Early Recognition & Management of Severe Sepsis

Kathleen M. Vollman RN, MSN, CCNS, CCRN, FCCM
Clinical Nurse Specialist/Educator/Consultant
ADVANCING NURSING
kvollman@comcast.net
Dearborn, Michigan
www.vollman.com
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Overview

- Significance of the Problem
- Defining the continuum
- Pathophysiologic derangements
- Prevention
- Early Recognition & Resuscitation
- Early Treatment
  - Supportive care

Surviving Sepsis Campaign

Public & Professional Awareness
Evidence Based Guidelines
Implementation Change Packet

Severe Sepsis: A Significant Healthcare Challenge

- Major cause of morbidity and mortality worldwide
  - Leading cause of death in noncoronary ICU (US)\(^1\)
  - 10th leading cause of death overall (US)\(^2\)
- More than 750,000 cases of severe sepsis in the US annually\(^3\)
- In the US, more than 500 patients die of severe sepsis daily\(^4\)

Surviving Sepsis Campaign

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Severe Sepsis Is Common*

*Based on data for sepsis
†Reflects hospital-wide cases of severe sepsis as defined by infection in the presence of organ dysfunction
\(^3\) National Vital Statistics Reports. 2005.

Severe Sepsis Campaign

Public & Professional Awareness
Evidence Based Guidelines
Implementation Change Packet
Begin Proven Care Strategies

- Early appropriate antibiotic use
- EGDT: Early Goal-Directed Therapy
- Low-tidal volume ventilation/ARDS/ALI
- Xigris if not contraindicated
- Tight glycemic control
- Low-dose steroid administration for refractory septic shock particularly in patients with relative adrenal insufficiency

Implementation Through Proven Change Strategies

IHI/VHA Change Strategy

- Care Bundles
  - Grouping of care elements for particular symptoms, procedures or treatments
  - Strong science, good methodology, poor process
  - Bundle characteristics
    - Solid evidence
    - Relatively easy & inexpensive
    - Individual components defined well
    - Process not defined well

Sepsis: 1991 ACCP / SCCM Definitions

- Infection
  - Inflammatory response to microorganisms, or
  - Invasion of normally sterile tissues
- Systemic Inflammatory Response Syndrome (SIRS)
  - Two or more of the following:
    - Core temperature >38°C or <36°C (>100.4°F or <98.8°F)
    - Elevated heart rate (>90 beats/min)
    - Respiratory rate >20 breaths/min or PaCO₂ <32 mmHg or mechanical ventilation for acute respiratory process
    - WBC count >12,000/mm³ or <4,000/mm³ or
      >10% immature neutrophils

Sepsis: 1991 ACCP / SCCM Definitions (cont)

- Sepsis
  - Known or suspected infection, plus
    - ≥2 SIRS criteria
- Severe Sepsis
  - Sepsis plus
    - ≥1 organ dysfunction

IHI/VHA Change Strategy Describe

- Care Bundles
  - Grouping of care elements for particular symptoms, procedures or treatments
- Strong science, good methodology, poor process
- Bundle characteristics
  - Solid evidence
  - Relatively easy & inexpensive
  - Individual components defined well
  - Process not defined well

Sepsis: 1991 ACCP / SCCM Definitions (cont)

- Septic Shock
  - Sepsis with
    - Hypotension despite fluid resuscitation, and
    - Perfusion abnormalities

Signs & Symptoms of Sepsis

- Chills
- Alteration in LOC
- Tachypnea
- Unexplained metabolic acidosis
- Heart rate
- Altered blood pressure
- Platelets
- Bands
- Skin perfusion
- Urine output
- Skin mottling
- Poor capillary refill
- Hypoglycemia
- Purpura/petechia

