Sepsis

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Why?

- It is common, lethal and expensive.
- Of the 750,000+ severe sepsis cases each year in the US, an estimated 215,000 (28.6%) pts die.
- Mortality associated with severe sepsis has been reported as high as 30-50%.
- The incidence is likely to increase even more
  - Aging population
  - Medical and technological advances
  - Widespread use of antibiotics
- It is costly
  - Accounts for ~ 40% of all ICU expenditures, totaling $16.7B in the US
  - Average LOS/cost per case: 19.6 days and $22,100
- With early recognition and aggressive treatment = better pt outcomes
**SIRS Criteria:**
- Temp > 38.3 C or < 36 C
- Heart Rate > 90
- Respiratory Rate > 20 or PaCO2 < 32
- WBC > 12K, < 4K or > 10% Bands

**Sepsis** = 2/4 SIRS + infection

**Severe sepsis** = sepsis-induced tissue hypoperfusion (inc lactate) / organ dysfunction (AMS, lungs, kidney, etc)

**Septic shock** = sepsis-induced hypotension (SBP < 90, MAP < 70, SBP dec > 40 from baseline) persisting despite adequate fluid resuscitation
What is Early Goal Directed Therapy?

- EGDT is a comprehensive strategy for identifying and treating septic pts that include:
  - **Identification of high risk pts**
    - Mobilization of resources for intervention
    - Performance of a consensus-derived protocol to reverse early hemodynamic disturbances

- The core objectives of EGDT in sepsis are to:
  - **Detect and treat occult global tissue hypoxia early** before organ damage becomes irreversible
  - Achieve a systemic oxygen delivery and demand balance
Landmark Literature (NEJM 2001)

EVALUATING THE USE OF AN EARLY GOAL-DIRECTED THERAPY APPROACH IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

Emanuel Rivers, M.D., M.P.H., Bryant N. Nguyen, M.D., Suzanne Havstad, M.A., Julie Ressler, B.S., Alexandra Muzzin, B.S., Bernhard Knobl, M.D., Edward Peterson, Ph.D., and Michael Tomlanovich, M.D., for the Early Goal-Directed Therapy Collaborative Group

The New England Journal of Medicine

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

SIRS criteria and systolic blood pressure $\leq 100$ mm Hg or increase $\leq 4$ mm Hg

Assessment and consent

Randomization

Sepsis criteria and systolic blood pressure $\leq 100$ mm Hg or increase $\leq 4$ mm Hg

Standard therapy in emergency department (n = 113)

Early goal-directed therapy (n = 120)

Vital signs, laboratory data, cardiac monitoring, pulse oximetry, urinary catheterization, arterial and central venous catheterization

CVP $\geq 8$ to 12 mm Hg

MAP $\geq 85$ mm Hg

Urine output $\geq 0.5$ ml/kg/hr

Standard care

Hospital admission

Did not complete 6 hr (n = 14)

Follow-up

Did not complete 6 hr (n = 13)

CVP $\geq 8$ to 12 mm Hg

MAP $\geq 85$ mm Hg

Urine output $\geq 0.5$ ml/kg/hr

SaO$_2$ $\geq 90$

Hematocrit $\geq 30$

Cardiac index

VO$_2$
Results

- In hospital Mortality
  - Standard therapy 46.5 % → EGDT 30.5 %

- Mean LOS in days (for pts who survived to hospital discharge)
  - Standard therapy 18.4 days → EGDT 14.6 days
Surviving Sepsis Campaign

The Society of Critical Care Medicine, the European Society of Intensive Care Medicine and the International Sepsis Forum joined forces to develop a three-phase Surviving Sepsis Campaign.

- **First phase:** six-point action plan to reduce global mortality from severe sepsis by 25% by 2009.

- **Second phase:** focused on creating guidelines for sepsis management.
  - Crit Care Med 2004; 32:858-873
  - Update → Crit Care Med 2008; 36(1):296-327
  - Updated 2012 → February 2013 issue of Critical Care Medicine and Intensive Care Medicine

- **Phase three:** translating the guidelines into clinical practice.
**Initial resuscitation (first 6 hours)**

- Begin resuscitation immediately in patients with hypotension or elevated serum lactate ≥4 mmol/L; do not delay pending ICU admission. (1C)

- Resuscitation goals: (2C)
  - Central venous pressure (CVP) 8–12 mm Hg*
  - Mean arterial pressure ≥65 mm Hg
  - Urine output ≥0.5 mL.kg⁻¹.hr⁻¹
  - Central venous (superior vena cava) oxygen saturation ≥70%, or mixed venous ≥65%

- If venous O₂ saturation target not achieved: (2C)
  - Consider further fluid
  - Transfuse packed red blood cells if required to hematocrit of ≥30% and/or
  - Dobutamine infusion max 20 μg.kg⁻¹.min⁻¹

* A higher target CVP of 12–15 mmHg is recommended in the presence of mechanical ventilation or pre-existing decreased ventricular compliance.
Controversy?

