Treatment of Septicemia & Immunomodulation

Davood Yadegarynia
Professor of Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences

Guidelines for Management of Sepsis and Septic Shock 2021

1. We recommend against using qSOFA compared with SIRS, NEWS, or MEWS as a single-screening tool for sepsis or septic shock.
2. For adults suspected of having sepsis, we suggest measuring blood lactate.
3. For adults with sepsis or septic shock who re-quire ICU admission, we suggest admitting the patients to the ICU within 6 hr.
4. For adults with possible sepsis without shock, we recommend rapid assessment of the likelihood of infectious versus noninfectious causes of acute illness.
5. 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.

Surviving Sepsis Campaign

In recent years

The care in sepsis is focused on prompt recognition and early treatment
“Shift of focus from inflammation to Organ Dysfunction ”

In 2016

Sepsis is now defined as
life-threatening organ dysfunction
caused by dysregulated host response to infection

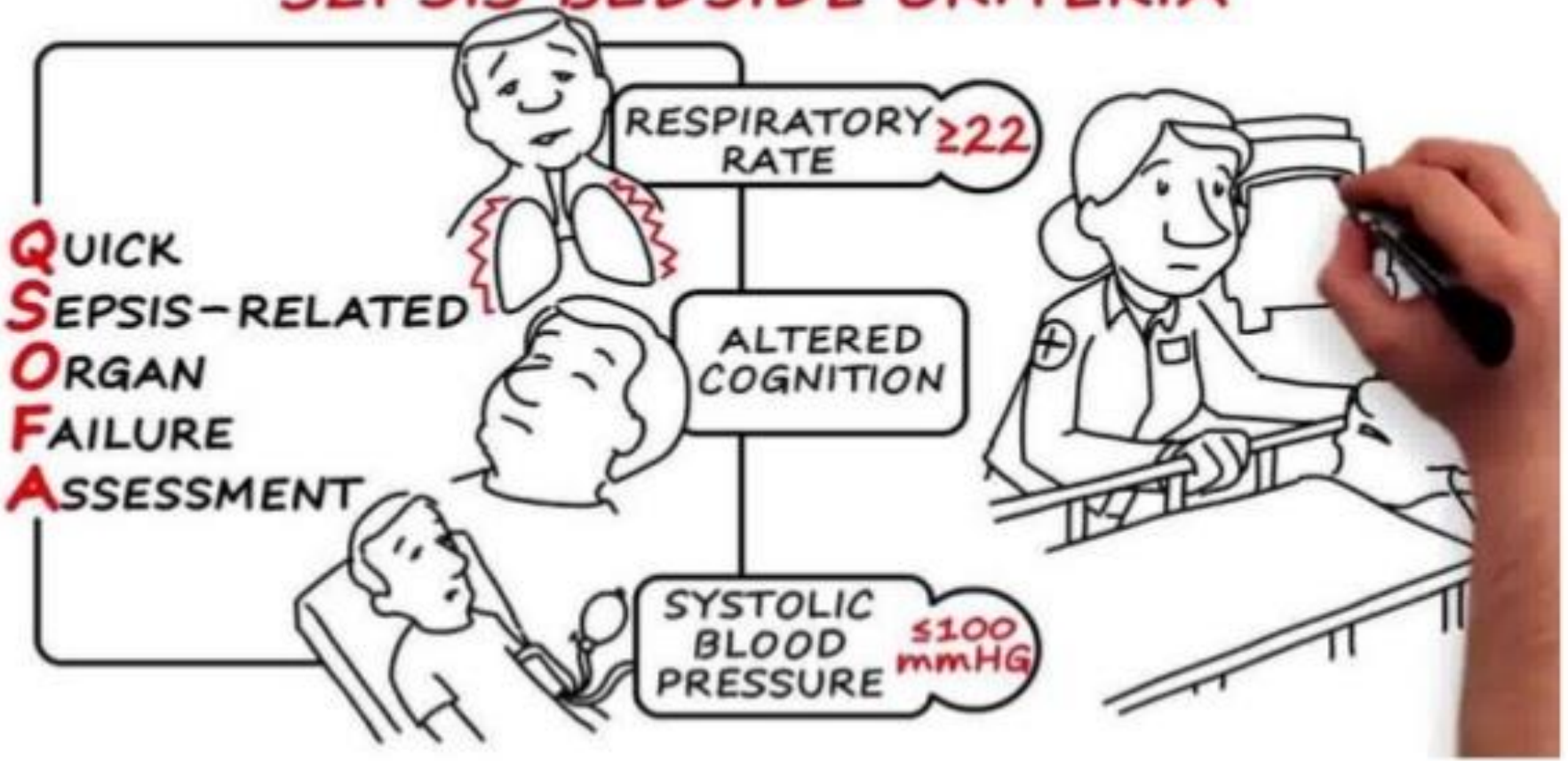
Why new scoring !!

