Surviving Sepsis 2012
International guidelines for management of severe sepsis and septic shock.

Review of the guidelines
Richard Taylor, MD

Severe Sepsis and Septic Shock

- Common, lethal, expensive
  - Severe sepsis: 3/1000 population per year
  - 22.6 per 1000 hospital discharges overall
  - 2 per 1000 pediatric hospital discharges
  - Mortality 28.6%
    - Pediatric 10%
    - Adults 38.4% (higher in many studies)
  - Annual cost 16.7 billion dollars in US in 2001

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- Evidence based review and expert consensus, published in Critical Care Medicine, January 2008.
- Guidelines explained with quality of evidence and strength of recommendation.
  - Quality:
    - A RCT
    - B Downgraded RCT or upgraded observational studies
    - C Well done observational studies
    - D Case series or expert opinion

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- Strength of recommendation
  - 1 Strong recommendation, "we recommend"
  - 2 Weak recommendation, "we suggest"

- Based on quality of evidence, and tradeoffs of desirable and undesirable effects.

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- Sepsis is infection plus systemic manifestations
- Severe sepsis is sepsis plus sepsis-induced organ dysfunction or tissue hypo-perfusion
- Septic shock is sepsis-induced hypotension and inadequate organ perfusion persisting despite adequate fluid resuscitation.
- These guidelines are for severe sepsis and septic shock


- On presentation to ER, and for initial 6 hours, randomized to standard therapy, at discretion of treating physicians, or to protocolized, goal directed therapy.
- Protocol:
  - Aggressive volume resuscitation, cvp ≥ 8
  - Mean arterial pressure ≥ 65
  - Urine output ≥ 0.5 cc/kg/hr
  - ScvO2 ≥ 70%

- Protocol
  - After aggressive volume resuscitation, used PRBC transfusion, inotoropes, sedation (to decrease oxygen requirements) to obtain goals
- Those on protocol had significant hospital survival advantage (mortality 30.5 versus 46.5%)
- My conclusion: time is of the essence!

Peter Marshall

- “Let us not be content to wait and see what will happen, but give us the determination to make the right thing happen.”

Andrew Jackson quoting Napoleon

- “Take time to deliberate, but when the time for action arrives, stop thinking and go in.”

Lorren Rus Stiles, Sr

- “Don't stop a parade to pick up a dime.”

Silius Italicus

- “Make haste! The tide of fortune soon ebbs.”

Leo Tolstoy

- “There is only one time that is important – NOW”
G K Chesterton

• “I do not believe in a fate that falls on men however they act, but I do believe in a fate that falls on them unless they act.”

Ralph Waldo Emerson

• “What you do speaks so loud that I cannot hear what you say.”

Benjamin Franklin

• “Drive thy business! Or it will drive thee!”

Peters and Waterman; In Search of Excellence.

• Ready, Fire!, Aim

Society of Critical Care Medicine

• Right care! Right Now!™
“We recommend routine screening of potentially infected seriously ill patients for severe sepsis...”

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- Initial resuscitation
  - Rationale, discussion
    - Early goal directed therapy decreased mortality (Rivers)
    - In mechanically ventilated patients or with known reasons for decreased ventricular compliance, use higher filling pressure (cpv 12 – 15)

- Diagnostics
  - Recommend obtaining appropriate cultures
  - Other body fluids if it does not delay treatment
  - Rapid influenza testing when prevalence is high

Pediatric note (not from guidelines)

  - Pediatric patients who were seen in physician offices presenting with septic shock were reviewed retrospectively
  - Those whose shock was successfully reversed in the pediatrician's office had a better survival; duh!
  - But also, those pediatricians who adhered more to the ACCM-PALS guidelines had significantly better outcome: 8% mortality versus 38%.
  - Begin resuscitation at point of first patient contact.

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- Initial resuscitation
  - Recommend if in first 6 hours Scvo2 not 70 or SVO2 not 65, then:
    - PRBCs
    - Dobutamine
    - Titrated to goal above
  - Rationale is Rivers study

- Diagnosis
  - Recommend obtaining appropriate cultures
  - Other body fluids if it does not delay treatment
  - Rapid influenza testing when prevalence is high
  - Imaging studies asap if patient can tolerate
Surviving Sepsis, 2012
• Biomarkers such as procalcitonin and C-reactive protein have not been shown to be helpful
• Suggest use of 1,3B-D-glucan, mannan and anti-mannan antibody assays to screen for invasive fungal infections