- Which part makes a difference?
- Does everyone need an invasive approach?
Which part makes a difference?

- **Early recognition of sepsis** → more aggressive txt / EGDT / better outcomes
  - The research supports it

- **Aggressive IVFs**
  - In Rivers original study, average total IVFs within first 6 hours:
    - Standard therapy: 3.5L → EGDT: 5L

- **Early antibiotics**
  - *Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock.*
  - Each hour of delay in antimicrobial administration over the first 6 hrs was associated with an average decrease in survival of 7.6%

- RBC transfusion, steroids, glycemic control, xigris ??
Is it necessarily Rivers/SSC guidelines that make a difference?

- **The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: a meta-analysis**
  - *Crit Care Med. 2008 Oct;36(10):2734-9*

- Applying an early quantitative resuscitation strategy (EGDT) to patients with sepsis imparts a significant reduction in mortality.

- They observed distinct variations in the goals / end points targeted among the studies.

- pts did better with just using **goals** (not necessarily Rivers/SSC guidelines/goals) and **early treatment**
Does everyone need an invasive approach?

Hemodynamic / Perfusion Goals

- Fluid resuscitation
  - CVP
  - IVC US
- MAP > 65
- Tissue oxygenation
  - ScvO2
  - Lactate clearance
**Fluid resuscitation: CVP vs IVC US**

- **CVP**
  - Invasive → can lead to complications, more time consuming & is typically started later (BP not responding to IVFs, increasing lactate).
  - Not reliable as 1 measurement → better to follow trends.
  - Made up numbers (based on EGDT recs)
    - How well does a CVP 8-12 translate to evidence that the tank is full? … the evidence is WEAK at best.

- **Bottom line:**
  - Even reaching CVP thresholds does not guarantee adequate fluid loading. While a very low CVP indicates an under-resuscitated pt, the opposite is not true.

- **IVC US**
  - Non-invasive
  - Can be used during initial evaluation / earlier in the course of resuscitation.
  - Can also assess global heart function and r/o pericardial effusion.
Emergency Department Bedside Ultrasonographic Measurement of the Caval Index for Noninvasive Determination of Low Central Venous Pressure

- Bedside ultrasonographic measurement of caval index (IVC collapsibility) $>50\%$ is strongly associated with a low CVP ($<8$ mm Hg).

- It could be a useful noninvasive tool in determining a patient's volume status/need for aggressive fluid replacement well before invasive monitoring can be established.

**Dr Scott Weingart - EMCrit Blog**
- Greater New York Hospital Association - STOP Sepsis Collaborative
Tissue Oxygenation

- Lactate
- Why use this?
- When to use it?
Clinical manifestations of disordered microcirculatory perfusion in severe sepsis.
Stephen Trzeciak and Emanuel P Rivers; Critical Care Aug 2005
Lactate

- Nonspecific for anaerobic metabolism
- Impaired microcirculatory flow is one of the many possible mechanisms for elevated lactate in severe sepsis
- Consensus recommendations advocate using lactate measurements to help identify normotensive pts who are in “cryptic shock” and in need of aggressive resuscitation.

**Cryptic Septic Shock: A Sub-analysis of Early, Goal-Directed Therapy**
- *Chest 2003*

Subgroup analysis of Rivers original study:

- MAP > 100 + lactate > 4 had mortality rate 60.9%
- MAP < 70 had mortality rate 42%
The Surviving Sepsis Campaign: results of an international guideline based performance improvement program targeting severe sepsis


- Hypotension and lactate > 4: 46.1%
- Hypotension alone: 36.7%
- Lactate > 4 alone: 30%

Prognostic value of incremental lactate elevations in emergency department patients with suspected infection.


- Mortality rose continuously across a continuum of incremental lactate elevations
  - 6% in pts with lactate levels <1.0 mmol/L
  - 39% in pts with levels of 19 to 20 mmol/L.
Are there false positives?

