INFEZIONI E SEPSI

Quale dovrebbe essere la gestione in Medicina d'Urgenza?

Dott. Enrico Mirante

Medicina d'Urgenza e Pronto Soccorso Ospedale Sant'Eugenio Roma

La gestione della sepsi nell'adulto in Pronto Soccorso ed in Medicina d'Urgenza.
Le raccomandazioni della Consensus SIMEU

CONSENSUS SIMEU – pubblicazione 29.11.2021

29) Il tempo consigliato per la permanenza del paziente settico in PS non dovrebbe superare le tre ore e il trasferimento del paziente nel setting assistenziale adeguato dovrebbe avvenire entro le 6 ore.
Tipo di raccomandazione: A (fortemente raccomandato) *Consenso: 100%* *Livello di evidenza: VI (opinione di esperti).*

La gestione della sepsi nell'adulto in Pronto Soccorso ed in Medicina d'Urgenza.
Le raccomandazioni della Consensus SIMEU

CONSENSUS SIMEU – pubblicazione 29.11.2021

32) Si ritiene appropriato il ricovero in Terapia Sub-Intensiva per la gestione dei pazienti che richiedano supporto avanzato per una singola o plurime funzioni d'organo, escluso il paziente con supporto respiratorio invasivo e/o che possono beneficiare di un più accurato monitoraggio rispetto a quanto consentito in una degenza ordinaria.
Tipo di raccomandazione: A (fortemente raccomandato) *Consenso: 100%* *Livello di evidenza: VI (opinione di esperti).*

Istituto Superiore di Sanità
Sorveglianza Nazionale Infezioni Correlate all'Assistenza

STUDIO DI PREVALENZA ITALIANO SULLE INFEZIONI CORRELATE ALL'ASSISTENZA E SULL'USO DI ANTIBIOTICI NEGLI OSPEDALI PER ACUTI – PROTOCOLLO ECDC

- Ottobre-novembre 2016 - 56 strutture - 14.773 pazienti distribuiti in vari reparti (medicina, chirurgia, terapia intensiva, ginecologia e ostetricia, pediatria, riabilitazione, neonatologia, geriatria, psichiatria, lungodegenze)
- Età media pari a 61 anni
- 76,4% portatore di almeno un dispositivo invasivo il giorno dello studio.
- La prevalenza di pazienti con almeno un'infezione correlata all'assistenza è risultata del 8,03% (calcolata come numero di pazienti con almeno un'ICA sul totale dei pazienti eleggibili).

Istituto Superiore di Sanità
Sorveglianza Nazionale Infezioni Correlate all'Assistenza

Variabili

- Dimensione degli ospedali (prevalenza più elevata per gli ospedali più grandi)
- disciplina di ricovero (23% terapia intensiva),
- età (prevalenza maggiore negli adulti),
- gravità delle condizioni cliniche,
- esposizione a dispositivi invasivi (32,5% negli intubati).

Le infezioni più frequentemente riportate sono risultate: respiratorie (23,5%), batteriemie (18,3%), urinarie (18%), infezioni del sito chirurgico (14,4%).

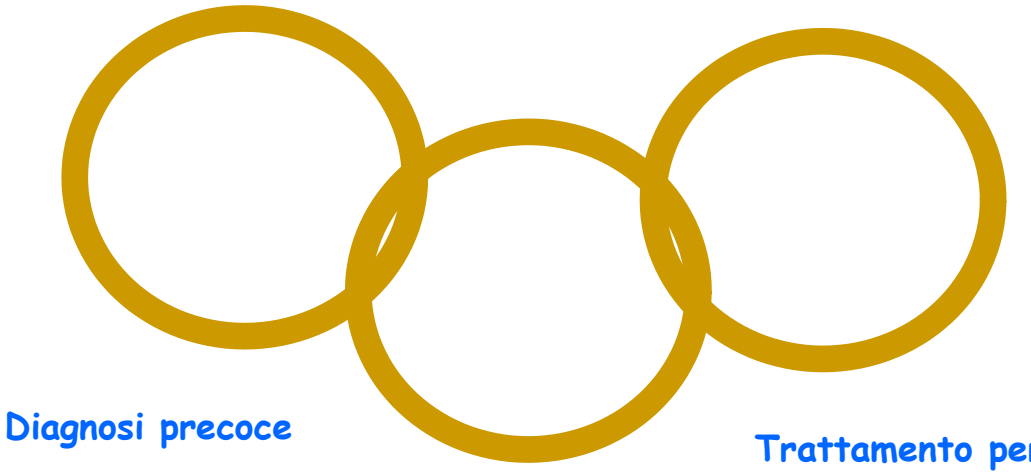
Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021

Critical Care Medicine November 2021 • Volume 49 • Number 11

INITIAL RESUSCITATION

4. Sepsis and septic shock are medical emergencies, and we recommend that treatment and resuscitation begin immediately. ***Best practice statement***

Sepsi: catena della sopravvivenza

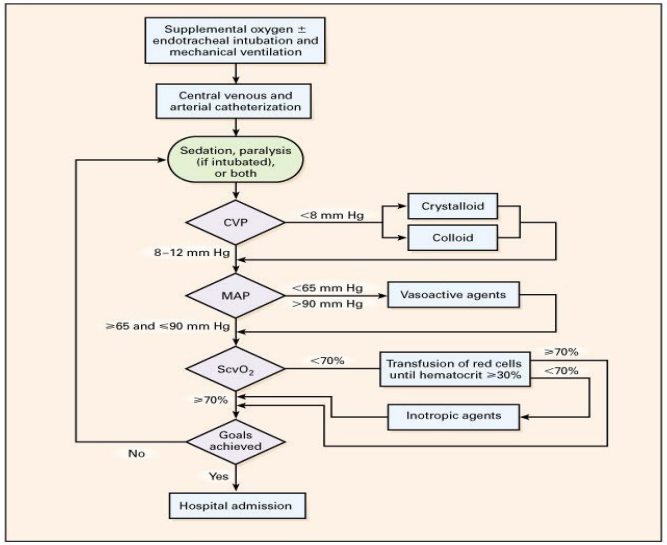


Diagnosi precoce

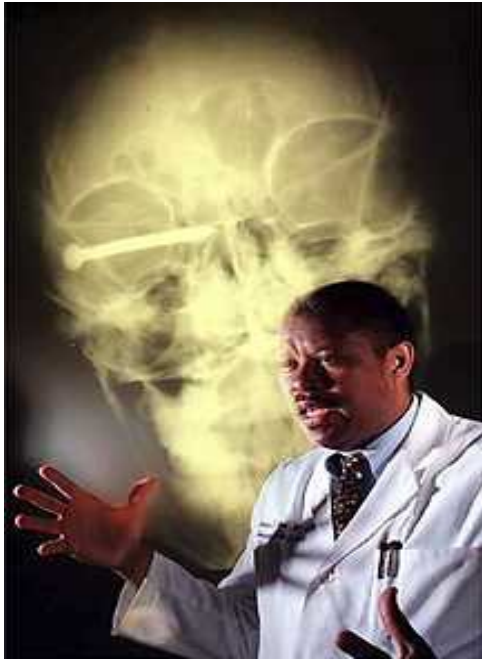
Antibioticoterapia precoce

Trattamento per obiettivi Precoce (EGDT)

Emanuel Rivers, Bryant Nguyen, Suzanne Havstad, et al.
Early goal-directed treatment in severe sepsis and septic shock.
New England Journal of Medicine
2001;345:1368-1377.



Department of Emergency Medicine
Henry Ford Hospital Detroit



2022

«USUAL CARE»

- *Early identification*
- *Lactate*
- *Cultures*
- *Antibiotics / Source Control*
- *Fluids*
- *Haemodynamic optimization*

CLINICAL DECISIONS
INTERACTIVE AT NEJM.ORG

Early Administration of Antibiotics for Suspected Sepsis

N ENGL J MED 380;6 NEJM.ORG FEBRUARY 7, 2019

- Fewer than 60% of patients admitted to intensive care units with a diagnosis of sepsis are ultimately confirmed to have definite or even probable infection

Most emergency department patients meeting sepsis criteria are not diagnosed with sepsis at discharge

Acad Emerg Med. 2021 July ; 28(7): 745–752. doi:10.1111/acem.14265.

John M. Litell, DO[1,2], Faheem Guirgis, MD[3], Brian Driver, MD[1,2], Alan E. Jones, MD[4], Michael A. Puskarich, MD[1,2]

interventions in those who do not. We sought to determine the proportion of patients meeting sepsis criteria in the emergency department (ED) that was ultimately diagnosed with sepsis and to quantify the subset of nonseptic patients with risk factors for harm from fluid resuscitation.

Methods: This retrospective cohort study of adult ED patients at a tertiary academic medical center included vital signs and laboratory results from the first 6 hours, plus administration of intravenous antibiotics, to determine if patients met 2016 Sepsis-3 consensus criteria. If these patients also had hypotension and lactic acidosis, we categorized them as Sepsis-3 plus shock. We used discharge ICD-9 codes to determine if patients were ultimately diagnosed with sepsis.

Results: Over 8 years, 3,121 ED patients met 2016 Sepsis-3 criteria in the first 6 hours. Of these, only 25% and 48% met explicit and implicit criteria for a discharge diagnosis of sepsis. Of 1,032 patients with Sepsis-3 plus shock, 48% and 62% met explicit and implicit criteria. Overall, 60% to 75% of ED patients meeting Sepsis-3 criteria with or without shock did not receive a sepsis discharge diagnosis. At least one plausible risk factor for harm from large-volume fluid resuscitation was identified among 19% to 36% of patients meeting sepsis criteria in the ED but not ultimately diagnosed with sepsis at discharge.

Reconsidering Vasopressors for Cardiogenic Shock

Everything Should Be Made as Simple as Possible, but Not Simpler

Pierre Squara, MD; Steven Hollenberg, MD; and Didier Payen, MD, PhD

CHEST 2019; 156(2):392–401

After time, in any shock state the symptoms can be dominated in different proportion by the systemic inflammatory response

Compensatory mechanisms may be less efficient →

alterations in myocardial contraction , lung function, microcirculation and organ function

The response to vasoactive mediators and drugs can be severely altered

Post cardiac arrest syndrome

Whole-body ischaemia/reperfusion:

- ✓ *activation of immune and caogulation pathways*
- ✓ *intravascular valume depletion*
- ✓ *vasodilation*
- ✓ *endothelial injury*
- ✓ *abnormalities of the microcirculation*
- ✓ *risk of infection*
- ✓ *multiple organ failure*

Most emergency department patients meeting sepsis criteria are not diagnosed with sepsis at discharge

Acad Emerg Med. 2021 July ; 28(7): 745–752. doi:10.1111/acem.14265.

John M. Litell, DO[1,2], Faheem Guirgis, MD[3], Brian Driver, MD[1,2], Alan E. Jones, MD[4], Michael A. Puskarich, MD[1,2]

- *Subset of patients plausibly at risk of harm from a protocolized administration of a rapid weight-based crystalloid bolus.*
  - *Systolic heart failure*
  - *Cirrhosis*
  - *Dialysis-dependent renal failure*
  - *Morbid obesity*

- *The most common noninfectious diagnoses included:*
  - *Poisoning/overdose*
  - *Inhalation pneumonitis*
  - *Acute respiratory failure (asthma / COPD / Heart Failure)*
  - *Diabetic Ketoacidosis*
  - *Acute renal failure*

Most emergency department patients meeting sepsis criteria are not diagnosed with sepsis at discharge

Acad Emerg Med. 2021 July ; 28(7): 745–752. doi:10.1111/acem.14265.