To know what distinguishes sepsis from uncomplicated infection as simple infection

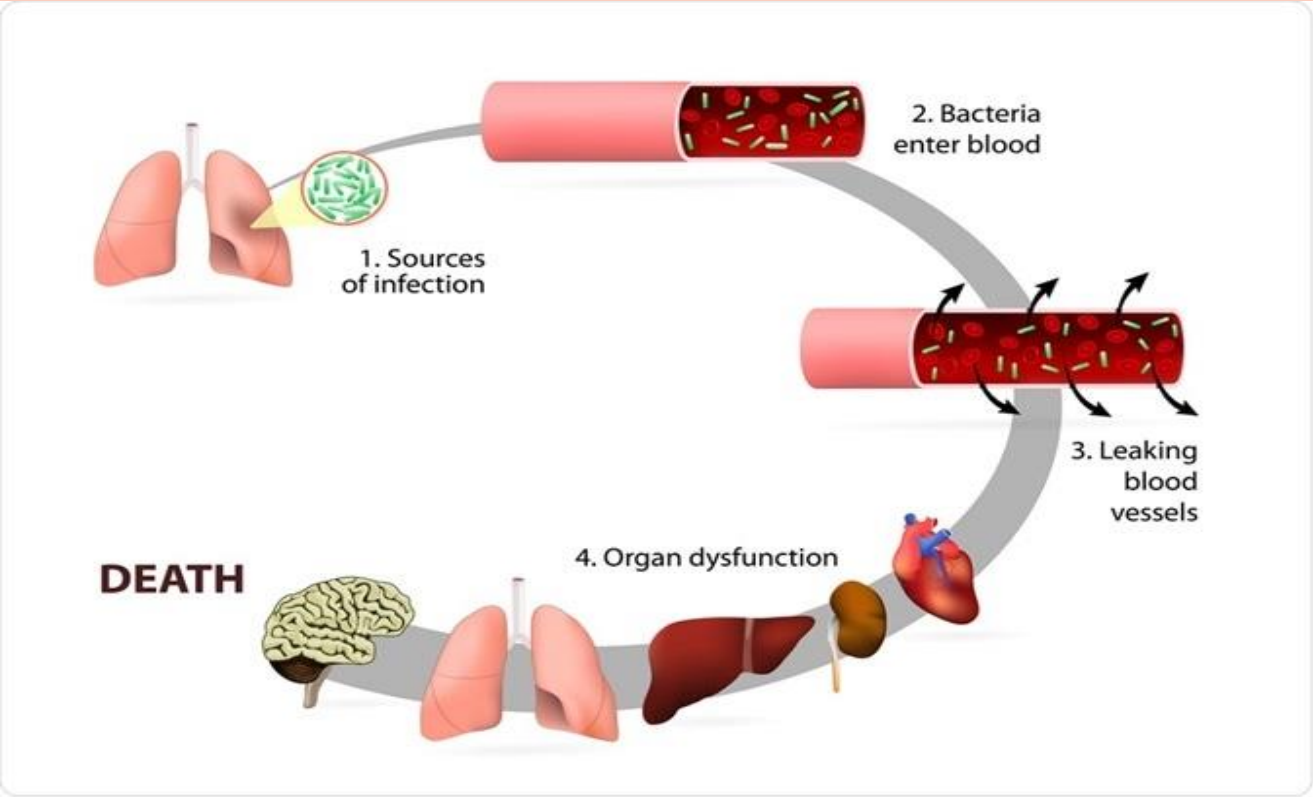
(which could simply controlled by rest and cup of hot tea!!)

- *“We need to differentiate a straightforward infection from one that can cause organ dysfunction or death”*

