

اللَّهُمَّ اغْفِرْ لِي الذُّنُوبَ الَّتِي تُنْزِلُ الْبَلَاءَ

دَعَاكَ كَمِيل

خدا یا بخشش آن گناها را که بر من باری فرستند

A T R E Q U R A N



*SARS-CoV-2 (COVID-19) and
intravascular volume management
strategies in the critically ill*



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TUMS , Shariati Hospital*

SARS-CoV-2 (COVID-19) and intravascular volume management strategies in the critically ill

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ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to spread across the globe, and millions of people may be affected. While knowledge regarding epidemiologic features and diagnostic tools of coronavirus disease 2019 (COVID-19) is rapidly evolving, uncertainties surrounding various aspects of its optimal management strategies persist. A subset of these patients develop a more severe form of the disease characterized by expanding pulmonary lesions, sepsis, acute respiratory distress syndrome, and respiratory failure. Due to lack of data on treatment strategies specific to this subset of patients, currently available evidence on management of the critically ill needs to be extrapolated and customized to their clinical needs. The article calls attention to fluid stewardship in the critically ill with COVID-19 by judiciously applying the evidence-based resuscitation principles to their specific clinical features such as high rates of cardiac injury. As we await more data from treating these patients, this strategy is likely to help reduce potential complications.

Covid-19 as a Critical Illness



- ✧ 14% patients with COVID-19 with more severe disease, additional manifestations (e.g., respiratory rate ≥ 30 /min and blood oxygen saturation $\leq 93\%$) were present, and 5% were critical, with respiratory failure, septic shock, and/or multiorgan dysfunction or failure.
- ✧ A significant subset of these patients develop acute respiratory distress syndrome (ARDS).
- ✧ Hypoxemic respiratory failure is the most common cause of admission to the intensive care unit (ICU).

Covid-19 as a Critical Illness



- ❧ Aberrancy in immune response can result in failure to clear virus and viral sepsis.
- ❧ While proinflammatory cytokines such as interleukin-6 are essential to mediate innate immunity, they can cause host damage as part of a maladaptive process.
- ❧ Viral sepsis remains highly heterogeneous and is likely to encompass a complex and not yet fully understood pattern of pathophysiologic pathways and immune responses that are distinct from bacterial infections.
- ❧ The current consensus guidelines are primarily based on studies of bacterial sepsis and are not pathogen specific

Covid-19 as a Critical Illness



- ∞ Respiratory failure due to expansion of pulmonary infiltrates and secondary bacterial infection, septic shock, and multiorgan failure are among the reasons for an untoward clinical course in this setting.
- ∞ The expression and distribution of angiotensin converting enzyme II (ACE-2), the primary host cell receptor of SARS-CoV2, in various systems make it possible for the virus to infect a variety of cells and induce multiple organ failure

Covid-19 as a Critical Illness



- Similar to other patients with hemodynamic instability, these patients are likely to undergo aggressive fluid administration as the mainstay of management.
- In fact, fluid resuscitation remains the most enduring of sepsis treatments, predating even antibiotics, although mounting evidence has recently challenged its central role in this setting.

Covid-19 as a Critical Illness



- ❧ A potentially simplistic and possibly incorrect reasoning at the foundation of such conjecture is the presumed hypoperfusion resulting in an increase in serum lactate levels accompanied by low blood pressure, oliguria, hepatic dysfunction, and altered mental status in patients with sepsis.
- ❧ In this hypoperfusion-centric paradigm, the microcirculatory dysfunction is the key driver of sequential pathophysiologic mechanisms ultimately leading to multiorgan failure

Covid-19 as a Critical Illness



- ∞ Due to known changes in the glycocalyx structure and hyperpermeability of vasculature in sepsis, the administered fluid is rapidly redistributed into an extravascular compartment.
- ∞ There is clinical evidence that the increase in intravascular volume after fluid bolus therapy might be small and short lived, leading to only transient improvement in hemodynamic parameters such as cardiac output

Covid-19 as a Critical Illness



- ❧ These observations coupled with the strong evidence on the association of adverse outcomes with extravascular volume overload make fluid stewardship a serious consideration for the care of these patients.
- ❧ This concept is even more crucial in critically ill patients with COVID-19 in whom expanding lung infiltrates, ARDS, and respiratory failure often coexist with sepsis.

Definition of Sepsis



∞ Sepsis :

Life-threatening organ dysfunction
caused by a
dysregulated host response
to infection

JAMA. 2016;315(8):762-774

Lancet Respir Med 2016; 4: 237-40

SSC 2016

Intensive Care Med (2017) 43:304-377

A large red speech bubble with a dark blue outline, pointing towards the bottom left.

10% Mortality

Definition of Septic Shock



∞ Septic shock:

A subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality

40% Mortality

qSOFA



Patient with suspected infection



$qSOFA \geq 2?^*$

Yes

Assess for evidence of organ
dysfunction

qSOFA*

RR>22

Systolic BP<100

Mental status

SOFA

Sequential (sepsis-related) Organ Failure Assessment



∞ The SOFA score  6 variables
each representing an organ system

∞ Each organ system



**A point value from 0 (normal)
to
4 (high degree of
dysfunction/failure)**

SOFA

Sequential (sepsis-related) Organ Failure Assessment



Organ system	SOFA score				
	0	1	2	3	4
Respiratory, PO ₂ /FiO ₂ , mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation, Platelets, ×10 ³ /mm ³	≥150	<150	<100	<50	<20
Liver, Bilirubin, mg/dL	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine <5 or dobutamine (any dose) ^b	Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1 ^b	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 ^b
Central nervous system, Glasgow Coma Scale	15	13–14	10–12	6–9	<6
Renal, Creatinine, mg/dL. Urine output, mL/d	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 <500	>5.0 <200

^a, adapted from Vincent *et al.* (7); ^b, Catecholamine doses are given as µg/kg/min for at least 1 hour. FiO₂, fraction of inspired oxygen; MAP, mean arterial pressure; PO₂, partial pressure of oxygen.