Surviving Sepsis, 2012
• Antibiotic therapy
  - Intravenous antibiotic therapy within the first hour (1B)
  - Appropriate cultures, but not if delays therapy (1D)
  - Discussion: each hour delay results in measurable decrease in chance of survival
  - Recommend that at least one antibiotic for all likely pathogens which penetrate to all likely sources

Surviving Sepsis, 2012
• Antibiotic therapy, continued
  - Recommend daily reassessment
  - Suggest combination therapy for patients with known or suspected pseudomonas
  - Suggest combination therapy for neutropenic patients
  - Combination empiric therapy should not be continued for more than 3 - 5 days
  - Recommend duration of therapy be 7 to 10 days, longer for select cases.
  - Discussion: remember that blood cultures will be negative in > 50% of cases that are very likely caused by bacteria or fungi

Surviving Sepsis, 2012
Double tap
• “Clinicians should be cognizant of blood cultures being negative in a significant percentage of cases of severe sepsis or septic shock, despite the fact that many of these cases are very likely caused by bacteria or fungi”

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Surviving Sepsis, 2012
Triple tap
• “Clinicians should be cognizant of blood cultures being negative in a significant percentage of cases of severe sepsis or septic shock, despite the fact that many of these cases are very likely caused by bacteria or fungi”
Surviving Sepsis, 2012

- "It should be kept in mind that the persistent mortality of febrile neutropenia is seldom caused by using too many antibiotics for too long; rather it is the result of antibiotics being started too late."
  
  Juan Gea-Banacloche, MD
  National Institutes of Health, Bethesda, MD
  Critical Care Medicine; May, 2011

Surviving Sepsis, 2012

- Recommend rate of fluid administration be
- Recommend fluid challenge begin with at least
- Recommend fluid challenge technique where
- Recommend target cvp >

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- Potential sources to think about:
  - Intra-abdominal abscess
  - Gastrointestinal perforation
  - Cholangitis
  - Pyelonephritis
  - Intestinal ischemia
  - Necrotizing soft tissue infection
  - Other deep space infection such as empyema, septic arthritis
- RCT showed surgical drainage of peri-pancreatic necrosis with delayed approach better, however.

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- Source control
  - Recommend that a specific anatomic source that would require control be identified as early as possible, within 12 hours.
  - Identify abscesses that need drainage and devices that may be infected
  - Recommend that when source control is required, least invasive effective intervention be done (such as CT guided percutaneous drainage versus laparotomy).
  - If intravascular device possible source of severe sepsis or septic shock, recommend it be removed promptly
  - Suggest that if peripancreatic infection is source - definitive intervention be delayed

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- Recommend resuscitation with crystalloids as initial fluid
- Suggest use of albumin in patients requiring substantial amounts of fluids
- Recommend NOT hydroxyethyl starch colloids.
- "SAFE" study showed no difference in outcome between colloid and crystalloids.
- Hydroxyethyl starch increased risk of AKI
- "Fluid therapy, continued"
  - Aggressive fluid resuscitation is often required for 24 hours.
  - Input is usually greater than output, and "input/output ratio is of no utility to judge fluid resuscitation needs during this time period."
  - Emphasis is on "fluid challenge." Give fluid and re-evaluate repetitively until optimized.
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• Vasopressors
  - Recommend that MAP be kept > 65
  - “supplementing end points, such as blood pressure, with assessment of regional and global perfusion, such as blood lactate concentrations and urine output, is important.”
  - “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…”

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• Vasopressors, cont.
  - Recommend norepinephrine as first choice. Dopamine is no longer recommended.
  - Suggest epinephrine, phenylephrine, and vasopressin should not be administered as first line
  - Vasopressin 0.03 units/min may be added subsequently
  - Suggest epinephrine be the first chosen alternative to shock poorly responsive to dopamine or norepinephrine

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• Vasopressors, continued, discussion
  - Dopamine increases BP and CO by increasing SV and HR. Survival worse than with NE, more arrthmogenic.
  - Norepinephrine increases BP and some increase in CO by increase in SV and little increase in HR
  - Norepinephrine is more potent
  - Phenylephrine does not increase CO and decreases SV

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• Inotropic therapy
  - Recommend dobutamine be used in presence of myocardial dysfunction evidenced by elevated filling pressures and low cardiac output.
  - Recommend against strategy to increase cardiac index to some predetermined supra-normal value.
**Surviving Sepsis, 2012**

- **Coricosteroids**
  - Shown in 1980s to not benefit and to increase secondary infections when used as anti-inflammatory doses by several large RCTs.
  - In past several years, use has been for “relative” insufficient stress response.
  - One RCT showed improved survival in patients with septic shock who did not respond to stress dose corticotropin stimulation, who were treated with stress dose steroids (Annane, JAMA, 2002).
  - The most recent larger trial did not show survival benefit (Sprung, NEJM, 2008).

