INTERNATIONAL GUIDELINES FOR MANAGEMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

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Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012

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- **Sepsis :** presence (probable or documented) of infection together with systemic manifestations of infection.
- **Severe sepsis** : sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion.
- **Septic shock :** sepsis-induced hypotension persisting despite adequate fluid resuscitation.
- **Sepsis-induced tissue hypoperfusion :** infection-induced hypotension, elevated lactate, or oliguria.

- Sepsis is characterized by a systemic inflammatory reaction which involves complex interactions between endothelial cells, platelets leukocytes, coagulation system, and multiple inflammatory mediators.

- Worldwide, the annual incidence of severe sepsis is considered to be in the range of 3/1000 inhabitants .

- In the United States, it is considered the most common cause of death in critically ill patients and is associated with a mortality rate of around 11%.

- Sepsis may proceed to severe sepsis, septic shock and, finally, to multiple organ failure (MOF).
- The progression to severe sepsis and septic shock has been associated with mortality rates of 50% and 68%,respectively

Diagnostic Criteria for Sepsis

Infection, documented or suspected, and some of the following:

General variables

- Fever (> 38.3°C)
- Hypothermia (core temperature < 36°C)
- Heart rate > 90/min–1 or more than two sd above the normal value for age
- Tachypnea
- Altered mental status
- Significant edema or positive fluid balance (> 20 mL/kg over 24 hr)
- Hyperglycemia (plasma glucose > 140 mg/dL or 7.7 mmol/L) in the absence of diabetes

Diagnostic Criteria for Sepsis(cont.)

Inflammatory variables

- Leukocytosis (WBC count > 12,000 μL–1)
- Leukopenia (WBC count < 4000 μL–1)
- Normal WBC count with greater than 10% immature forms
- Plasma C-reactive protein more than two sd above the normal value
- Plasma procalcitonin more than two sd above the normal value

Hemodynamic variables

- Arterial hypotension (SBP < 90 mm Hg, MAP < 70 mm Hg, or an SBP decrease > 40 mm Hg in adults or less than two sd below normal for age)

Diagnostic Criteria for Sepsis(cont.)

Organ dysfunction variables

- Arterial hypoxemia (Pao2/Fio2 < 300)
- Acute oliguria (urine output < 0.5 mL/kg/hr for at least 2 hrs despite adequate fluid resuscitation)
- Creatinine increase > 0.5 mg/dL or 44.2 μmol/L
- Coagulation abnormalities (INR > 1.5 or aPTT > 60 s)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count < 100,000 μL–1)
- Hyperbilirubinemia (plasma total bilirubin > 4 mg/dL or 70 μmol/L)

Tissue perfusion variables

- Hyperlactatemia (> 1 mmol/L) Decreased capillary refill or mottling

Adapted from Levy MM, Fink MP, Marshall JC, et al: 2001 CCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003; 31:

Severe Sepsis

- Severe sepsis definition = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)
  - Sepsis-induced hypotension
  - Lactate above upper limits laboratory normal
  - Urine output < 0.5 mL/kg/hr for more than 2 hrs despite adequate fluid resuscitation
  - Acute lung injury with PaO2/FIO2 < 250 in the absence of pneumonia as infection source
  - Acute lung injury with PaO2/FIO2 < 200 in the presence of pneumonia as infection source
  - Creatinine > 2.0 mg/dL (176.8 μmol/L)
  - Bilirubin > 2 mg/dL (34.2 μmol/L)
  - Platelet count < 100,000 μL
- Coagulopathy (international normalized ratio > 1.5)

Adapted from Levy MM, Fink MP, Marshall JC, et al: 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003; 31

Recommendations: Initial Resuscitation and Infection Issues

1. Goals during the first 6 hrs of resuscitation:
   - a) Central venous pressure 8–12 mm Hg
   - b) Mean arterial pressure (MAP) ≥ 65 mm Hg
   - c) Urine output ≥ 0.5 mL/kg/hr
   - d) Central venous (superior vena cava) or mixed venous oxygen saturation 70% or 65%, respectively (grade 1C).
2. In patients with elevated lactate levels targeting resuscitation to normalize lactate (grade 2C)