John M. Litell, DO[1,2], Faheem Guirgis, MD[3], Brian Driver, MD[1,2], Alan E. Jones, MD[4], Michael A. Puskarich, MD[1,2]

Sepsis resuscitation involves the urgent application of intervention that may harm a subset of patients when applied indiscriminately to those with milder infections or alternative diagnoses → large volume fluid resuscitation – invasive procedures – broad spectrum empiric antibiotic therapy

CLINICAL DECISIONS
INTERACTIVE AT NEJM.ORG

Early Administration of Antibiotics for Suspected Sepsis

N ENGL J MED 380;6 NEJM.ORG FEBRUARY 7, 2019

- *Sepsis is defined by Sepsis-3 as «life threatening organ dysfunction caused by a dysregulated host response to infection».*
- *Clinician must take two steps:*

✓ *decide whether infection is present or suspected*

✓ *assess whether the patient has acute organ dysfunction attributable to the known or suspected infection*

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INFECTION

11. For adults with suspected sepsis or septic shock but unconfirmed infection, we recommend continuously re-evaluating and searching for alternative diagnoses and discontinuing empiric antimicrobials if an alternative cause of illness is demonstrated or strongly suspected.

Best practice statement

Intensive Care Med (2018) 44:925–928

The Surviving Sepsis Campaign Bundle: 2018 update

Mitchell M. Levy[1*], Laura E. Evans[2] and Andrew Rhodes[3]

- Measure lactate level. Remeasure if initial lactate is >2 mmol/L.
- Obtain blood cultures prior to administration of antibiotics.
- Administer broad-spectrum antibiotics.
- Begin rapid administration of 30ml/kg crystalloid for hypotension or lactate ≥4 mmol/L.
- Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥65 mm Hg.

*"Time zero" or "time of presentation" is defined as the time of triage in the Emergency Department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of sepsis (formerly severe sepsis) or septic shock ascertained through chart review.

Fig. 1 Hour-1 Surviving Sepsis Campaign Bundle of Care

Table 1 Bundle elements with strength of recommendations and under-pinning quality of evidence [12, 13]

Bundle element	Grade of recommendation and level of evidence
Measure lactate level. Re-measure if initial lactate is > 2 mmol/L	Weak recommendation, low quality of evidence
Obtain blood cultures prior to administration of antibiotics	Best practice statement
Administer broad-spectrum antibiotics	Strong recommendation, moderate quality of evidence
Rapidly administer 30 ml/kg crystalloid for hypotension or lactate ≥ 4 mmol/L	Strong recommendation, low quality of evidence
Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥ 65 mm Hg	Strong recommendation, moderate quality of evidence

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021

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3. For adults suspected of having sepsis, we suggest measuring blood lactate. **Weak**, *low quality of evidence*

- *The association of lactate level with mortality in patients with suspected infection and sepsis in well estabilished*
- *The lactate cutoff determining an elevated level ranges from 1.6 – 2.5 mmol/L*
- *Its use is currently recommended as part of the SSC Hour-1 sepsis bundle for patients with sepsis*
- *An elevated lactate is part of the Sepsis-3 definition of septic shock*
- *Elevated or normal lactate level significantly increases or decreases, respectively, the likelihood of a final diagnosis of sepsis in patients with suspected sepsis (adjunctive test to modify the pretest probability of sepsis)*
- *Lactate alone is neither sensitive nor specific enough to rule in or rule out the diagnosi on its own*

Surviving Sepsis Campaign

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12. For adults with possible septic shock or a high likelihood for sepsis, we recommend administering antimicrobials immediately, ideally within 1 hr of recognition.	***Strong,*** *low quality of evidence (Septic shock)* ***Strong,*** *very low quality of evidence (Sepsis without shock)*	**CHANGED from previous:** "We recommend that administration of intravenous antimicrobials should be initiated as soon as possible after recognition and within one hour for both a) septic shock and b) sepsis without shock" ***strong recommendation,*** *moderate quality of evidence*
13. For adults with possible sepsis without shock, we recommend rapid assessment of the likelihood of infectious versus noninfectious causes of acute illness.	***Best practice statement***	
14. For adults with possible sepsis without shock, we suggest a time-limited course of rapid investigation and if concern for infection persists, the administration of antimicrobials within 3 hr from the time when sepsis was first recognized.	***Weak,*** *very low quality of evidence*	**NEW from previous:** "We recommend that administration of IV antimicrobials should be initiated as soon as possible after recognition and within 1 hr for both a) septic shock and b) sepsis without shock" ***strong recommendation,*** *moderate quality of evidence*
15. For adults with a low likelihood of infection and without shock, we suggest deferring antimicrobials while continuing to closely monitor the patient.	***Weak,*** *very low quality of evidence*	**NEW from previous:** "We recommend that administration of IV antimicrobials should be initiated as soon as possible after recognition and within 1 hr for both a) septic shock and b) sepsis without shock" ***strong recommendation,*** *moderate quality of evidence*

La gestione della sepsi nell'adulto in Pronto Soccorso ed in Medicina d'Urgenza.
Le raccomandazioni della Consensus SIMEU

CONSENSUS SIMEU – pubblicazione 29.11.2021

11) Disponibilità tempestiva di antibiotici ad ampio spettro, utilizzabili in Pronto Soccorso 24 ore su 24 e sette giorni su sette, in grado di agire anche sui principali patogeni multi resistenti.
Tipo di raccomandazione: A (fortemente raccomandato) *Consenso: 100%* *Livello di evidenza: VI (opinione di esperti).*

12) Considerare la sede probabile di infezione responsabile della sepsi, i fattori di rischio del paziente inerenti a patogeni Multi Drug Resistant (MDR) e lo stato immunologico del paziente Per la scelta del tipo di antibiotico da usare empiricamente.
Tipo di raccomandazione: A (fortemente raccomandato) *Consenso: 100%* *Livello di evidenza: VI (opinione di esperti).*

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021

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27. For adults with sepsis or septic shock, we recommend rapidly identifying or excluding a specific anatomical diagnosis of infection that requires emergent source control and implementing any required source control intervention as soon as medically and logistically practical.	***Best practice statement***
28. For adults with sepsis or septic shock, we recommend prompt removal of intravascular access devices that are a possible source of sepsis or septic shock after other vascular access has been established.	***Best practice statement***

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021

Critical Care Medicine November 2021 • Volume 49 • Number 11

29. For adults with sepsis or septic shock, we suggest daily assessment for de-escalation of antimicrobials over using fixed durations of therapy without daily reassessment for de-escalation.	***Weak,*** *very low quality of evidence*
31. For adults with an initial diagnosis of sepsis or septic shock and adequate source control where optimal duration of therapy is unclear, we suggest using procalcitonin AND clinical evaluation to decide when to discontinue antimicrobials over clinical evaluation alone.	***Weak,*** *low quality of evidence*

GESTIONE DEI FLUiDI

Surviving Sepsis Campaign

5. For patients with sepsis induced hypoperfusion or septic shock we suggest that at least 30 mL/kg of IV crystalloid fluid should be given within the first 3 hr of resuscitation.	**Weak**, *low quality of evidence*	**DOWNGRADE** from ***Strong***, low quality of evidence "We **recommend** that in the initial resuscitation from sepsis-induced hypoperfusion, at least 30 mL/kg of IV crystalloid fluid be given within the first 3 hr"

- *There are no prospective intervention studies comparing different volumes for initial resuscitation in sespis and septic shock*

- *In the PROCESS, ARISE and PROMISE trials the average volume of fluid received pre randomization was also in the range of 30 ml/kg suggesting that this fluid volume has been adopted in routine clinical practice*

Martin et al. BMC Anesthesiology (2018) 18:200

Choice of fluids in critically ill patients

- ✓ Fluids are the most commonly administred treatment in inpatient care
- ✓ Recent evidence on long term effects
  Intravenous fluids are drugs affecting the cardiovascular, renal, gastrointestinal and immune systems
- ✓ Should not be administered «blindly»

Malbrain et al. Ann. Intensive Care (2020) 10:64

Annals of Intensive Care

INTERNATIONAL FLUID ACADEMY
The four Ds of fluid therapy

- ✓ *Drugs: Fluids are drugs with indications, contraindications and side effects; different indications need different types of fluids*

- ✓ *Dosing: timing and administration rate is equally important for fluids; there is no standard therapeutic dose for fluids*

- ✓ *Duration: the duration of fluid therapy is crucial and volume must be tapered when shock is resolved; «starting triggers» for fluid resuscitation are quite clear; «stopping triggers» are less clear.*

- ✓ *De-escalation: the final step is withhold/ withdraw fluids when they are no longer required, thus reducing the risk of fluid overload*

Choice of fluids in critically ill patients

Low chloride concentration solutions Vs High chloride concentration solutions

- ✓ Results are conflicting
- ✓ Reduced rates of mortality and AKI have been described with balanced solutions
- ✓ Balanced solutions remain preferred over 0.9% saline for the treatment of hemodynamically unstable septic patients

HEMODYNAMIC MANAGEMENT		
32. For adults with sepsis or septic shock, we recommend using crystalloids as first-line fluid for resuscitation.	***Strong,*** *moderate-quality evidence*	
33. For adults with sepsis or septic shock, we suggest using balanced crystalloids instead of normal saline for resuscitation.	***Weak,*** *low quality of evidence*	**CHANGED from *weak recommendation*,** *low quality of evidence.* "We suggest using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock"

However, the use of balanced solutions in sepsis may be associated with improved outcomes compared with chloride-rich solutions. No cost-effectiveness

Malbrain et al. Ann. Intensive Care (2020) 10:64

Annals of Intensive Care

RESUSCITATION FLUIDS

OPTIMAL FLUID MANAGEMENT SHOULD TARGET EFFICIENT CENTRAL HEMODYNAMICS AND TISSUE PERFUSION WHILE AVOIDING POSITIVE NET FLUID BALANCE

J Thorac Dis 2020;12(Suppl 1):S37-S47

Fluid resuscitation in sepsis: the great 30 mL per kg hoax

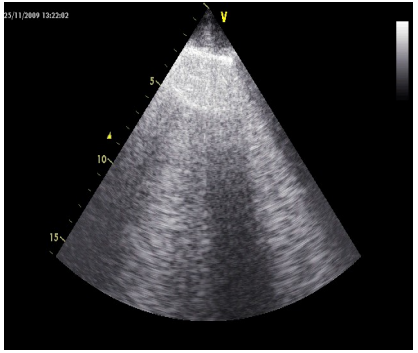
Paul E. Marik[1], Liam Byrne[2,3], Frank van Haren[2,3]

Second, the recommendation of a fixed resuscitation volume of 30 mL/kg in all patients with septic shock is an example of a "one-size-fits-all" approach. This approach contradicts the current paradigm that medical treatments, including fluid administration, should be individualized and personalized (9,20). In one study conducted in

emerging data suggests that at presentation only about 50% of patients with septic shock (who are fluid naive) will demonstrate a clinically significant increase in stroke volume in response to a fluid bolus (i.e., are fluid responsive) (24). Furthermore, this study demonstrated that those patients who were initially fluid responders rapidly become non-responsive to fluid challenges (*Figure 1*). It is therefore

P.E. Marik 2011

Progressive volume loading



Severe tissue edema

Compromised tissue oxygenation

Further compromised microvascular dysfunction

FLUID OVERLOAD!