**Surviving Sepsis, 2008**

- **Corticosteroids**
  - Suggest that iv hydrocortisone be given only to adult septic shock patients after failure to respond to fluids and pressors.
  - CORTICUS study failed to show mortality benefit, but did show faster resolution of septic shock.
  - Enthusiasm tempered by known side effects of increased risk of infection and myopathy.

**Surviving Sepsis, 2012**

- **Steroids, continued**
  - Suggest ACTH stimulation test not be done.
  - Cortisol levels or response to stimulation test do not predict who will respond clinically to steroids with hemodynamic improvement.

**Surviving Sepsis, 2012**

- **rhAPC (activated protein c)**
  - Suggest use in high risk patients, APACHE >25, multiorgan failure (2C!).
  - PROWESS showed 6.1% absolute risk reduction of death.
  - ADDRESS stopped early for futility (to show effect).
  - ENHANCE suggested benefit.
  - Quality of evidence given a “C” because of conflicting results not easily explainable.

**Surviving Sepsis, 2012**

- **Steroids, continued**
  - Suggest that doses greater than 300 mg per day of hydrocortisone not be used.
  - Recommend that corticosteroids not be used for sepsis in the absence of shock unless another indication (adrenal disease, etc).
Surviving Sepsis, 2012

• Blood product administration
  - After resuscitation, transfuse PRBCs when Hb is ≤ 7 to target level 7 – 9.
  - Recommend not to use erythropoietin as specific therapy in sepsis.
  - Suggest FFP not be used in absence of bleeding or planned procedures
  - Recommend against using AT3
  - Suggest platelets be administered when <5k; consider when 5 – 30k if significant risk of bleeding.

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• Mechanical ventilation
  - Recommend 6ml/kg tidal volumes
  - Recommend plateau pressures be measured and upper limit allowed be 30
  - Recommend permissive hypercapnia if needed for goals above
  - Recommend PEEP set to avoid extensive lung collapse at end expiration
  - Suggest prone positioning for patients requiring injurious ventilator settings and who are not at high risk for adverse events with repositioning

Surviving Sepsis, 2012

• Mechanical ventilation, continued
  - Recommend, unless contraindicated, that all patients who are intubated have head of bed elevated to prevent ventilator associated pneumonia
  - Suggest 30 to 45 degrees
  - “Patients should not be fed with the head of the bed at 0 degrees.”

Surviving Sepsis, 2012

• Recommend a weaning protocol
  - Periodic “breathing trials” with low peep and ps, for patients who:
    * Arousable
    * Hemodynamically stable
    * No new potentially serious conditions
    * Low ventilatory and end expiratory pressures
    * FiO2 that can be safely delivered by face mask
  - Extubate those who tolerate breathing trial

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• Mechanical ventilation, continued
  - Recommend against routine use of pulmonary artery catheter for patients with ALI/ARDS
  - Recommend conservative fluid strategy for patients not showing evidence of tissue hypoperfusion
Surviving Sepsis, 2012

- Sedation, analgesia, NMB
  - Recommend sedation protocols with explicit sedation goals
    - Studies have shown reduced length of MV, LOS, tracheostomy rates, cost per day, and improved sedation quality
  - Recommend either intermittent bolus dosing or continuous infusions with daily interruption, defined goals, allowing awakening and retitration of drip

Surviving Sepsis, 2012

- Sedation, analgesia, and NMB, continued
  - Studies have shown longer duration of MV with continuous drips. A daily interruption decreased length of MV and hospital LOS
  - Recommend that NMBs be avoided if possible, and if used, either intermittent dosing or monitoring with train of four.