Resuscitation Fluids



Typical Hemodynamics in Various Shock States and Their Differential Diagnosis



	CVP or Preload	CO	SVR	Examples
Distributive	↓	↑	↓↓	<ul style="list-style-type: none"> • Septic • Neurogenic • Anaphylaxis • Adrenal insufficiency
Hypovolemic or hemorrhagic	↓↓	↓	↑	<ul style="list-style-type: none"> • Hemorrhagic • Other volume depletion (diarrhea, vomiting, overdiuresis, inadequate intake)
Cardiogenic	↑	↓↓	↑	<ul style="list-style-type: none"> • Acute myocardial infarction • Heart failure • Valvular disease • Post cardiopulmonary bypass • Arrhythmia
Obstructive	NA	↓↓	↑	<ul style="list-style-type: none"> • Massive pulmonary embolism • Tamponade • Tension pneumothorax • Mechanical ventilation with excess PEEP

Viral Sepsis

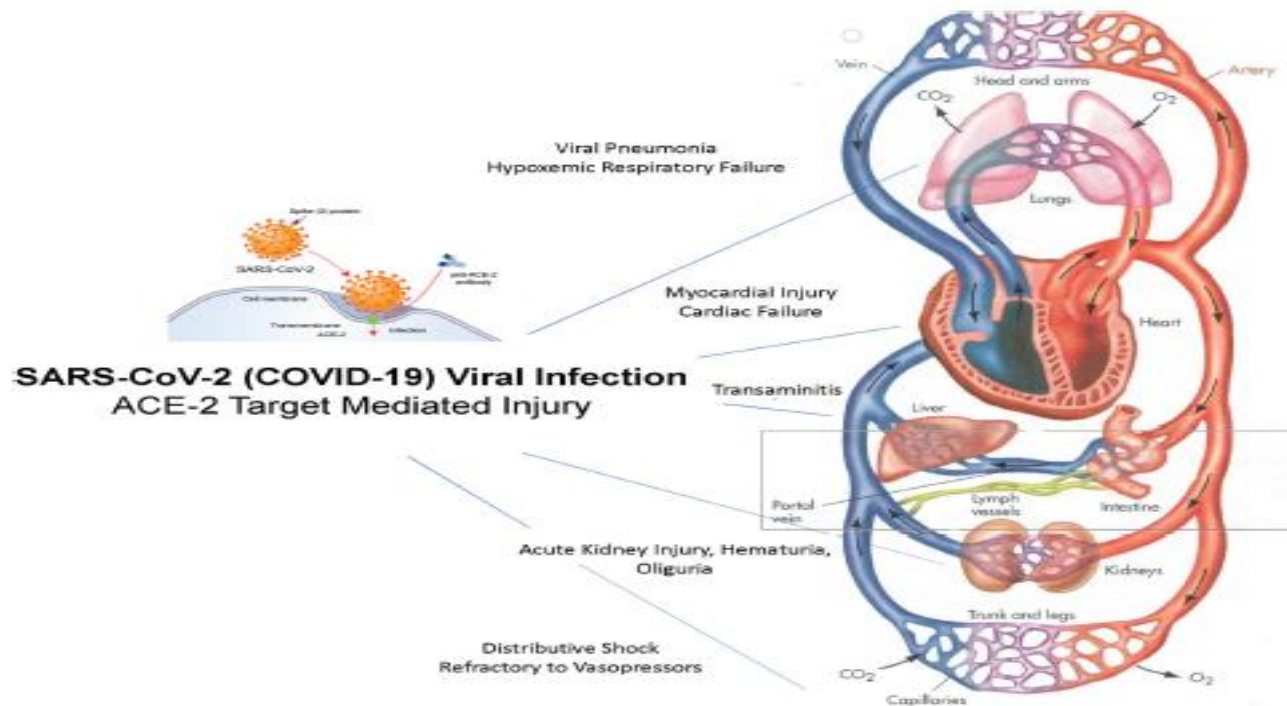


Figure 1. SARS-CoV-2 (COVID-19)-mediated organ injury in critically ill patients mediated by viral entry and target mediated destruction of the angiotensin converting enzyme II (ACE-2) receptor enzyme.

4 Phases of Septic Shock



- ∞ Rescue : Recommended goal of 30 mL/Kg of IV crystalloid
- ∞ Optimization phase : Ischemia and reperfusion phase . Repeated assessments of intravascular fluid status and determination for further fluid administration
- ∞ Stabilization : Maintain intravascular volume, replace ongoing fluid losses, support organs dysfunction, avoid iatrogenic harm with unnecessary fluid administration
- ∞ De-escalation

Intravenous Fluids



- ❧ Along with timely administration :
- ❧ Antibiotics and source control
- ❧ Appropriate volume resuscitation remains an important determinant of outcomes in septic patients
- ❧ **Vasoactive agents , Norepinephrine has emerged as the first-line agent for septic shock** due to trials and meta-analyses showing that norepinephrine causes fewer tachyarrhythmias (mostly atrial fibrillation) and may be associated with decreased overall mortality compared to dopamine.

