)

How to personalize the decision to add a vasopressor to fluid?

Norepinephrine:

- Likely to be considered early administration in most hypotensive septic patients
- Most powerful in marked vasodilation: a low diastolic pressure (e.g. <40 mmHg).

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How to personalize therapeutic targets?

Aim of fluid boluses: increase mean SP, cardiac preload, SV, CO, and tissue oxygenation.

Outside the ICU (wards, pre-hospital or emergency department)

Look for clinical signs of improvement in **tissue perfusion :**

- Disappearance of skin mottling,
- Shortening of capillary refill time; disappears and might change even after a single fluid bolus.
- Increased diuresis, is rarely available because of the very short observation time.

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How to personalize therapeutic targets?

<u>The effect of bolus fluid:</u>

- **Increase CO**.
- **Arterial pressure** increases only **incidentally**.
- The **decrease in heart rate** is **unreliable** to detect the fluid-induced increase in CO

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How to personalize therapeutic targets?

Effect of fluid boluses…

In the ICU:

- **CO** measured either by transpulmonary thermodilution, pulmonary arterial catheter, or by echocardiography.
- Increase in end-tidal carbon dioxide parallels the increase in CO.
- The reduction of lactate is a valid therapeutic objective.
- Venous oxygen saturation show improved tissue oxygenation.

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How to customize the criteria for stopping fluid infusion?

- ***In patients with ARDS***
  Lung ultrasound evidences interstitial lung edema by B-lines.
- ***In patients with intra-abdominal hypertension***
  - Impairs the perfusion of abdominal organs, mainly the kidneys,
  - Independently influences the prognosis of ICU patients,
  - Must be considered before deciding to administer a fluid bolus during the stabilization phase

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How to customize the criteria for stopping fluid infusion?

Don't forget CVP!

- CVP is the backward pressure of organ blood flow.
- Increased CVP levels are associated with organ dysfunction.
- Limiting the increase in CVP may be a reasonable goal.

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In which patients should fluid removal be undertaken?

- High LV filling pressure,
- High CVP,
- Signs of pulmonary congestion on CT scan
- Elevated IAP.

The presence of soft tissue edema does not necessarily have to be required, may on the contrary be accompanied by a depleted intravascular sector.

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How to remove fluid?

- Diuretics.
- Ultrafiltration during renal replacement therapy (oliguria or anuria).
- 20% hyperoncotic albumin (in low albumin) a synergistic effect on fluid removal.

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How to choose the dose of fluid to withdraw?

Too much fluid withdrawal alter the hemodynamic state.

- **First** the **hemodynamic state must be stable**, and the **vasopressors** must be at **low dose or stopped**.
- **Preload unresponsive, fluid removal** must be well tolerated.
- In a study in a stabilized phase of shock, fluid removal by ultrafiltration did not induce intra-dialytic hypotension (did not have preload responsiveness by a negative PLR test before depletion).
- The existence of a preload responsiveness must urge not to withdraw additional fluid.

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AKI and sepsis

AKI is a common complication of sepsis

Mechanisms:

- Hypotension leading to hypoperfusion,
- Inflammation
- Oxidative stress

Early management of sepsis, early volume resuscitation and vasopressors in patients with septic shock.

BRENNER & RECTOR'S THE KIDNEY, 2020-p: 2121

Fluid Management and its Impact on Acute Kidney Injury

Fluid excess adverse consequences in critically ill and AKI patient:

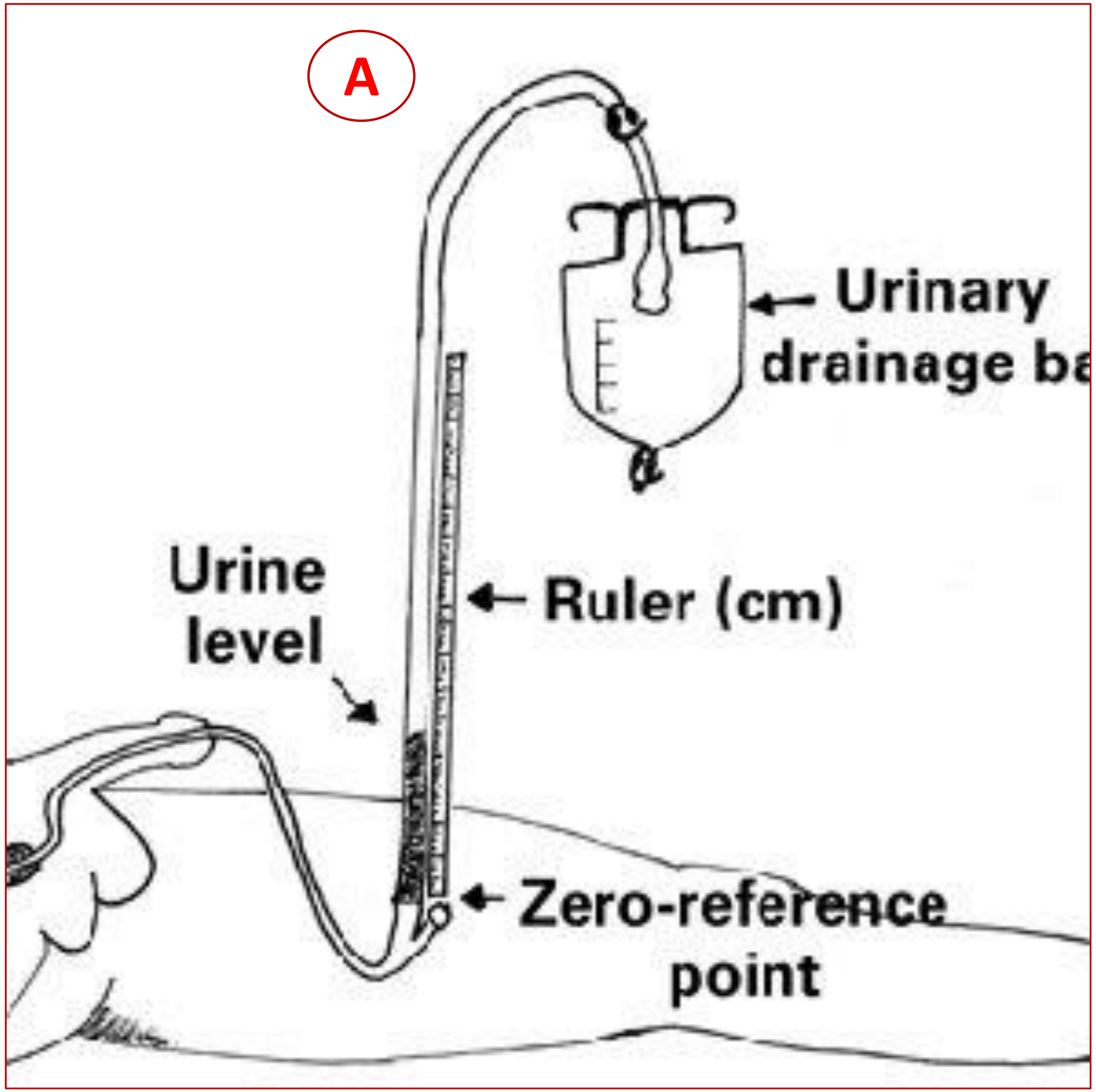
1. Decreased gastrointestinal absorption
2. Impaired wound healing.
3. Increased risk of new sepsis
4. Increased short- and long-term risks of death
5. Dilute serum creatinine concentration and mask AKI
6. Intraabdominal hypertension and the abdominal compartment syndrome