- *Early goal-directed therapy*, was evaluated in a multicenter trial of 314 patients with severe sepsis in eight Chinese centers . This trial reported a 17.7% absolute reduction in 28-day mortality (survival rates, 75.2% vs. 57.5%)
  - There are limitations to CVP as a marker of intravascular volume status and response to fluids :
    - In mechanically ventilated patients
    - Known preexisting decreased ventricular compliance
    - Increased abdominal pressure
    - Preexisting clinically significant pulmonary artery hypertension.
  - Stroke volume variation, pulse pressure variation, and/or stroke volume variation and the change in stroke volume/cardiac index after a fluid or positive end-expiratory pressure challenge .
  - Utility of pulse pressure variation and stroke volume variation is limited in the presence of atrial fibrillation, spontaneous breathing, and low pressure support breathing.
  - Ultrasound can be used to assess the fullness of I.V.C.
  - Echocardiography ,is an accessible way to judge the volume status.
  - Pulmonary artery catheter may be used as well ?

Fluid Therapy of Severe Sepsis

6S Trial Group

Scandinavian multicenter study in septic patients showed increased mortality rates with 6% HES 130/0.42 fluid resuscitation compared to Ringer's acetate (51% vs. 43% $p = 0.03$)

Perner A,et al.*N Engl J Med* 2012;367:124–134

The CHEST study

Conducted in intensive care (HES vs. isotonic saline, $n = 7000$ critically ill patients), showed no difference in 90-day mortality between resuscitation with 6% HES with a molecular weight of 130 kD/0.40 and isotonic saline (18% vs. 17%,$p = 0.26$); the need for renal replacement therapy was higher in the HES group (7.0% vs. 5.8%)

Myburgh et al.*N Engl J Med* 2012; 367:1901–191

(*Continued*) Fluid Therapy of Severe Sepsis

CRYSTAL trial

Patients with severe sepsis assigned to fluid resuscitation with HES 130/0.42 had an increased risk of death at day 90 and were more likely to require renal replacement therapy compared with those receiving Ringer's acetate. At 90 days after randomization, 201 of 398 patients (51%) assigned to HES 130/0.42 had died, as compared with 172 of 400 patients (43%) assigned to Ringer's acetate;. In the 90-day period, 87 patients (22%) assigned to HES 130/0.42 were treated with renal replacement therapy versus 65 patients (16%) assigned to Ringer's acetate and 38 patients (10%) and 25 patients (6%), respectively, had severe bleeding .

Estrada et al, *Critical Care* 2013, **17**:310

- A meta-analysis aggregated data from 17 randomized trials (n = 1977) of albumin vs. other fluid solutions in patients with severe sepsis/septic shock 279 deaths occurred among 961 albumin-treated patients vs. 343 deaths among 1.016 patients treated with other fluids, thus favoring albumin

Delaney et al.*Crit Care Med* 2011; 39:386–391

Vasopressors

- Adequate fluid resuscitation is a fundamental aspect of the hemodynamic management of patients with septic shock and should ideally be achieved before vasopressors and inotropes are used; however, using vasopressors early as an emergency measure in patients with severe shock is frequently necessary.
- Vasopressor therapy initially target a MAP of 65 mm Hg
- **Norepinephrine** as the first-choice vasopressor.
- **Epinephrine** (added to and potentially substituted for Norepinephrine) when an additional agent is needed to maintain adequate blood pressure.
- **Vasopressin** (up to 0.03 U/min) can be added to norepinephrine with the intent of raising MAP to

(*Continued*) Vasopressors

Dopamine may be particularly useful in patients with compromised systolic function but causes more tachycardia and may be more arrhythmogenic than Norepinephrine.

- Dopamine may also influence the endocrine response via the hypothalamic pituitary axis and have immunosuppressive effects.

- Comparing Norepinephrine to Dopamine does not support the routine use of dopamine in the management of septic shock .

Phenylephrine is the adrenergic agent least likely to produce tachycardia, but it may decrease stroke volume and is therefore not recommended for use in the treatment of septic shock .

Low doses of **Vasopressin** may be effective in raising blood pressure in patients, refractory to other vasopressors .

Higher doses of vasopressin have been associated with cardiac, digital,and splanchnic ischemia.

Inotropic Therapy

Dobutamine infusion administered or added to vasopressor (if in use) in the presence of:

- Myocardial dysfunction, as suggested by elevated cardiac filling pressures and low cardiac output, or
- Ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP.

