Sepsis: Keeping Your Patients Safe from a Deadly Disease

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Disclaimer/Disclosures

- Grant funding from Association of Organ Procurement Organizations for investigation of Lung Protective Strategies in brain dead organ donors to improve yield of lung procurement.
Objectives

- Understand updated criteria for diagnosing sepsis and septic shock
- Describe diagnostic tools to make an early diagnosis of sepsis
- Early Goal Directed Therapy and Bundles – what are they, how they are implemented, and what it means for patients.
- Understand how early recognition and management of sepsis reduces morbidity and mortality
- Describe early clinical interventions to mitigate sepsis and septic shock

Sepsis Glossary

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Infection</td>
<td>Microorganism invasion of a normally sterile site</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>Presence of viable microorganisms in the blood</td>
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</tbody>
</table>
| Systemic Inflammatory Response Syndrome (SIRS) | A systemic inflammatory response to a pathologic insult, such as a burn, trauma, pancreatitis, or infection. SIRS requires two or more of the following conditions:
  - Temperature >38°C or <36°C
  - Heart rate >90 beats/min
  - Respiratory rate >20 breaths/min or PaCO2 <32 mm Hg
  - WBC >12,000/mm³, <4000 cells/mm³, or >10% immature (band) forms |
| Sepsis (= 1 + 3)              | The syndrome caused by a systemic inflammatory response secondary to infection |
| Severe sepsis                | Sepsis associated with organ dysfunction. Specific organ dysfunctions include, but are not limited to, hypotension, renal dysfunction, respiratory failure, and altered mental status. |
| Septic shock (= 5 + 7)       | Sepsis with hypotension or hypoperfusion despite adequate fluid resuscitation. |
Epidemiology of Sepsis

- Approximately 230,000 sepsis associated deaths in 2009
- At risk populations – Age extremes, Immunosuppressed, Cancer
- Mortality is decreasing (35% → 26%) between 2004 and 2009
  - Improvement may plateau with rising age of population.
- One year all cause mortality among sepsis patients ~ 44%
  - All cause mortality risk persists for up to 5 years after survival


Sepsis rate by age category

![Graph showing sepsis rate by age category](image)
2001 Aggregate cost of Sepsis:
- $16,700,000,000

Multiple studies indicate longer ICU-LOS and higher costs in septic patients
- $22,000 - $104,000 per patient
- Surgical patients cost more than medical patients
- Cost increases paralleled presence of and number of organ system dysfunction(s)
- Cost per admission decreases with age

### $epsis – top 10 DRG CMD discharges 6/1/2015

<table>
<thead>
<tr>
<th>Diagnostic Related Group Code and Description</th>
<th>Total Discharges</th>
<th>Total Allowed Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>470 - MAJOR JOINT REPLACEMENT OR REATTACHMENT OF LOWER EXTREMITY W/O MCC</td>
<td>446,148</td>
<td>$6,600,501,280</td>
</tr>
<tr>
<td>871 - SEPTICEMIA OR SEVERE SEPSIS W/O MV 95+ HOURS W MCC</td>
<td>398,004</td>
<td>$5,580,910,280</td>
</tr>
<tr>
<td>392 - ESOPHAGITIS, GASTROENT &amp; MISC DIGEST DISORDERS W/O MCC</td>
<td>219,212</td>
<td>$1,089,866,661</td>
</tr>
<tr>
<td>292 - HEART FAILURE &amp; SHOCK W CC</td>
<td>188,463</td>
<td>$1,427,086,058</td>
</tr>
<tr>
<td>201 - HEART FAILURE &amp; SHOCK W MCC</td>
<td>184,697</td>
<td>$2,114,205,003</td>
</tr>
<tr>
<td>194 - SIMPLE PNEUMONIA &amp; PLEURISY W CC</td>
<td>162,368</td>
<td>$1,295,140,342</td>
</tr>
<tr>
<td>690 - KIDNEY &amp; URINARY TRACT INFECTIONS W/O MCC</td>
<td>175,529</td>
<td>$982,540,814</td>
</tr>
<tr>
<td>883 - RENAL FAILURE W CC</td>
<td>154,289</td>
<td>$1,028,578,709</td>
</tr>
<tr>
<td>190 - CHRONIC OBSTRUCTIVE PULMONARY DISEASE W MCC</td>
<td>152,880</td>
<td>$1,274,787,567</td>
</tr>
<tr>
<td>183 - SIMPLE PNEUMONIA &amp; PLEURISY W MCC</td>
<td>145,391</td>
<td>$1,005,092,023</td>
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</table>
Sepsis: Bench to Bedside