BRENNER & RECTOR'S THE KIDNEY, 2020-p: 2121

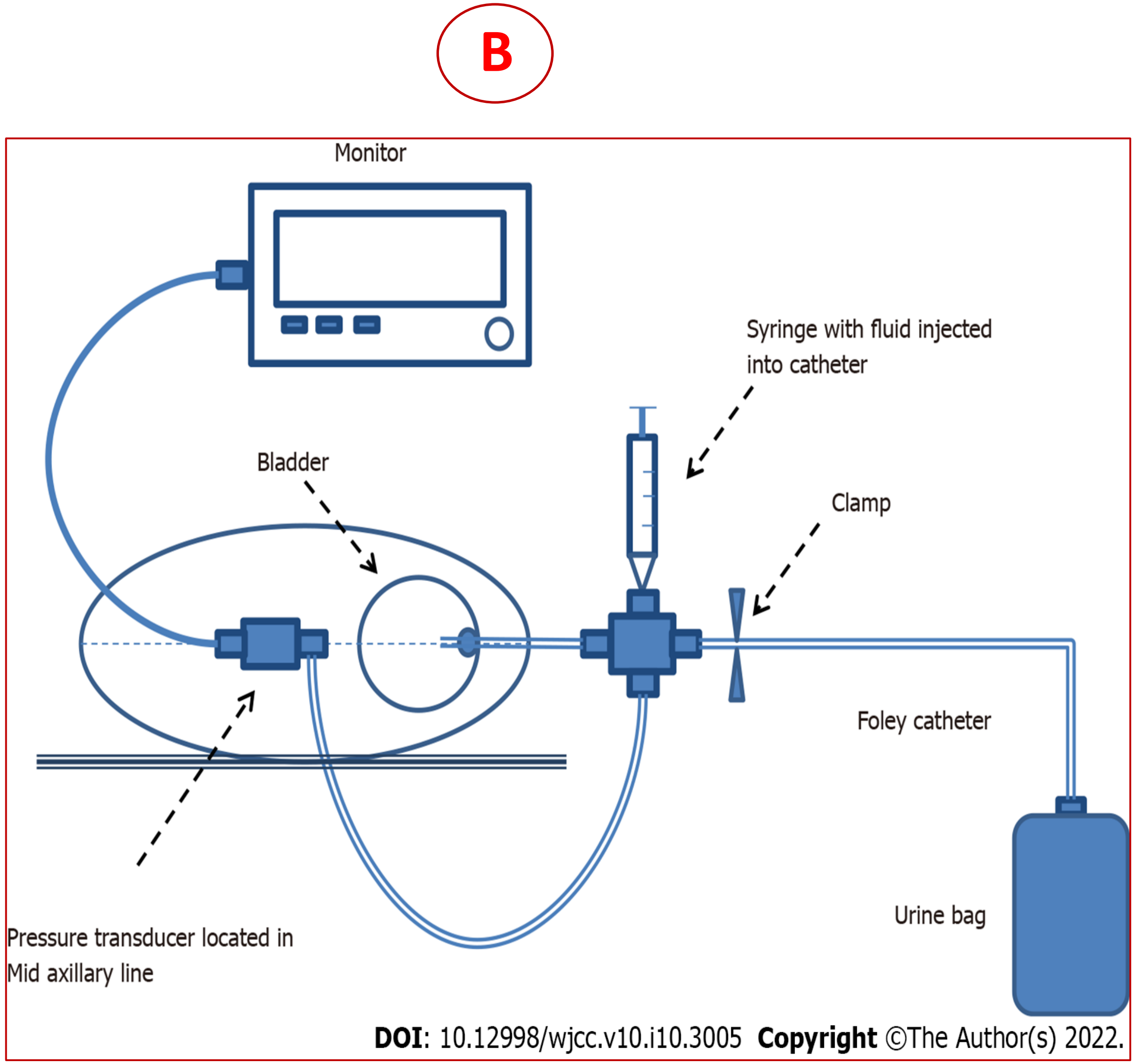
Intraabdominal hypertension (IAH)

- IAH: intraabdominal pressure (IAP) > 12 mm Hg.
- **Measurement:** instilling a of 30 mL water into the urinary bladder via a foley catheter and using pressure tubing to transduce a bladder pressure.
- Abdominal compartment syndrome: an IAP > 20 mm Hg with associated end-organ dysfunction.
- IAH: direct compression of the IVC, impaired venous return and venous stasis throughout the abdominal cavity, including the renal veins results AKI.