Initial Resuscitation



- ∞ At least 30 mL/Kg of IV crystalloid fluid within first 3 hours
- ∞ After initial resuscitation, additional fluids guided by frequent reassessment
- ∞ MAP >65 mm Hg
- ∞ Guiding resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.

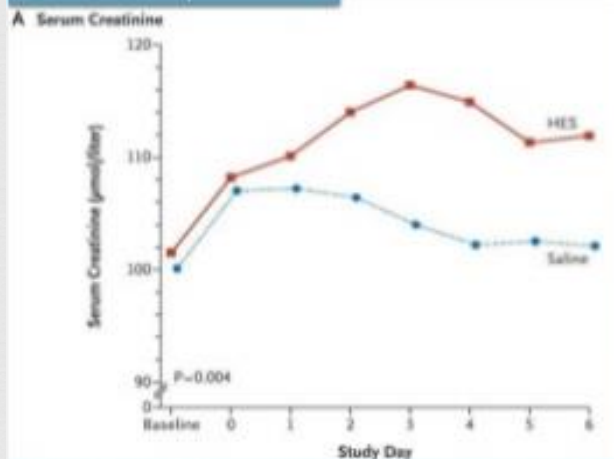
Colloids Versus Crystalloids



Crystalloid versus HES (CHEST) Trial 2012 : 7000 ICU patients



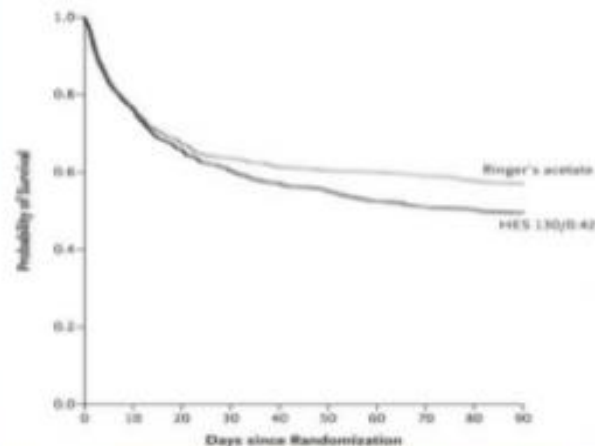
The NEW ENGLAND
JOURNAL of MEDICINE



Significant increase in the rate of RRT
and AKI with HES.
No significant increase in mortality .

The Scandinavian Starch for Severe Sepsis/Septic Shock Trial (6S) 2012 :

800 patients with severe sepsis



Significant increase in mortality with HES

Colloids Versus Crystalloids



❑ The Nature Of IV Fluids :

- ❖ **Crystalloids** : don't remain in vascular space for long .
After 90 min : The intravascular volume effect of Ringer's lactate is below 20% in normal condition , decreases to 5% in critical illness eg: sepsis .
- ❖ **Colloids** : increased capillary permeability > extravasation into extracellular space > increasing interstitial oncotic pressure > worsen edema .
accumulation of low-molecular-weight fractions in renal tubules and osmotic nephrosis .

The intravascular volume effect of Ringer's lactate is below 20%; a prospective study in humans

Critical Care 2012, 16:R66 | DOI: 10.1186/cc11344 | © Jacobs et al.; licensee BioMed Central Ltd. 2012



Critical Care

Intravenous Fluids



Surviving Sepsis
Campaign



Intensive Care Medicine
March 2017, Volume 45, Issue 3, pp 304-377



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

- ☐ **We recommend crystalloids as the fluid of choice for resuscitation in patients with sepsis and septic shock** (Strong recommendation, moderate quality of evidence).
- ☐ **We suggest using albumin in addition to crystalloids when patients require substantial amounts of crystalloids** (weak recommendation, low quality of evidence).

Intravenous Fluids



Saline Versus Balanced Solutions

-  The pathophysiology underlying the purported negative effect of saline solution on the kidneys remains unclear, but it is thought to be related to the high chloride content proposed mechanisms include:
-  Reduced glomerular filtration rate (GFR) through activation of tubuloglomerular feedback:
 - ☐ Triggered by increased chloride delivery to the macula densa
 - ☐ Vasoconstriction caused by chloride-induced thromboxane release
 - ☐ Increased inflammatory cytokine expression induced by acidosis.

Intravenous Fluids



☞ Saline Versus Balanced Solutions

- ☞ Epidemiologic data suggest that 0.9% saline solution , when compared with balanced salt solutions such as lactated Ringers or Plasma-Lyte (Baxter), may **increase the risk for AKI, need for RRT, and mortality in ICU patients.**
- ☞ Two recent large trials examined the use of balanced crystalloids versus 0.9% saline solution:
 - ❑ Non-ICU setting (SALT-ED; n > 13,000), and the other evaluated ICU patients (SMART; n > 15,000).
 - ❑ In both trials , the use of balanced solutions resulted in an ~1% absolute reduction in the rate of “MAKE-30,” a composite outcome of death, need for RRT, or persistent doubling of creatinine level at 30 days.