- Vasoplegic shock (Distributive)
  - Lack of smooth muscle tone $\rightarrow$ venous dilation $\rightarrow$ ↑ capacitance $\rightarrow$ ↓ preload $\rightarrow$ ↓ cardiac output
- Myocardial depression
- Altered Microvascular Flow
- Diffuse endothelial injury
  - Loss of integrity between cells, breakdown of endothelial glycolcalyx
- No high-quality trials showing that interventions to treat or prevent pathophysiologic changes alter outcomes
Cytokine storm

Uncontrolled pro-inflammatory response
Uncontrolled anti-inflammatory response
Immunosuppression

Pre-Hospital Sepsis

- Time to diagnosis
- Time to treatment
- Educational Barriers
- Bringing the next level of critical care management to the field
- Outreach to referring facilities
311 patients received EGDT – 160/311 arrived by EMS

EMS patients

- ↑ SOFA scores
- ↓ time to abx
- ↓ time to starting EGDT

EMS provider concern for sepsis associated specifically with earlier EGDT and antibiotics
• 48% (67/112) patients who eventually diagnosed with severe sepsis were correctly identified by EMS SAP
• Unadjusted mortality reduced from 26.7% to 13.6 among patients who met SAP criteria
3 years, 263 patients
- SIRS (2/4) & SBP < 90 OR Lactate > 4 mmol/L
- EGDT = STD therapy + SCVO2 goal > 70 for AT LEAST 6 hours
- Excluded – Immediate surgery, uncured Ca (chemo), immunosuppressed
- Sepsis Team and Area ***
- Antibiotics at discretion of Sepsis Unit Attending

Surgical patients tended to be excluded throughout trial
- EGDT received average of 1.7 hours more ‘directed therapy’
- MAP target
  - All groups met targets
  - Average MAP in initial 6 hours lower in STD therapy
- SCVO2 target
  - 99.4% EGDT vs 60.2% STD
- Combined targets (CVP, MAP, UOP ± SCVO2)
  - 99.2% EGDT vs 86.1% STD
<table>
<thead>
<tr>
<th></th>
<th>EGDT</th>
<th>Equivocal</th>
<th>STD</th>
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<tbody>
<tr>
<td><strong>Initial 6 hours</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>↑ Fluids</td>
<td>✔</td>
<td></td>
<td></td>
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<tr>
<td>Blood</td>
<td>✔</td>
<td></td>
<td></td>
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<tr>
<td>Inotropes</td>
<td>✔</td>
<td></td>
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<tr>
<td>Pressors</td>
<td>✔</td>
<td></td>
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<tr>
<td>Mechanical Ventilation</td>
<td>✔</td>
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<td><strong>7 → 72 hours</strong></td>
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<tr>
<td>↑ Fluids</td>
<td></td>
<td>✔</td>
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<tr>
<td>Blood</td>
<td></td>
<td>✔</td>
<td></td>
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<tr>
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<td></td>
<td>✔</td>
</tr>
<tr>
<td>Mechanical Ventilation</td>
<td></td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td><strong>Baseline → 72 hours</strong></td>
<td></td>
<td></td>
<td>✔</td>
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<tr>
<td>↑ Fluids</td>
<td></td>
<td>✔</td>
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<td>Blood</td>
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<td>✔</td>
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</table>
EGDT – Primary Endpoint

- Increased Mortality in STD therapy
  - In-house Mortality
  - 28 day
  - 60 day

ProMise of a ProCeSS to ARiSE

- Attempt to validate Rivers' EGDT Trial

CLEAR AS MUD

- Locations/Environments
- Role of Antibiotics
- Time to enrollment
Why time matters...