Identifying Acute Organ Dysfunction as a Marker of Severe Sepsis

- Respiratory
  - PaO₂/FiO₂<200 if lung only dysfunction/site of infection
  - PaO₂/FiO₂<250 with other organ dysfunction/lung not site of infection
- Cardiovascular
  - Tachycardia
  - SBP<90mmHg
  - MAP < 75mmHg (despite fluid)
  - Need for Vasopressors
- Renal
  - UO <0.5 ml/kg per hr (despite fluid)
- Metabolic
  - Unexplained metabolic acidosis
    - pH<7.30 or Base deficit ≥ 5.0 mEq/l
    - Lactate > 1.5 times upper normal
- Hematologic
  - Platelets <80,000/mm³
  - Decline in platelet count of 50% over 3 days
### PaO₂/FiO₂ Ratio
- User friendly tool
- Crude assessment of the severity of lung injury
- Used in the definition of ALI/ARDS
  - ALI: PaO₂ < 300 regardless of PEEP
  - ARDS: PaO₂ < 200 regardless of PEEP

### Identifying Acute Organ Dysfunction as a Marker of Severe Sepsis
- Respiratory
  - PaO₂/FiO₂ < 200 if lung only dysfunction/site of infection
  - PaO₂/FiO₂ < 250 with other organ dysfunction/lung not site of infection
- Cardiovascular
  - Tachycardia
  - MAP < 70 mmHg
- Renal
  - UO > 0.5 ml/kg per hr
- Metabolic
  - Unexplained metabolic acidosis
    - pH < 7.30 or Base deficit > 5.0 mEq/l
    - Lactate > 1.5 times upper normal
- Hematologic
  - Platelets < 80,000/mm³

### Homeostasis Is Unbalanced in Severe Sepsis
- COAGULATION
- INFLAMMATION
- FIBRINOLYSIS

### SEVERE SEPSIS PATHOPHYSIOLOGY
- Microvascular dysfunction → Hypoperfusion/hypoxia → Organ dysfunction
- Inflammation
- ↑ Coagulation
- ↓ Fibrinolysis
- Microvascular thrombosis
- Endothelial dysfunction
- Global tissue hypoxia
- Direct tissue damage

### MICROCIRCULATION: SUBLINGUAL BLOOD FLOW
- Septic Shock Patient
  - Resuscitated with fluids and dopamine
    - HR: 82 BPM
    - BP: 90/35 mmHg
    - SaO₂: 96%
    - CVP: 25 mmHg

### Pathophysiologic Characteristics in Severe Sepsis
- Maldistribution of blood flow
- Imbalance of oxygen supply & demand
- Metabolic alterations & activation of the stress response
**Maldistribution of Blood Flow**
- Mechanical obstruction
  - Micro-emboli
  - Increased blood viscosity
  - Compression
- Systemic & local mediator & ion influence
  - Constriction vs. dilation
- Loss of regulatory activities/endothelial cell injury
  - Reactive hyperemia
  - Anticoagulation

**Imbalance of Oxygen Supply & Demand**

**O₂ Supply/Demand Compensatory Mechanisms**
- Improve pulmonary gas exchange
- Increase oxygen delivery
- Alter the distribution of blood flow

**O₂ Supply Debt**

**Metabolic Alterations & The Stress Response**

**Initiation of the Stress Response**
- Sympathetic Nervous System Activation
- Hypothalamus Activation

**Metabolic Alterations & The Stress Response**
- SNS Activation
  - Gut hypothesis
  - ↑ BMR
  - Inhibition of insulin secretion
  - Inhibition of glucose uptake by the tissues
- Hypothalamus Activation
  - Adrenal cortex stimulation
  - Changes in carbohydrate, protein & fat metabolism resulting in ↑ glucose concentration
Except on few occasions, the patient appears to die from the body’s response to infection rather than from it.”

Sir William Osler – 1904
The Evolution of Modern Medicine

Cornerstones of Management
- Prevention
- Early recognition & resuscitation
- Early antibiotic administration
- Early resuscitation
- Transport to appropriate care area for early treatment using evidence based care

PREVENTING THE INVASION
- Handwashing
- Line care
- Oral care
- HOB

Michigan Keystone Prevention of Infection (127 ICU’s)
- VAP’s
  - March 2004
    5.44/per 1000 ventilator days
  - July 2004
    5.36/per 1000 ventilator days
  - December 2004
    4.14 per/1000 ventilator days
- 1/3 hospitals 5 months with no VAP’s
- Prevented 73 deaths
- Cost saved $2,000,000.00

Michigan Keystone Prevention of Infection (103 ICU’s data reported)
- BSI’s
  - June 2004/Baseline
    Median 2.7 (mean 7.7) /per 1000 catheter days
  - At 18 months
    Median 0 (mean 1.4) per/1000 catheter days
- 66% reduction using the BSI bundle concept


