SURVIVING SEPSIS 2015

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Sepsis – The Problem

- Septic shock is the leading cause of mortality in patients admitted to the ICU
- In the United States alone there are over 750,000 cases of severe sepsis and septic shock annually
- At least 20% mortality in septic shock (37%, 43%, 46%)
- Over 17 billion dollars spent annually for the treatment of sepsis in the USA
- Increasing in incidence

Sepsis – The Definitions

- SIRS
- Sepsis
- Severe Sepsis
- Septic Shock

Systemic Inflammatory Response Syndrome (SIRS)

Need 2 or more of the following:

- Temperature >38.3 (100.9 F) or <36.0 (96.8)
- Heart rate >90 beats per minute,
- Respiration >20 breaths/min
- White blood cell count >12,000 or <4000/mm3, >10% bandemia

Sepsis

SIRS (2 or more of the following)

- Temperature >38.3 (100.9 F) or <36.0 (96.8)
- Heart rate >90 beats per minute,
- Respiration >20 breaths/min
- White blood cell count >12,000 or <4000/mm3, >10% bandemia

PLUS

Suspected or documented infection

Severe Sepsis

- Sepsis + at least one end organ dysfunction or tissue hypoperfusion
  - SBP <90 mm Hg or MAP < 65 or drop in SBP > 40
  - Encephalopathy
  - Hypoxemia (Lung injury)
  - Creatinine > 2.0 mg/dl or Urine Output < 0.5 ml/kg/hour for > 2h
  - Bilirubin > 2 mg/dl
  - Platelet count < 100,000
  - Coagulopathy (INR > 1.5 or aPTT > 60 seconds)
  - Lactate > 2 mmol/L

Septic Shock

- Severe Sepsis

PLUS

- Hypoperfusion (persistently low blood pressure) despite adequate fluid resuscitation

OR

- lactate > 4mmol/L.

The New England Journal of Medicine

EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

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2001 single center RCT (263 patients)

- Early goal-directed therapy (EGDT) vs. standard therapy
- Lower mortality (30.5% vs. 46.5%)

EGDT:

- Central line: monitor CVP and Scvo2 to guide the use of IVFs
- Vasopressors, pRBC transfusions, and dobutamine for pre-specified physiological goals

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

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Objective: To provide an update to the "Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock," last published in 2008.

Design: A consensus committee of 68 international experts representing 30 international organizations was convened. Nominal groups were assembled at key international meetings (for those committee members attending the conference). A formal conflict of interest policy was developed at the onset of the process and enforced throughout. The entire guidelines process was conducted independent of any industry funding. A stand-alone meeting was held for all subgroup heads, co- and vice-chairs, and selected individuals. Teleconferences and electronic-based discussion among subgroups and among the entire committee served as an integral part of the development.

Methods: The authors were advised to follow the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to guide assessment of quality of evidence from high (A) to very low (D) and to determine the strength of recommendations as strong (1) or weak (2). The potential drawbacks of making strong recommendations in the presence of low-quality evidence were emphasized. Some recommendations were ungraded (UG). Recommendations were classified into three groups: 1) those directly targeting severe sepsis; 2) those targeting general care of the critically ill patient and considered high priority in severe sepsis; and 3) pediatric considerations.

Results: Key recommendations and suggestions, listed by category, include: early quantitative resuscitation of the septic patient during the first 6 hrs after recognition (1C); blood cultures

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* Members of the 2012 SSC Guidelines Committee and Pediatric Subgroup are listed in **Appendix A** at the end of this article.

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- Published in the journal Critical Care Medicine in February 2013
- 58 pages
- An international committee with 68 members of both the Society of Critical Care Medicine and the European Society of Intensive Care Medicine

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A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*

ProCESS: multicenter, RCT, 31 US academic hospitals

- Randomized 1341 patients with early septic shock to:
  - Protocol-based EGDT (Rivers)
  - Protocol-based standard therapy
  - Usual care

RESULT: no difference in mortality

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*

- Published in October 2014, ARISE Trial
- Conducted at 51 centers (mostly in Australia or New Zealand)
- Randomized 1600 patients presenting to the ED with early septic shock to receive EGDT or usual care
- No difference in mortality

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Early, Goal-Directed Resuscitation for Septic Shock

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- Published in April 2015, ProMISE Trial
- Randomized 1260 patients with early septic shock in 56 hospitals in England to EGDT vs usual care
- No difference in mortality

Sepsis - Treatment

- As in trauma, acute myocardial infarction and stroke – the speed and appropriateness of initial management affects outcome
- These studies demonstrate that although strict adherence to the initial EGDT protocol may not be necessary, early recognition, volume resusitation, and appropriate antibiotics are critical