"Patients who have the largest cumulative fluid balance have an increased mortality"

Malbrain et al. Ann. Intensive Care (2020) 10:64

Annals of Intensive Care

FLUID OVERLOAD

- ✓ *worsening gas exchange*
- ✓ *worsening renal function*
- ✓ *worsening wound healing*
- ✓ *associated with worse outcome in:*
  - patients with septic shock
  - patients admitted in ICU after surgery
  - various groups of intensive care patients

Restricitve fluid strategy aiming for negative fluid balance in patients with ACUTE LUNG INJURY is associated with improved outcomes

COMPLICATIONS OF FLUID OVERLOAD

Central nervous system	Cerebral oedema ↑ Altered consciousness, stupor, coma Impaired cognition Delirium Intracranial hypertension (ICP ↑) Intracranial compartment syndrome Decreased cerebral perfusion pressure (CPP ↓ = MAP – ICP) Increased intraocular and intra-orbital pressure (IOP ↑) Intra-orbital compartment syndrome
Cardiovascular system	Myocardial oedema ↑ Conduction disturbance Impairment in cardiac contractility Diastolic dysfunction
Peripheral	Tissue oedema ↑ Poor wound healing ↑ Wound infection ↑ Pressure ulcers ↑ Abdominal wall compliance ↓
Gastrointestinal system	Ascites formation ↑ Gut oedema ↑ Malabsorption ↑ Ileus ↑ Bowel contractility ↓ IAP ↑ and APP (= MAP – IAP) ↓ Abdominal compartment syndrome
Hepatic system	Hepatic congestion ↑ Impaired synthetic function Cholestasis ↑ Cytochrome P450 activity ↓ Hepatic compartment syndrome Lactate clearance ↓

ACCESSI VASCOLARI!

Malbrain et al. Ann. Intensive Care (2020) 10:64

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TOO MUCH FLUIDS ?

DIFFERENT PATIENTS WILL HAVE DIFFERENT NEEDS AND DIFFERENT BASELINE FLUID STATUS:

- ✓ age
- ✓ co-morbid disease
- ✓ current diagnosis

In healthy volunteers, only 25% of a crystalloid bolus remains in the intra-vascular space at 3 h.

Chowdhury AH. Ann Surg 2012; 256: 18–24

In patients with sepsis less than 5% of a crystalloid bolus remains intravascular an hour after the end of the infusion.

Sanchez M. Anaesth Intensive Care 2011; 39: 1022–9

Malbrain et al. Ann. Intensive Care (2020) 10:64

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Shedding of the glycocalyx

Loss of barrier function is associated with the formation of edema

- Common in critically ill parients
- Occurs in presence of:
  - *Reactive oxygen species*
  - *Hyperglycemia*
  - *Cytokines*
  - *Endotoxin*

Diabetes, surgery, trauma, and ***sepsis***

Annals of Intensive Care

Shedding of the glycocalyx

- *Fluid therapy itself is known to be potentially deleterious for endothelial function because of the resulting oxidative stress*

- *The risk relates to the specific clinical context*

53], the amount of glycocalyx shedding was proportional to the volume of fluid given in septic shock patients [54].

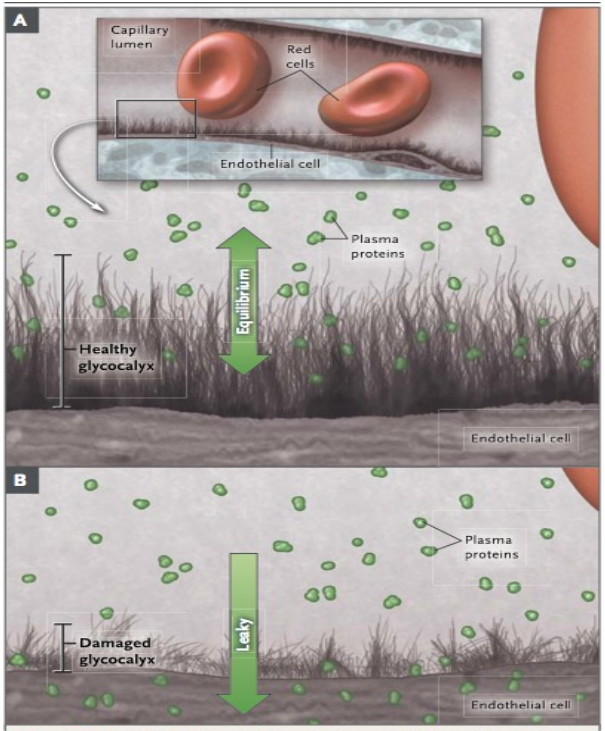


Figure 1. Role of the Endothelial Glycocalyx Layer in the Use of Resuscitation Fluids.

CONSENSUS SIMEU – pubblicazione 29.11.2021

MONITORAGGIO DEL PAZIENTE SETTICO

PS → MU/TSI

CLINICA – ECOGRAFIA – METODICHE NON INVASIVE O MINI/INVASIVE

VALUTAZIONE INIZALE SEMPLICE: CHE PAZIENTE E'?

RISPOSTA ALLA TERAPIA INIZIALE

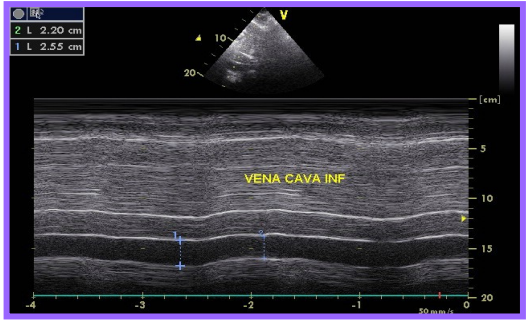
METODICHE PIU' COMPLESSE NEI PAZIENTI CHE NONOSTANTE LA TERAPIA RESTANO INSTABILI

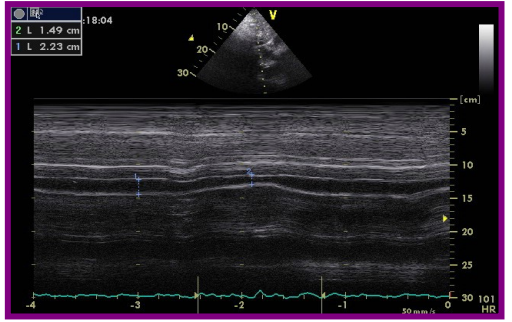
OPTIMAL FLUID MANAGEMENT SHOULD TARGET EFFICIENT CENTRAL HEMODYNAMICS AND TISSUE PERFUSION WHILE AVOIDING POSITIVE NET FLUID BALANCE

INDICES OF *FLUID TOLERANCE*

FLUID ADMINISTRATION AT LEAST WILL NOT LEAD TO PULMONARY OEDEMA OR RIGHT HEART FAILURE

- ✓ PVC
- ✓ LUNG WATER
- ✓ OXYGENATION





Diametro VCI (cm)	Riduzione inspiratoria	PVC (mmHg)
< 1,5	Collasso	0 – 5
1,5 – 2,0	>50	5 - 10
1,5 – 2,0	33-50%	10 - 15
2,0 – 2,5	0-33%	15 - 20
>2,5	Assente	>20

G. Soldati, R. Copetti. Ecografia toracica
C. G. Edizioni Medico Scientifiche S. r. l. Torino, 2006

Anile et al. Crit Ultrasound J (2017) 9:13
DOI 10.1186/s13089-017-0068-x

Critical Ultrasound Journal

LUNG ULTRASOUND

B LINES

- ✓ vertical echoid comet-tail artefacts detected by lung ultrasonography
- ✓ correlated with the loss of pulmonary aeration and an increase in lung water

- Agricola 2005: Good correlation between the number of B – lines at lung ultrasonography and EVLW (invasive hemodynamic monitoring)
- Zaho 2015: very good correlation between lung ultrasound score (LUS) and EVLW (trans-pulmonary thermodilution in ARDS patients

echo research and practice | A Miller and J Mandeville | Predicting and measuring fluid responsiveness | ID: 16-0008; June 2016 DOI: 10.1530/ERP-16-0008

FLUID TOLERANCE

Echocardiography

Fluid administration at least will not lead to pulmonary oedema or right heart failure

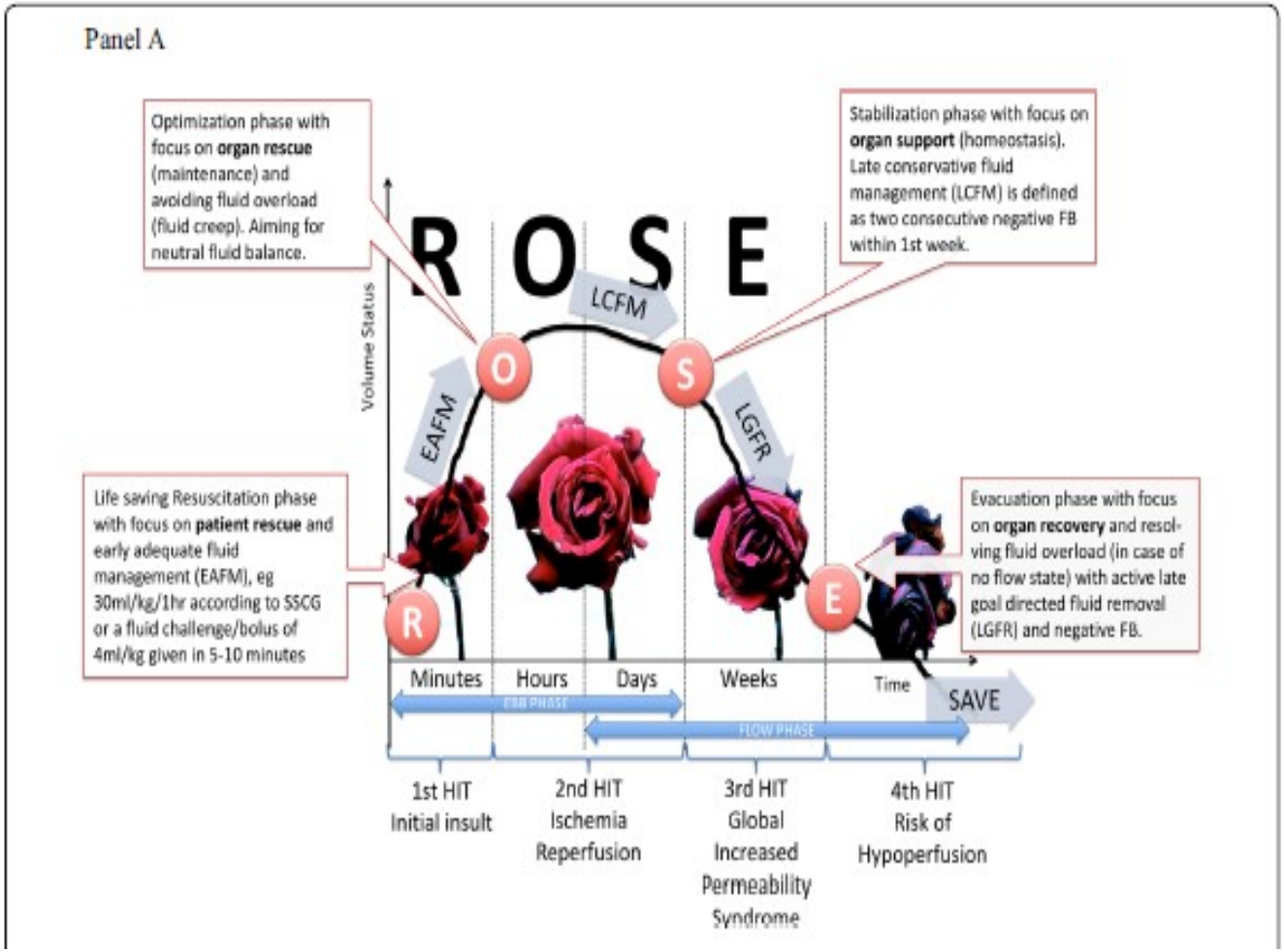
- ✓ Small IVC that varies in size with respiration
- ✓ non dilated right heart chambers
- ✓ a non displaced interventricular septum
- ✓ absence of right or left systolic failure
- ✓ absence of markers of raised LVEDP

Malbrain et al. Ann. Intensive Care (2020) 10:64

Annals of Intensive Care

HOW MUCH FLUIDS ?