EARLY MANAGEMENT
Screening for Severe Sepsis

Yes

Screen for Severe Sepsis

No

Standard care

Confirm Diagnosis of Severe Sepsis

Surviving Sepsis Guidelines

Monitor Q24H floor; Monitor every shift in the ICU

“Triggers” for Identifying Severe Sepsis

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<tbody>
<tr>
<td>Emergency Department</td>
<td>• Triage: Criteria-Based Early Response</td>
<td>Concurrent order in case manager</td>
<td>Upon pharmacy entry of vasopressor antibiotic</td>
</tr>
<tr>
<td></td>
<td>• Lactate as a screen</td>
<td>Order sheets antibiotic/vasopressor for</td>
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<td>• Change in lactate</td>
<td>Change in lab values (lactate)</td>
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Clinical Surrogates for High Risk of Death

Remember these care issues:
- Cultures, antibiotics, source control
- Vasopressors
- Mechanical ventilation
- Supplemental O₂
- Risk of death 30% to 50% or higher

Changes in Cardiovascular Function on Day 1 Were Associated With Increased Mortality

Data on file, Eli Lilly and Company.

Make it Process Dependent

- Weave into fabric of current practice
- Assess for daily
- Identify strategies for initiation of therapy response once patient is identified
To provide prompt, consistent nursing interventions for the patient with SIRS or...

**IMPLEMENTATION:**

**PURPOSE:**

**Labs:**

- WBC: 11.5
- Hgb: 15.8
- Hct: 47.4
- BUN: 28 Creatinine: 1.6
- Glucose: 158
- BNP: 78 (moderate CHF); troponin: 0.03
- Lactic acid: 4.6
- UA: positive for bacteria
- Svo2: 49.1%
- Blood cultures X 2 drawn

**Early Recognition Models**

**Shock Program**

**MET Team**

**Critical Care Nurse Consultant Service**

**Advanced Treatment Guidelines**

**Department of Emergency Services**

**Purposes:** To provide prompt, consistent nursing interventions for the patient with SIRS or sepsis prior to physician evaluation, to enable rapid diagnosis and slow the progression of illness.

**Implementation:** The nursing staff may implement these interventions for patients who present with the following criteria. The nurse should take into consideration the patient's baseline vital signs when evaluating as a potential candidate. Also, these interventions should not conflict with the patient/family goals. (i.e. DNR, comfort care)

1. Clinical suspicion of systemic infection
2. At least two of the following:
   - Hypothermia: Temperature less than < 36 °C (96.8 °F)
   - Hyperthermia: Temperature greater than 38 °C (100.4 °F)
   - Tachycardia Pulse > 90 bpm
   - Tachypnea: RR > 20
3. SBP < 90

**Positive Screen for severe sepsis:**

- SIRS: HR > 90; RR > 20; Temp > 38
- Organ dysfunction: SBP < 90 mmHg

**Early Treatment**

- IV started
- Received 500 cc NS bolus over 30 minutes
- Labs drawn

**Case Study: Early Identification and Intervention**

**Initial VS:**

- Temp: 101.6 F
- RR: 31
- HR: 109, atrial fib with occasional SVT
- B/P: 79/51
- 2L of O2, O2 sat of 96%

**Positive Screen for severe sepsis:**

- SIRS: HR > 90; RR > 20; Temp > 38
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**Advanced Treatment Guidelines**

**Department of Emergency Services**

**Treatment**

1. Notify Physician
2. Place Intermittent Infusion Device (large bore catheter) in 2 sites
3. Place on cardiac monitor
4. Continuous pulse oximetry
5. Vital signs every 15 minutes
6. Administer oxygen at 2 L/min per nasal cannula if O2 sat < 92%
7. Draw and hold blood cultures x 2, Type & screen
8. Draw and hold tube for serum lactate and place on ice.
10. Portable CXR
11. Intravenous hydration: Administer 500 ml bolus of normal saline over 15 minutes.

