The Surviving Sepsis Campaign (SSC) is a global initiative to bring together professional organizations to reduce mortality from sepsis (45-50% for septic shock) \(^1\). Phase I was initiated in October 2002 with the Barcelona Declaration. In Phase II, a group of international critical care and infectious disease experts representing 11 organizations developed evidence-based guidelines that the bedside clinician could use to improve outcome in severe sepsis and septic shock. They gathered data from June-December 2003 and published the guidelines in 2004 \(^2\) with a stated goal to achieve 25% reduction in sepsis mortality by 2009.

In 2006 and 2007, the Committee met for updates resulting in “SSC-International guidelines for management of severe sepsis and septic shock: 2008” \(^3\) which adapted the Modified Delphi method and used the GRADE system to qualify evidence from high (A) to very low (D) and to determine the strength of recommendations as mentioned in Table I. They are applicable for both ICU and pre ICU settings.

The recommendations are outlined below (with their grades in bold):
I. Management of severe sepsis
II. Supportive Therapy of severe sepsis

I. Management of severe sepsis
A. Initial resuscitation:
Early Goal Directed Therapy (EGDT) is given in Fig.1. Briefly, it advocates a 20-40 ml/kg fluid challenge if SBP < 90 mmHg or lactic acid > 4 mmol/lit, without pending ICU admission (1C), followed by antibiotic coverage within 1st hour (1D for severe sepsis, 1B for septic shock), Central Venous Pressure (CVP) goal of > 8-12 mmHg (1C), vasopressors if Mean Arterial Pressure (MAP) < 65 mmHg (1C) and packed cells to maintain hematocrit > 30% (1C). Ionotropes may be used if central venous oxygen saturation (ScvO2) of ≥ 70% or mixed venous oxygen ≥ 65% is not achieved \(^3,4\).

B. Diagnosis:
To optimize identification of causative organisms, at least two blood cultures >10ml should be obtained with at least one drawn percutaneously and one drawn through each vascular access device, unless the device was recently (48 hrs) inserted. Other cultures (urine, respiratory secretions, wounds) are obtained in relevant settings. Imaging studies (preferably bedside ultrasound) may be useful to determine source of infection for sampling (1C). \(^5\)

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**Table I. Determination of the quality of evidence: SSC 2008**

<table>
<thead>
<tr>
<th>Underlying methodology</th>
<th>Evidence strength</th>
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<tbody>
<tr>
<td>A. RCT</td>
<td>A</td>
</tr>
<tr>
<td>B. Downgraded RCT or upgraded observational studies</td>
<td>B</td>
</tr>
<tr>
<td>C. Well-done observational studies</td>
<td>C</td>
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<tr>
<td>D. Case series or expert opinion</td>
<td>D</td>
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Main factors that may increase the strength of evidence:
1. Large magnitude of effect (direct evidence, RR > 2 with no plausible confounders)
2. Very large magnitude of effect with RR > 5 and no threats to validity (by two levels)
3. Dose-response gradient

Venous Pressure (CVP) goal of > 8-12 mmHg (1C), vasopressors if Mean Arterial Pressure (MAP) < 65 mmHg (1C) and packed cells to maintain hematocrit > 30% (1C). Ionotropes may be used if central venous oxygen saturation (ScvO2) of ≥ 70% or mixed venous oxygen ≥ 65% is not achieved \(^3,4\).
Fig. 1: Suspected Infection

The high risk patient:
SBP < 90 mmHg after 20-40 cc/kg volume challenge or lactic acid > 4 mmole/liter