Saline Versus Balanced Solutions

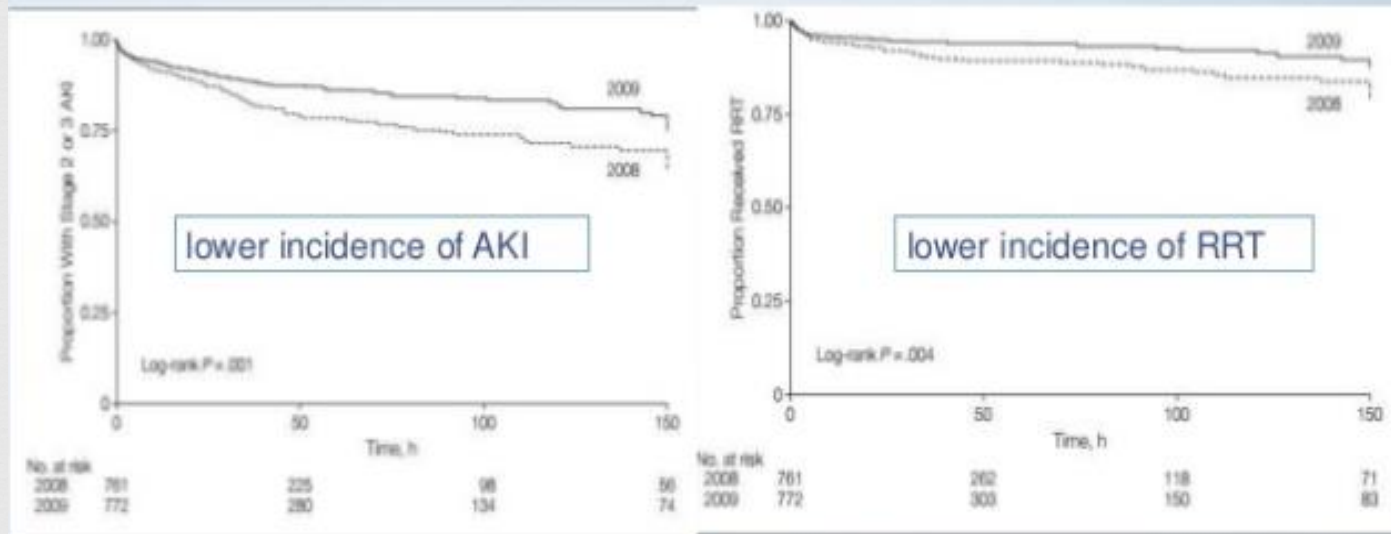


JAMA. 2012 Oct 17;308(15):1566-72. doi: 10.1001/jama.2012.13356.

JAMA, October 17, 2012—Vol 308, No. 15

Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults.

1500 patients in the two groups



Intravenous Fluids



- 
- A vertical line with five white circles, each containing a small black dot in the center. The line starts at the top circle and ends at the bottom circle, with a small diagonal tick mark at the top and bottom. The circles are connected by a thin line, and each circle is positioned to the left of a horizontal bar.
- HES : Don't USE (HARM) .
 - Dextran and Gelatin : NOT Studied .
 - Albumin : No Beneficial Effect .
 - Normal Saline: still the standard ?!
 - Balanced Crystalloids : No harmful effect . May decrease Risk of AKI



How To Assess Volume Status ?

Is it the volume status what matters ?



Fluid Responsiveness



- ⌘ Retrospective trial of 3686 patients.
- ⌘ Fluid responsiveness defined as a static measurement of sustained reversal of hypotension with resultant:
 - ❑ systolic blood pressure >90 mmHg or
 - ❑ MAP > 65 mmHg after initial fluid resuscitation without the use of vasopressors for 24 hours
- ⌘ 36.2% refractory to fluid bolus.
- ⌘ Fluid refractory patients had higher in-hospital mortality, mechanical ventilation, longer ICU stays, longer hospital length of stay.
- ⌘ **Predictors of being fluid refractory: delayed fluid resuscitation with time to fluid > 120 minutes*, CHF, hypothermia, lactate > 4, coagulopathy, immunocompromised.**

Fluid Responsiveness



- ✎ Following initial fluid resuscitation, additional fluids be guided by frequent reassessment of hemodynamic status
- ✎ **We suggest that dynamic over static variables be used to predict fluid responsiveness, where available**
- ✎ In contrast to static measures (eg, CVP, ScVO₂, or pulmonary artery occlusion pressure)
- ✎ Dynamic measures of volume responsiveness – in which the response to a transient or small change in cardiac filling is assessed – appear to be more useful.

For example, variations in stroke volume (or a surrogate such as pulse pressure) as assessed by pulse contour analysis,

- ❑ Transthoracic or esophageal Doppler
- ❑ Bioimpedance in response to changes in intrathoracic pressure during the respiratory cycle
- ❑ **Passive leg raise (equivalent to 500cc fluid bolus)** , appear to be useful.

Passive Leg Raise

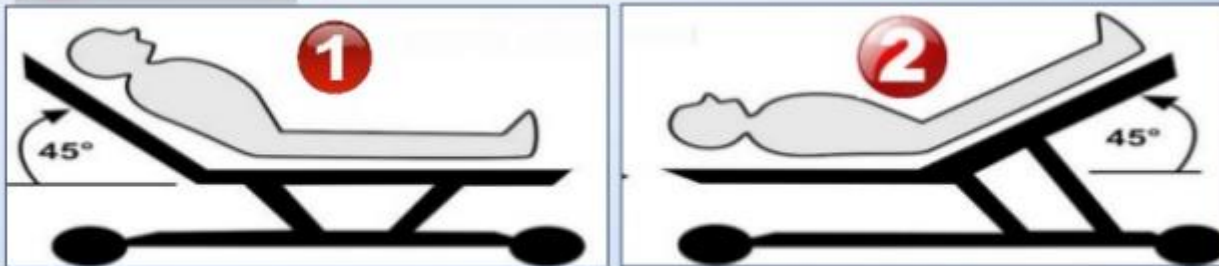


Passive Leg Raising (PLR) Test



Passive leg raising: five rules, not a drop of fluid!