- ✓ Fluid requirements vary during the course of illness
- ✓ Fluids must be prescribed on an **individual patient basis**
- ✓ The prescription should be regularly reviewed and tailored to the *evolving clinical stage*


Panel A
Optimization phase with focus on organ rescue (maintenance) and avoiding fluid overload (fluid creep). Aiming for neutral fluid balance.
Stabilization phase with focus on organ support (homeostasis). Late conservative fluid management (LCFM) is defined as two consecutive negative FB within 1st week.
ROSE
LCFM
EAFM
LGFR
Volume Status
O
S
R
E
Life saving Resuscitation phase with focus on patient rescue and early adequate fluid management (EAFM), eg 30ml/kg/1hr according to SSCG or a fluid challenge/bolus of 4ml/kg given in 5-10 minutes
Evacuation phase with focus on organ recovery and resolving fluid overload (in case of no flow state) with active late goal directed fluid removal (LGFR) and negative FB.
Minutes
Hours
Days
Weeks
Time
SAVE
EAR PHASE
FLOW PHASE
1st HIT
Initial insult
2nd HIT
Ischemia
Reperfusion
3rd HIT
Global
Increased
Permeability
Syndrome
4th HIT
Risk of
Hypoperfusion

Malbrain et al. Ann. Intensive Care (2020) 10:64

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EVOLVING CLINICAL STAGES

Resuscitation

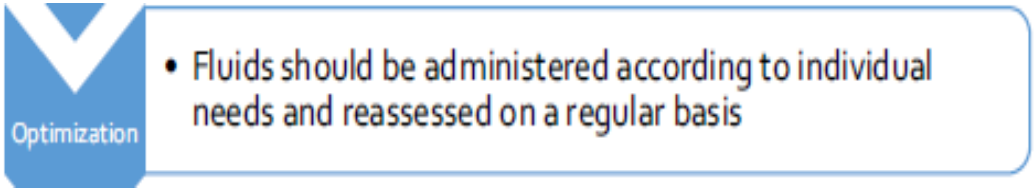
- Aim of the fluid treatment is resuscitation and correction of shock with the achievement of an adequate perfusion pressure

- ✓ IN THE ***ACUTE RESUSCITATION/SALVAGE PHASE*** FLUID ADMINISTRATION IS GENEROUS
- ✓ WHILE FLUID OVERLOAD IS ALWAYS A CONCERN, ***A POSITIVE FLUID BALANCE*** IS A SPECIFIC TARGET OF THIS PHASE
- ✓ Fluid challenge bolus of 4 ml/kg given in 5 – 10 min repeated when necessary normally in association with vasopressor administration

Malbrain et al. Ann. Intensive Care (2020) 10:64

Annals of Intensive Care

EVOLVING CLINICAL STAGES



- ✓ THE ***OPTIMIZATION PHASE*** STARSTS WHEN THE PATIENT IS NO LONGER IN OVERT ABSOLUTE/RELATIVE HYPOVOLEMIA BUT REMAINS HEMODYNAMICALLY UNSTABLE
- ✓ *FLUIDS SHOULD BE ADMINISTRED USING FLUID CHALLANGE TECHNIQUES (TROL)*
- ✓ *PATIENT MUST BE CAREFULLY MONITORED TO OBTAIN THE MOST COMPLETE PICTURE OF HEMODYNAMIC STATUS*

Annals of Intensive Care

FLUID CHALLANGE TECHNIQUE (TROL)

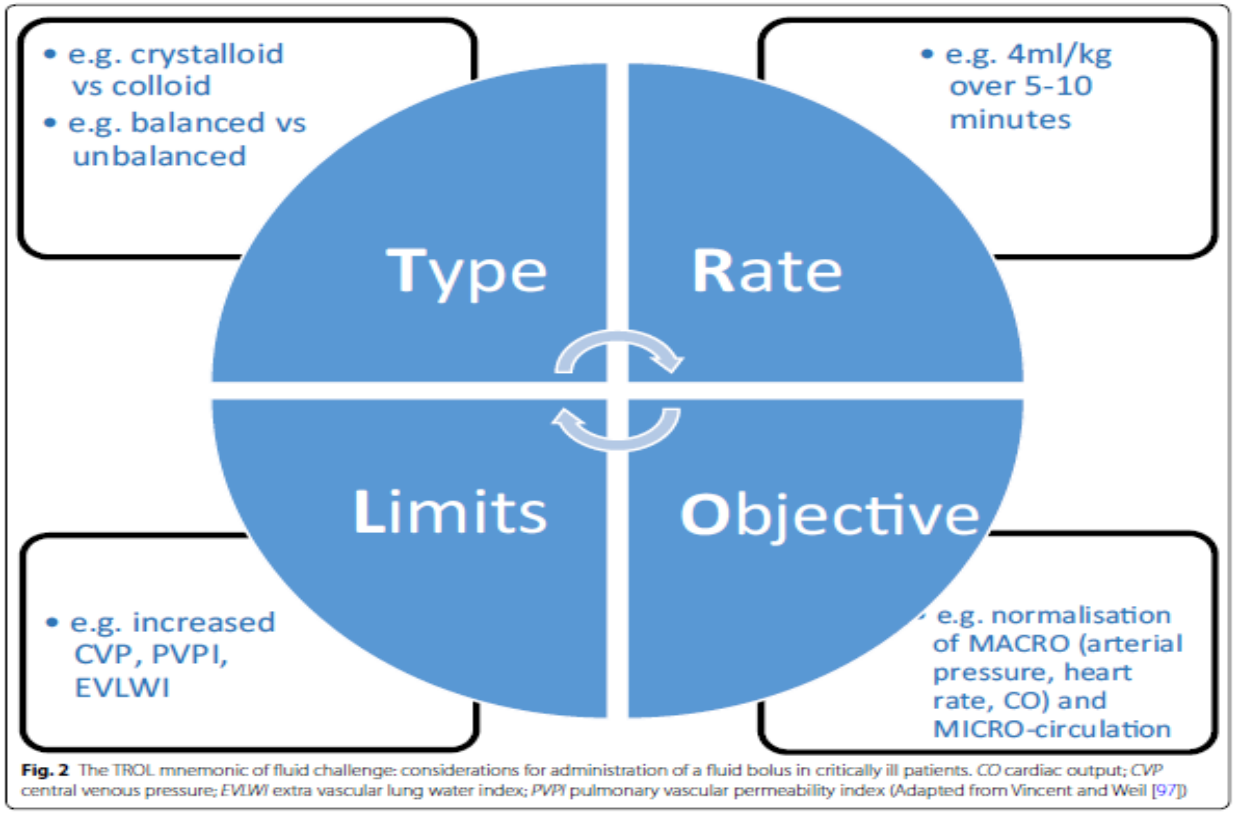


Fig. 2 The TROL mnemonic of fluid challenge: considerations for administration of a fluid bolus in critically ill patients. *CO* cardiac output; *CVP* central venous pressure; *EVLWI* extra vascular lung water index; *PVPI* pulmonary vascular permeability index (Adapted from Vincent and Weil [97])

If fluid therapy beyond the initial 30 mL/kg administration is required, clinicians may use repeated small boluses guided by objective measures of SV and/or CO. In post-cardiac surgery patients, fluid challenges of 4 mL/kg compared to 1 to 3 mL/kg increased the sensitivity of detecting fluid responders and nonresponders based on measurement of CO (70). In resource-limited

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021

Critical Care Medicine November 2021 • Volume 49 • Number 11

6. For adults with sepsis or septic shock, we suggest using dynamic measures to guide fluid resuscitation, over physical examination, or static parameters alone.	***Weak,*** *very low quality of evidence*

echo research and practice | A Miller and J Mandeville | Predicting and measuring fluid responsiveness | ID: 16-0008; June 2016 DOI: 10.1530/ERP-16-0008

FLUID RESPONDER

- Someone who increases his Stroke Volume by 15% after a 500 ml fluid challenge

Around 50% of fluid challenges administred in critically ill patient do not result in an increase in Stroke Volume exposing these patients to potential harm

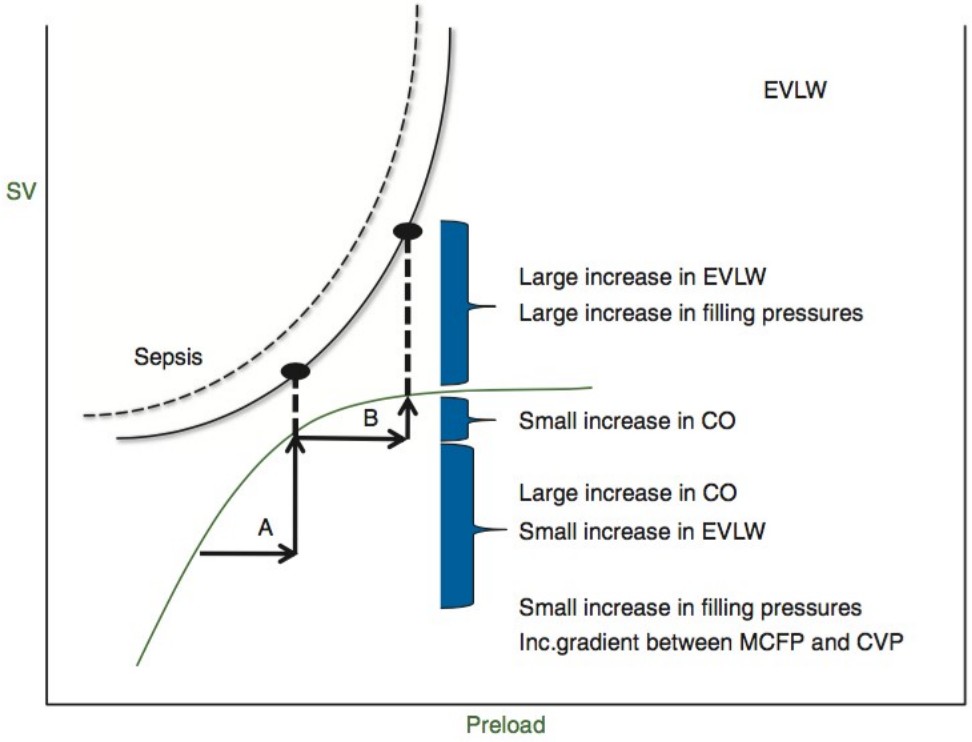


Fig 1 Superimposition of the Frank-Starling and Marik-Phillips curves demonstrating the effects of increasing preload on stroke volume and lung water in a patient who is pre-load responsive (A) and non-responsive (B). With sepsis the EVLW curve is shifted to the left.[51] EVLW=extra-vascular lung water; CO=cardiac output; SV=stroke volume. MCFP=mean circulating filling pressure. Reproduced with permission from the British Journal Anaesthesia; 2014;12:620–622.