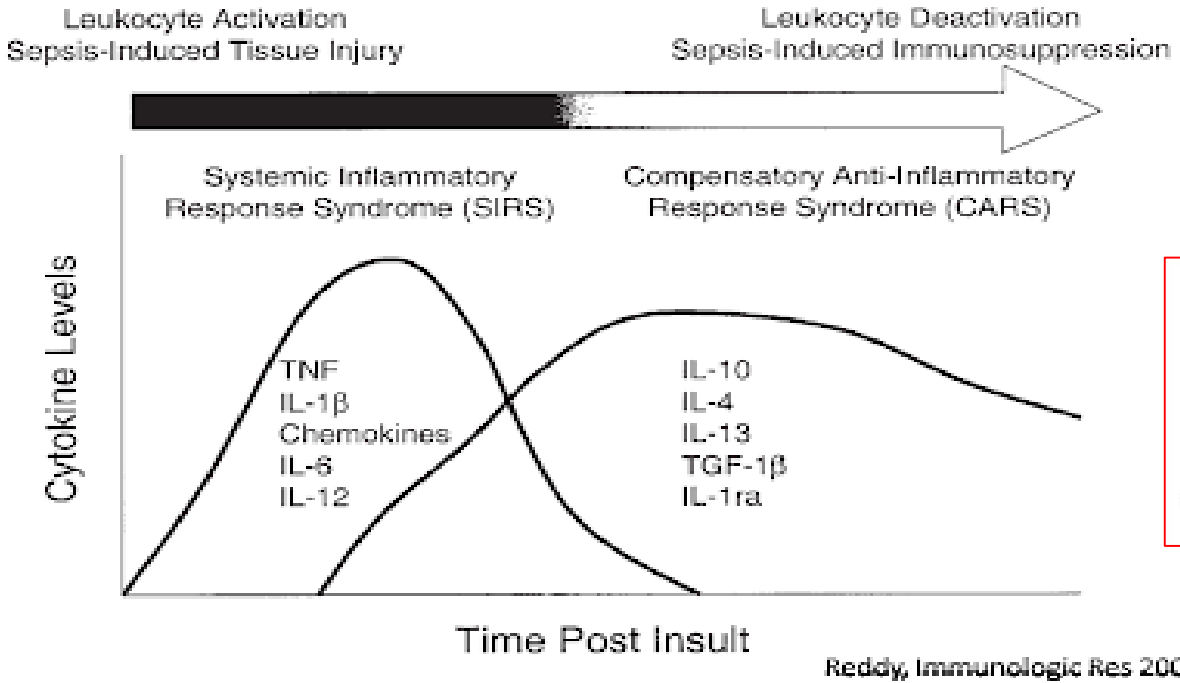
SEPSIS BEDSIDE CRITERIA



What Happens in Sepsis



ROLE OF CYTOKINES IN SEPSIS



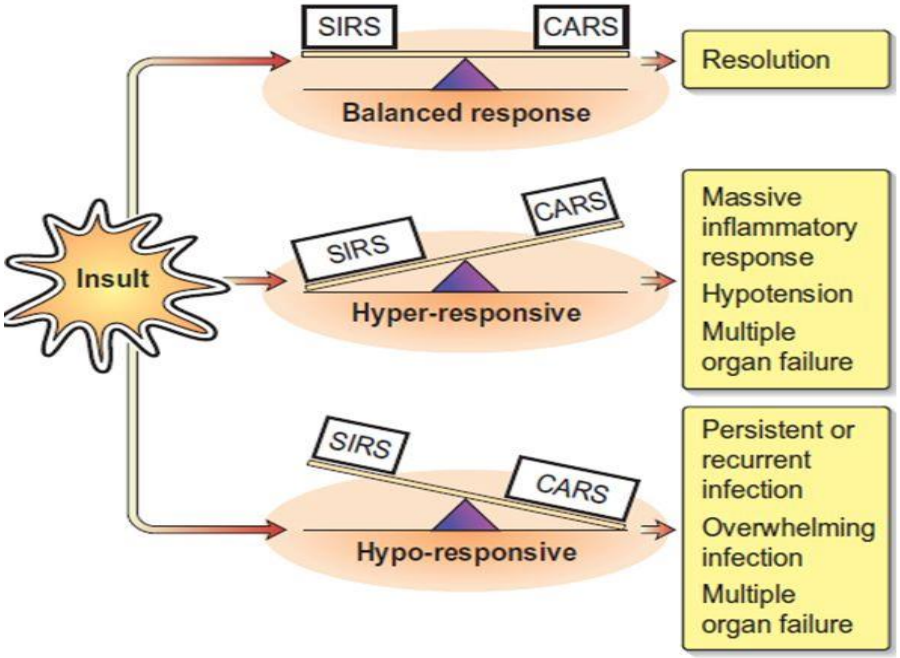
Reddy, Immunologic Res 2009

Proinflammatory	Antiinflammatory
TNF-alfa	TNF-ra
IL-1	IL-1ra
IL-6	IL-4
IL-8	IL-10
PAF	IL-13
Endothelium-derived relaxing factor	

The immunopathology of sepsis and potential therapeutic targets , NATURE REVIEWS/ IMMUNOLOGY-2017

In acute phase of sepsis

Pattern of systemic inflammatory response



CARS: compensatory anti-inflammatory response syndrome;

SIRS: systemic inflammatory response syndrome.