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Case Study: Early Identification and Intervention--MICU

**Additional Interventions: Day 1**
- Continued fluid resuscitation—7 L
- Low dose vasopressor
- Low dose steroids
- Remained on 2 L nasal canula
- Not eligible for Xigris (renal failure resolved and vasopressor weaned off within 12 hours after ICU admission)

**Labs:**
- ScvO2: 72.8 (after resuscitation)
- Lactic acid: 4 hours after ICU admission: 6.7
  12 hours after ICU admission: 3.0

Bleeding is most common adverse effect associated with Xigris therapy, please see important safety information in this presentation

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|                      | Change in lactate or surrogate
|                      | During MD, RN, RPh, rounds
|                      | Criteria-Based Early Response
|                      | From concurrent coder or case manager
|                      | Nurse MAR review antibiotic/vasopressor
|                      | Change in lab values (lactate or surrogate)
|                      | Place on all ICU charts, daily
|                      | Upon pharmacy entry of vasopressor/antibiotic
|                      | In note field on computerized MAR
|                      | In note field of vasopressor computerized label
|                      | Upon withdrawal of need from Automated Dispensing Cabinet
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**Criteria-Based Early Response**

Patient Care Units
- Upon admission
- During MD, RN, RPh, rounds
- Criteria-Based Early Response teams

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**Triggers**

**Sepsis Screening (To be completed every shift)**

A. **SIRS**

- Does patient have an infection or suspicion of infection?
- Is patient on antibiotics (not prophylaxis)?

B. **SIRS** (Systemic Inflammatory Response Syndrome)

Does patient meet ≥2 or more of the following SIRS criteria?
- T > 38°C (100.4°F) or < 36°C (96.8°F)
- HR > 90 BPM
- RR > 20 breaths/min
- WBC > 12,000, < 4000, or > 10% immature neutrophils

C. **Assess Organ Dysfunction**

Does patient meet one or more of the following criteria?
- SBP < 90 mmHg or MAP < 65 mmHg
- SBP decreases ≥40 mmHg from baseline
- Bilateral pulmonary infiltrates with a new or increased oxygen requirement to maintain SpO2 < 90%
- Bilateral pulmonary infiltrates with PaO2/FiO2 ratio < 300
- Creatinine >2.0 mg/dL or Urine Output <0.5 mL/kg/hour for ≥2 hours
- Bilirubin >2 mg/dL
- Platelet count < 100 000
- Coagulopathy (PT >15.5 or aPTT >50 seconds)
- Lactate >4 mmol/L
- Altered consciousness or radiated SOAS

If all criteria met for A, B, C, screen is positive for severe sepsis

Time: [ ] Time: [ ] Time: [ ]

O. If positive screen for severe sepsis

- MO notified
- Time: [ ]
- SBIRT team notified
- Time: [ ]

---

Case Study: Early Identification and Intervention

**Day 2:**
- Vasopressor weaned off
- Lasix to assist with fluid mobilization
- Lactic acid: 3.0

**Day 3:**
- Lactic acid: 1.2
- O2 sat 93% on room air
- Central line discontinued
- Transferred to intermediate care on Day 3
- Discharged from hospital on day 7
EARLY MANAGEMENT

- Early Recognition /Screening
- Source Control/ Early Antibiotics
- Prompt/Aggressive Resuscitation
- ICU/Additional Evidence Based Therapies

Early Treatment: Source Control

(grade E: case series, uncontrolled studies, expert opinion)

- Appropriate cultures including 2 blood cultures prior to initiation of antibiotics
- Early aggressive surgical intervention
- Early fracture fixation

Antibiotics and Sepsis: Necessary but Not Sufficient for Survival

- Intention
- Immune/Inflammatory Activation
- Severe Sepsis
- Death

- Appropriate antibiotics decrease evolution to severe sepsis by ~50%

Antibiotic Therapy

- Start intravenous antibiotic therapy within the first hour of recognition of severe sepsis after obtaining appropriate cultures  
  Grade E
- Empirical choice of antimicrobials should include one or more drugs with activity against likely pathogens, both bacterial or fungal  
  Grade D
  - Penetrate presumed source of infection
  - Guided by susceptibility patterns in the community and hospital
  - Continue broad spectrum therapy until the causative organism and its susceptibilities are defined