Xavier Monnet^{1,2} and Jean-Louis Teboul^{1,2}



- ☐ Increases preload and acts like a transient reversible “self-Fluid challenge” - mimic increase 500-700 ml .
- ☐ In patients on MV : without any invasive device by the changes in end-tidal CO₂ .
- ☐ Intra-abdominal hypertension could be an obstacle


Passive Leg Raise



- ❧ A passive leg raise (positioning a patient at zero degrees, then raising both legs to about 45") returns a reservoir of venous blood into the central circulation relatively quickly (30-90 seconds). It's the original, all-natural fluid bolus.
- ❧ **Patients with a positive test have a 10% increase in cardiac output or stroke volume.**
- ❧ Passive leg raise testing (with cardiac output measured invasively or by echocardiography during the PLR) performed the best by far in the pooled analyses: patients with **positive PLR were about 11 times more likely to respond to IV fluids.**
- ❧ Only about 1 in 8 patients with a negative PLR responded to fluids.

Static and Dynamic Hemodynamic Parameters



<div>  <div> KIREPORTS <small>KIRereports.org</small> </div> <div> <small>Available online 26 April 2017</small> Prevention and Therapy of Acute Kidney Injury in the Developing World </div> </div>			
<input type="checkbox"/> Every patient with AKI should be assessed for volume status as a part of hemodynamic optimization.			
Clinical parameters	Paraclinical parameters	Static measures	Dynamic measures
Body weight changes	Urinary indices (i.e. UNa, FeNa, FeUrea, specific gravity and osmolality)	Central venous pressure IVC diameter	Stroke volume variation and pulse pressure variation
Input/output balance	Hematologic changes	Pulmonary artery occlusion pressure	Aortic flow velocity and stroke volume
Blood pressure, heart rate and orthostasis	Bioelectrical impedance	RV end-diastolic volume	Positive pressure ventilation induced changes in IVC diameter
Urine volume	Lactates, SVO ₂	LV end-diastolic area	Microcirculation evaluation
Capillary refill, skin turgor	Extravascular lung water index	Intra-aortic blood volume index	
Organomegaly		Global end-diastolic volume index	
Pulmonary edema			

Fluid Challenge



Fluid challenge :

- ❑ The “common” fluid challenge : 500-1000mL or 30mL/kg
Performing it several times a day leads to a significant fluid overload.

- ❑ A “mini fluid challenge” has been described .
In an interesting study, the effects of only 100 mL of colloid on stroke volume can predicted the response of cardiac output to a 500 mL volume expansion.
Changes in stroke volume were estimated by Echo .



Fluid Challenge



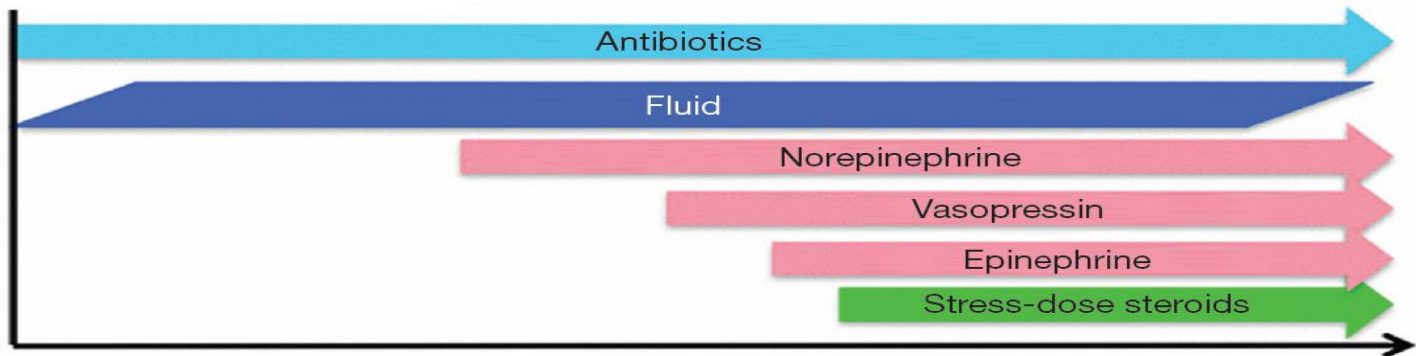
- ☐ Only patients who show a significant increase in SV following a fluid challenge are considered to benefit : fluid responders (50% of critically ill patients)
- ☐ In the non-responder , volume expansion will only exert adverse effects, without any hemodynamic benefit.
- ☐ We need to determine whether a patient will be fluid responsive or not before Fluid administration ?
- ☐ Observing if changes in cardiac preload will change of cardiac output or stroke volume .

Dynamic Measures

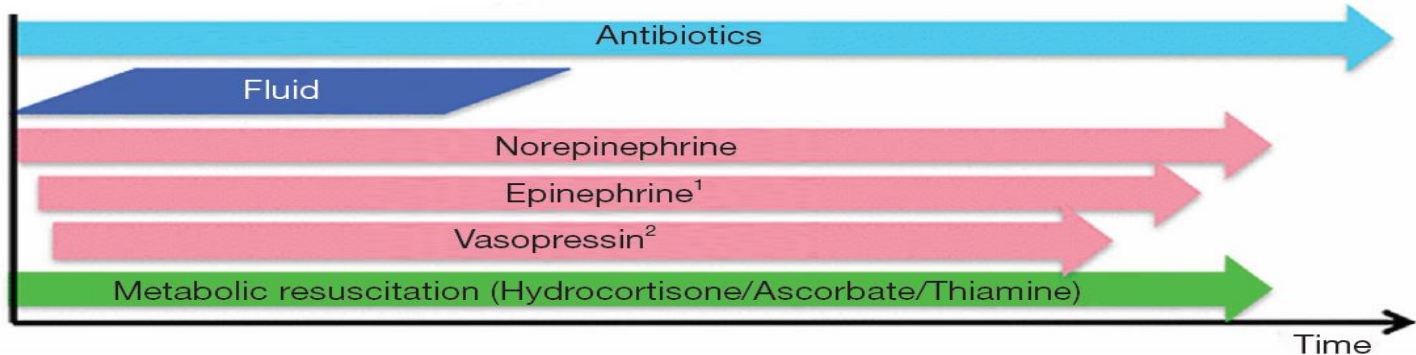
The Changing Paradigm of Sepsis: Early Diagnosis, Early Antibiotics, Early Pressors, and Early Adjuvant Treatment