How do we manage sepsis and septic shock?

1) Investigate and treat sepsis
   - Try and find and treat source
   - Early blood cultures
   - Start antibiotics asap ideally within 1 hour and after cultures taken
2) Assess extent of end organ hypoperfusion and improve oxygen delivery (early goal directed therapy)

Fluid therapy

Fluid therapy

- Administer **30 mL/kg crystalloids** within three hours of confirmed or suspected sepsis or sepsis related hypo-perfusion. **(FLUID OF CHOICE)**

- ***Tip*:** Crystalloids refer to IV fluids with a balanced electrolyte composition, such as **normal saline** or **ringer lactate solution** (as opposed to colloids, such as albumin or hetastarch).

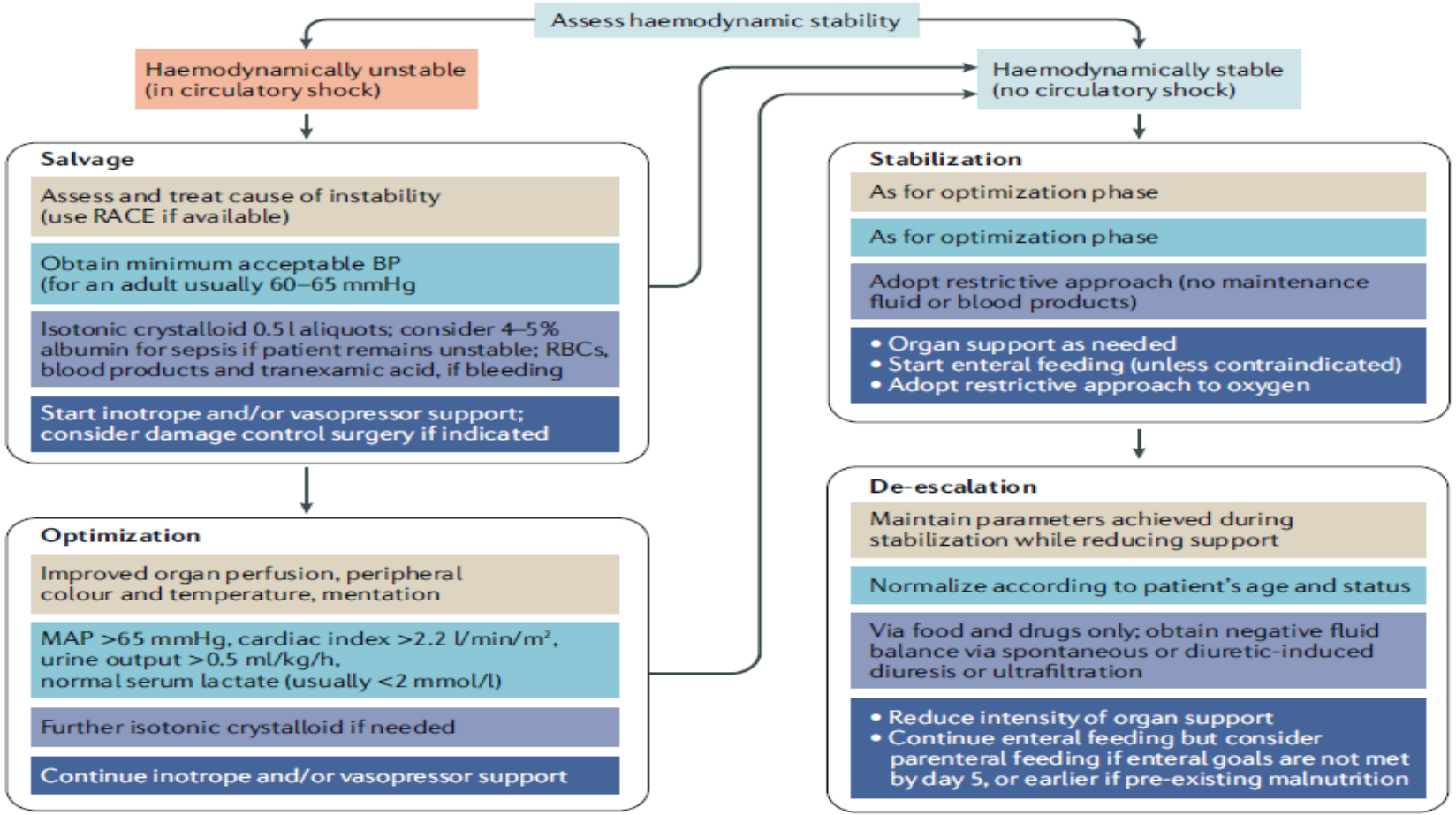
- in most patients, **buffered salt solutions** seem to **offer benefits over normal saline.**

Fluid therapy

Fluid management differs in the four phases of shock:

1) salvage
2) optimization
3) stabilization
4) de- escalation

Administration of fluid boluses is appropriate in the salvage and optimization phases, but each bolus should be followed by reassessment of the need for ongoing fluid administration.