- Delay between recognition and initiation of appropriate treatment results in INCREASED organ failure and higher mortality

Reduction in Time to First Action as a Result of Electronic Alerts for Early Sepsis Recognition

- ‘Pop-out’ Alerts in EMR
- 30 patients diagnosed with sepsis before alerts and 30 patients case matched who had alerts
- EMR alerts associated with ↓ time to first intervention by 3.5 hours

Kurczewski, Lisa PharmD, BCPS; Sweet, Michael PharmD, BCPS; McKnight, Richard PharmD; Halbritter, Kevin MD

Kurczewski. Crit Care Nurs Q. 2015 Apr
MARS, Sepsis, and the EMR

- Use of EMR generated Sepsis pop-out alerts based upon transfer criteria
  - How many patients meet criteria not recognized by referring facility
  - Foundation for outreach
- Priority transportation and bed assignment
- Analogous to Stroke or Trauma Team activation
- Initiation of protocol based sepsis care

Earl-ier Goal Directed Therapy

- Identification by EMS, Critical Access Hospital, or Flight Crew
  - App Based & POC Lactic Acid
- Protocol-based therapy initiated at diagnosis of severe sepsis
  - ‘Sepsis-Pack’
    - Fluids, Antibiotics, Norepinephrine, Culture collection material, Hydrocortisone
  - Sepsis Alert – Priority Transportation, Acceptance, Bed Availability
  - Access to Resource Physicians via Regional MedCom Centers
Earl-ier Goal Directed Therapy

- Targets – Change the Goals
  - Early restoration of optimal perfusion pressures
  - Conservative and controlled fluid management
  - Early cultures and antibiotics
  - Early access to facilities with 24-hour source control capabilities

- Statewide Database
  - Data Collection & Analysis

SIRS...measuring the measuring stick

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. SIRS Criteria Met</th>
<th>( \geq 1 )</th>
<th>( \geq 2 )</th>
<th>( \geq 3 )</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No. (%)</td>
<td>2,763 (99.9)</td>
<td>2,659 (96.2)</td>
<td>1,617 (56.5)</td>
<td>343 (12.4)</td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>63.0 ± 14.6</td>
<td>63.0 ± 14.7</td>
<td>62.4 ± 15.5</td>
<td>60.0 ± 17.3</td>
<td></td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>1,977 (71.6)</td>
<td>1,860 (71.1)</td>
<td>1,107 (68.5)</td>
<td>212 (61.8)</td>
<td></td>
</tr>
<tr>
<td>Severity of illness scores, mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Day 1 APACHE II</td>
<td>15.1 ± 4.7</td>
<td>15.1 ± 4.7</td>
<td>15.7 ± 5.1</td>
<td>16.9 ± 5.9</td>
<td></td>
</tr>
<tr>
<td>Day 1 SOFA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6.0 ± 2.3</td>
<td>6.0 ± 2.3</td>
<td>6.3 ± 2.5</td>
<td>7.0 ± 2.8</td>
<td></td>
</tr>
<tr>
<td>Respiratory domain</td>
<td>2.3 ± 0.8</td>
<td>2.3 ± 0.6</td>
<td>2.3 ± 0.9</td>
<td>2.3 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular domain</td>
<td>2.1 ± 1.2</td>
<td>2.2 ± 1.2</td>
<td>2.3 ± 1.2</td>
<td>2.6 ± 1.3</td>
<td></td>
</tr>
<tr>
<td>Neurologic domain</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td></td>
</tr>
<tr>
<td>Renal domain</td>
<td>0.4 ± 0.6</td>
<td>0.4 ± 0.6</td>
<td>0.4 ± 0.7</td>
<td>0.5 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>Coagulation domain</td>
<td>0.8 ± 0.5</td>
<td>0.8 ± 0.5</td>
<td>0.5 ± 0.8</td>
<td>0.8 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>Liver domain</td>
<td>0.5 ± 0.7</td>
<td>0.5 ± 0.7</td>
<td>0.5 ± 0.7</td>
<td>0.7 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOS, median (IQR), d</td>
<td>1.1 (0.9-2.7)</td>
<td>1.1 (0.9-2.7)</td>
<td>1.7 (0.9-2.9)</td>
<td>1.9 (0.9-5.0)</td>
<td></td>
</tr>
<tr>
<td>ICU mortality, No. (%)</td>
<td>2.68</td>
<td>2.78</td>
<td>4.21</td>
<td>10.2</td>
<td></td>
</tr>
</tbody>
</table>
Test Dataset
- ≥ 2 criteria for 6 consecutive hours
  - BEST predictive model for mortality, organ dysfunction, and ICU-LOS
- Total # of hours, NOT consecutive hours within first 24 hours of sepsis where ≥ 2 or 3 criteria met was best predictor of mortality

Drawbacks to study
- Patient population much different than MICU/SICU
- Otherwise ‘healthy’ before elective CT surgery