Mortality as a Function of Adequacy of Empiric Antimicrobial Therapy

- Hospital Mortality (%)
- All causes
- Infection-related

- Adequate Therapy
- Inadequate Therapy

P<0.001

Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock

- Effective antimicrobial administration within the 1st hour of documented hypotension was associated with increased survival in patients with septic shock.
- Each hour of delay over the next 6 hours was associated with an average decrease in survival of 7.6% (range 3.6-9.9%)

CCM 2006 Vol. 34 No.6
Antibiotic Challenges

✓ Appropriate selection – determined based upon consensus guidelines and pathogen sensitivity at your institution

✓ Timing issues
  ➢ How? Delivery time challenges of antibiotics
  ➢ Possible solutions

Sepsis Resuscitation Bundle

(To be accomplished as soon as possible over first 6 hours):

1. Serum lactate measured.
2. Blood cultures obtained prior to antibiotic administration.
3. From the time of presentation, broad-spectrum antibiotics administered within 3 hours 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) of > 8 mm Hg.
   b) Achieve central venous oxygen saturation (ScvO2) of > 70%.

PROMPT AGGRESSIVE RESUSCITATION

“Early Goal Directed Therapy”

Early Goal Directed Therapy

Methodology: 263 severe sepsis patients

- Early Goal-Directed Therapy (EGDT)
  - Continuous ScvO2 monitoring & tx with fluids, blood, inotropes &/or vasoactives to maintain:
    - ScvO2 ≥ 70%, SaO2 ≥ 93%, Hct ≥ 30%, CI/VO2
    - CVP ≥ 8-12
    - MAP ≥ 65
    - UO ≥ 0.5 ml/kg/hr

- Standard Therapy
  - CVP ≥ 8-12
  - MAP ≥ 65
  - UO ≥ 0.5 ml/kg/hr

Evidence of Early Goal Directed Therapy

First 6 hours of EGDT:

- 1500cc more fluid
- 64% received blood products vs. 18.5%
- 13.7% received inotropes vs. 0.8%
- No difference in vasopressor use or mechanical ventilation

Resuscitation should begin as soon as severe sepsis or sepsis induced tissue hypoperfusion is recognized.

Elevated Serum lactate identifies tissue hypoperfusion in patients at risk who are not hypotensive.

Initial Resuscitation (Grade B)

- Resuscitation should begin as soon as severe sepsis or sepsis induced tissue hypoperfusion is recognized.
- Elevated Serum lactate identifies tissue hypoperfusion in patients at risk who are not hypotensive.

EGDT: Revisited

- Outcomes Survey: 12 programs
- 1,298 patients with severe sepsis and septic shock
- Treated with EGDT and/or the sepsis bundles
- Pre implementation mortality: 44.8 ± 7.8%
- Post implementation mortality: 24.5 ± 5.5%

20.3% Reduction in Mortality, NNT 5

Otero RM. et al Chest; 2006:130:1579-1595

EGDT: Revisited

- Cost Effectiveness of EGDT/Guideline Based Care (ED, ICU or RRT initiated)
- 23.4% reduction in hospital cost (incorporated additional training, personnel and equipment)
  Huang et al Crit Care Med 2003:7(suppl S116)
- Henry Ford Hospital: ↓ 4 day Hospital LOS (32.6% reduction)
- Reduction in hospital charges from $135,199 to $82,233 (39.2% reduction)

Otero RM. et al Chest; 2006:130:1579-1595

Challenges to Adequate Fluid Resuscitation

- How does your institution do fluid boluses?
- Is low urine output still measured by < 30cc/hr?
- Are resuscitation goals based on CVP, MAP & UO and do your practitioners still believe this is adequate?
**Challenges to Adequate Fluid Resuscitation**

- What are your average wait times for an ICU bed?
- Will you be able to shorten those?
- Initiation of EGDT must be early
- Do you routinely measure lactate, and how?
- What resources and education/training is required? (catheter, fluid administration per kg & dobutamine use)

**EARLY MANAGEMENT BUNDLE**

- Early Recognition
- Source Control/Early Antibiotics
- Prompt/Aggressive Resuscitation
- ICU/Additional Evidence Based Therapies