Antibiotics within 1 hr and Source control

- **CVP**
  - < 8 mmHg: Crystalloid
  - > 8-12 mmHg

- **MAP**
  - < 65 or > 90 mmHg: Vasoactive Agent(s)
  - > 90 mmHg

- **ScvO₂**
  - < 70%

Goals Achieved

No

EARLY GOAL DIRECTED THERAPY

Packed red Blood cells to Hct > 30%

Ionotrope (s)
C. Antibiotic Therapy:
1) Intravenous antibiotic therapy should be started within the first hour of recognition of severe sepsis, after appropriate cultures have been obtained.
2) Initial empirical anti-infective therapy should include one or more drugs that have activity against the likely pathogens (bacterial or fungal) and that penetrate into the presumed source of sepsis, their choice guided by the susceptibility patterns of microorganisms in the community and in the hospital. Broad-spectrum antibiotics are warranted only in severe sepsis or septic shock till antibiotic susceptibilities of causative organism are defined.
3) Later, de-escalation in both choice and number of antibiotics is an important and responsible strategy to minimize the development of resistant pathogens and costs.
4) The duration of therapy should be 7-10 days with dose adjustment as per renal and hepatic profile. A narrow spectrum antibiotic should be substituted to minimize development of superinfection with pathogenic or resistant organisms such as Candida species, Clostridium difficile, or vancomycin-resistant Enterococcus (VRE). Consider combination therapy in Pseudomonas infections and neutropenic patients.
5) Stop antimicrobial therapy, if the cause is found to be non-infectious.

D. Source Control:
A specific anatomic site of infection should be established as rapidly as possible and within first 6 hrs of presentation. Healthcare professionals should engage specialists in other disciplines to obtain diagnostic samples and to drain, debride, or remove the infection source including lines.

E. Fluid Therapy:
Fluid challenge in patients with hypovolemia may be given at a rate of 500-1000 mL of crystalloids or 300-500 mL of colloids over 30 mins and repeated based on response and tolerance. With venodilation and ongoing capillary leak, input is typically greater than output, and input/output ratio is of no utility to judge fluid resuscitation needs. The SAFE study indicated that albumin administration was safe and equally as effective as crystalloid.

F. Vaspressors:
1. Vasopressor agents should be started when fluid challenge fails or to maintain perfusion in life-threatening hypotension during an ongoing fluid challenge. Loss of autoregulation in vascular beds in the setting of low MAP requires vaspressors to maintain adequate flow.
2. The first-choice is either norepinephrine or dopamine through a central catheter. They are preferred over epinephrine (less tachycardia and splanchnic vasoconstriction) and phenylephrine (decrease in stroke volume). Dopamine increases MAP and cardiac output while norepinephrine increases MAP due to its vasoconstrictive effects, with little change in heart rate and stroke volume. Norepinephrine is more potent and preferred in septic shock as it causes less tachycardia and is less arrhythmogenic than dopamine which may be useful in patients with compromised systolic function.
3. Low-dose dopamine should not be used for renal protection in severe sepsis.
4. All patients requiring vaspressors should have an arterial catheter as measurement of BP using a cuff is inaccurate in shock. These, however, can cause hemorrhage and damage to arterial vessels.
5. Vasopressin in dose of 0.01-0.04 units/min may be considered in refractory shock. It is avoided in cardiac dysfunction (cardiac index <2.5L/min/m²) (2C). Higher doses can induce myocardial and visceral ischaemia and cardiac arrest. The recent VASST trial, a randomized, controlled trial comparing norepinephrine alone to norepinephrine plus vasopressin at 0.03 units/min, showed no difference in outcome in the intent to treat population.

G. Inotropic Therapy:
Dobutamine is the first-choice inotrope for patients with low CO in the setting of adequate left ventricular filling pressure, in fluid unresponsive hypotension, in combination with vaspressors. A vasopressor such as norepinephrine and an inotrope such as dobutamine may be used separately to target specific levels of MAP and CO respectively, if CO can be separately monitored.

H. Steroids:
1. Intravenous hydrocortisone 200-300 mg/day for 7 days is recommended in patients with septic shock who require vasopressor therapy to maintain adequate BP based on European CORTICUS and French trials (2C) with proper weaning. Some recommend a 250ug ACTH stimulation test to identify potential steroid-responders.
2. Dose of hydrocortisone daily should not be >300 mg in severe sepsis.
3. Stress doses of steroids do not improve the outcome of
sepsis in the absence of shock unless the patient was on prior steroid therapy (1D).