Surviving Sepsis, 2012

- Glucose control
  - Recommend that after stabilization hyperglycemia be treated with insulin infusion therapy
  - Suggest validated protocol, target glucose less than 180
  - Recommend all patients treated with insulin receive glucose energy source with monitoring of blood sugar Q 1-2 hours until stable, then Q 4
  - Recommend caution in interpreting low glucose levels by point of care testing as they may overestimate true blood sugar
  - Acknowledge some uncertainty because of new trials showing lack of benefit and increased hypoglycemic episodes

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- Renal replacement
  - 5 prospective randomized studies comparing continuous and intermittent RRT
    - 4 found no difference, 1 found higher mortality in CRRT, but patients sicker, multivariate analysis concluded no difference
    - “there is no current evidence to support the use of continuous therapies in sepsis independent of renal replacement needs.”
  - Suggest that continuous renal replacement therapy and intermittent therapy are equivalent
  - Suggest use of continuous therapy in hemodynamically unstable patients

Surviving Sepsis, 2008

- Bicarbonate therapy
  - Recommend against the use of bicarbonate if pH > 7.15
  - Studies comparing bicarbonate to saline showed no difference in hemodynamics
  - Associated with sodium and fluid overload, increased lactate, decrease in iCa
Surviving Sepsis, 2012

DVT Prophylaxis (for adults)
- Recommend, unless contraindication, unfractionated heparin 2 to 3 times a day, or LMWH daily
- Suggest, if heparin contraindicated, use mechanical intermittent compression devices
- Suggest, very high risk patients (orthopedic surgery, h/o dvt, severe sepsis, etc) receive both heparin and mechanical device
- Suggest LMWH is superior to unfractionated heparin in very high risk patients

Stress ulcer prophylaxis
- Recommend H2 blocker or proton pump inhibitor, but weigh risks of GI hemorrhage with risk of acid suppression and VAP
- Studies have shown carafate to be inferior. Also have not shown decreased mortality, but have shown decreased risk of GI hemorrhage.
- Suggest ppi better than H2 blockers

Selective Digestive Tract Decontamination
- Committee tied, so no recommendation
- Evidence suggestive of some benefit in preventing VAP, and maybe mortality in trauma patients

Consideration for limitation of support
- Recommend advance planning and communication with patients and families.

Pediatric Considerations
- Mortality much lower (about 10%) than adults
- Recommend antibiotics within 1 hour
- Mechanical ventilation - no graded recommendations
- Fluid resuscitation: recommend fluid challenges start with boluses of crystalloids of 20cc/kg titrated to hemodynamics

Pediatric considerations, continued
- Suggest dopamine as initial pressor
  - Pediatric patients may have high CI, low SVR: low CI and high SVR; or low CI and low SVR. Suggest tailoring pressor/inotropes to the patient
  - Suggest epinephrine or norepinephrine if fails dopamine
  - If low CI and increased SVR (by exam) be given dobutamine
  - When normotensive, low CI, high SVR despite fluid and inotrope, consider vasodilator and or inodilator such as phosphodiesterase inhibitor (milrinone)
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*Pediatric considerations: therapeutic endpoints*
- Suggest use: normalization of heart rate, capillary refill < 2 seconds, normal pulses with no differential between proximal and distal, warm extremities, urine output > 1/kg/hr, and normal mental status.
- Goals used in adults (SvO2, etc) may have benefit in children

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*Pediatric considerations*
- Steroids
  - Suggest hydrocortisone be reserved for patients with catecholamine resistance AND suspected or proven adrenal insufficiency
  - Studies have shown that use of any adrenal steroid is independent risk factor for death
  - "given the lack of data in children and potential risk, steroids should not be used in children who do not meet minimal criteria for adrenal insufficiency."

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*Pediatric Considerations*
- rhAPC
  - We recommend against the use of rhAPC in children
  - Pediatric study stopped for futility
    - Mortality: 18% placebo, 17% rhAPC
    - Major amputations: 3% placebo, 2% rhAPC
    - Bleeding: 6% placebo, 7% rhAPC
  - But........

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*Pediatric issues*
- Recommend DVT prophylaxis in post-pubertal children with severe sepsis
- Stress ulcer prophylaxis - no recommendation due to lack of evidence. Rate of bleed similar to adults
- Renal replacement therapy - no graded recommendations, but did say should be initiated before significant fluid overload occurs

**Infants - not all that looks like septic shock is**
- Ductal dependent cardiac lesions
  - Consider PGE infusion in babies less than 4 wks with recalcitrant shock
- Congenital adrenal hyperplasia
- Pulmonary hypertension complicating sepsis
Surviving Sepsis, 2012

- Pediatric issues
  - Suggest use of clindamycin and "antitoxin" therapies in toxic shock syndromes, possibly IVIG.
  - "Children are more prone to toxic shock than adults."
- ECMO – suggest it should be reserved for those who cannot otherwise be supported