- These guidelines are NOT strictly for implementation in the ICU, in fact the greatest impact can be achieved if initiated in the emergency department or bedside

Diagnostic Criteria

- General Variables
- Inflammatory Variables
- Hemodynamic Variables
- Organ Dysfunction Variables
- Tissue Perfusion Variables

General Variables

- Fever (>38.3 C) (100.9 F)
- Hypothermia (core temp < 36 C) (96.8 F)
- Heart Rate > 90
- Tachypnea
- Altered mental status
- Significant edema or positive fluid balance (>20 mL/kg over 24 hours)
- Hyperglycemia (>140 mg/dL) in absence of diabetes

Inflammatory Variables

- Leukocytosis (WBC > 12,000)
- Leukopenia (WBC < 4000)
- Normal WBC with > 10% bands
- Plasma CRP > 2 standard deviations above normal
- Plasma procalcitonin > 2 standard deviations above normal

Hemodynamic Variables

- Arterial hypotension (SBP < 90 mm Hg, MAP < 65 mm Hg or decrease in SBP > 40 mm Hg)

Organ Dysfunction Variables

- Arterial hypoxemia ($PaO_2/FiO_2 < 300$)
- Acute oliguria (urine output < 0.5 mL/kg/hr for at least 2 hours despite adequate fluid resuscitation)
- Creatinine increase > 0.5 mg/dL
- Coagulation abnormalities (INR > 1.5 or PTT > 60)
- Ileus (absent bowel sounds)
- Thrombocytopenia (< 100,000)
- Hyperbilirubinemia (total bilirubin > 4 mg/dL)

Tissue Perfusion Variables

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

Management of Severe Sepsis

Diagnosis

Screening

First Steps

- Measure Lactate
- Obtain Cultures
- Administer Broad Spectrum Antibiotics
- Administer 30 mL/kg crystalloid for hypotension
- If hypotension does not respond to fluids apply pressors to achieve MAP>65
- If hypotension persists measure CVP or SVO2 and re-measure lactate

Targets during the first 6 hours of resuscitation:

- CVP 8-12 mm Hg
- MAP > 65 mm Hg
- Urine output >0.5 ml/kg/hr
- Mixed venous oxygen saturation (SVO2) > 65%
- Normalize lactate if elevated

Efforts should be initiated as soon as hypoperfusion is recognized, not pending ICU admission

Treat Hemodynamics

Fluid Therapy

- Crystalloid as initial fluid (no benefit to colloids but increased cost)
- Recommend AGAINST HES (increased mortality)
- Suggest albumin after a substantial amount of crystalloid required
- Initial fluid challenge of 30 mL/kg of crystalloid
- Continue challenge as long as hemodynamic improvement is demonstrated

Vasopressors

- Target a MAP of 65 mm Hg
- Norepinephrine is drug of choice
- Epinephrine if an additional agent is needed
- Vasopressin may be added but not recommended as a single agent
- Dopamine only with bradycardia – arrhythmogenic; recommend AGAINST low dose treatment
- Phenylephrine only if arrhythmias from norepinephrine or salvage therapy

Inotropic Therapy

- Recommend a trial of dobutamine in the presence of elevated cardiac filling pressures, low cardiac output or signs of hypoperfusion despite adequate volume and MAP
- If patient is volume resuscitated but SVO2 remains < 65%, then Dobutamine infusion or transfusion of packed red blood cells to achieve hematocrit of 30% or greater in attempt to achieve SVO2 goal are options

Corticosteroids

- Use only if adequate fluid resuscitation and vasopressors do NOT restore hemodynamic stability (dose of 200 mg/day)
- Use of ACTH test was not an accurate predictor
- Taper when vasopressors no longer required
- Not be administered for sepsis in the absence of shock
- Consider infusion rather than bolus to minimize side effects (hyperglycemia)

Treat Source

Cultures

- Obtain cultures prior to antibiotics (if no more than 45 minute delay)
- At least 2 sets with aerobic and anaerobic
- At least one peripheral and one from each vascular access device
- Other body fluid cultures as appropriate
- Imaging studies as appropriate

Antimicrobial Therapy

- Goal of therapy is within 1 hour of recognition of sepsis
- Multiple studies show mortality increases for each hour of delay
- Start with broad spectrum coverage against all likely pathogens
- Consider patient risk factors, presenting symptoms, local prevalence, recent antibiotic use (type and duration within 3 months)

De-escalation

- Assess daily for potential de-escalation to prevent development of resistance, reduce toxicity and reduce cost
- Limit treatment to 7-10 days in most cases
- Stop antimicrobial therapy if infection is not confirmed