- Usually a lactate $\geq 4$ is associated with badness.

- However, in patients using beta-agonists, e.g. an acute asthma exacerbation, the lactate may be quite high.

- If you take the lactate of any patient who has just completed extreme exercise, their lactates will be high.

- Patients with seizures will also have remarkably high lactates immediately after their ictal period.
  - In all of these cases, the lactate should quickly clear after the inciting situation.

- Patients with hepatic failure can have elevated lactate from decreased clearance.
  - They are also prone to sepsis or hypotension.

- Non-septic possibilities: any shock state, dead bowel, necrotizing fasciitis, and a multitude of toxicological causes.
ScvO2 -or- SmvO2

- Normal ScvO2 > 70% (drawn from IJ / SCL catheter)
- Normal SmvO2 > 65% (drawn from pulmonary artery catheter)

If low = tissue not seeing enough hgb (so it is taking more O2)
1. Not enough hgb to come around (relative anemia)
2. Hgb not coming around fast enough (cardiac output inadequate)
Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy

*JAMA.* Feb 2010; 303(8):739-746.

- To test the hypothesis of non-inferiority between lactate clearance and central venous oxygen saturation (ScvO2) as goals of early sepsis resuscitation
- **ScvO2 group:** resuscitated to normalize CVP, MAP & ScvO2 > 70%
- **Lactate clearance group:** resuscitated to normalize CVP, MAP & lactate clearance of at least 10%.
- Lactate clearance was not inferior to ScvO2 and did not result in significantly different in-hospital mortality.

**Lactate clearance: 17% vs ScvO2: 23%**
Metabolic goals

**Adrenal replacement txt:** Hydrocortisone 50 mg IV q6
- Vasopressor-refractory hypotension, suspect adrenal insufficiency (if pts endocrine / steroid history warrants it, got etomidate ?)
- ACTH stim test, cortisol levels no longer recommended

**Glycemic control**
- Controversial history but most recent studies / recommendations (tight control → no change in mortality, increased incidence of mod-severe hypoglycemia)
- Insulin therapy when 2 consecutive glucose levels > 180 with a goal ≤ 180 (NICE-SUGAR study)

**Activated Protein C (xigris)**
- On October 25, 2011, Eli Lilly announced a voluntary-recall of Xigris following the results of the PROWESS-SHOCK trial, which demonstrated no survival benefit when using the drug when compared to placebo.
Blood Controversy

- Original Rivers study and SSC recommendations were to transfuse pRBCs to hgb > 10
  - Increase the O2 carrying capacity
- Multiple studies: has not shown a mortality benefit
- + potential transfusion risks/reactions
- Now more conservative approach
  - If Hgb < 7: transfuse 1 unit pRBC
  - If Hgb 7-10: consider transfusion especially in elderly pts or with CAD
Airway/O2

- Maximize O2 delivery with supplemental O2 to keep O2 sats > 90%

- Indications for Intubation
  - Airway protection
  - Oxygenation / Ventilation
  - *Expected clinical course*

- 75% of pts with sepsis (severe/shock) require mechanical ventilation
  - Increased work of breathing d/t hypoxia + compensation for metabolic/lactic acidosis

- **ARDSNET**
  - Compared TV: 12 cc/kg/IBW vs 6 cc/kg/IBW with goal plateau pressure < 30 cm H2O
  - 22% dec mortality, inc in ventilator-free / organ failure-free days

- Maintain HOB 30-45 … decrease risk of aspiration PNA
Cultural Change

- We have Stroke / STEMI / Trauma protocols/teams… Sepsis viewed just as important
- To be successful we need a multidisciplinary team approach + acceptance within
Loyola University Medical Center

Early Recognition of Sepsis

Two or more SIRS Criteria:
1. Temp > 38.3°C or < 36°C
2. Heart Rate > 90
3. Respiratory Rate > 20 or PaCO₂ < 32
4. WBC > 12K, < 4K or > 10% Bands

Suspected Infection?