I. Recombinant Human Activated Protein C (rhAPC)

Drotrecogin Alpha:
rhAPC is a novel anti-inflammatory, anti-thrombin and pro-fibrinolytic drug for the pathophysiologic derangements of severe sepsis (Fig.2). rhAPC in doses of 24μg/kg/hour for 96 hours was approved by USFDA for severe sepsis in patients with APACHE II score ≥ 25 or with ≥ 2 organ dysfunctions (2B). This was based on 19.4% reduction in relative risk of death (absolute RR of 6.1%) in PROWESS study. The ADDRESS trial showed no significant benefit if patients with sepsis had a low risk of death. The risk of intracranial hemorrhage (ICH) was 0.2% -1.5%. A European regulatory mandated RCT of rhAPC vs. Placebo in patients with septic shock is now ongoing 12.

J. Blood Product Administration:

1. Red blood cell transfusion is advocated only when hemoglobin decreases to 7.0 g/dL to target a haemoglobin of 7.0-9.0 g/dL (1B).

2. Clinical trials of erythropoietin in critically ill patients show some decrease in red cell transfusion requirement with no effect on clinical outcome (1B). 13

3. Fresh frozen plasma should not be used to correct laboratory clotting abnormalities in the absence of bleeding or planned invasive procedures (2D). 14

4. Antithrombin administration for the treatment of severe sepsis and septic shock is not recommended (1B).15

5. Maintain higher platelet counts (>50,000) for planned surgical or invasive procedures with platelet transfusion for counts <5000 and at higher levels if clinical bleeding (2D).

II. SUPPORTIVE THERAPY OF SEVERE SEPSIS

A. Mechanical Ventilation of Sepsis-Induced Acute Lung Injury (ALI)/Acute Respiratory Distress Syndrome (ARDS):

1. Clinicians should target a lower tidal volume of 6 mL/kg (predicted) body weight in patients with ALI/ARDS (1B).

2. Permissive hypercapnia can be tolerated in patients with ALI/ARDS if required to minimize plateau pressures and tidal volumes. (1C).

3. A minimum amount of positive end expiratory pressure

"Fig.2: Mechanism of action of Recombinant Activated Human APC"
(PEEP) through an endotracheal tube or face mask should be set to prevent lung collapse at end-expiration. (1C) 16.

4. Prone positioning should be considered in ARDS patients in the settings of high FiO2 but accidental dislodgment of the endotracheal tube and central venous catheters can be disastrous (2C) 17.

5. Mechanically ventilated patients should be maintained semi recumbent, with the head of the bed raised to 30-45° to prevent the development of ventilator-associated pneumonia (2C) 18.

6. Non-invasive ventilation (NIV) should only be considered in that minority of ALI/ARDS patients with mild-moderate hypoxemic respiratory failure with stable hemodynamics who are easily arousable, and able to protect and spontaneously clear the airway of secretions. A low threshold for airway intubation should be maintained (2B). 19

7. A weaning protocol should be in place and mechanically ventilated patients should undergo a spontaneous breathing trial (SBT) when they satisfy the following criteria: a) arousable; b) hemodynamically stable (without vasopressor agents); c) no new potentially serious conditions; d) low ventilatory and end-expiratory pressure requirements; and e) requiring levels of FiO2 that could be safely delivered with a face mask or nasal canula. SBT options include a low level of pressure support with continuous positive airway pressure 5 cm H2O or a T-piece (1A). 19

8. Routine use of the pulmonary artery catheter for patients with ALI/ARDS is not recommended (1A) 20.

B. Sedation, Analgesia, and Neuromuscular Blockade in Sepsis:
Intermittent bolus or continuous infusion to predetermined end points with daily lightening of continuous infusion are recommended methods for administration of sedatives (1B) 21 and even for neuromuscular blocking agents (NMBA) like pancuronium if needed for beyond 1st few hours (1B). NMBA can prolong skeletal muscle weakness in critically ill patients 22.

C. Glucose Control:
Following initial stabilization, IV insulin to maintain blood glucose <150 mg/dL (8.3 mmol/L) is recommended. With Leuven protocol (glucose-insulin drip), glucose should be monitored frequently once levels of 80-110 mg/dL are reached (VISEP and NICE-SUGAR trials) (1B) 21.