Assess haemodynamic stability
Haemodynamically unstable (in circulatory shock)
Haemodynamically stable (no circulatory shock)
Salvage
Assess and treat cause of instability (use RACE if available)
Obtain minimum acceptable BP (for an adult usually 60–65 mmHg
Isotonic crystalloid 0.5 l aliquots; consider 4–5% albumin for sepsis if patient remains unstable; RBCs, blood products and tranexamic acid, if bleeding
Start inotrope and/or vasopressor support; consider damage control surgery if indicated
Optimization
Improved organ perfusion, peripheral colour and temperature, mentation
MAP >65 mmHg, cardiac index >2.2 l/min/m², urine output >0.5 ml/kg/h, normal serum lactate (usually <2 mmol/l)
Further isotonic crystalloid if needed
Continue inotrope and/or vasopressor support
Stabilization
As for optimization phase
As for optimization phase
Adopt restrictive approach (no maintenance fluid or blood products)
• Organ support as needed
• Start enteral feeding (unless contraindicated)
• Adopt restrictive approach to oxygen
De-escalation
Maintain parameters achieved during stabilization while reducing support
Normalize according to patient's age and status
Via food and drugs only; obtain negative fluid balance via spontaneous or diuretic-induced diuresis or ultrafiltration
• Reduce intensity of organ support
• Continue enteral feeding but consider parenteral feeding if enteral goals are not met by day 5, or earlier if pre-existing malnutrition
Therapeutic goals
Haemodynamic and other targets
Fluid therapy
Additional treatments

Conservative Versus Liberal Approach to Fluid Therapy of Septic Shock

- In support of a conservative approach, the results of the pilot Conservative Versus Liberal Approach to Fluid Therapy of Septic Shock in Intensive Care (CLASSIC) trial showed that AKI occurred less often in patients with septic shock who were randomly assigned to a restrictive fluid strategy.

- In this trial, the median volume of resuscitation fluid given in the fluid restriction group was 500 ml compared with 2,200 ml in the standard care group.
- Similar findings were reported in a study of patients with acute lung injury, in whom the mean cumulative fluid balance during the first 7 days was −136 ml in the restrictive strategy group and +6,692 ml in the liberal strategy group

Hjortrup, P. B. et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel- group, multicentre feasibility trial. *Intensive Care Med.* **42**, 1695–1705 (2016)14

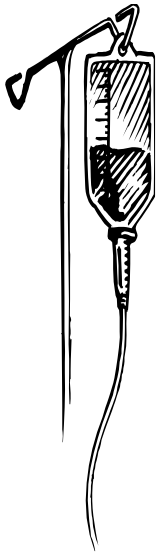
Fluid therapy

- The aggregated data from three large trials of early goal-directed therapy (EGDT), which mandates the use of aggressive fluid therapy in patients who present to emergency departments with septic shock, found no beneficial effect of EGDT on mortality or organ function, including renal function.

- Collectively, these trials call into question the assumption that liberal use of high-volume fluid resuscitation is beneficial, particularly in patients with septic shock, the most common cause of AKI in critically ill patients

Intravenous fluid therapy in critically ill adults;Nature reviews,nephrology;2018

Fluid therapy



- Following initial resuscitation, hemodynamic assessment should be used to guide further fluid administration using invasive and non-invasive measures.
- Include clinical exam and evaluation of available physiologic variables including HRT, BP, MAP arterial oxygen saturation, RR, rapid assessment by cardiac echocardiography, temperature, and urine output.

Severe Sepsis/Septic Shock Bundle

Activate Within ONE hour of presentation

A-Blood cultures x 2 sets

Drawn before antibiotic and within 1 hr after **TOP** (time of presentation)

4 bottles total with minimum 8-10 mL/bottle

B-IV Broad Spectrum Antibiotic

Start within **1 hr** after **TOP** unless given within past 24 hours

C-Lactate

Drawn within 1 hr after **TOP**

Require 2-5mL blood in GREY top tube: Immediately put sample on ICE & transport to lab for analysis.