**Corticosteroids In Septic Shock: SSC Recommendations**

- Intravenous corticosteroids are recommended in patients with septic shock who, despite adequate fluid therapy, require vasopressor therapy to maintain adequate blood pressure
- Administer intravenous hydrocortisone 200-300 mg/day for 7 days in three or four divided doses by continuous infusion
- Shown to reduce mortality rate and reverse shock in patients with relative adrenal insufficiency
- NNT=17

*Annane D et al. JAMA 2000;283:1038-1045

**Xigris (drotrecogin alfa [activated]) in Severe Sepsis: Indication**

- Drotrecogin alfa (activated) is indicated for the reduction of mortality in adult patients with severe sepsis (sepsis associated with acute organ dysfunction) who have a high risk of death (e.g., as determined by APACHE II*)
- Drotrecogin alfa (activated) is not indicated in adult patients with severe sepsis and lower risk of death. Safety and efficacy have not been established in pediatric patients with severe sepsis.

*APACHE (Acute Physiology And Chronic Health Evaluation). For more information on using the APACHE II scoring system, please see [http://www.sfr.org/scores2/index.html](http://www.sfr.org/scores2/index.html).

See important safety information in this presentation.

**THE ROLE OF ENDOGENOUS ACTIVATED PROTEIN C IN SEVERE SEPSIS**

**Recombinant human Activated Protein C**

- Recombinant human Activated Protein C (Drotrecogin alfa [activated]) is recommended in patients at a high risk of death Grade B
  - APACHE II score ≥ 25, or
  - Sepsis-induced multiple organ failure, or
  - Septic shock, or
  - Sepsis induced acute respiratory distress syndrome
- Treatment with drotrecogin alfa (activated) should begin as soon as possible once a patient has been identified as being at high risk of death
- Patients should have no absolute or relative contraindication related to bleeding risk that outweighs the potential benefit of rhAPC

Drotrecogin Alfa (Activated) In Severe Sepsis: PROWESS Results

- 29% reduction in relative risk of death with Xigris™

PROWESS 28-Day Mortality – High Risk of Death Patients*

<table>
<thead>
<tr>
<th>Mortality Rate</th>
<th>Placebo</th>
<th>Drotrecogin alfa (activated)</th>
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<td>0%</td>
<td>44%</td>
<td>31%</td>
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</table>

Absolute Risk Reduction = 13%

Rate of serious bleeding events during infusion in high-risk patients:
- PROWESS: 2.2% (9 of 414) in drotrecogin alfa (activated) patients vs 0.7% (3 of 403) in standard therapy patients

- Rate of ICH in high-risk patients during infusion:
  - PROWESS: 0.2% (1 of 414) in drotrecogin alfa (activated) patients
  - Associated with severe thrombocytopenia (platelet count < 30,000/mm³)

- Not associated with other adverse events

*Defined by APACHE II ≥ 25. Incidence risk reduction at 28 days.

See important safety information in this presentation.

Safety Profile

- Low incidence of serious bleeding events*
- Rate of serious bleeding events during infusion in high-risk patients:
  - PROWESS: 2.2% (9 of 414) in drotrecogin alfa (activated) patients vs 0.7% (3 of 403) in standard therapy patients
- Rate of ICH in high-risk patients during infusion:
  - PROWESS: 0.2% (1 of 414) in drotrecogin alfa (activated) patients
  - Associated with severe thrombocytopenia (platelet count < 30,000/mm³)
- Not associated with other adverse events

*Serious bleeding events were defined as any intracranial hemorrhage, any life-threatening bleeding, any bleeding event resulting in the administration of 10 units of packed red blood cells per day for 2 consecutive days, or any bleeding event associated with a serious adverse event.

At the time of enrollment in the PROWESS study, the patient had a platelet count above 30,000/mm³. The patient's platelet count fell to less than 30,000/mm³ after drotrecogin alfa (activated) therapy was initiated.

See important safety information and full prescribing information in this presentation.

IMPORTANT SAFETY INFORMATION

Drotrecogin alfa (activated) is contraindicated in patients with the following clinical situations in which bleeding could be associated with a high risk of death or significant morbidity:

- Active internal bleeding
- Recent (within 3 months) hemorrhagic stroke
- Recent (within 2 months) intracranial or intraspinal surgery, or severe head trauma
- Trauma with an increased risk of life-threatening bleeding
- Presence of an epidural catheter
- Intracranial neoplasm or mass lesion or evidence of cerebral herniation

Drotrecogin alfa (activated) is contraindicated in patients with known hypersensitivity to drotrecogin alfa (activated) or any component of this product.