YES

NO

Check Lactate

Obtain Appropriate Cultures

MAP < 65 after IVF bolus?
(30 ml/Kg over 30 mins)

NO

Lactate ≥ 4 mmol/L or ≥ 2 Organ Dysfunction

Septic Shock

YES

Severe Sepsis

If goals of care are curative, proceed to:
EARLY GOAL DIRECTION THERAPY (EGDT)
SEPSIS GUIDELINES (Non-Invasive/Invasive)
and consider notification of the ICU

Antibiotics and Re-Assess

Re-Assess

Exceptions: Age < 18 years, STEMI, Acute Pulmonary Edema, Trauma.
Two or more SIRS Criteria:
1. Temp > 38.3° C or < 36° C
2. Heart Rate > 90
3. Respiratory Rate >20 or PaCO2 <32
4. WBC >12K, <4K or >10%Bands

Suspected Infection?

YES

Check Lactate
Obtain Appropriate Cultures

NO

Re-Assess

YES

Re-Assess

NO

Re-Assess
MAP < 65 after IVF bolus? (30 mL/kg over 30 min)

- NO
  - Lactate ≥4 mmol/L or ≥1 Organ Dysfunction
    - NO
      - Sepsis
    - YES
      - Antibiotics and Re-Assess
  - YES
    - Septic Shock

If goals of care are curative, proceed to
EARLY GOAL DIRECTED THERAPY (EGDT) SEPSIS GUIDELINES (Non-Invasive/Invasive) and consider notification of the ICU
LUMC Non-Invasive Sepsis Guidelines

- Initiate Sepsis Order Set
  - Think of Source Control and seed cultures
  - Initiate Broad Spectrum Antibiotics within 1 hour
  - Supplemental O2: If hypotension despite non-rebreather mask, consider intubation and switch to Invasive Guidelines.
- Establish 2 large bore IVs and give IVF Bolus: Isotonic crystalloid 30 mL/kg boluses over 30 minutes

**Fluid Resuscitation**

**Fluid loaded, not responsive**

MAP

**MAP < 65**

**MAP ≥ 60**

**Repeat Lactate**

≥ 10% Lactate Clearance

- Consider Transfusion
  - If Hgb < 7, transfuse 1 unit pRBC
  - If Hgb ≥ 10, consider transfusion especially in elderly pts or with CAD

- Lactate increasing or ≤ 10% Clearance

**Dynamic IVC Ultrasound**

Keep giving 500-1000 mL boluses of isotonic crystalloid until <30% change in IVC size with inspiration

**Empirc Fluid Loading**

Most pts will require ~ 4-6 L fluid during initial resuscitation (first 6 hours)

- Start Vasopressors and switch to Invasive guidelines

<table>
<thead>
<tr>
<th>Disposition</th>
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</thead>
<tbody>
<tr>
<td>Admission (ICU vs monitored bed)</td>
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<tr>
<td>Periodically recheck for MAP &gt; 65, good mental status, good UOP</td>
</tr>
<tr>
<td>Trend lactate q2-4 hours until it is normal (if rises again, restart guidelines)</td>
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</tbody>
</table>

| Additional fluids: If had empric IVF loading, give an additional liter of crystalloid |

goals achieved

**No**

**Yes**

**Yes**
- Initiate Sepsis Order Set
  - Think of Source Control and send cultures
  - Initiate Broad Spectrum Antibiotics within 1 hour
  - Supplemental O2. If hypoxemia despite non-rebreather mask, consider intubation and switch to Invasive Guidelines
  - Establish 2 large bore IVs and give IVF Bolus: Isotonic crystalloid 30 mL/kg bolus over 30 minutes

Fluid Resuscitation

- Fluid loaded/not responsive

Dynamic IVC Ultrasound:
Keep giving 500-1000 mL boluses of isotonic crystalloid until <30% change in IVC size with inspiration

Empiric Fluid Loading:
Most pts will require ~ 4-6 L fluid during initial resuscitation (first 6 hours)
MAP:

- **MAP < 65**
  - Start Vasopressors and switch to **Invasive** guidelines

- **MAP ≥ 65**
  - Lactate increasing or ≤ 10% Clearance
    - **Consider Transfusion**
      - If Hgb < 7: transfuse 1 unit pRBC
      - If Hgb 7-10: consider transfusion especially in elderly pts or with CAD
    - **Inotropes** (especially if heart appears hypodynamic on echo/US)
      - If Ca low, replete that first (500-1000 mg)
      - If Ca normal, then administer Dobutamine (2.5-20 mcg/kg/min)
  - ≥ 10% Lactate Clearance
    - **Additional fluids:** If had empiric IVF loading, give an additional liter of crystalloid
Continue with above or Switch to Invasive Guidelines