Traditional approach



Revised approach



Timing of Vasopressor Administration



- ✧ A very early start of vasopressor support seems to be safe, might limit the amount of fluids to resuscitate septic shock, and could lead to better clinical outcomes.
- ✧ Early norepinephrine initiation can increase MAP shorten the duration of hypotension and, thereby, may improve vital organ perfusion and decrease serum lactate levels.

Ospina-Tascón et al. *Critical Care* (2020) 24:52
<https://doi.org/10.1186/s13054-020-2756-3>

Critical Care

RESEARCH

Open Access

Effects of very early start of norepinephrine in patients with septic shock: a propensity score-based analysis



Bai et al. *Critical Care* (2014) 18:532
<http://ccforum.com/content/18/5/532>



RESEARCH

Open Access

Early versus delayed administration of norepinephrine in patients with septic shock

Xiaowu Bai, Wenkui Yu*, Wu Ji, Zhiliang Lin, Shanjun Tan, Kaipeng Duan, Yi Dong, Lin Xu and Ning Li*



FLUID OVERLOAD



Fluid Overload



Why Interstitial Edema occurs during acute illness ?

"The 3rd Space : Where has all the fluid gone?"



- ☐ Hypotension, pain and tissue injury > + **sympathetic system** > + **RAS** , ADH > trigger sodium and water retention.
- ☐ **Hypoalbuminemia** > Increased vascular permeability in sepsis > capillary 'leakiness' > distributive shock
- ☐ Vascular endothelium is disrupted : **dysfunction of glycocalyx** > increase in capillary leak, and interstitial edema > fluid overload > More dysfunction "vicious cycle"
- ☐ The relationship between fluid input and **natriuresis** is weak > Fluid overload .

Fluid Overload



- Several retrospective studies have found associations between **positive fluid balance and mortality in critically ill patients**.
- In a large multicenter cohort focused on critically ill patients, those **with fluid overload (10% weight gain)** at the time of dialysis therapy initiation had an odds ratio(OR) for death of 2.07 (95% confidence interval [CI],1.27-3.37); findings were similar in those with AKI who did not require dialysis.

Fluid Overload



Proven by many studies :

Fluid overload at initiation of renal replacement therapy is associated with lack of renal recovery in patients with acute kidney injury FREE

Nephrol Dial Transplant. 2012 Mar;27(3):956-61. doi: 10.1093

ndt NEPHROLOGY
DIALYSIS
TRANSPLANTATION

Oliguria is an early predictor of higher mortality in critically ill patients

Etienne Macedo, Rakesh Malhotra, Josée Bouchard, Sus
published online 29 June 2011

ISN kidney
INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

Research

A positive fluid balance is associated with a worse outcome in patients with acute renal failure

Crit Care. 2008;12(3):R74. doi: 10.1186/cc6916. Epub 2008 Jun 4.

C Critical Care

Fluid Overload



- ❧ While the primary focus of the first phase is to reach the minimum effective blood volume through fluid administration, the main goal of the de-escalation phase is to reach a negative fluid balance.
- ❧ Interestingly, not only has early fluid resuscitation been shown to reduce mortality in patients with sepsis, but **earlier negative volume balance during the de-escalation phase is also associated with an improved survival**

Fluid Overload



❧ Murphy et al reported that among patients with **acute lung injury secondary to septic shock**, those who received both adequate initial fluid resuscitation as well as conservative late fluid management (i.e., negative to even fluid balance on 2 consecutive days during the first week after sepsis) had the best survival rates compared with those who achieved only one of these goals or neither of the two.

Fluid Overload



∞ Dynamic approach and optimal timing:

☐ **Early administration followed**

☐ **Early termination or active removal**

∞ appear to be the key in fluid resuscitation of patients with sepsis.

Excessive Resuscitation



CARDIOVASCULAR SYSTEM*

Myocardial oedema ↑
Conduction disturbance
Impaired contractility
Diastolic dysfunction
CVP ↑ and PAOP ↑
Venous return ↓
SV ↓ and CO ↓
Myocardial depression
GEF ↓ GEDVI ↑
Pericardial effusion ↑
CARS ↑

CENTRAL NERVOUS SYSTEM

Cerebral oedema ↑
Impaired cognition ↑
Delirium ↑
Intracranial pressure ↑
Cerebral perfusion pressure ↓
Intra-ocular pressure ↑
ICH, ICS, OCS

RESPIRATORY SYSTEM

Pulmonary oedema ↑
Pleural effusion ↑
Altered pulmonary and chest wall elastance (cfr IAP ↑)
Impaired gas exchange:
Hypercarbia ↑
PaO₂ ↓ and PaO₂/FIO₂ ↓
Extravascular lung water ↑
Lung volumes ↓ (cfr IAP ↑)
Prolonged ventilation ↑
Difficult weaning ↑
Work of breathing ↑