Diagnosis made... Now what???
- Initial Resuscitation
- Infection Diagnosis
- Antibiotic Therapy
- Infection Source Control
- Fluids
- Pressors & Inotropes
- Corticosteroids
- Blood products
Fluid Therapy…the science

- Large Volumes often administered (5-10 liters)
- No human data that ≥ 30 cc/kg reliably improves blood pressure or end-organ perfusion
- Large Volumes/Short Duration
  - ↑ cardiac filling pressures → release natriuretic peptides → cleave membrane proteins → third spacing
  - Transient ↑ cardiac output → Vasodilation/Endotoxin Release/↓ SVR → NO production (refer same MOI as "little blue pill")

Fluid therapy…the science

- Responders vs Non-Responders
  - Sounds like trauma resuscitation
  - Make assessment early → continuing ineffective treatments → iatrogenesis
  - 5% of infused colloid remains intravascular after 3 hours
Fluids...too much, too little, just right??

- Brandt
  - 2 treatment arms for each study group (moderate- and high-volume)
    - Moderate → 10 cc/kg/hr of LR
    - High → 15 cc/kg/hr + 5 cc/kg/hr HES
  - Boluses allowed to maintain goal UOP and hemodynamics
  - High-volume resuscitation improved hemodynamics early but associated with INCREASED MORTALITY
VASST
- A priori subgroup analysis
- Optimal survival was with +3 liter fluid balance @ 12 hours
- Fluid balance and CVP were @ 12 and 96 hour \(\rightarrow\) independent predictor of death

Micek
- 24 hours fluid balance assessment
  - Survivors: 37.5 cc/kg positive
  - Dead: 55 cc/kg positive

Fluids...choosing from the menu

- True isotonic solutions \(\rightarrow\) LR, Hartmann’s Solution, PlasmaLyte
  - NSS \(\rightarrow\) ↑ risk renal dysfunction, metabolic acidosis (NAGA), Death

- Colloid Solutions
  - Hetastarch
    - ↑ risk renal dysfunction, Death
  - Albumin
    - ALBIOS trial \(\rightarrow\) 25% albumin ↓’d mortality when given AFTER resuscitation
    - SAFE trial \(\rightarrow\) 25% albumin may restore endothelial glycocalyx
Inopressors...what?

- Scott Weingart – Combined Inotrope and vasopressor effect
- When to start pressors?
  - If hemodynamics not improved with 20-30 cc/kg/hr of fluids
  - Start EARLY if presenting DBP ≤ 40 mmHg
  - Do NOT wait to start pressors – achieve goal MAP for end organ perfusion as early as possible
- Autoregulatory threshold
  - Ideal MAP for end organ perfusion (heart, brain, kidney) → > 60 mmHg
  - Take into account chronic HTN and effect on day-to-day MAP
    - RELATIVE HYPOTENSION

Inopressors...what?

- SEPSISPAM Trial – assess goal MAP for sepsis resuscitation
  - Establish goal of 65-70 mmHg vs 80-85 mmHg
  - A priori subgroup of patients with chronic hypertension
  - Organ failure (Renal) highest in the 65-70 group who had chronic hypertension
  - Time below MAP <65 is an independent predictor of death
Chosing a vasoactive medication

- **Norepinephrine**
  - Increases BP, cardiac output, and global blood flow; minimal effect on HR
  - Venoconstriction $\rightarrow$ ↓ capacitance $\rightarrow$ ↑ preload/venous return $\rightarrow$ ↑ CO
  - Abid: Early use of NE in septic shock $\rightarrow$ strong predictor of survival
- **Dopamine**
  - Increases mortality
  - Urban myth of positive impact on renal function
- **Phenylephrine**
  - Decreases cardiac output and splanchnic blood flow

Enough is Enough...End Points

- **Surviving Sepsis Campaign**
  - CVP goal 8-12 mmHg (12-15 if vented) – no proven relationship between CVP and fluid responsiveness
  - SCVO2 > 70 – value typically high in sepsis due to mitochondrial dysfunction, value > 90 independent predictor of death
  - UOP > 0.5 cc/kg/hr – altered in face of AKI
  - Nee & Rivers: achieving goals of SSC did NOT influence survival
Enough is Enough…End Points

- Lactic Acid
  - Not produced by tissue hypoxia → anaerobic production from metabolic stress response
  - ↑ in DO2 → No Δ in VO2 (Mitochondria)
  - Effect of shock liver and ineffective Cori Cycle
  - Best outcome was use of esmolol to decrease HR, CO, and DO2
    - Increased survival
    - Decreased Lactic acid