- Large prospective clinical trials, which included critically ill ICU patients who had severe sepsis, failed to demonstrate

Corticosteroids

- Vasopressor-unresponsive septic shock (hypotension despite fluid resuscitation and vasopressors for more than 60 mins) showed significant shock reversal and reduction of mortality rate in patients with relative adrenal insufficiency .

Annane et al. *JAMA* 2002; 288:862–871

- ACTH stimulation test to identify the subset of adults with septic shock who should receive hydrocortisone?

- Etomidate,when used for induction for intubation, will suppress the hypothalamic-pituitary-adrenal axis. The CORTICUS revealed that the use of Etomidate before application of low-dose steroids was associated with an increased 28-day mortality rate.

(*Continued*)Recommendations: Initial Resuscitation and Infection Issues

Screening for Sepsis and Performance Improvement

- Routine screening of potentially infected seriously ill patients for severe sepsis to allow earlier implementation of therapy (grade 1C).

- Hospital–based performance improvement efforts in severe sepsis (UG).

(*Continued*)Recommendations: Initial Resuscitation and Infection Issues

- **Diagnosis**

- Cultures as clinically appropriate before antimicrobial therapy if no significant delay (> 45 mins) in the start of antimicrobial(s) (grade 1C). At least 2 sets of blood cultures (both aerobic and anaerobic bottles) be obtained before antimicrobial therapy with at least 1 drawn percutaneously and 1 drawn through each vascular access device, unless the device was recently (<48 hrs) inserted (grade 1C).
- Use of the 1,3 beta-D-glucan assay (grade 2B), mannan and anti-mannan antibody assays (2C), if available and invasive candidiasis is in differential diagnosis of cause of infection.
- Imaging studies performed promptly to confirm a potential source of infection (UG).

(*Continued*)Recommendations: Initial Resuscitation and Infection Issues

- Administration of effective intravenous antimicrobials within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C) as the goal of therapy.
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- Initial empiric anti-infective therapy of one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis (grade 1B).
- Antimicrobial regimen should be reassessed daily for potential de-escalation (grade 1B).
- Use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection (grade 2C).
- Combination empirical therapy for neutropenic patients with severe sepsis (grade 2B) and for patients with difficult-to-treat, multidrugresistant bacterial pathogens (grade 2B).
- Empiric combination therapy should not be administered for more than 3–5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known (grade 2B).
- Duration of therapy typically 7–10 days; (grade 2C).
- Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin (grade 2C).
- Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of noninfectious cause (UG).

(*Continued*)Recommendations: Initial Resuscitation and Infection Issues

- **Infection Prevention**

- Selective oral decontamination and selective digestive decontamination should be introduced and investigated as a method to reduce the incidence of ventilator-associated pneumonia. (grade 2B).

- Oral chlorhexidine gluconate be used as a form of oropharyngeal decontamination to reduce the risk of ventilator-associated pneumonia in ICU patients with severe sepsis (grade 2B).

- The efficacy of SDD, its safety, propensity to prevent or promote antibiotic resistance, and cost-effectiveness remain
- debatable despite a number of favorable meta-analyses and controlled clinical trials.
- There is a reduction with SDD in VAP but no consistent improvement in mortality, except in selected populations in some studies.
- Oral CHG is relatively easy to administer, decreases

Blood product administration

- During the resuscitative phase of septic shock, Hematocrit of 30% is recommended to increase the oxygen delivery.
- Once tissue hypoperfusion has resolved ,red blood cell transfusion occurs when the hemoglobin concentration decreases to 70.0 g/L .
- No significant differences in 30-day mortality rates were observed when the target level is 100g/L.
- Top up the hemoglobin level to 100g/L does not increase the oxygen

Blood product administration(Cont.)

- In the absence of apparent bleeding, platelets be administered prophylactically when counts are less than 10 x 109/L .
- Fresh frozen plasma, do we really need it?
- Immunoglobulins !

(*Continued*) Recommendations: Mechanical ventilation of sepsis-induced acute respiratory distress syndrome

- Target a tidal volume of 6 mL/kg predicted body weight in patients with sepsis-induced ARDS .
- Plateau pressures be ≤30 cm H2O (grade 1B).
- Positive end-expiratory pressure (PEEP) be applied to avoid alveolar collapse at end expiration (atelectotrauma) (grade 1B).
- Strategies based on higher rather than lower levels of PEEP be used for patients with sepsis- induced moderate or severe ARDS (grade 2C).
- Recruitment manoeuvres be used in sepsis patients with severe refractory hypoxemia (grade 2C).
- Prone positioning be used in sepsis-induced ARDS patients with a PaO2/FIO2 ratio ≤100 mm Hg(grade 2B).