HEPATIC SYSTEM

Hepatic congestion ↑
Impaired synthetic function
Cholestasis ↑
Impaired Cytochrome P 450 activity
Hepatic compartment syndrome

RENAL SYSTEM

Renal interstitial oedema
Renal venous pressure ↑
Renal blood flow ↓
Interstitial pressure ↑
Glomerular filtration rate ↓
Uremia ↑
Renal vascular resistance ↑
Salt retention ↑
Water retention ↑
Renal compartment syndrome

GASTRO-INTESTINAL SYSTEM

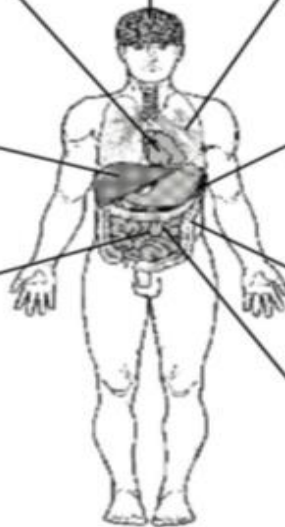
Ascites formation ↑
Gut oedema ↑
Malabsorption ↑
Ileus ↑
Abdominal perfusion pressure ↓
Bowel contractility ↓
IAP ↑ and APP (=MAP-IAP) ↓
IAH and ACS ↑
Successful enteral feeding ↓
Intestinal permeability ↑
Bacterial translocation ↑
Splanchnic microcirculatory flow ↓
ICG-PDR ↓, pH_i ↓

ABDOMINAL WALL

Tissue oedema ↑
Impaired lymphatic drainage ↑
Microcirculatory derangements ↑
Poor wound healing ↑
Wound infection ↑
Pressure ulcers ↑
Skin oedema ↑
Abdominal compliance ↓

ENDOCRINE SYSTEM

Release pro-inflammatory cytokines ↑
(IL-1b, TNF-α, IL-6)



Liberal Fluid Administration Associated with Poor Outcomes



- ❧ Boyd. CCM 2011. Patients with lower quartiles of fluid balance had lower risk of mortality
- ❧ Micek. CCM 2013. Positive fluid balance at 24 hours had increased hospital mortality compared to those with lowest fluid
- ❧ Sedaka. J Int Care Med 2014. Patients with > 6 liters of fluid had higher mortality compared to those with < 6 liters of fluid
- ❧ Acheampong. CCM 2015. More positive fluid balance associated with higher mortality
- ❧ De Oliverira. J Crit Care 2015. Net fluid balance > 3 liters associated with increased hospital mortality
- ❧ Kelm. Shock 2017. Higher fluid balance at 72 hours but not 24 hours associated with increased mortality
- ❧ FEAST Trial. NEJM 2011. Higher mortality in with liberal fluids.

Fluid Overload



- ☐ Diuretics should be used to treat FO ; however, they should not be continued if there is no an adequate response
- ☐ Unresponsive patients should be considered for early initiation of RRT .
- ☐ From a renal standpoint: unless there is clinically evident dehydration, there is no No clear evidence that aggressive hydration can change renal outcome, except in contrast-induced AKI.

Fluid Overload



- ☐ We do not recommend diuretics for prevention and/or treatment of AKI but may be used in the setting of fluid overload .
- ☐ We recommend a furosemide stress test (FST) after adequate fluid repletion under monitored conditions .
- ☐ Volume depletion is a major risk factor for AKI and Volume overload can worsen renal function .

Role of the Furosemide Stress Test in Renal Injury Prognosis



- ∞ The dose of intravenous bolus furosemide administered was 1 mg/kg for loop diuretic naïve patients and 1.5 mg/kg for those previously treated with loop diuretics.
- ∞ **FST-induced urine output was a significant predictor of the primary outcome.**
- ∞ FST failed to predict in-hospital patient survival

Active Fluid Removal



- ❧ Negative fluid balance in the de-escalation phase would be crucial in order to avoid complications associated with lingering congestion.
- ❧ Loop diuretics are often used to counter positive fluid balance in ICU patients.
- ❧ Studies evaluating the impact of loop diuretics in the ICU have yielded inconsistent results, with some showing benefit, others reporting no benefit, and some suggesting harm

Active Fluid Removal



- ☞ In the face of positive fluid balance during the de-escalation phase of sepsis management, one might consider earlier application of renal replacement therapy (RRT) especially in those patients with :
- ☐ More severe volume overload
 - ☐ Progressive metabolic alkalosis with diuretic use
 - ☐ Suboptimal diuretic response or diuretic refractoriness
 - ☐ Development of oliguric AKI.

Fluid Overload



Fluid Overload is extremely HARMFUL !



Your tests reveal that
you are retaining fluids!

1 in 5 patients suffers harm
through injudicious fluid use.

Chart fluid input and output
more accurate than measuring
BW changes with a scale

Fluid overload (FO) = the total
input - total output / initial BW
Adverse outcomes occur when
reaching more than 10%

Estimation of fluid status changes in critically ill patients: fluid balance chart or
electronic bed weight?

Padhi S, Bullock I, U I, Stroud M, National Institute for Health Care Excellence
Guideline Development Group. Intravenous fluid therapy for adults in hospital:
summary of NICE guidance. *Bmj*. 2013;347:f7073

Fluid Therapy in AKI : Where do we stand ?



Aggressive Fluid
Replacement

Static Measures
Is the patient
hypovolemic ?

Normal Saline

Protocolized
Approach



Aggressive prevention
of Fluid Overload

Dynamic Measures
Will the patient be
Fluid responsive ?