MONITORAGGIO STATO VOLEMICO E FLUID RESPONSIVENESS

LA METODICA GIUSTA NEL SETTING GIUSTO

La gestione della sepsi nell'adulto in Pronto Soccorso ed in Medicina d'Urgenza.
Le raccomandazioni della Consensus SIMEU

CONSENSUS SIMEU – pubblicazione 29.11.2021

24) Tecniche di monitoraggio raccomandate in TSI nel paziente settico: - **monitoraggio clinico (stato di coscienza, tempo di Refill, variazione marezzatura cutanea, monitoraggio diuresi oraria)**
Tipo di raccomandazione: A (fortemente raccomandato) *Consenso: 100%* *Livello di evidenza: I (più studi randomizzati).*
- **monitoraggio dei lattati.**
Tipo di raccomandazione: B (esecuzione attentamente considerata) *Consenso: 100%* *Livello di evidenza: III (studi di coorte non randomizzati).*
- **ecografia clinica integrata**
Tipo di raccomandazione: A (fortemente raccomandato) *Consenso: 100%* *Livello di evidenza: VI (opinione di esperti).*
- **monitoraggio pressione arteriosa cruenta con incannulazione arteria nei casi di shock che richiedono infusione di vasopressori**
Tipo di raccomandazione: B (esecuzione attentamente considerata) *Consenso: 100%* *Livello di evidenza: VI (opinione di esperti).*

Lactate guided resuscitation—nothing is more dangerous than conscientious foolishness

Paul E. Marik

J Thorac Dis 2019;11(Suppl 15):S1969-S1972

and death (4). Lactate guided resuscitation in patients with severe sepsis and septic shock is based on the cascading myths that an elevated blood lactate level is a consequence of organ hypoperfusion with inadequate oxygen delivery and with the consequent anaerobic production of lactate.

- ✓ *Hyperlactatemia in sepsis is caused more frequently by impaired tissue oxygen utilization, rather than by impaired oxygen transport*
- ✓ *Hyperlactatemia in sepsis is unlikely to be associated with inadequate oxygen delivery and attempts at increasing oxygen delivery may be harmfull*

J Thorac Dis 2020;12(Suppl 1):S37-S47

Fluid resuscitation in sepsis: the great 30 mL per kg hoax

Paul E. Marik[1], Liam Byrne[2,3], Frank van Haren[2,3]

Cerebral, cardiac, renal and hepatic dysfunction in sespis is largely caused by bioenergetic failure rather than microcirculatory dysfunction and impaired organ perfusion

MONITORING IN THE EMERGENCY DEPARTMENT
MACROVASCULAR ASPECTS

0 – No mottling
1 – Coin sized mottling area on the knee.
2 – To the superior area of the knee cap.
3 – Mottling up to the middle thigh
4 – Mottling up to the fold of the groin
5 – Severe mottling that extends beyond the the groin.

Quelle: Ait-Oufella et al., Intensive Care Med 2011

7. For adults with sepsis or septic shock, we suggest guiding resuscitation to decrease serum lactate in patients with elevated lactate level, over not using serum lactate.	***Weak,*** *low quality of evidence*	

8. For adults with septic shock, we suggest using capillary refill time to guide resuscitation as an adjunct to other measures of perfusion.	***Weak,*** *low quality of evidence*	***NEW***

When advanced hemodynamic monitoring is not available, alternative measures of organ perfusion may be used to evaluate the effectiveness and safety of volume administration. Temperature of the extremities, skin mottling and capillary refill time (CRT) have been validated and shown to be reproducible signs of tissue perfusion (76, 77). The ANDROMEDA-SHOCK

Open Access Emergency Medicine 2018:10 183–191

Approach of minimal invasive monitoring and initial treatment of the septic patient in emergency medicine

G. Devia Jaramillo et al.

Table 1 Macrovascular aspects for evaluating perfusion in septic patients in the emergency department

Variable	Advantages	Disadvantages
Capillary refill	Easy to do, no equipment required	May occur late in presentation, inter-observer variability
Temperature	Does not require complex equipment. Temperature gradient is preferable over peripheral temperature	May occur late in presentation, not associated with low organ pulsatility index
Mottling score	Easy to do, no equipment required	Inter-observer variability; cannot be used in burn patients or amputees; and may occur late in presentation
Urinary output	Easy to do, no complex equipment required	False positives (urinary obstruction), and false negatives (diuretic therapy) may occur
Mental state	Easy to do, no equipment required	May occur late in presentation. False positives are common (stroke, metabolic encephalopathy, electrolytic disturbance)
Left ventricular strain	Direct evaluation of cardiac contraction, may be undertaken at the bedside	Requires minimal training; has inter-observer variability and false positives (baseline systolic dysfunction)
Vital signs (Shock Index)	Easy to do, no complex equipment required	May be a cause or consequence of hypoperfusion

La gestione della sepsi nell'adulto in Pronto Soccorso ed in Medicina d'Urgenza.
Le raccomandazioni della Consensus SIMEU

CONSENSUS SIMEU – pubblicazione 29.11.2021

25) Utilizzo dell'ecocardiografia per la valutazione sequenziale della funzione cardiaca durante lo shock in TSI nel paziente settico
Tipo di raccomandazione: B (esecuzione attentamente considerata) *Consenso: 100%* *Livello di evidenza: VI (opinione di esperti).*

26) Non è raccomandato l'utilizzo del PLR in PS per la valutazione della fluido responsività del paziente settico
Tipo di raccomandazione: D (non raccomandato) *Consenso: 100%* *Livello di evidenza: VI (opinione di esperti).*

27) L'uso del passive leg raising in TSI per valutazione della fluid responsiveness può essere considerato
Tipo di raccomandazione: B (esecuzione attentamente considerata) *Consenso: 100%* *Livello di evidenza: II (studio randomizzato)*

echo research and practice | A Miller and J Mandeville | Predicting and measuring fluid responsiveness | ID: 16-0008; June 2016 DOI: 10.1530/ERP-16-0008

PASSIVE LEG RAISING

- Tilting a patient from a 45- degree semi-recumbent head up position to a 45 degree leg-up position
- Transfers up to 300 ml of blood to the central circulation
- Stroke volume or simply VTI across outflow tract is measured before and 1 min after the PLR
- An increment of 10% suggests Fluid Responsiveness

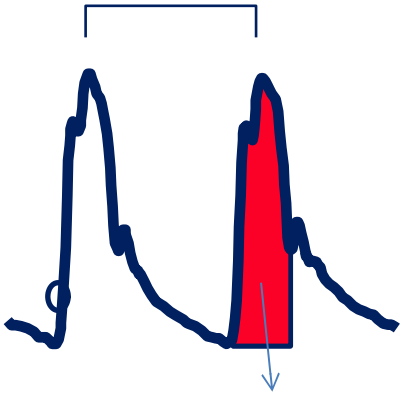
Crit Care Med. 2018 November ; 46(11): e1040–e1046.

Ultrasound assessment of the change in Carotid Corrected Flow Time in Fluid Responsiveness in Undifferentiated Shock

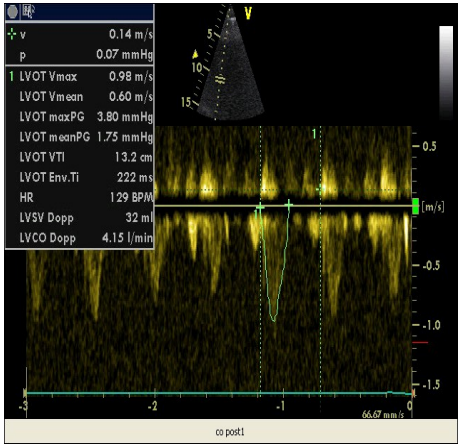
I. Barjaktarevic et al

Suboptimal or potentially harmful Passive Leg Raising

- ✓ lower extremity thromboembolism
- ✓ recent abdominal surgery
- ✓ hip fracture
- ✓ suspected elevated intracranial pressure
- ✓ significant peripheral vascular disease



Stroke volume



BIOIMPEDENCE AND BIOREACTANCE

Vincent et al. Critical Care 2011, 15:229
http://ccforum.com/content/15/4/229

Fluid Response Evaluation in Sepsis Hypotension and Shock

A Randomized Clinical Trial

CHEST 2020; 158(4):1431-1445

CHEST

FRESH TRIAL

BACKGROUND: Fluid and vasopressor management in septic shock remains controversial. In this randomized controlled trial, we evaluated the efficacy of dynamic measures (stroke volume change during passive leg raise) to guide resuscitation and improve patient outcome.

STUDY DESIGN AND METHODS: We conducted a prospective, multicenter, randomized clinical trial at 13 hospitals in the United States and United Kingdom. Patients presented to EDs with sepsis that was associated hypotension and anticipated ICU admission. Intervention arm patients were assessed for fluid responsiveness before clinically driven fluid bolus or increase in vasopressors occurred. The protocol included reassessment and therapy as indicated by the passive leg raise result. The control arm received usual care. The primary clinical outcome was positive fluid balance at 72 hours or ICU discharge, whichever occurred first.

Fluid Response Evaluation in Sepsis Hypotension and Shock

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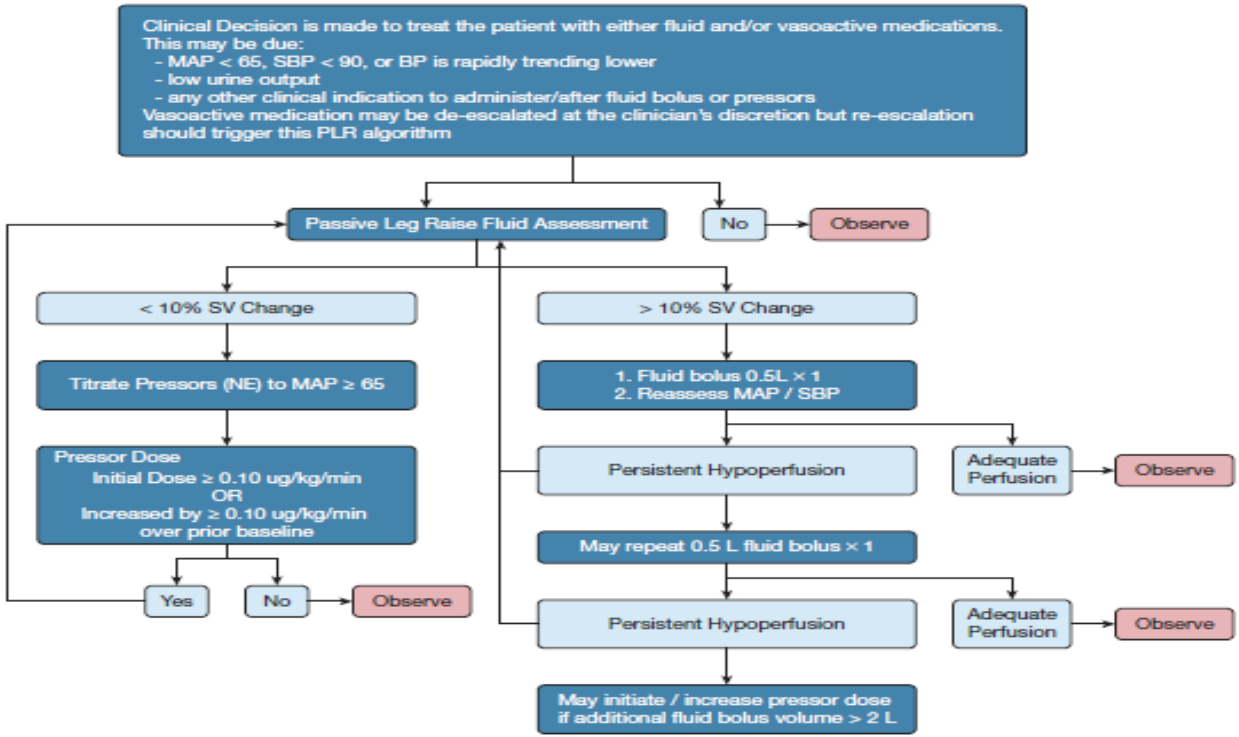

Figure 1 – Flow chart model of the algorithm used to guide treatment in the Fluid Responsiveness Evaluation in Sepsis-associated Hypotension study. MAP = mean arterial pressure; NE = norepinephrine; PLR = passive leg raise; SBP = systolic BP; SV = stroke volume.