If initial Lactate >18, then repeat within 3 hrs after 1st lactate draw

C-IV fluid bolus (0.9% NS or LR)

Min 30 mL/kg only if Septic Shock present

Start within 1 hr after **TOP** and complete within 3 hrs

The Surviving Sepsis Campaign Bundle:2018 Update,critical care medicine,2018

ANTIMICROBIAL THERAPY

The empiric choice of antimicrobials should consider:

- Site of infection
- Previous antibiotic use
- Local pathogen susceptibility patterns
- Immunosuppression
- Risk factors for resistant organisms

ANTIMICROBIAL THERAPY

- **Double gram-negative coverage may be appropriate when a high degree of suspicion exists for infection with multi-drug-resistant organisms such as Pseudo-monas or Acinetobacter.**

- **If a nosocomial source of infection is suspected to be the cause of sepsis, anti-MRSA agents are recommended.**

Guidelines for Management of Sepsis and Septic Shock 2021

1. For adults with sepsis or septic shock and high risk for multidrug resistant (MDR) organisms, we suggest using two antimicrobials with gram-negative coverage for empiric treatment over one gram-negative agent.
2. For adults with sepsis or septic shock and low risk for multidrug resistant (MDR) organisms, we suggest against using two gram-negative agents for empiric treatment, as compared to one gram-negative agent.
3. For adults with sepsis or septic shock at high risk of fungal infection, we suggest using empiric antifungal therapy over no antifungal therapy

Guidelines for Management of Sepsis and Septic Shock 2021

4. 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.

5. 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.

Empiric Antimicrobials with MRSA Coverage

- Prior history of MRSA infection or colonization
- Recent IV antibiotics
- History of recurrent skin infections or chronic wounds
- Presence of invasive devices
- Hemodialysis
- Recent hospital admissions
- Severity of illness

Consider antifungals

- The last few decades have seen a 200% rise in the incidence of sepsis due to fungal organisms.
- Antifungals should be considered for patients at risk, such as those who have had total parenteral nutrition, recent broad-spectrum antibiotic exposure, perforated abdominal viscus, or immunocompromised status, or when clinical suspicion of fungal infection is high.
- Risk factors for fungal infection in septic shock should trigger the addition of echinocandins or liposomal amphotericin B. Azoles are considered appropriate for hemodynamically stable patients

Examples of Risk Factors for Fungal Infection

Risk Factors for Candida Sepsis

- ✓ Candida Colonization at Multiple Sites
- ✓ Surrogate Markers Such as Serum Beta-D-Glucan Assay
- ✓ Neutropenia
- ✓ Immunosuppression
- ✓ Severity of Illness (High APACHE score
- ✓ Longer ICU Length of Stay
- ✓ Central Venous Catheters and Other Intravascular Devices
- ✓ Persons Who Inject Drugs
- ✓ Total Parenteral Nutrition
- ✓ Broad Spectrum Antibiotics
- ✓ Gastrointestinal Tract Perforations and Anastomotic Leaks
- ✓ Emergency Gastrointestinal or Hepatobiliary Surgery
- ✓ Acute Renal Failure and Hemodialysi
- ✓ Severe Thermal Injur
- ✓ Prior Surgery

Lactate level as a resuscitation guide

- Lactate-guided resuscitation can significantly lessen the high mortality rate associated with elevated lactate levels (> 4 mmol/L).36,37 A rise in lactate during sepsis can be due to tissue hypoxia, accelerated glycolysis from a hyper-adrenergic state, medications (epinephrine, beta-2 agonists), or liver failure.

- Measuring the lactate level is an objective way to assess response to resuscitation, better than other clinical markers.

Guidelines for Management of Sepsis and Septic Shock 2021

1. For adults with sepsis or septic shock we recommend using a restrictive (over liberal) transfusion strategy.
2. For adults with sepsis or septic shock we suggest against using IV immunoglobulins.
3. For adults with sepsis or septic shock, and who have risk factors for gastrointestinal (GI) bleeding, we suggest using stress ulcer prophylaxis.
4. For adults with sepsis or septic shock, we recommend using pharmacologic venous thromboembolism (VTE) prophylaxis unless a contraindication to such therapy exists.
5. For adults with sepsis or septic shock, we recommend using low molecular weight heparin over unfractionated heparin for VTE prophylaxis

Guidelines for Management of Sepsis and Septic Shock 2021

6. For adults with septic shock and an ongoing requirement for vasopressor therapy we suggest using IV corticosteroids.
7. In adults with sepsis or septic shock and AKI, we suggest using either continuous or intermit-tent renal replacement therapy.
8. For adults with sepsis or septic shock, we recommend initiating insulin therapy at a glucose level of ≥ 180mg/dL (10 mmol/L).
9. For adults with septic shock and severe metabolic acidemia (pH ≤ 7.2) and acute kidney injury (AKIN score 2 or 3), we suggest using sodium bicarbonate therapy.
10. For adult patients with sepsis or septic shock who can be fed enterally, we suggest early (within 72 hr) initiation of enteral nutrition.