Mechanical Ventilation

- The use of lung-protective strategies for patients with ARDS showed an absolute 9 % decrease in all-cause mortality in patients with ARDS ventilated with tidal volumes of 6 mL/kg compared with 12 mL/kg of predicted body weight.

Ranieri et al (2012) JAMA 307:25226–25233

- Patients with profound metabolic acidosis, high obligate minute ventilations, or short stature may require additional manipulation of tidal volumes.

- Permissive Hypercapnia.

- Patients with moderate or severe ARDS (Pao2/FIo2 ratio ≤200 mm Hg) had decreased mortality with the use of higher PEEP, whereas those with mild ARDS did not.

Briel M, Meade et al,(2010) JAMA 303:865–873

Mechanical Ventilation (Cont.)

- Extracorporeal membrane oxygenation , may be considered as rescue therapies in centers with expertise and experience with their use .
- Inhaled nitric oxide does not improve mortality rates in patients with ARDS.
- Conservative fluid strategy for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion.

β2-agonist therapy in patients with ARDS

In BALTI-2 study, Salbutamol increased 28-day mortality (55 [34%] of 161 patients died in the salbutamol group vs 38 (23%) of 163 in the placebo group.

Gao et al,(2012) Lancet. 21;379(9812):229-3

ALTA trial.7(2012) This prospective, randomized, multicenter trial of aerosolized albuterol (5 mg four-hourly) versus placebo for acute lung injury (defined as PaO2/FiO2 <300 mm Hg . clinical outcomes were worse in the albuterol group.

http://clinicaltrials.gov/ct2/show/NCT00434993

β2-agonist therapy in patients with ARDS should be limited to the treatment of clinically

Glucose Control

- **The *NICE-SUGAR trial* (2009): A blood glucose target of 4.5 – 6.0 mmol/L (81-108 mg/dL) resulted in increased mortality compared to a target of <10.0mmol/L (180 mg/dL)**. Griesdale DEG, de Souza RJ, van

Dam RM et al (2009) CMAJ 180:821–827

- Intensive insulin therapy was not associated with a mortality benefit in surgical, medical, or mixed ICU patients.

Marik PE (2010) Chest 137:544–551

- A meta-analysis using between-trial comparisons found that intensive insulin therapy was beneficial in surgical ICU patients [risk ratio 0.63 (0.44–0.9)].

Griesdale et al(2009) CMAJ180:821–827

- The meta- analysis by, using within-trial comparisons, showed no benefit for surgical patients in mixed medical-surgical ICUs [risk ratio 0.99 (0.82–1.11)] and no subgroup of surgical patients who benefited from intensive insulin therapy.

Nutrition

Early enteral nutrition has theoretical advantages in:

- Integrity of gut mucosa and prevention of bacterial translocation and organ dysfunction
- Reduced incidence of infectious complications.
- Reduced length of mechanical ventilation.
- Reduced ICU stays.
- Reduced hospital stays.

EDEN randomized trial Underfeeding (60–70 % of target) or trophic feeding (upper limit of 500 kcal) is probably a better nutritional strategy in the first week of severe sepsis/septic shock.

Rice et al (2012) JAMA 137:795–803

Early initiation of parenteral nutrition led to longer hospital and ICU stays, longer duration of organ support, and higher incidence of ICU-acquired

Renal Replacement Therapy

- Severe sepsis and septic shock are associated with AKI in 5–50% of the patients and the risk increases with positive blood cultures and worsening clinical signs of sepsis .
- 50% of the cases of newly onset AKI in the intensive care unit (ICU) do occur as a consequence of sepsis.
- 70% of patients with AKI developed MOF, whereas this was only the case in 10% of the patients without AKI.
- ICU mortality of critically ill patients with AKI is reported as roughly 60% .Mortality from septic shock in combination with AKI is even higher at roughly 75%.
- The role of continuous renal replacement therapy (CRRT) in sepsis and MOF has two major aspects:

First : from the point of renal replacement therapy (RRT) per se

second : as an immunomodulatory tool helping to influence the systemic consequences of severe sepsis

THANK YOU