Fluid Response Evaluation in Sepsis Hypotension and Shock
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We evaluated SV responses to PLR using noninvasive surface-electrode bioreactance technology. Average SV is assessed over a minute and is reliable even with strong respiratory variations and irregular heartbeat, including atrial fibrillation. The bioreactance-derived SV measurement has been validated against invasive flow-directed catheter-derived CO[26,28-30] and echo-Doppler measurements.[27,34]

Fluid Response Evaluation in Sepsis Hypotension and Shock

A Randomized Clinical Trial

CHEST 2020; 158(4):1431-1445

CHEST

Results: In this multicenter randomized controlled trial of 124 patients with septic shock, treatment that was guided by a dynamic assessment of fluid responsiveness (passive leg raise) compared with usual care resulted in a decreased fluid balance (0.65 L vs 2.02 L). Fewer patients required renal replacement therapy (5.1% vs 17.5%) or mechanical ventilation (17.7% vs 34.1%), and patients were more likely to be discharged home alive (63.9% compared with 43.9%).

Interpretation: Personalized, dynamic fluid responsiveness monitoring enhances appropriate resuscitation fluid and vasopressors administration and improves patient outcomes.

Malbrain et al. Ann. Intensive Care (2020) 10:64

Annals of Intensive Care

EVOLVING CLINICAL STAGES

PROPER TREATMENT

SHOCK REVERSAL

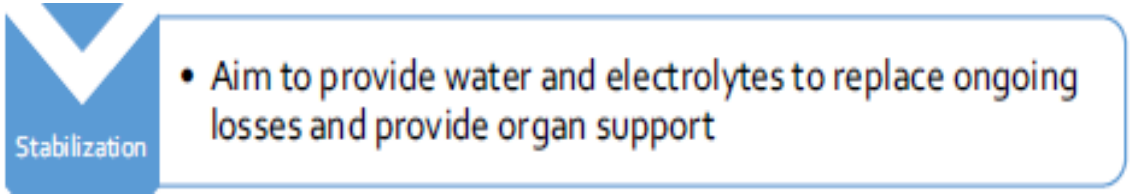
EXCESS FLUIDS MOBILIZED

EBB PHASE → FLOW PHASE

Malbrain et al. Ann. Intensive Care (2020) 10:64

Annals of Intensive Care

EVOLVING CLINICAL STAGES



- ✓ THE ***STABILIZATION PHASE*** *BEGINS WHEN THE PATIENT IS STABLE AND EVOLVES OVER DAYS*
- ✓ *THE TARGET SHOULD BE A* ***ZERO OR SLIGHTLY NEGATIVE FLUID BALANCE***

Malbrain et al. Ann. Intensive Care (2020) 10:64

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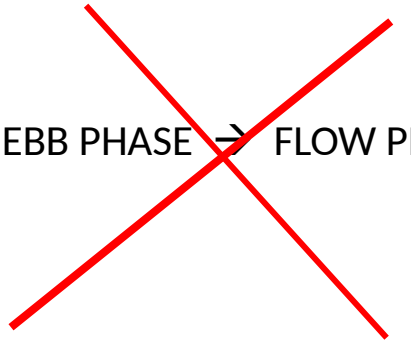
EVOLVING CLINICAL STAGES



UNRESOLVED SHOCK

POSITIVE CUMULATIVE FLUID BALANCE

DERESUSCITATION/DE-ESCALATION

- ✓ Furosemide
- ✓ 20% albumin?
- ✓ PEEP?
- ✓ Renal replacement therapy/Ultrafiltration

Annals of Intensive Care

EVOLVING CLINICAL STAGES

DERESUSCITATION/DE-ESCALATION

Right targets

✓ *Ensure that indication for fluid resuscitation no longer exist*

Furthermore, the *5 steps of Deresuscitation/De-Escalation* need to be kept in mind: (1) define a clinical endpoint (e.g., improvement in oxygenation); (2) set a fluid balance goal (e.g., 1 L negative balance in 24 h); (3) set perfusion and renal safety precautions (e.g., vasopressor need, 25% serum creatinine increase); (4) re-evaluate after 24 h unless safety limits reached; (5) adjust the plan accordingly.

Lactate guided resuscitation—nothing is more dangerous than conscientious foolishness

Paul E. Marik

J Thorac Dis 2019;11(Suppl 15):S1969-S1972

- *The primary haemodynamic goal in patients with sepsis is to achieve a mean arterial pressure (MAP) > 65 – 70 mmHg*
- *This is best achieved by a physiologically guided, conservative fluid strategy followed by the early use of norepinephrine*
- *Apart from increasing venous return and arterial tone, unlike crystalloids, norepinephrine has been demonstated to increase microcirculatory flow*

Early norepinephrine use in septic shock

J Thorac Dis 2020;12(Suppl 1):S72-S77

Olfa Hamzaoui[1], Rui Shi[2,3]

- ✓ *It has been shown that early (within a median time interval of 1.3 hours after admission in the ICU) and exclusive administration of norepinephrine restored adequate MAP within a relatively a short period of time (30 min) in all patients and was associated with a fovorable survival rate*

Morimatsu H, Singh K, Uchino S, et al. Early and exclusive use of norepinephrine in septic shock. Resuscitation 2004;62:249-54.

- ✓ *THE TIMING TO START NOREPINEPHRINE IS CRUCIAL*

- ✓ *European Society of Intensive Care Medicine (ESICM)*

  Administer Norepinephrine in the initial phase of sepstic shock even when hypovolemia is not completely corrected by fluid administration

Scheeren TWL, Bakker J, De Backer D, et al. Current use of vasopressors in septic shock. Ann Intensive Care 2019;9:20.

Early norepinephrine use in septic shock

J Thorac Dis 2020;12(Suppl 1):S72-S77

Olfa Hamzaoui[1], Rui Shi[2,3]

NE is an α_1-adrenergic agent with β_1-adrenergic properties.

Table 1 Arguments in favor of the early use of norepinephrine in septic shock

Consequences of early use of norepinephrine	Rational	References
Prevention of prolonged severe hypotension	Septic shock is characterized by a depressed arterial tone. fluid administration alone cannot be sufficient to correct severe hypotension	(10,11)
Increase in cardiac output	Increase in cardiac preload due to an increase in stressed blood volume	(12-16)
	Increase in cardiac contractility	(17)
Improvement of microcirculation	Improvement of microvascular blood flow in pressure-dependent vascular beds through increase in MAP in severely hypotensive patients	(13)
Prevention of fluid overload	Early administration of norepinephrine limits the volume of fluids infused	(18)
Improvement of outcome	Likely in relation to the preceding effects	(18,19)

Early norepinephrine use in septic shock

THERE IS NO UNIQUE HEMODYNAMIC PATTERN

THE THERAPEUTIC APPROACH MUST BE PERSONALIZED

differences in pathophysiologic and clinical patterns. For example, sepsis of abdominal origin is more often associated with profound hypovolemia than sepsis of lung origin. In some patients, hypovolemia is the predominant mechanism responsible for the hemodynamic failure, in some others vascular tone depression or myocardial depression are the predominant mechanisms. As there is no unique

Low DAP (e.g.< 40 mmHg) is strongly suggestive of a markedly depressed arterial tone and should prompt initiation of norepinephrine urgently

Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021

Vasoactive agents

Recommendations
37. For adults with septic shock, we **recommend** using norepinephrine as the first-line agent over other vasopressors. *Strong recommendation* Dopamine. *High quality evidence* Vasopressin. Moderate-quality evidence Epinephrine. Low-quality evidence Selepressin. *Low-quality evidence* Angiotensin II. *Very low-quality evidence* **Remark** In settings where norepinephrine is not available, epinephrine or dopamine can be used as an alternative, but we encourage efforts to improve the availability of norepinephrine. Special attention should be given to patients at risk for arrhythmias when using dopamine and epinephrine
38. For adults with septic shock on norepinephrine with inadequate MAP levels, we **suggest** adding vasopressin instead of escalating the dose of norepinephrine *Weak recommendation, moderate-quality evidence* **Remark** In our practice, vasopressin is usually started when the dose of norepinephrine is in the range of 0.25–0.5 µg/kg/min
39. For adults with septic shock and inadequate MAP levels despite norepinephrine and vasopressin, we **suggest** adding epinephrine *Weak recommendation, low-quality evidence*
40. For adults with septic shock, we **suggest against** using terlipressin *Weak recommendation, low quality of evidence*

USO DELLA VASOPRESSINA E DEI SUOI ANALOGHI NEI PAZIENTI CRITICI

Buone pratiche cliniche
SIAARTI

Shock settico

- Nei pazienti con shock settico non è appropriato l'utilizzo di vasopressina come vasopressore di prima linea
- Nei pazienti con shock settico refrattario, che ricevono già noradrenalina, è appropriata l'associazione di vasopressina/terlipressina come vasopressore di seconda linea per raggiungere una pressione arteriosa media di 65 mmHg
- Nei pazienti con shock settico che ricevono noradrenalina con indicazione ad associare vasopressina/terlipressina, l'infusione continua di vasopressina è da preferire rispetto all'utilizzo della Terlipressina
- Nei pazienti con shock settico meno severo (dosaggi di noradrenalina da 5 a 14 mcg/min), è appropriata la precoce associazione di vasopressina alla noradrenalina per ridurre la mortalità
- Nei pazienti con shock settico trattati con noradrenalina e steroidi, l'appropriatezza di associare la vasopressina per trarre vantaggio dall'attività sinergica non è chiara
- Nei pazienti con shock settico, è appropriata l'associazione della vasopressina alla noradrenalina per ridurre l'incidenza di danno renale acuto
- Nei pazienti con shock settico l'appropriatezza dell'utilizzo precoce di vasopressina per ridurre l'incidenza di fibrillazione atriale non è chiara.
- Nei pazienti con shock settico e cirrosi epatica è appropriato l'utilizzo precoce di vasopressina/terlipressina per ridurre le complicanze e la mortalità