Guidelines for Management of Sepsis and Septic Shock 2021

1. For adults with septic shock, we recommend using norepinephrine as the first-line agent over other vasopressors.
2. For adults with septic shock and inadequate mean arterial pressure levels despite norepinephrine and vasopressin, we suggest adding epinephrine.
3. For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we suggest either adding dobutamine to norepinephrine or using epinephrine alone.

Source control

1. Rainage of an abscess
2. Debriding infected necrotic tissue, removal of a potentially infected device
3. Intra-abdominal abscesses
4. Gastrointestinal perforation
5. Ischemic bowel or volvulus
6. Cholangitis
7. Cholecystitis
8. Pyelonephritis associated with obstruction

Immunomodulation as a treatment for sepsis

New Insights

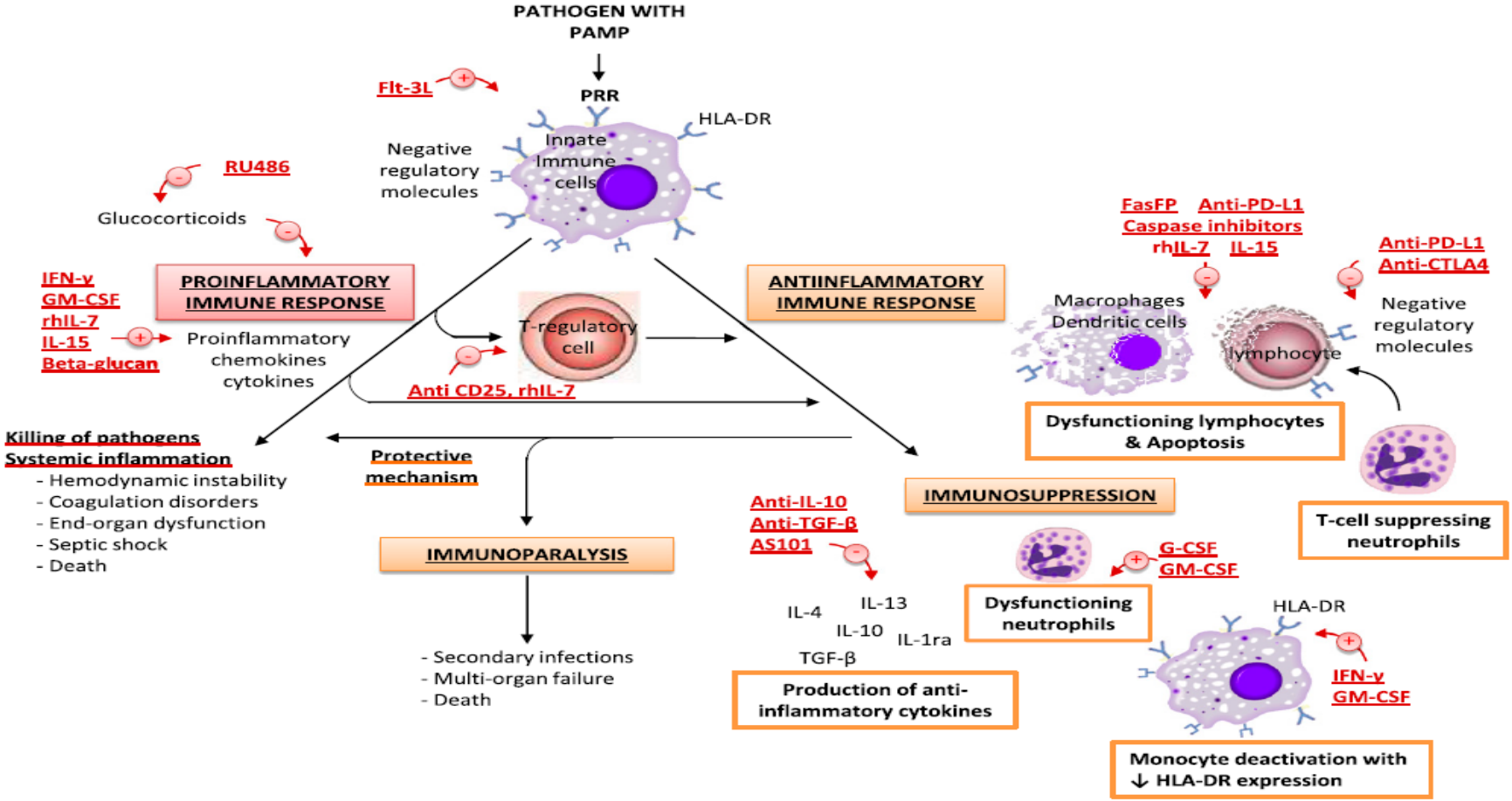
Immunomodulation as a treatment for sepsis