≥ 10% Lactate Clearance

Goals Achieved

No

Yes

Disposition
- Admission (ICU vs monitored bed)
- Periodically recheck for MAP>65, good mental status, good UOP
- Trend lactate q2-4 hours until it is normal (if rises again, restart guidelines).
LUMC Invasive Sepsis Guidelines

- Initiate Sepsis Order Set
- Think of Source Control and send cultures
- Initiate Broad Spectrum Antibiotics within 1 hour
- Supplemental O2: If hypoxemia persists, consider non-rebreather mask (see bottom right)
- IV Fluids: Isotonic crystalloid 30 mL/kg bolus over 30 minutes
- Place full sterile central line (IF or subclavian)

Fluid Resuscitation

MAP

MAP < 65

MAP ≥ 65

MAP < 65

MAP ≥ 65

Lactate < 10%

Consent Tranfusion

or

Consent Tranfusion

or

Consent Tranfusion

or

Consent Tranfusion

Consent Tranfusion

and

SvO2 > 70%

≥ 10% Lactate

Consent Tranfusion

and

SvO2 > 70%

≥ 10% Lactate

SvO2 > 70%

SvO2 > 70%

Goals Achieved

No

Yes

Disposition

- Admission (ICU vs monitored bed)
- Periodically recheck for MAP > 65
- Good mental status, good UOP
- Trend lactate q2-4 hours until it is normal (if rises again, restart guidelines)

Dynamic IVC Ultrasound:
Administer 500-1000 mL boluses of isotonic crystalloid until there is >30% change in IVC size or if not intubated or >12% if intubated

CVP:
Administer 500-1000 mL boluses of isotonic crystalloid until CVP 8-12 mmHg (if not intubated) and 12-15 mmHg (if intubated)

Vasopressors:
1. Titrate Norepinephrine (0.01 mcg/kg/minute)
2. Place static A-line
3. If MAP < 65 after Norepi between 0.5 - 1 mcg/kg/minute:
   - Add Hydrocortisone 50 mg iv & Vasopressin 0.04 units/minute
4. Next purveyor of choice: Epinephrine 0.01 mcg/kg/minute (max dose 0.5 mcg/kg/minute)

Consent Tranfusion

- If Hgb < 7: transfuse 1 unit RBC
- If Hgb 7-10: consider transfusion especially in elderly pts or with CAD

Consent Tranfusion

- If Ca low, replete that first (500-1000 mcg)
- If Ca normal, then administer Dobutamine (2.5-20 mcg/kg/min)

Additional fluids:
If you were using CVP to determine fluid status, give an additional liter of crystalloid

Intubate to decrease pulmonary metabolic load (see below)

Lung Protective Mechanical Ventilation

- Ketamine is the preferred induction agent (1-1.5 mg/kg IV)
- Etomidate is acceptable (0.5 mg/kg IV)
- Low TV (consider 6 mL/kg IBW) with a goal
  PEEP < 10
  - Autoregulation + Sedation (see LUMC protocols)
  - Raise HOB to 30-45°

*Note that SvO2 is ordered as Mixed Venous Blood Gas (SwanG)

A MEMBER OF TRINITY HEALTH
- Initiate Sepsis Order Set
- Think of Source Control and send cultures
- Initiate Broad Spectrum Antibiotics within 1 hour
- Supplemental O2: If hypoxemia despite non-rebreather mask, consider intubation (see bottom right)
- IVF Bolus: Isotonic crystalloid 30 mL/kg bolus over 30 minutes
- Place full-sterile central line (IJ or subclavian)

Fluid Resuscitation

- Fluid loaded/ not responsive

Dynamic IVC Ultrasound:
Administer 500-1000 mL boluses of isotonic crystalloid until there is < 30% change in IVC size if not intubated or > 12% if intubated

CVP:
Administer 500-1000 mL boluses of isotonic crystalloid until CVP 8-12 mmHg (if not intubated) and 12-15 mmHg (if intubated)

Vasopressors:
Fluid loaded/not responsive

MAP

MAP ≤ 65

MAP ≥ 65

Lactate < 10%
Clearance OR SevO2 < 70%

Repeat Lactate + SevO2

≥ 10%
Lactate Clearance AND SevO2 ≥ 70%

Vasopressors:
1. Titrate Norepinephrine (0.01 mcg/kg/minute)
2. Place sterile A-line
3. If MAP < 65 after Norepi between 0.5 - 1 mcg/kg/minute: add Hydrocortisone 50 mg q6 & Vasopressin 0.04 units/minute
4. Next pressor of choice: Epinephrine 0.01 mcg/kg/minute (max dose 0.5 mcg/kg/minute)