See full prescribing information available at this presentation.

Survival Benefit Consistent across High-risk Severe Sepsis Patients

Xigris™ (drotrecogin alfa [activated]) benefits consistent

<table>
<thead>
<tr>
<th>Survival Benefit Consistent across High-risk Severe Sepsis Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FAVORS XIGRIS</strong></td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>251</td>
</tr>
</tbody>
</table>

**FAVORS XIGRIS** vs **FAVORS PLACEBO** results were consistent across subgroups.

Note the consistency between the overall trial result and the subgroup analyses.

Important Safety Information

CONTRAINdications

Drotrecogin alfa (activated) increases the risk of bleeding. Drotrecogin alfa (activated) is contraindicated in patients with the following clinical situations in which bleeding could be associated with a high risk of death or significant morbidity:

- Active internal bleeding
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See full prescribing information available at this presentation.

Fine-Tuning Xigris Therapy in Adult High-Risk Severe Sepsis Patients

Right Patient, Right Drug, Right Time

New: Clinical trials to help advance care of adult patients with severe sepsis at high risk of death:

RESPOND Targeted Enrollment = 500

Phase 2 trial investigating a biomarker (Protein C) to help guide Xigris therapy in adult patients with severe sepsis at high risk of death.

NEW Placebo Controlled Trial in Adult High-Risk Severe Sepsis

Help clinicians better identify patients who are most likely to benefit from Xigris, as well as to further clarify the benefit/risk profile of the drug.

Contact 1-800-LILLY-RX for more information.

Bleeding is the most common adverse effect associated with Xigris therapy. Please see important safety information in this presentation and accompanying full prescribing information.
Low Tidal Volume Ventilation: SSC Recommendations

- High tidal volumes, >6 mL/kg, coupled with high plateau pressures, >30 cm H2O, should be avoided  
- Hypercapnia can be tolerated in patients with ALI/ARDS if required to minimize plateau pressures and tidal volumes  
- A minimum amount of positive end expiratory pressure should be used to prevent lung collapse at end-expiration

---

The Role of Dopamine in Hemodynamic Support

- No evidence of increased renal perfusion at low doses
- Tachycardia more common than with norepinephrine
- May impair splanchnic blood flow
- Stimulates vasopressin release
- Does not confer clinically significant protection against renal dysfunction

---

Potential Advantages of Norepinephrine

- Minimal tachycardia response
- No interference with hypothalamic pituitary axis
- Evidence of increased cardiac output, renal blood flow and urine output when used in septic shock
- More potent agent than dopamine in refractory septic shock

---

Glucose Control: SSC Recommendations

- Following initial stabilization of patients with severe sepsis, maintain blood glucose to <150 mg/dL
- Glycemic control strategy should include a nutrition protocol with the preferential use of the enteral route
  - Minimize the risk of hypoglycemia by providing a continuous supply of glucose substrate
  - Accomplished by using 5% or 10% dextrose IV infusion and followed by initiation of feeding preferably by enteral route

---

Intensive Insulin Therapy in the Critically Ill

- Hyperglycemia & insulin resistance are common
- In diabetics with acute myocardial infarct, therapy to maintain the blood glucose level < 215mg/dL improves long term outcomes
- In the SICU, tight glycemic control to maintain a blood glucose of < 110mg/dL reduces morbidity & mortality (Grade B)
- The greatest reduction in mortality involves deaths due to multiple organ failure with a proven septic focus.
Sepsis Evidence Implementation

Making it a Reality Sepsis Bundle

Develop Protocols & Order Sets to Implement Resuscitation in Medical-Surgical Area

- Draw blood
  - Lactate Level
- Obtain blood cultures before administration of antibiotic
- Broad spectrum antibiotics administered within three hours of presentation
- In the event of hypotension (SBP < 90, MAP < 70) or lactate > 4 mmol/L, begin initial fluid resuscitation with 20-40 ml of crystalloid (or colloid equivalent) per estimated kg of body weight
- Vasopressors employed for hypotension ((MAP) < 65 mm Hg) during and after initial fluid resuscitation