Balanced Crystalloids

Individualized Approach



THE TAKE-HOME MESSAGE

It is a Question of Balance



Volume status

Both Hypervolemia and hypovolemia are Bad

One Size Doesn't Fit All



Personalized

Covid-19 & AKI



- ∞ The incidence of AKI in COVID-19 varies widely; estimates range from 0.5% to 29%.
- ∞ It is noteworthy that a subset of patients experiences fever, malaise, nausea, vomiting, and possibly diarrhea for several days before seeking medical care.
- ∞ They are prone to intravascular volume depletion and prerenal AKI.
- ∞ In these patients, early aggressive volume resuscitation is indicated to avoid development of extensive acute tubular injury due to prolonged severe renal hypoperfusion

Covid-19 & AKI



∞ While it has been suggested that **direct cellular injury via ACE-2 that is expressed in proximal renal tubules could contribute to AKI**, it remains likely that shock (and in some cases cytokine storm) are the primary causes of acute tubular necrosis in this setting

Covid-19 & AKI



- ❧ Yaghoubi et al reported that among patients hospitalized for COVID-19 from February 2020 through April 2020 in Shariati Hospital:
- ❧ 200 patients were included in the final analysis, with a mean age of 60.5 years.
- ❧ **126 (63%) developed AKI.**
- ❧ **Among 68 ICU-admitted patients, 50 (73.5%) developed AKI.**
- ❧ **Patients with AKI were 4.29 times more likely to die.**
- ❧ Pre-existing CKD, being treated with immunosuppressants, ICU admission, and the need for hemodialysis, were also associated with mortality.

Covid-19 & AKI



- ❧ Right-sided heart failure, following aggressive fluid administration the increased right atrial pressure is transmitted retrograde, leading to elevated venous pressure in abdominal organs such as the kidney, liver, and the guts.
- ❧ Kidneys are particularly vulnerable to a rise in interstitial pressure and tubular compression due to the capsule surrounding them (i.e., renal intracapsular tamponade).

Covid-19 & AKI



- ∞ In the Fluids and Catheters Treatment Trial (FACCT), the incidence of AKI was similar between restrictive and liberal fluid management groups.
- ∞ However, Liu et al showed that after correcting serum creatinine levels for fluid balance, the incidence of AKI was lower with a restrictive fluid strategy.

Covid-19 & AKI



- ❧ **Venous wall stretch is a stimulus for activation of endothelium and subsequent release of inflammatory mediators, which in turn may lead to interstitial damage and functional abnormalities such as diminished tubular reabsorption and retention of sodium and water.**
- ❧ Increasing intra abdominal pressure due to progressive volume overload can also contribute to further impairment of renal hemodynamics and function.

Sepsis Associated AKI



- ❧ Intravenous fluids should be used judiciously in patients with AKI who are not “volume responsive.”
- ❧ After significant volume resuscitation, even if patients remain volume responsive, vasopressor support should be considered to avoid markedly positive fluid balance.
- ❧ In those requiring volume resuscitation, the choice of solution is controversial.

Conclusion



- ✧ A significant subset of patients with COVID-19 develops ARDS, which is characterized by pulmonary edema resulting from increased capillary permeability, making these patients even more vulnerable to resuscitation-induced lung congestion.

Amir Kazory, MD, Claudio RoncoBaylor, Baylor University Medical Center
Proceedingsaylor, doi.org/10.1080/08998280.2020.1754700.

Conclusion



- ❧ Increased atrial pressure is associated with an increase in pulmonary and venous hydrostatic pressures, leading to a shift of fluid into the interstitial space, further disturbing capillary blood flow and oxygen diffusion.
- ❧ This effect is more pronounced in those clinical settings, such as COVID-19, where lung tissue architecture is already disturbed by an active and rapidly expanding inflammatory process.

Conclusion



Surviving Sepsis
Campaign



Intensive Care Medicine

March 2017, Volume 43, Issue 3, pp 304-377

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

- ☐ We recommend that in the resuscitation from sepsis-induced hypo-perfusion, at least **30ml/kg of intravenous crystalloid** fluid be given **within the first 3 hours**. (Strong recommendation; low quality of evidence)
- ☐ We recommend that following initial fluid resuscitation, **additional fluids be guided by frequent reassessment of hemodynamic status**. (Best Practice Statement)
- ☐ We suggest that **dynamic over static variables** be used to predict fluid responsiveness, where available. (Weak recommendation; low quality of evidence)

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Conclusion



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MEETING REPORT

Available online 26 April 2017

Prevention and Therapy of Acute Kidney Injury in the Developing World

- ☐ A combination of all parameters (both static and dynamic) should be performed .
- ☐ The amount of fluid to be given should be individualized .
- ☐ Vasopressors should be considered as soon as possible if volume repletion has not achieved the hemodynamic goal.
- ☐ We recommend a target of MAP of 65 to 85 mm Hg

Conclusion



- ❧ Evidence has established **positive fluid balance as a strong and independent predictor of poor outcomes in the critically ill.**
- ❧ For example, a large international study on more than 1800 patients with sepsis found that a higher cumulative fluid balance 3 days after ICU admission was proportionately associated with an increased risk of death.

Conclusion



- ✧ We should remain mindful that fluid resuscitation exerts its potentially therapeutic effect mainly by increasing the stressed volume of the circulation, leading to improved venous return and cardiac output.
- ✧ Aggressive fluid administration is likely to result in volume overload and its extensive adverse consequences in patients with already diminished respiratory reserve due to pulmonary infiltrates.
- ✧ It has been reported that a restricted initial resuscitation strategy (i.e., “preventing” overload) might be advantageous compared to fluid removal after more liberal administration.

Thank You!