Consider Transfusion
If Hgb < 7: transfuse 1 unit pRBC
If Hgb 7-10: consider transfusion especially in elderly pts or with CAD

Inotropes (especially if heart appears hypodynamic on echo/US)
If Ca low, replete that first (500-1000 mg)
If Ca normal, then administer Dobutamine (2.5-20 mcg/kg/min)

Additional fluids: If you were using CVP to determine fluid status, give an additional liter of crystalloid

Intubate to decrease pulmonary metabolic load (see below)

*Note that SevO2 is ordered as Mixed Venous Blood Gas (Smvo2)*
Continue with above trending lactates & ScvO2 q1 hr until these two goals are met

≥ 10% Lactate Clearance AND ScvO2 ≥70%

Disposition
- Admission (ICU vs monitored bed)
- Periodically recheck for MAP>65, good mental status, good UOP
- Trend lactate q2-4 hours until it is normal (if rises again, restart guidelines)

Goals Achieved

Yes

No
Lung Protective Mechanical Ventilation

- Ketamine is the preferred induction agent (1-1.5 mg/kg IV): Etomidate is acceptable (0.3 mg/kg IV)
- Low TV (consider 6 mL/kg/IBW) with a goal Plateau Pressure < 30
- Analgesia + Sedation (see LUMC protocols)
- Raise HOB to 30-45°
Order Set: “Adult Sepsis”

**REFERENCE LINKS:**
- Sepsis Antibiotic Guidelines
- Early Recognition of Sepsis Guidelines
- Non-Invasive Sepsis Guidelines
- Invasive Sepsis Guidelines
- Sepsis Resuscitation Bundle

**REFERENCES:**
- Criteria for Sepsis/Severe Sepsis/Septic Shock

**SEPSIS:**
Two or more of the SIRS Criteria listed below:
1. Temperature over 38.3 degrees Celsius
2. Temperature under 36 degrees Celsius
3. Heart Rate over 90 beats per min
4. Resp Rate over 20 resp per min
5. PaCO2 under 32
6. WBC over 12K
7. WBC under 4K
8. Blasts greater than 10%
PLUS Documented / Suspected Infection

**SEVERE SEPSIS:**
1. Lactate greater than or equal to 4 mmol/L
2. One or more new organ dysfunction

**SEPTIC SHOCK:**
1. MAP less than 65 after IVF bolus (30 mL/kg over 30 min)

Reference Link:
Early Recognition of Sepsis

**TREATMENTS / PROCEDURES**

**RADIOLOGY**

**LABORATORY**

**MEDICATIONS**

**ANTIBIOTIC USE**
Only An Initial Dose of Antibiotics Are Allowed Without Infectious Disease Approval in Patients With Sepsis/Severe Sepsis/Septic Shock.

**ANTIBIOTICS:**
- Abdomen Source
- Central Nervous System - Community Acquired
- Central Nervous System - Hospital Acquired
- Diabetic Foot Infection or Ulcer
- Genitourinary - Community Acquired
- Genitourinary - Hospital Acquired
- Line or Device Related Infection
- Neutropenic Fever (patients with ANC<500/mm3 and Temp >101F)
- Pulmonary - Community Acquired
- Pulmonary - Healthcare Associated
- Unknown Etiology
### Medications

#### Intravenous Fluid Resuscitation
- **NaCl 0.9% “fluid bolus” infusion (ADULT)**
  - Intravenous, STAT
- **Lactated ringers “fluid bolus” infusion (ADULT)**
  - Intravenous, STAT
- **Albumin (human) 5% infusion**
  - Intravenous, STAT

#### Steroids
- **Hydrocortisone sodium succinate injection**
  - 50 mg, Intravenous, STAT
- **Hydrocortisone sodium succinate injection**
  - 50 mg, Intravenous, EVERY 6 HOURS

#### Vasopressors / Inotropes

**Norepinephrine (0.01 mcg/kg/min) is the vasopressor of choice.**

- Once norepinephrine is titrated between 0.5 - 1 mcg/kg/minute (MAX norepinephrine dose is 3 mcg/kg/min) AND MAP < 65 consider adding hydrocortisone 50 mg IV Q8h AND vasopressin 0.04 units/min IV

