**Overview**

- Significance of the Problem
- Defining the continuum
- Brief overview of Pathophysiologic derangements
- Prevention
- Early Recognition & Resuscitation
- Case Studies
- Outcome studies

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**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 annually³
- In the US, more than 500 patients die of severe sepsis daily

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**Severe Sepsis: Comparison with Other Diseases**

- Mortality from severe sepsis remains unacceptably high, even with the best standard care⁴

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**Background Information: Surviving Sepsis Campaign**

- Mission of the Surviving Sepsis Campaign (SSC)
  - Increase awareness and improve outcomes in severe sepsis
- Members of the SSC
  - Initial guidelines in 2004 were developed by a group of international experts representing 11 international organizations
  - 2008 revised guidelines using a modified Delphi method with a consensus of 55 international experts.
  - SSC members recognized that while evidence-based recommendations have been frequently published, documentation of impact on patient outcomes may be limited.
  - IHI is a leader and partner that strives to create measurable and continual progress of health care systems throughout the world. So they partnered with the IHI and put the guidelines into two bundles of care.
Institute for Healthcare Improvement (IHI): Care Bundles

- What is a “bundle”?  
  - A structured way of improving the processes of care and patient outcomes: a small, straightforward set of practices  
  - When performed collectively and reliably, are proven to improve patient outcomes  
  - A bundle focuses on how to deliver the best care

The Severe Sepsis Bundles: Surviving Sepsis

**Resuscitation Bundle**
- Delivered as soon as possible
  - Serum lactate measured.
  - Blood cultures obtained prior to antibiotics administered (1C)
  - Perform imaging studies promptly to define source of infection  
  - For hypotension and/or lactate > 4 mmol/L: antibiotics within 3 hours for ED admissions and 1 hour for non-ED ICU admissions. (1D/1B)
  - For persistent hypotension despite initial fluid resuscitation (septic shock) and/or lactate > 4 mmol/L: 1C
  - For persistent hypotension despite initial fluid resuscitation (septic shock) and/or lactate > 4 mmol/L: 1C
  - Administer low-dose steroids for refractory septic shock particularly in patients with relative adrenal insufficiency

**Management Bundle**
- High risk of death (2B)
  - Give vasopressors for hypotension not responding to initial fluid resuscitation to maintain MAP > 65 mmHg.
  - Low-tidal volume ventilation/ARDS/ALI
  - Low-dose steroid administration for refractory septic shock.
  - Tight glycemic control
  - Metabolic: glucose control maintained

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**

Severe Sepsis: Defining a Disease Continuum

**SIRS**
- Systemic Inflammatory Response Syndrome
- Examples: Cardiovascular (refractory hypotension), Respiratory, Hematologic, Neurologic, Renal, Unexplained metabolic acidosis

**Severe Sepsis**
- SIRS with ≥ 2 sign of organ dysfunction/hyperperfusion or hypotension.

Identifying Acute Organ Dysfunction as a Marker of Severe Sepsis

- **Respiratory**
  - Increasing O2 requirements
  - PaO_2/FiO_2 <250 with other organ dysfunction/lung not site of infection

- **Cardiovascular**
  - Tachycardia
  - SBP < 90 mmHg
  - MAP < 70 mmHg (despite fluid)

- **Neurologic**
  - Change in LOC

- **Metabolic**
  - Unexplained metabolic acidosis

- **Hematologic**
  - Platelets < 100,000/mm^3

Signs & Symptoms of Sepsis

- Chills
- Alteration in LOC
- Tachypnea
- Unexplained metabolic acidosis
- Heart rate
- Altered blood pressure
Homeostasis Is Unbalanced in Severe Sepsis

Inflammation, Coagulation and Impaired Fibrinolysis In Severe Sepsis

MICROCIRCULATION: SUBLINGUAL BLOOD FLOW

In Sepsis, the Microcirculation is Under Attack

Pathophysiologic Characteristics in Severe Sepsis

- Maldistribution of blood flow
- Imbalance of oxygen supply & demand
- Metabolic alterations & activation of the stress response

Cornerstones of Multidisciplinary Management of Severe Sepsis/MODS

- Prevention
- Screening and Early Identification
- Early Intervention: Source control, Blood cultures and broad spectrum antibiotics
- Resuscitation Bundle
- Management Bundle

References:

Registered with permission from the National Initiative in Sepsis Education (NISE).