D. Renal Replacement:
In acute renal failure, and in the absence of hemodynamic instability, continuous venovenous hemofiltration and intermittent hemodialysis are considered equivalent (2B). Continuous hemofiltration offers easier management of fluid balance in hemodynamically unstable septic patients (2D) 24.

E. Bicarbonate Therapy:
Bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements is not recommended for treatment of hypoperfusion induced lactic acidemia with pH >=7.15 (1B).

F. Deep Vein Thrombosis Prophylaxis:
Severe sepsis patients should receive deep vein thrombosis (DVT) prophylaxis with either low-dose unfractionated heparin or low-molecular weight heparin (1A). For septic patients who have a contraindication for heparin use (i.e., thrombocytopenia, severe coagulopathy, active bleeding, recent intracerebral hemorrhage), the use of a mechanical prophylactic device (graduated compression stockings or intermittent compression device) is recommended (unless contraindicated by the presence of peripheral vascular disease) (2C) 25,26.

G. Stress Ulcer Prophylaxis:
Stress ulcer prophylaxis using H2 blocker (1A) or proton pump inhibitor (1B) should be given to patients with severe sepsis to prevent upper gastrointestinal (GI) bleed and are more efficacious than sucralfate 27.

H. Selective Digestive Tract Decontamination (SDD):
Prophylactic use of SDD (enteral nonabsorbable antimicrobials and short-course intravenous antibiotics) reduces infections, mainly pneumonia, and mortality in the general population of critically ill and trauma patients 28 without promoting emergence of resistant Gram negative bacteria.

I. Consideration for Limitation of Support:
Advance care planning, including the communication of likely outcomes and realistic goals of treatment should be discussed with patients and families (1D) 29.

Apart from rhAPC, the immunomodulatory agents tested in sepsis in clinical trials like TNF alpha antibodies, soluble TNF alpha receptors, recombinant IL-1Ra, endotoxin monoclonal antibody, G-CSF, GM-CSF, IVIg, Tissue Factor Pathway inhibitor (TFPI) have shown no survival benefit. 30
CONCLUSION: Implementation of SSC Guidelines and Outcome: 2010

A multifaceted intervention comprising ‘Sepsis Bundles’ with 2 sets of targets to be completed within 6 hours and within 24 hours (Table II) was voluntarily implemented in 165 sites across US, Europe and South America. Data from 15022 subjects revealed significant rise in compliance for resuscitation bundle (p< 0.0001) and for management bundle (p=0.008) at the end of 2 years. The unadjusted hospital mortality decreased from 37% to 30.8% over 2 years (p= 0.001), thus showing that implementation of SSC can result in sustained, continuous quality improvement in sepsis care.

A. 6 hr Sepsis Resuscitation Bundle:
1) Serum lactate measured
2) Blood cultures obtained prior to antibiotic administration
3) From the time of presentation, broad-spectrum antibiotics administered within 3 hours for ED admissions and 1 hour for non-ED ICU admissions
4) In the event of hypotension and/or lactate > 4 mmol/L (36 mg/dl):
   i. Deliver an initial minimum of 20 ml/kg of crystalloid (or colloid equivalent)
   ii. Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) > 65 mm Hg
5) In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate > 4 mmol/L (36 mg/dl):
   i. Achieve central venous pressure (CVP) of > 8 mm Hg
   ii. Achieve central venous oxygen saturation (ScvO2) of > 70%

B. 24 hr Sepsis Management Bundle:
1. Low-dose steroids administered for septic shock in accordance with a standardized ICU policy
2. Drotrecogin alfa (activated) administered in accordance with a standardized ICU policy
3. Glucose control maintained > lower limit of normal, but < 180 mg/dl (10 mmol/L)
4. Inspiratory plateau pressures maintained < 30 cm H2O for mechanically ventilated patients

Table II. Surviving Sepsis Campaign: Bundles

REFERENCES
16. Villar J, Kacmarek RM, Pérez-Méndez L, et al, for the ARIES Network: A high PEEP-l0w tidal volume ventilatory strategy improves outcome