Fluids, Inopressors…Now what

- Check the pump – coexistent cardiogenic shock
- Global BiVentricular Dysfunction
  - Present in 60% of patients with septic shock – acidosis cardiopresive
- Methods
  - Ultrasound
  - Non-Invasive Methods for Hemodynamic Monitoring
    - Tissue oxygenation (S1O2)
    - Arterial dilution/waveform (LiDCO, FloTrac, etc.)
Fluids, Inopressors...Now what

Treatment
- Dobutamine (DBA) titrate from 2.5 mcg/kg/min to goal CO 2.5 LPM
- Consider PDE (Milrinone, Amrinone)
- Vasopressin (0.03 units/min) – Do NOT titrate
  - VASST trial → NO difference in outcome of NE vs NE+Vaso
  - If you choose to start, START EARLY

To transfuse...or not to transfuse

- SSC → if SCVO2 < 70 in 1st 6 hours → transfuse to a Hb ≥ 7
- Increased Hct → NO change in VO2 (O2 consumption)
  - Increased viscosity → worse flow at microvascular level → ↓ tissue oxygenation
- Increased risk of secondary infection, MODS, and Death
Bugs & Drugs

- Antimicrobial Therapy
  - Attempt to obtain cultures PRIOR to antibiotics***
  - Early antibiotics – DOOR to DRUG time
    - Pre-DOOR antibiotics???
  - 5-15% DECREASE in survival with each hour delay after first 6 hours

Antimicrobial Therapy

- Right Drug
- Right Route
  - Concentration above MIC for > 40% of dosing interval necessary
- Right mechanism
  - Cidal vs Static
  - Pharmacokinetics
- Tissue Penetration
- Local Anti-biogram Guidance
- De-escalation
Source control

- Most effective intervention with the least physiologic insult

Steroids...the circle of life continues

- Beneficial EARLY, detrimental LATE
- Timing of administration NOT considered in Annane or Springer papers
- Park → 178 patients & retrospective
  - Only benefit shown if received within 6 hours of shock onset
- CORTICUS – 60% were surgical/postop
  - Patient population may be factor
Resuscitation done... Now what???

- Mechanical Ventilation – Dx/Tx/Prevention of ALI/ARDS
- Sedation, Analgesia, Delirium (SAD) Management/Prevention
- Glucose Control
- Renal preservation and replacement
- Acid-Base management
- DVT prophylaxis
- Stress ulcer prophylaxis
- Co-Morbid Management
- Treatment end-points and limitations (POST, Advance Directives)

Bundles...

Sepsis resuscitation bundle: Tasks to be completed within 6 hours of presentation
1. Measure serum lactate.
2. Obtain blood cultures before antibiotic administration.
3. Administer broad-spectrum antibiotics within 3 hours from time of presentation 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):
   a. Deliver an initial minimum of 20 mL/kg of crystalloid (or colloid equivalent).
   b. 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):
   a. Achieve central venous pressure (CVP) ≥8 mm Hg.
   b. Achieve central venous oxygen saturation (ScvO2) ≥70% (or SvO2 ≥65%).
More Bundles...

Sepsis management bundle: Tasks to be completed within 24 hours of presentation
1. Administer low-dose steroids for septic shock in accordance with standardized ICU policy.
2. Standardized ICU protocol.
3. Maintain glucose control greater than or equal to the lower limit of normal, but <150 mg/dL (8.3 mmol/L).
4. Maintain inspiratory plateau pressures <30 cm H₂O for mechanically ventilated patients.

Introspection

- Take stock of where you are
  - Patient population – HIM
  - Resources – Physical, Human, Financial
- Who has a seat at the table - Decision and Implementation authority
- Vision & Sustainability
- Rollout – target your audience
  - Short, focused, attention-grabbing
  - Stake in the outcome
Changing culture

- ACLS, ATLS, SSCG are structured, evidence (good & bad) based methodical approaches to complex and stressful situations not regularly encountered by providers
- Focused on achieving key clinical goals
- Foundation for validation and study of local and population based outcomes
- Marketing and Selling
Opportunities to Change

- Push the envelope for early diagnosis
- Sepsis survival is getting better – Why?
- Treatment should continue in parallel
- Early interventions seem to have most profound impact
- Sepsis management paralleling Trauma, Stroke, and Cardiac Care
- Sepsis in rural & community environments