Inflammation
Coagulation
Fibrinolysis

Endothelium

MIMIL-6

TNF-α

PAI-1

Factor VIIIa

Tissue Factor

Thrombin

Factor Xa

Factor V

Plasminogen

TAFI

Fibrin clot

Factor Va

THROMBIN

Fibrin

COAGULATION CASCADE

Fibrinolytic Response

Thrombotic Response

Inflammatory Response to Infection

Tissue Factor

Meninges

Neutrophil

MOnocyte

Healthy Volunteer

BP: 120/80 mm Hg
SaO₂: 98%

Septic Shock Patient
Resuscitated with fluids and dopamine
HR: 82 BPM
BP: 90/35 mmHg
SaO₂: 98%
CVP: 25 mmHg

Regional areas of hypoxia and dysoxia

Very difficult to detect clinically

Maldistribution of blood flow
Imbalance of oxygen supply & demand
Metabolic alterations & activation of the stress response

Healthy Volunteer

BP: 120/80 mm Hg
SaO₂: 98%
The Nurse’s Role

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

Strategies for Prevention: 5 Key “Best Practices”

- Remove Unnecessary Lines
- Hand Hygiene
- Use of Maximal Barrier Precautions
- Chlorhexidine for Skin Antisepsis
- Avoid femoral lines

Ventilator Bundle

- HOB at 30 degrees
- WAKE UP AND BREATH
  - Daily Spontaneous Breathing Trials
  - Appropriate Sedation
- PUD Prophylaxis
- DVT Prophylaxis
- Tight Glucose Control
- Oral Care q 2 hours with CHG rinse q 12 hrs
- Don’t routinely instill NS with suctioning
- Handling of suctioning and oral care equipment
- Use of pulmonary specialty beds
- Subglottal suctioning
- Progressive Mobility

EARLY MANAGEMENT

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

ICU SEVERE SEPSIS SCREENING TOOL

- Daily Spontaneous Breathing Trials
- Appropriate Sedation
- PUD Prophylaxis
- DVT Prophylaxis
- Tight Glucose Control
- Oral Care q 2 hours with CHG rinse q 12 hrs
- Don’t routinely instill NS with suctioning
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Strategies for Prevention: 5 Key “Best Practices”

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MMWR. 2002;51:RR-10
Reaching Outside the ICU: Early Recognition Models

- Shock Program/Rapid Response Team
- Medical Emergency Response Team (MET)
- Critical Care Nurse Consultant Service

Serum Lactate is associated with mortality in severe sepsis independent of organ failure and shock

Mikkelsen, Mark et al, CCM 2009 Vol 37 No 5

Objective:
- Test whether the association between initial serum lactate level and mortality in patients presenting to the ED with severe sepsis is independent of organ dysfunction and shock

Design:
- Retrospective, single center cohort study
- Academic teaching hospital

Patients:
- 830 adults admitted with severe sepsis in the ED
- Stratified lactate into 3 groups: low (<2), intermediate (2-3.9) and high (≥ 4)

Early Recognition: A Screening Process

- TIME IS TISSUE!!
  - If you identify patients early then you can intervene and prevent further tissue damage
- To screen effectively, it must be part of the nurses’ daily routine
- Must define a process for what to do with the results of the screen

Results:
- Intermediate and high serum lactate significantly associated with mortality regardless of the presence of shock or other organ dysfunction
- A single serum lactate seems to risk-stratify patients independent of organ dysfunction or hemodynamic instability

If you don’t screen you will miss patients that could have benefited from the interventions
Make it Process Dependent

- Weave into fabric of current practice
- Assess for daily
- Identify strategies for initiation of therapy response once patient is identified

Screening

- Lesson Learned: Bedside nurse must do screening
- Education/Simulation/Education
  - Every 6 months
  - Build into orientation
  - Must be part of their documentation structure
  - Practice-Practice-Practice

The END RESULT—anytime patient has 2 or more SIRS—will think that this patient might have sepsis and can screen at that time

EARLY MANAGEMENT

![Diagram](early_management_diagram.png)

Antibiotic Therapy

- Start intravenous antibiotic therapy within the first hour of recognition of severe sepsis after obtaining appropriate cultures (1D) for Septic shock (1B)
- Broad spectrum: include one or more agents active against likely bacterial/fungal pathogens, & with good penetration into presumed source (1B)
- Reassess regimen daily to optimize efficacy, prevent resistance, avoid toxicity & minimize costs. (1C)

The Severe Sepsis Bundles: Surviving Sepsis Campaign/IHI

Resuscitation Bundle
-Low-dose steroids administered for septic shock in accordance with a standardized ICU policy. (2C)
-Drotrecogin alfa (activated) administered in accordance with a standardized ICU policy. (2C)
-Serum lactate measured. (1C)
-Blood cultures obtained prior to antibiotics administered. (1C)
-Perform imaging studies promptly to identify source. (1C)
-Administer antibiotics within 3 hours for ED admissions and 1 hour for non-ED ICU admissions. (1D/1B)

Management Bundle
-Low-dose steroids administered for septic shock in accordance with a standardized ICU policy. (2C)
-Drotrecogin alfa (activated) administered in accordance with a standardized ICU policy. (2C)
-Volume expansion with crystalloids, colloids or blood products as needed. (C)
-Fever control maintained to < 38°C (98.6°F) or 38°C (101°F). (C)
-Tidal volume 6 ml/kg (1B) Inspiratory plateau pressures < 30 cmH2O for mechanically ventilated patients. (1C)

Mortality as a Function of Adequacy of Empiric Antimicrobial Therapy
### Initiation of Inappropriate Antimicrobial Therapy Result in a 5-Fold Reduction of Survival in Human Septic Shock