- The unsuccessful clinical trials that tested various anti-inflammatory agents have shown that curbing excessive inflammation cannot improve outcome in all patients with sepsis and identification of sub-cohorts on the basis of the disease severity itself is not optimal.

- Conversely, the more functionally specific immune status based criteria should be better suited to stratify patients for immunotherapy.

- Other investigators advocate the use of immune-stimulatory approaches to restore defective immune functions, subsequently reducing susceptibility to secondary infection and late sepsis mortality

Current gaps in sepsis immunology: new opportunities for translational research. *Ignacio Rubio, Marcin F Osuchowski, Manu Shankar-Hari, Tomasz Skirecki ;et al ;2019*



Immunotherapy for the Adjunctive Treatment of Sepsis:From Immunosuppression to ImmunostimulationAMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE,2013

Biomarkers to Stratify the Immune Status in Sepsis Patients

- **Evaluate PD-1 and PD-L1 expression and lymphocytes counts** to select potential patients for treatment with **Check-point inhibitors;**
- **Evaluate expression of IL-7 in plasma or expression of its receptor** to select potential patients for treatment with **IL-7;**
- **Assess concentrations of endogenous immunoglobulins** to select patients for treatment with intravenous **Immunoglobulins;**
- **Assess expression of HLA-DR in monocytes** to identify patients for treatment with **GM-CSF**

Current gaps in sepsis immunology: new opportunities for translational research. *Ignacio Rubio, Marcin F Osuchowski, Manu Shankar-Hari, Tomasz Skirecki ;et al ;2019*

Examples of immunotherapy in sepsis.

	Mechanism of action	Summary of evidence
IMMUNOSUPPRESSIVE COMPOUNDS		
anti-TNFα (various)	Blocks pro-inflammatory effects of TNFα	- Individual studies: no beneficial effects (94) - Meta-analysis: reduced 28-day mortality, OR = 0.91 [95% CI 0.83–0.99] (94)
IL-1RA (anakinra)	Blocks IL-1 receptor → inhibits downstream pro-inflammatory effects	- Study in unselected population of severe sepsis patients: no effect on mortality (21) - *Post-hoc* analysis in subgroup of hyperinflamed patients with macrophage activation syndrome: lower mortality (93)
IMMUNOSTIMULATORY COMPOUNDS		
GM-CSF	Enhances antigen presenting capacity and pro-inflammatory cytokine production	- Meta-analysis: no effect on 28-day mortality in sepsis patients (probably underpowered) (107) - Biomarker-guided study (based on mHLA-DR expression): restoration of monocytic immunocompetence, shorter duration of mechanical ventilation, and more swift improvement of disease severity scores as exploratory endpoints (95)
IFN-γ	Enhances antigen presenting capacity and pro-inflammatory cytokine production	- Human endotoxemia model (mimicking sepsis-induced immunoparalysis): increased mHLA-DR expression, restored TNFα production and further attenuated IL-10 production (43) - Case series in patients suffering from opportunistic infections not responding to regular treatment: increased mHLA-DR expression and cytokine production by *ex vivo*-stimulated leukocytes (97)
Recombinant human IL-7	Reduces apoptosis and enhances lymphocyte function	- Phase 2 trial in septic shock patients with severe lymphopenia: safe, well-tolerated and reversal of lymphopenia (111)
anti-PD-(L)1	Inhibits PD-1-PD-L1 interaction → reduces apoptosis and promotes T-cell responses	- Preclinical data in sepsis models: promising results (e.g., prevention of sepsis-induced depletion of lymphocytes, increased TNF-α and IL-6 production, decreased IL-10 production, enhanced bacterial clearance, improved survival (102) - Clinical data in the oncology field: effective, especially in advanced melanoma and non-small cell lung cancer. - No clinical trials in sepsis patients yet.

Precision Immunotherapy for Sepsis;Frontier in immunology,2018

Sepsis-3
Surviving sepsis campain