- Next vasopressor of choice is epinephrine 0.01 mcg/kg/min (MAX 0.6 mcg/kg/min)

- Norepinephrine 4 mg in dextrose 5% 250 ml infusion
  - Intravenous, CONTINUOUS, Starting 10/4/13
  - Titrate by 0.1 mcg/kg/min increments every 2 minutes (or as clinically indicated) to HR and BP goals as instructed by physician. MAX of 3 mcg/kg/min or as instructed by physician

- Vasopressin 100 units in dextrose 5% 100 ml infusion
  - 0.04 Units/min, intravenous, CONTINUOUS

- Epinephrine 4 mg in dextrose 5% 250 ml infusion (Next pressor of choice following Norepinephrine & Vasopressin)
  - 0.01 mcg/kg/min, intravenous, CONTINUOUS, Starting 10/4/13

- Dobutamine 250 mg in dextrose 5% 250 ml infusion
  - 2.5 mcg/kg/min, intravenous, CONTINUOUS, Titrate by 2.5 mcg/kg/min increments every 30 minutes (or as clinically indicated) to HR and BP goals as instructed by physician. MAX dose of 20mcg/kg/min
**ANTIBIOTICS:** Central Nervous System - Hospital Acquired

**ANTIBIOTICS:** Diabetic Foot Infection or Ulcer

**ANTIBIOTICS:** Genitourinary - Community Acquired

**ANTIBIOTICS:** Genitourinary - Hospital Acquired

**ANTIBIOTICS:** Line or Device Related Infection

**ANTIBIOTICS:** Neutropenic Fever (patients with ANC<500/mm3 and Temp >101F)

**ANTIBIOTICS:** Pulmonary - Community Acquired

Choose ONE of the following regimens:

**Sepsis Antibiotic Guidelines**

**Pulmonary Source - Community Acquired: NOT Penicillin Allergic**

**Order:** Ceftriaxone AND Azithromycin

- Ceftriaxone 2 g in dextrose 5% 50 mL IVPB
- Azithromycin 500 mg in dextrose 5% 250 mL IVPB

Order if patient has no erythromycin allergy. Cautions if hepatic impairment or known prolonged QT.

**Pulmonary Source - Community Acquired: Penicillin Allergy**

**Order:** Aztreonam AND Moxifloxacin

- Aztreonam in dextrose 5% 100 mL IVPB
- Moxifloxacin 400 mg in 250 mL IVPB

400 mg, intravenous, STAT. Starting 10/4/13

**ANTIBIOTICS:** Pulmonary - Healthcare Associated

**ANTIBIOTICS:** Unknown Etiology
A formal **conflict of interest policy** was developed at the onset of the process and enforced throughout.

The entire guideline process was conducted **independent** of any industry funding.

The recommendations in this document are intended to **provide guidance** for the clinician …. cannot replace the clinicians decision-making capability when he or she is presented with a patients unique set of clinical variables.

These recommendations are intended to be **best practice** and not created to represent standard of care.

The committee believes that the greatest outcome improvement can be made through **education and process change**.

Emphasize **routine screening** for earlier identification/txt
Routine screening → earlier recog

- Changed the way lactates drawn/run (grey top → VBG)
- ED Triage Sepsis Screening tool
- Bedside POC lactate in ED
- Lactate added to blood culture panel
- Lactate > 4 added to Critical Call list from Core lab
- Sepsis screening question added to most admission orders
- Inpatient Nursing Sepsis Screening tool
- Added Sepsis Screening to the Rapid Response team
ED Triage Sepsis Screening tool
Lactate added to blood culture panel
Sepsis screening question added to most admission orders
Inpatient Nursing Sepsis Screening tool

Patient has screened POSITIVE for Severe Sepsis, Call the Primary Physician/LIP/Service to notify of the screen result.
SSC - Fluid Resuscitation?

- Recognized limitations of static measures (CVP) and that targeting dynamic measures of fluid responsiveness may have advantages.
  - However the efficacy of these techniques remains incomplete and requires further study before endorsement.