M. Girardis et Al. 2021

Arginin-vasopressina – LG SSC

CONFERENCE REPORTS AND EXPERT PANEL

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

Andrew Rhodes[1*], Laura E. Evans[2], Waleed Alhazzani[3], Mitchell M. Levy[4], Massimo Antonelli[5], Ricard Ferrer[6], Anand Kumar[7], Jonathan E. Sevransky[8], Charles L. Sprung[9], Mark E. Nunnally[7], Bram Rochwerg[3], Gordon D. Rubenfeld[10], Derek C. Angus[11], Djillali Annane[12], Richard J. Beale[13], Geoffrey J. Bellinghan[14], Gordon R. Bernard[15], Jean-Daniel Chiche[16], Craig Coopersmith[8], Daniel P. De Backer[17], Craig J. French[18], Seitaro Fujishima[19], Herwig Gerlach[20], Jorge Luis Hidalgo[21], Steven M. Hollenberg[22], Alan E. Jones[23], Dilip R. Karnad[24], Ruth M. Kleinpell[25], Younsuk Koh[26], Thiago Costa Lisboa[27], Flavia R. Machado[28], John J. Marini[29], John C. Marshall[30], John E. Mazuski[31], Lauralyn A. McIntyre[32], Anthony S. McLean[33], Sangeeta Mehta[34], Rui P. Moreno[35], John Myburgh[36], Paolo Navalesi[37], Osamu Nishida[38], Tiffany M. Osborn[39], Anders Perner[40], Colleen M. Plunkett[25], Marco Ranieri[41], Christa A. Schorr[42], Maureen A. Seckel[43], Christopher W. Seymour[44], Lisa Shieh[45], Khalid A. Shukri[46], Steven Q. Simpson[45], Mervyn Singer[46], B. Taylor Thompson[47], Sean R. Townsend[48], Thomas Van der Poll[49], Jean-Louis Vincent[50], W. Joost Wiersinga[49], Janice L. Zimmerman[51] and R. Phillip Dellinger[22]

Vasopressin levels in septic shock have been reported to be lower than anticipated for a shock state [266]. Low doses of vasopressin may be effective in raising blood pressure in patients refractory to other vasopressors and may have other potential physiologic benefits [266–271]. Terlipressin has similar effects, but is long-acting [272]. Studies show that vasopressin concentrations are elevated in early septic shock, but decrease to normal range in the majority of patients between 24 and 48 h as shock continues [273]. This finding has been called *relative vasopressin deficiency* because, in the presence of hypotension, vasopressin would be expected to be elevated. The significance of this finding is unknown. The VASST trial, an RCT comparing norepinephrine alone to norepinephrine plus vasopressin at 0.03 U/min, showed no difference in outcome in the intent-to-treat population [274]. An a priori defined subgroup analysis demonstrated improved survival among patients receiving <15 μg/min norepinephrine at randomization with the addition of vasopressin; however, the pretrial rationale for this stratification was based on exploring potential benefit in the population requiring ≥15 μg/min norepinephrine. Higher doses

G. VASOACTIVE MEDICATIONS

1. **We recommend norepinephrine as the first-choice vasopressor (strong recommendation, moderate quality of evidence).**
2. **We suggest adding either vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) or epinephrine (weak recommendation, low quality of evidence) to norepinephrine with the intent of raising MAP to target, or adding vasopressin (up to 0.03 U/min) (weak recommendation, moderate quality of evidence) to decrease norepinephrine dosage.**
3. **We suggest using dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (weak recommendation, low quality of evidence).**
4. **We recommend against using low-dose dopamine for renal protection (strong recommendation, high quality of evidence).**
5. **We suggest using dobutamine in patients who show evidence of persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents (weak recommendation, low quality of evidence).**

Vasoactive Agent Management

!! Use norepinephrine as first-line vasopressor

For patients with septic shock on vasopressor

!! Target a MAP of 65mm Hg

! Consider invasive monitoring of arterial blood pressure

If central access is not yet available

! Consider initiating vasopressors peripherally*

If MAP is inadequate despite low-to-moderate-dose norepinephrine

! Consider adding vasopressin

If cardiac dysfunction with persistent hypoperfusion is present despite adequate volume status and blood pressure

! Consider adding dobutamine or switching to epinephrine

!! Strong recommendations ! Weak recommendations

*When using vasopressors peripherally, they should be administered only for a short period of time and in a vein proximal to the antecubital fossa.

Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021

Additional therapies

Corticosteroids

Recommendation
58. For adults with septic shock and an ongoing requirement for vasopressor therapy we **suggest** using IV corticosteroids *Weak recommendation; moderate quality of evidence*

Remark

The typical corticosteroid used in adults with septic shock is IV hydrocortisone at a dose of 200 mg/day given as 50 mg intravenously every 6 h or as a continuous infusion. It is suggested that this is commenced at a dose of norepinephrine or epinephrine ≥ 0.25 mcg/kg/min at least 4 h after initiation

Blood Purification

Recommendations
59. For adults with sepsis or septic shock, we **suggest against** using polymyxin B haemoperfusion *Weak recommendation; low quality of evidence*
60. There is **insufficient evidence to make a recommendation** on the use of other blood purification techniques

Red blood cell (RBC) transfusion targets

Recommendation
61. For adults with sepsis or septic shock, we **recommend** using a restrictive (over liberal) transfusion strategy *Strong recommendation; moderate quality of evidence*

Remark

A restrictive transfusion strategy typically includes a haemoglobin concentration transfusion trigger of 70 g/L; however, RBC transfusion should not be guided by haemoglobin concentration alone. Assessment of a patient's overall clinical status and consideration of extenuating circumstances such as acute myocardial ischaemia, severe hypoxemia or acute haemorrhage is required

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021

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47. For adults with sepsis-induced hypoxemic respiratory failure, we suggest the use of high flow nasal oxygen over noninvasive ventilation.	***Weak,*** *low quality of evidence*
48. There is insufficient evidence to make a recommendation on the use of noninvasive ventilation in comparison to invasive ventilation for adults with sepsis-induced hypoxemic respiratory failure.	***No recommendation***

Grazie per l'attenzione

Diagnosi precoce

Critical Care Medicine November 2021 • Volume 49 • Number 11

2. We recommend against using qSOFA compared with SIRS, NEWS, or MEWS as a single-screening tool for sepsis or septic shock. ***Strong***, *moderate-quality evidence*

qSOFA

- GCS < 15
- RR ≥ 22
- PA s ≤ 100 mmHg

If two of these variables are present simultaneously qSOFA is positive

- ✓ *qSOFA is a predictor of poor outcome in patients with known or suspected infection*
- ✓ *qSOFA is more specific but less sensitive than having two of four SIRS criteria for early identification of infection induced organ dysfunction*
- ✓ *Neither SIRS nor qSOFA are ideal screening tools for sepsis*
- ✓ *The presence of a positive qSOFA should alert the clinician to the possibility of sepsis in all resource settings*

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021

Critical Care Medicine November 2021 • Volume 49 • Number 11

16. For adults with suspected sepsis or septic shock, we suggest against using procalcitonin plus clinical evaluation to decide when to start antimicrobials, as compared to clinical evaluation alone.	***Weak,*** *very low quality of evidence*

Istituto Superiore di Sanità
Sorveglianza Nazionale Infezioni Correlate all'Assistenza

I patogeni identificati come responsabili di ICA sono stati nel complesso 67, di cui *Escherichia coli* (13%), *Klebsiella pneumoniae (10.4%), Pseudomonas aeruginosa* (8,1%), *Staphylococcus aureus* (8,9%) e *Staphylococcus epidermidis* (6,3%) rappresentano più del 45% di tutti gli isolamenti, spesso anche resistenti o multiresistenti agli antimicrobici.

La gestione della sepsi nell'adulto in Pronto Soccorso ed in Medicina d'Urgenza.
Le raccomandazioni della Consensus SIMEU

CONSENSUS SIMEU – pubblicazione 29.11.2021

3) Uso combinato del qSOFA con criteri di allerta aggiuntivi per aumentarne la sensibilità per l'identificazione del paziente settico al Triage di Pronto Soccorso

Tipo di raccomandazione: A (fortemente raccomandato)
Consenso: 100%
Livello di evidenza: VI (opinione di esperti).

4) Tra i criteri di allerta aggiuntivi utilizzati per la precoce identificazione al Triage dei pazienti con sospetta sepsi, NEWS e NEWS2 sembrano garantire la migliore accuratezza

Tipo di raccomandazione: A (fortemente raccomandato)
Consenso: 100%
Livello di evidenza: III (studi di coorte retrospettivi non randomizzati).

Carta 1: National Early Warning Score (NEWS)

PARAMETRI FISIOLOGICI	3	2	1	0	1	2	3
Frequenza del respiro	≤8		9 - 11	12 - 20		21 - 24	≥25
Saturazione d'ossigeno	≤91	92 - 93	94 - 95	≥96			
Ossigeno supplementare		Sì		No			
Temperatura corporea	≤35.0		35.1 - 36.0	36.1 - 38.0	38.1 - 39.0	≥39.1	
Pressione sistolica	≤90	91 - 100	101 - 110	111 - 219			≥220
Frequenza cardiaca	≤40		41 - 50	51 - 90	91 - 110	111 - 130	≥131
Stato di coscienza				Vigile			Risponde a stimoli verbali, dolore provocato, confuso

NEWS2 Score		Clinical risk		Response		
3			Low-Medium		Urgent ward-based response	
3	2	1	0	1	2	3
Respiration rate (per minute)						
≤8		9-11	12-20		21-24	≥25
SpO_2 Scale 1 (%)						
≤91	92-93	94-95	≥96			
SpO_2 Scale 2 (%)						
≤83	84-85	86-87	88-92 ≥93 on	93-94 on O_2	95-96 on O_2	≥97on O_2
Air or O_2						
	O_2		Air			
Systolic blood pressure (mmHg)						
≤90	91-100	101-110	111-219			≥220
Pulse (per minute)						
≤40		41-50	51-90	91-110	111-130	≥131
Consciousness						
			Alert			CVPU
Temperature (°C)						
≤35.0		35.1-36.0	36.1-38.0	38.1-39.0	≥39.1	

BIOMARKERS NELLA SEPSI?

H.H. Dolin et. Al

SHOCK, Vol. 49, No. 4, pp. 364–370, 2018

PCT

- ✓ Is a peptide precursor of calcitonin which is involved in calcium homeostasis
- ✓ It is often combine with CRP in order to make a putative diagnosis of sespis
- ✓ PCT levels are increased in greater magnitude by bacterial infections than CRP
- ✓ Shows a marked increase within 2 – 4 hours of the initiation of an inflammtory response
- ✓ Normal serum levels are below 0.05 ng/ml
- ✓ A value of 2.0 ng/mL suggests a significantly increased risk of sepsis and/or septic shock

BIOMARKERS NELLA SEPSI?