Source Control

- Identify possible anatomic sources of infection
- Use intervention of least physiologic insult
- If vascular access device – establish new vascular access and remove

Infection Prevention

- Selective oral decontamination (SOD) with chlorhexidine gluconate (CHG) – reduces risk of VAP
- Selective digestive decontamination (SDD)?
- Hand washing
- Catheter care
- Barrier precautions
- Airway management
- Elevation of head of bed
- Subglottic suctioning

Supportive Therapy

Blood Products

- Transfuse for hgb < 7.0 (unless active myocardial ischemia, severe hypoxemia, acute hemorrhage)
- Recommend against erythropoetin
- Recommend against FFP to correct lab abnormalities in absence of bleeding
- Platelets –

Transfuse < 10,000

Transfuse < 20,000 with risk of bleeding

Transfuse < 50,000 for bleeding or surgery

Recommend against

- Antithrombin administration
- Immunoglobulin administration
- Selenium administration
- Activated protein C

Mechanical Ventilation

- Target a tidal volume of 6 mL/kg in sepsis induced ARDS
- Plateau pressure < 30 cm H2O
- Permissive hypercapnea
- PEEP applied to avoid alveolar collapse
- High PEEP for moderate to severe ARDS
- Recruitment maneuvers in refractory hypoxemia
- Prone positioning for PaO2/FiO2 < 100
- Elevate HOB between 30 and 45 degrees

- NIV used if possible (minority)
- Weaning protocol with spontaneous breathing trials once – arousable, off vasopressors, no new conditions, low PEEP requirement, low FiO2 requirement
- Recommend against pulmonary artery catheter in ARDS
- Recommend conservative fluid strategy in ARDS without hypoperfusion
- Recommend against beta agonists without bronchospasm

Sedation

- Minimize sedation – use intermittent
- Use targeted endpoints
- Use of protocols
- Daily interruption
- Avoid neuromuscular blockers (due to prolonged effect)

- Why? Reduce length of mechanical ventilation, length of stay, tracheostomy rate

Glucose Control

- Use of protocols
- Target < 180 mg/dL (NOT 110)
- Monitor every 1 to 2 hours until stable, then every 4 hours

Renal Replacement Therapy

- CRRT and intermittent dialysis are equivalent (same short term survival rates)
- Suggest CRRT in hemodynamically unstable patients

Bicarbonate Therapy

- Recommend against sodium bicarbonate in patients with lactic acidemia and pH > 7.15

DVT Prophylaxis

- Recommend prophylaxis with LMWH
- For creatinine clearance < 30, suggest dalteparin
- Suggest combination of pharmacologic and intermittent pneumatic compression devices
- Contraindication to pharmacologic, use mechanical UNTIL risk decreases

Stress Ulcer Prophylaxis

- Suggest prophylaxis for those with risk factors
- Suggest prophylaxis with proton pump inhibitors rather than H2 antagonists
- Patients without risk factors should not receive prophylaxis

- Risks – coagulopathy, mechanical ventilation, hypotension

Nutrition

- Enteral feeding, as tolerated, rather than fasting within first 48 hours
- May avoid full calorie feeding (if not tolerated)
- Suggest enteral feeding rather than TPN in the first 7 days

Setting Goals of Care

- Goals of care and prognosis be discussed with patients and families
- Goals of care be incorporated into treatment and end-of-life care planning
- Utilize palliative care principles where appropriate
- Address goals of care as early as feasible, no later than 72 hours after admission

Sepsis Core Measures

- Began October 1, 2015
- Any patient discharged with an ICD 10 diagnosis related to sepsis

Severe Sepsis Core Measures

- Severe Sepsis core measure is triggered if all 3 criteria are met within 6 hours –
- SIRS

PLUS

- Infection

PLUS

- Organ dysfunction

Within 3 hours:

- Measure lactate level
- Obtain blood cultures prior to administration of appropriate broad spectrum antibiotics

Within 6 hours:

- Repeat lactate if initial level > 2

Septic Shock Core Measures

- Within 3 hours - Administer 30ml/kg of crystalloids
- Within 6 hours - Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation within 1 hour) to maintain a mean arterial pressure (MAP) ≥65mmHg

Within 6 hours:

- Patient must have a documented assessment by clinician to re-assess volume status and tissue perfusion for either

- persistent hypotension after initial fluid administration

OR

- initial lactate was ≥4 mmol/L,.

Assessment Requirements

- Vital Signs
- Cardiopulmonary Exam
- Capillary Refill Evaluation
- Peripheral Pulse Evaluation
- Skin Evaluation

Or 2 of :

- Central venous pressure
- Central venous oxygen
- Cardiovascular ultrasound
- Passive leg raise or fluid challenge

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