- In patients with elevated lactate, they suggest targeting resuscitation to normalize lactate.
SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:
1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L

TO BE COMPLETED WITHIN 6 HOURS:
5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation (Scvo₂)*
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, Scvo₂ of ≥70%, and normalization of lactate.
LUMC SEPSIS RESUSCITATION BUNDLE

TO BE COMPLETED WITHIN 3 HOURS

1) Measure lactate (WBLA) level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics within 1 hour of diagnosis
4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L

TO BE COMPLETED WITHIN 6 HOURS

5) Non-invasive guidelines resuscitation goals:
   a. Lactate clearance of ≥ 10 % if initial lactate was elevated (with ultimate goal being normalization of lactate)

6) Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
   - a full-sterile central line should be placed

7) Invasive guidelines resuscitation goals:
   a. CVP 8-12 mmHg (non-intubated pts) or CVP 12-15 mmHg (intubated pts)

   PLUS

   b. Lactate clearance of ≥ 10 % if initial lactate was elevated (with ultimate goal being normalization of lactate) AND ScvO2 ≥ 70% (ordered as SmvO2)
EMCrit Lessons from the STOP Sepsis Collaborative

- Dec 2012 – 10,000 patient mark
- Screening → Send lots of lactates
- Make lactate ≥ 4 a panic value
- Non-invasive protocols have evidence and seem to be working
- Early appropriate antibiotics → Simultaneous Infusions
- Check Your Work → Mandate repeat lactates
Headline news –
New York State Adopts Sepsis Rules

NY Times Dec 2012: One Boy’s Death Moves State to Action to Prevent Others
WSJ Jan 2013: NY plans new hospital rules for treating sepsis

- Jan 2013, in a precedent-setting statement during his State of the State Message, New York’s Governor Andrew M. Cuomo announced:

  "New York will become the first state in the nation to require our hospitals to adopt best practices for the early identification and treatment of sepsis."

- Went effective: 5/1/13  (NY State Dept of Health)

  “Rory’s Regulations”  ➔ Sept 2013, Senator Tom Harkin, the chairman of the Senate Health committee, promised action on sepsis at a Senate Committee Hearing.
SSC – antibiotics?

- Should be reassessed daily for potential de-escalation to prevent the development of resistance, to reduce toxicity, and to reduce costs (grade 1B).
- Collaboration with antimicrobial stewardship programs is encouraged.
- In the near future, rapid, non-culture-based diagnostic methods (PCR, mass spectroscopy, microarrays) might be helpful for a quicker identification of pathogens and major antimicrobial resistance determinants.
Micro lab to implement a rapid identification (within 1 hour) of bacteria and relevant antibiotic resistant markers from blood culture bottles that signal positive.

Laboratory will use a combination of Cepheid GeneXpert Blood Culture MRSA/MSSA kit (if Gram stain shows Gram-positive cocci in clusters) or BioFire FilmArray for all other types of organisms observed in Gram stain.

+ result → CODE SEPSIS pager

Interrogate the patient EMR and recommend appropriate changes in antibiotic coverage in order to tailor therapy to the specific pathogen and resistance markers identified.
27 Targets that can be identified within 1h following positive blood culture signal:

- **Gram-Positive Bacteria**
  - Enterococcus
  - Listeria monocytogenes
  - Staphylococcus
    - Staphylococcus aureus
  - Streptococcus
    - Streptococcus agalactiae
    - Streptococcus pneumoniae
    - Streptococcus pyogenes

- **Yeast**
  - Candida albicans
  - Candida glabrata
  - Candida krusei
  - Candida parapsilosis
  - Candida tropicalis

- **Gram-Negative Bacteria**
  - Acinetobacter baumannii
  - Haemophilus influenzae
  - Neisseria meningitidis
  - Pseudomonas aeruginosa
  - Enterobacteriaceae
    - Enterobacter cloacae complex
    - Escherichia coli
    - Klebsiella oxytoca
    - Klebsiella pneumoniae
    - Proteus
    - Serratia marcescens

- **Antimicrobial Resistance Genes**
  - mecA - methicillin resistance
  - vanA/B - vancomycin resistance
  - KPC - carbapenem resistance
Conclusion

- Sepsis is common, lethal and expensive → EGDT can make a difference
- Have a high index of suspicion (SIRS + suspected infection)
- Send lactate early and often
- Be more aggressive with IVFs
- Early Antibiotics & De-escalate asap
- Use the ultrasound early and often if available
- Not everyone needs an Invasive strategy … Non-invasive guidelines have evidence and seem to be working
- Treat it as important as a Stroke / STEMI / Trauma
We also treat the human spirit.®