H.H. Dolin et. Al

SHOCK, Vol. 49, No. 4, pp. 364–370, 2018

PCT

- ✓Rises higher in correlation of the severity of an infection
- ✓Higher PCT level correlates with Gram-negative rods
- ✓Antibiotic resistant bacteria induce higher levels of PCT than either Gram positive cocci or Gram-negative rods
- ✓May be used in algorithms to stop antibiotic therapy

FALSE POSITIVE RESULTS

- Acute Respiratory Distress Syndrome
- Trauma
- Chemical Pneumonitis
- Severe Falciparum Malaria

La gestione della sepsi nell'adulto in Pronto Soccorso ed in Medicina d'Urgenza.
Le raccomandazioni della Consensus SIMEU

CONSENSUS SIMEU – pubblicazione 29.11.2021

7) Determinazione della procalcitonina in PS nel paziente con sospetta sepsi
Tipo di raccomandazione: B (esecuzione attentamente considerata) *Consenso: 89%* *Livello di evidenza: III (studi di coorte non randomizzati).*

La determinazione della procalcitonina già nelle prime fasi dell'inquadramento del paziente settico permette di ottenere il tempo 0 ed il trend temporale, che, con le successive determinazioni a 24-48 ore, fornisce elementi utili per le successive scelte terapeutiche in termini di de-escalation o modifica della terapia antibiotica

Choice of fluids in critically ill patients

HETASTARCH (HES)

- ✓ RCTs have associated administration of HES with AKI and the need for RRT in ICU patients, especially in those with sepsis
- ✓ Results are conflicting on mortality
- ✓ Intraoperative HES administration did not increase the incidence of AKI or mortality

Recommendations 2021	Recommendation Strength and Quality of Evidence	Changes From 2016 Recommendations
36. For adults with sepsis and septic shock, we suggest against using gelatin for resuscitation.	***Weak,*** *moderate-quality evidence*	**UPGRADE from *weak recommendation***, *low quality of evidence* "We suggest using crystalloids over gelatins when resuscitating patients with sepsis or septic shock."

(RR, 1.10; 95% CI, 0.86–1.41). Therefore, in the face of inconclusive effect on mortality, increased adverse effects, and higher costs, the panel issued a weak recommendation against the use of gelatin for acute resuscitation. More high-quality studies are needed to inform future guideline updates.

34. For adults with sepsis or septic shock, we suggest using albumin in patients who received large volumes of crystalloids.	***Weak,*** *moderate-quality evidence*
35. For adults with sepsis or septic shock, we recommend against using starches for resuscitation.	***Strong,*** *high-quality evidence*

Although albumin is theoretically more likely to maintain oncotic pressure than crystalloids, it is more costly and there is no clear benefit with its routine use

Malbrain et al. Ann. Intensive Care (2020) 10:64

Annals of Intensive Care

Albumin

- *Colloids should remain in the intravascular space longer than crystalloids, provided that the endothelial barrier is intact, which is not often the case of the critically ill patients*

- *To* date *no randomized controlled trial has shown any significant benefit of fluid resuscutation using albumin over other types of fluids, including crystalloids*

- *The significant cost and the availability of equally effective low cost alternatives do not play in favor of albumin*

- *Up to date, the theoretical benefits of albumin are not supported by sound clinical evidence and the case of albumin remains controversial*

Intensive Care Med (2018) 44:925–928

The Surviving Sepsis Campaign Bundle: 2018 update

Mitchell M. Levy[1*], Laura E. Evans[2] and Andrew Rhodes[3]

Fluid administration beyond initial resuscitation requires careful assessment of the likelihood that the patient remains fluid responder

Early norepinephrine use in septic shock

J Thorac Dis 2020;12(Suppl 1):S72-S77 Olfa Hamzaoui[1], Rui Shi[2,3]

- ✓ *Septic Shock is characterized by hypovolemia (both relative and absolute) and decreased vascular tone, which contributes much to the severity of hypotension*

- ✓ *Organ blood flow depends on perfusion pressure when mean arterial pressure (MAP) decreases below a certain critical value*

- ✓ *Thus, at the early phase, both fluid resuscitation - aiming to correct hypovolemia and vasopressors - mainly norepinephrine as a first line agent – aiming to restore vasculare tone are important to ensure organ perfusion*

Early norepinephrine use in septic shock

J Thorac Dis 2020;12(Suppl 1):S72-S77

Olfa Hamzaoui[1], Rui Shi[2,3]

EARLY ADMINISTRATION OF NOREPINEPHRINE INCREASES CARDIAC OUTPUT IN SEPTIC SHOCK

- ✓ *The increase in stroke volume following early administration of norepinephrine is associated with an increase in global end diatolic volume – a marker of cardiac preload- and a reduced pulse pressure variation (PPV), which is a marker of preload responsiveness*

Hamzaoui O, Georger JF, Monnet X, et al. Early administration of norepinephrine increases cardiac preload and cardiac output in septic patients with life-threatening hypotension. Crit Care 2010;14:R142.

- ✓ *The significant increase in LVEF with norepinephrine, in spite of an increased left ventricular afterload, strongly suggests that norepinephrine increases the left ventricular contractility*

Early norepinephrine use in septic shock

J Thorac Dis 2020;12(Suppl 1):S72-S77

Olfa Hamzaoui[1], Rui Shi[2,3]

LOW DIASTOLIC ARTERIAL PRESSURE (DAP) IS CONSIDERED AS A MARKER OF LOW ARTERIAL TONE

- ✓ Beneficial effects of norepinephrine on CO:
  - Improved ventricular perfusion in relation to the increased DAP
  - Left ventricular consequence of β_1 adrenergic receptor stimulation (time dependent –early phase)

Early norepinephrine use in septic shock

J Thorac Dis 2020;12(Suppl 1):S72-S77

Olfa Hamzaoui[1], Rui Shi[2,3]

EARLY INITIATION OF NOREPINEPHRINE MAY IMPROVE MICROCIRCULATION IN SEVERE SEPTIC SHOCK

- ✓ *Increasing the MAP in severely hypotensive patients improves microvascular blood flow in pressure dependent vascular beds and hence improves muscle oxygenation and microcirculatory recruitment capacities*

- ✓ *Impairment of microcirculation due to potential norepinephrine induced excessive vasoconstriction is not reality when MAP is low*

Hemodinamic management
Monitoraggio

Valutazione iniziale con metodiche semplici

Ecografia - lattati - riempimento capillare - mottling score

diuresi

Maggiore complessità ed eventuale invasività nei pazienti che restano critici ed instabili nonostante il trattamento inziale (TSI/TI)

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8. For adults with septic shock, we suggest using capillary refill time to guide resuscitation as an adjunct to other measures of perfusion.	***Weak,** low quality of evidence*

Early norepinephrine use in septic shock

J Thorac Dis 2020;12(Suppl 1):S72-S77

Olfa Hamzaoui[1], Rui Shi[2,3]

EARLY INITIATION OF NOREPINEPHRINE MAY IMPROVE MICROCIRCULATION IN SEVERE SEPTIC SHOCK

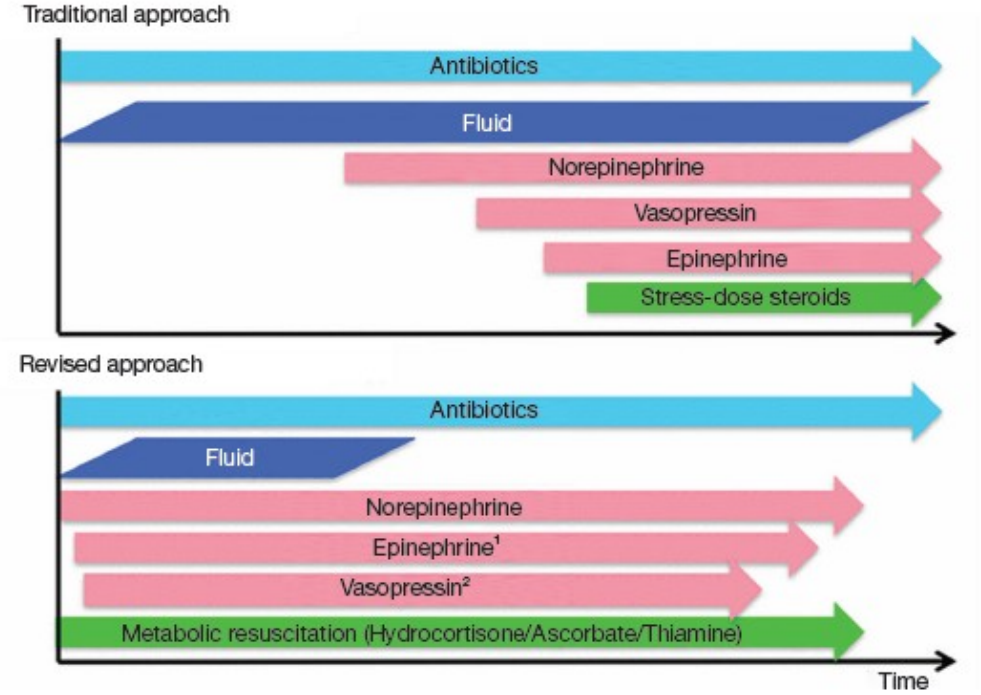
- ✓ Septic shock is associated with impaired microcirculation even in patients with preserved or corrected macrocirculation
- ✓ In severely hypotensive patients an improvement of microvascular blood flow could be expected with correction of hypotension due to correction of low organ perfusion pressure
  (MAP → STO_2)

Georger JF, Hamzaoui O, Chaari A, et al. Restoring arterial pressure with norepinephrine improves muscle tissue oxygenation assessed by near-infrared spectroscopy in severely hypotensive septic patients. Intensive Care Med 2010;36:1882-9.

Lactate guided resuscitation—nothing is more dangerous than conscientious foolishness

Paul E. Marik

J Thorac Dis 2019;11(Suppl 15):S1969-S1972



[Original Research **Critical Care**]

CHEST

Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock

A Retrospective Before-After Study

PODCAST

Paul E. Marik, MD, FCCP; Vikramjit Khangoora, MD; Racquel Rivera, PharmD; Michael H. Hooper, MD; and John Catravas, PhD, FCCP

BACKGROUND: The global burden of sepsis is estimated as 15 to 19 million cases annually, with a mortality rate approaching 60% in low-income countries.

METHODS: In this retrospective before-after clinical study, we compared the outcome and clinical course of consecutive septic patients treated with intravenous vitamin C, hydrocortisone, and thiamine during a 7-month period (treatment group) with a control group treated in our ICU during the preceding 7 months. The primary outcome was hospital survival. A propensity score was generated to adjust the primary outcome.

RESULTS: There were 47 patients in both treatment and control groups, with no significant differences in baseline characteristics between the two groups. The hospital mortality was 8.5% (4 of 47) in the treatment group compared with 40.4% (19 of 47) in the control group ($P < .001$). The propensity adjusted odds of mortality in the patients treated with the vitamin C protocol was 0.13 (95% CI, 0.04-0.48; $P = .002$). The Sepsis-Related Organ Failure Assessment score decreased in all patients in the treatment group, with none developing progressive organ failure. All patients in the treatment group were weaned off vasopressors, a mean of 18.3 ± 9.8 h after starting treatment with the vitamin C protocol. The mean duration of vasopressor use was 54.9 ± 28.4 h in the control group ($P < .001$).

CONCLUSIONS: Our results suggest that the early use of intravenous vitamin C, together with corticosteroids and thiamine, are effective in preventing progressive organ dysfunction, including acute kidney injury, and in reducing the mortality of patients with severe sepsis and septic shock. Additional studies are required to confirm these preliminary findings.

CHEST 2017; 151(6):1229-1238

Vitamin C

Recommendation
70. For adults with sepsis or septic shock, we **suggest against** using IV vitamin C
Weak recommendation, low quality of evidence