BRENNER & RECTOR'S THE KIDNEY, 2020-p: 2121



Transvesical system for measuring intra-abdominal pressure



Intra-abdominal pressure measurement using the U-tube technique

Intraabdominal hypertension

- Impaired venous return, decreased C.O. and increased RAAS signaling, renal vasoconstriction and prerenal state, low urinary sodium concentration and oliguria.
- Decompression of the abdominal compartment (typically via a surgical approach) may lead to an improvement of kidney function.
- Identification of patients whose kidney function will benefit from decompression remains elusive.

BRENNER & RECTOR'S THE KIDNEY, 2020-p: 2121

Fluid management and its impact on acute kidney injury

Type of fluid administered:

Chloride-rich solutions:

- May cause hyperchloremic acidosis, renal vasoconstriction and exacerbate renal medullary hypoxia.
- Greater **fluid retention** and **reduced kidney perfusion** than administration of balanced salt solutions [plasma-lyte (chloride concentration, 98 mmol/l) or lactated ringer's]
- **No benefit** to the **use of normal saline** and possibly **some** potential **harm**

BRENNER & RECTOR'S THE KIDNEY, 2020-p: 2121

nature reviews nephrology
https://doi.org/10.1038/s41581-023-00683-3

Consensus statement

Check for updates

Sepsis-associated acute kidney injury: consensus report of the 28th Acute Disease Quality Initiative workgroup

Nature Reviews Nephrology | Volume 19 | **June 2023** | 401–417

Fluid management in SA-AKI Consensus statement

- SA-AKI should be considered when AKI occurs within 7 days of sepsis diagnosis.
- Urine output should be closely monitored but should not be used to guide fluid therapy in patients with SA-AKI.
- Daily and cumulative fluid balance should inform, fluid overload excess mortality.
- Injury to the endothelial glycocalyx layer might lead to increased rates of fluid loss and further fluid administration could cause fluid overload.

Sepsis-associated acute kidney injury Nature Reviews Nephrology | Volume 19 | June 2023 | 401–417

Fluid management in SA-AKI Consensus statement

- In patients with SA-AKI, haemodynamic management should be similar to that recommended by the Surviving Sepsis Guidelines (grade 2C)
- The significance of central venous pressure as a marker of congestion in SA-AKI is uncertain, although a high central venous pressure has been associated with AKI.
- We suggest using measures of fluid status assessment and fluid responsiveness to assess the need for fluid administration (grade 1C)

Sepsis-associated acute kidney injury Nature Reviews Nephrology | Volume 19 | June 2023 | 401–417

Fluid management in SA-AKI Consensus statement

- We suggest that balanced solutions and 0.9% saline be used for resuscitation based on the biochemical profile of individual patients (grade 2B).
- Albumin and bicarbonate might be of benefit in SA-AKI (grade 1C), but we recommend against the use of starch, gelatin and dextran (grade 1A).
- We recommend that norepinephrine be used as the first-line vasopressor for sepsis with organ dysfunction (grade 1A).
- We suggest that combining vasopressors with volume administration might have a net fluid-sparing effect (grade 1C)

Sepsis-associated acute kidney injury Nature Reviews Nephrology | Volume 19 | June 2023 | 401–417

Take home message-1

- In patients with sepsis less than 5% of a crystalloid bolus remains intravascular an hour after the end of the infusion.
- Increased mortality in ICU patients with hyperchloremia.
- SSC guidelines suggested to prefer balanced crystalloids in all septic shock patients.
- Red blood cell transfusion to maintain a hemoglobin target of ≥7 g/dl.
- Chest radiography, CVP, ScvO2, serum lactate, vena-caval collapsibility index and physical examination have limited value in guiding fluid management.

Take home message-2

- Passive leg raise maneuver is the choice of test or index of preload responsiveness.
- An increase in cardiac output of 10%–15% or more suggests an increase in cardiac output with IV fluid bolus
- Norepinephrine considered early administration in most hypotensive septic patients (MAP < 65 mm Hg), have a net fluid-sparing effect.
- IAP must be considered before deciding to administer a fluid bolus.
- The presence of soft tissue edema does not necessarily have to be required to diagnose volume overload.

Thanks a lot for your patience