Surviving Sepsis 2008
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

eMedicine, Septic Shock

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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, inotropes, 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!™

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Initial resuscitation of shock (hypotension after initial fluid challenge or lactate greater than 4)

Protocolized resuscitation
Immediately, do not wait for ICU
First 6 hours

- CVP 8 – 12
- MAP greater than 65
- UO greater than 0.5 ml/kg/h
- Central Venous sat > 70 or mixed venous > 65%
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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 (cvp 12 – 15)

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

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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- Diagnosis
  - Recommend:
    - Obtain appropriate cultures
    - At least 2 blood cultures, one peripheral and at least one from every vascular device
    - Other body fluids if it does not delay treatment
  - Discussion: if both peripheral blood and catheter are positive, high likelihood the organism is responsible. If catheter grows more than 2 hours sooner, likely catheter infection. Also rec quantitative or semi-quantitative cultures of respiratory tract specimens
  - Recommend imaging studies asap if patient can tolerate

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- 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

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- 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
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• “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

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• Source control
  — Recommend that a specific anatomic source that would require control be identified as early as possible, within 6 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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• 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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• 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 either norepinephrine or dopamine as first choice
  – 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
  – 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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• Vasopressors, cont
  – Vasopressin is depleted after initial hours of septic shock, giving rationale for low dose continuous infusion of vasopressin at 0.03 units/minute.
  – VASST trial showed no difference in intention to treat analysis, but did show improvement in those requiring less than 15mic/k/min of norepi
  – Higher doses of vasopressin associated with cardiac, digital and splanchnic ischemia

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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.

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• 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 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)
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• 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

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• 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

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• Steroids, continued
  – Suggest that dexamethasone not be used if hydrocortisone is available (concern about prolonged suppression of hypothalamic-pituitary-adrenal axis)
  – Suggest fludrocortisone is optional if hydrocortisone is used, but should be added if steroid without mineralocorticoid activity is used
  – Suggest weaning steroids when vasopressors not required. One study showed hemodynamic and immunologic rebound when steroids stopped abruptly

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• 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

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• 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

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- Mechanical ventilation
  - 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.”

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- Mechanical Ventilation, continued
  - Suggest that non-invasive mask ventilation be considered only in minority of ALI/ARDS patients
    - Mild, responsive to low levels peed and ps
    - Comfortable, easily arousable, able to protect airway
    - Anticipated to recover quickly
    - Low threshold for intubation

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- 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

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- 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
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- 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.

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- Glucose control
  - Recommend that after stabilization hyperglycemia be treated with insulin infusion therapy
  - Suggest validated protocol, target glucose less than 150
  - Recommend all patients treated with insulin receive glucose energy source with monitoring of blood sugar Q 1 - 2 hours until stable, then Q4
  - 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
  - Suggest that continuous renal replacement therapy and intermittent therapy are equivalent
  - Suggest use of continuous therapy in hemodynamically unstable patients

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- Renal replacement therapy
  - 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.”

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- 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

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- 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
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• 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. Two studies show equivalency of H2 blockers and proton pump inhibitors

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

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

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• 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

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• 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
Pediatrics Grand Rounds
29 July 2011

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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

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- Pediatric issues
  - Glycemic control – no graded recommendations
  - Sedation – recommend protocols
  - Blood products – no graded recommendations. Note study showing threshold of Hb 7 as good as 9.5

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

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- Pediatric issues
  - Suggest use of IVIG in children with severe sepsis
  - Recent RCT showed improved mortality, shorter los, reduced complications
  - ECMO – suggest it should be reserved for those who cannot otherwise be supported