Medical ICU Glycemic Management

Methodology

- 1200 MICU patients
- Maintain serum glucose levels 80-110mg/dl
- Measure 28 day mortality for patients >3 days in the ICU
- Measured morbidity factors: renal failure/dialysis use, vent days & ICU LOS

Results

- No difference in mortality within looking at all patients
- >3 days in the ICU with effective glucose control demonstrated improved mortality (43% vs 52.5% (p=0.009)
- Reduce use of dialysis, earlier weaning & discharge from the ICU in pts receiving glycemic control


Sepsis Bundles

Screen for Severe Sepsis

Standard care

Within 6 hrs (Transport is ICU is Key)

- In the event of septic shock or lactate > 4 mmol/L, CVP and ScvO2 or SVO2 measured. (line inserted)
- In the event of septic shock or lactate > 4 mmol/L, CVP maintained 8-12 mmHg
- Inotropes (and/or PRBC's if hematocrit <= 30 percent) delivered for ScvO2 < 70 percent or Svo2 < 65 percent if CVP >= 8 mmHg

www.ihi.org
Develop Protocols & Order Sets to Implement Management 24-Hour Severe Sepsis Bundles

- Maintain serum glucose levels on average < 150 mg/dl (8.3 mmol/L)
- Drotrecogin alfa (activated) administered in accordance with hospital guidelines
- Steroids given for septic shock requiring continued use of vasopressors for equal to or greater than 6 hours
- Adoption of a lung protective strategy (tidal volumes < 6ml/kg) with plateau pressures of 30 cm H2O for mechanically ventilated patients

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Severe Sepsis Bundle Implementation Results

- England
- Germany
- St. Louis, Missouri
- Colorado Coalition
- TICU

Severe Sepsis Protocol in Use

- Germany
- 60 patients (30 consecutive receiving SOP severe sepsis management compared to historical controls)
- Measured: Primary endpoint 28 day mortality
- Measured: Secondary endpoints: ABG’s, lactate, glucose, creat, WBC, Plat, time to dx & 7am on day 2 & 4 SOFA scores
- Results: In SOP group:
  - ↑ use of dobutamine, glucose control, steroids & rhAPC
  - Mortality: Control vs SOP (53% vs. 27% p <.05)
- Independent predictors of survival: lactate on admission, age, gender, blood glucose < 150 mg/dl, adm of rhAPC & steroids


Standardized Order Set-Sepsis Bundles

- St. Louis, Missouri
- Before-after study design with prospective consecutive data collection of 120 patients
- 1,200 bed academic medical center
- Primary endpoint: 28 day mortality
- Other measures: hospital LOS, IV fluid intact for shock, appropriate antibiotic
- Results: after group: received more IV fluids in ED (p=0.002); more likely to receive >20ml/kg of fluid prior to vasopressors; had lower risk of mortality (48.3% vs 30%, p=0.04); lower hospital LOS (12.1 vs 8.9 days, p=0.038)
- Independent predictors of survival: increased pt age and not receiving >20 ml/kg of IV fluid prior to vasopressors

Micek, Scott et al., Critical Care Medicine, 2006; 34:2707-2714

Colorado Coalition: Statewide Network

<table>
<thead>
<tr>
<th></th>
<th>Deceased</th>
<th>Alive</th>
<th>Total Receiving Bundle</th>
<th>% died who got the bundle</th>
<th>% Total Charts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality: All Patients</td>
<td>110</td>
<td>399</td>
<td>509</td>
<td>22%</td>
<td>100%</td>
</tr>
<tr>
<td>Resuscitation Bundle</td>
<td>11</td>
<td>87</td>
<td>98</td>
<td>11%</td>
<td>19%</td>
</tr>
<tr>
<td>Management Bundle</td>
<td>21</td>
<td>116</td>
<td>137</td>
<td>15%</td>
<td>27%</td>
</tr>
</tbody>
</table>

Presented by Dr. M. Levy at ASPEN National Meeting, 1/07
The Nurses Role

- Early recognition of patients with signs of sepsis
- Early initiation of evidence-based practice therapies appropriate for your area of practice (antibiotics, fluids/blood & pressors)
- Swift disposition to care areas where the rest of the bundle can be started.