- 5,715 patients in septic shock in three countries
- 55% of cases were from community acquired infection
- Decrease in survival with inappropriate initial antibiotics was fivefold

<table>
<thead>
<tr>
<th>Survival</th>
<th>Inappropriate</th>
<th>Appropriate</th>
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<td>20</td>
<td>60</td>
</tr>
<tr>
<td>1</td>
<td>185</td>
<td>8</td>
</tr>
</tbody>
</table>

### 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

### Initial Resuscitation (1C)

- Protocolized resuscitation should begin as soon as sepsis induced tissue hypoperfusion is recognized
- Elevated Serum lactate identifies tissue hypoperfusion in patients at risk who are not hypotensive
- Initial fluid challenges be started at > 1000 mL/kg or 300-500 mL of colloid over 30 minutes (1C)

### Early Goal Directed Therapy

- Standard Therapy
  - CVP > 8-12
  - MAP > 65
  - UO > .5ml/kg/hr

- 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 ≥ .5ml/kg/hr

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

- 2,154 septic shock patients
- 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%)

### Prompt Aggressive Resuscitation

“Early Goal Directed Therapy”
Early Goal-Directed Therapy Results

28-day Mortality

<table>
<thead>
<tr>
<th></th>
<th>Standard Therapy n=133</th>
<th>EGDT n=130</th>
</tr>
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<tbody>
<tr>
<td>28-day Mortality</td>
<td>49.2%</td>
<td>33.3%</td>
</tr>
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</table>

*NNT = 7-8

*Key difference was in sudden CV collapse, not MODS


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


Occult Tissue Hypoxia

- Tissue hypoxia is often occult, reaches an advanced and lethal stage before its presence is known and resuscitation is attempted.
- Vital signs are inadequate for detecting global tissue hypoxia and not adequate as a resuscitation end point.
- Up to 50% of patients resuscitated from shock may have continued global tissue hypoxia (elevated lactate and decreased ScvO2) despite normalized vital signs and central venous pressure.


Inadequacy of Arterial Pressure

- Adequate pressure does not always mean adequate flow to tissues.
- Systemic hypoperfusion usually precedes hypotension, especially in patients with sepsis.

OXYGEN SUPPLY/DEMAND DYNAMICS

ScvO2

CVP, CO, SV, SVV

Hemodynamic Monitoring

- Preload
  - Volume status
  - Currently measured by CVP, PAOP (PCW)
  - Normal: 8-12
- Afterload
  - Resistance that heart has to pump against
  - Currently use SVR which is a calculated variable (need pulmonary artery catheter)
  - Normal: 800-1200
- Contractility
  - How effectively the heart is pumping
  - Currently measured by obtaining CO, CI and SV from pulmonary artery catheter
  - CO= SV x HR
  - Normal: CO= 4-8 L; CI=2.5-4 L; SV= 60-100ml; SVI=33-47 ml

Optimize Cardiac Performance

Fluid Bolus to define place on curve:
- Record CI and SV
- Give 250-500 NS bolus over 15 minutes
- Record CI and SV
- If see greater than a 10% increase in SV or CI—it is on steep portion of curve and will still respond to fluid

Stroke Volume Variation (SVV)

- Using a continuous measurement of the 'swing' in arterial pulse pressure often observed with mechanically ventilated patients, the FloTrac/Vigileo system calculates the Variation of Stroke Volume (SVV) associated with each inspiration & expiration.
- This variation is expressed as SVV (Stroke Volume Variation), & is recalculated every 20 seconds, and reported as a % (stroke volume max - stroke volume minimum / Mean stroke volume over a single respiratory cycle)
- SVV has been shown to be an important predictor of a patients fluid responsiveness & when used with other reported indices (CI,SVI,MAP& HR) a valuable guide to optimizing volume in a patient.
- Research indicates that mechanically ventilated patient exhibiting a SVV of >13% would respond favorably to fluid. (Increase in SVI,CI, & CO).
- Limitations: Presence of arrhythmias, use of differing tidal volumes & rates, and non mechanically-control ventilated patients limits the predictive value of SVV.
Application of Minimally invasive Hemodynamic monitoring in Sepsis

- Assist in differentiation of type of shock
- Assist with optimal fluid resuscitation
  - When target CVP of 8-12 or 12-15: use of SVV or SV changes with fluid bolus will help to decide optimal filling pressures to achieve maximum stroke volume
- Identify patients with myocardial dysfunction with sepsis
- Assist with fluid resuscitation in patients in which central line insertion is contraindicated or delayed

Monitoring Oxygen Dynamics

- Lactates every 6 hrs
  - Correlates with mortality;
  - Expect clearance within 24 hours
- ScvO2
  - subclavian or IJ triple lumen or PreSep catheter
  - baseline and then hourly till > 70%

Multicenter Study of Central Venous Oxygen Saturation (ScvO2) as a Predictor of Mortality in Patients With Sepsis

Pope; et al

- Objective:
  - Primary: an abnormal (both low and high) ScvO2 is associated with increased mortality in emergency department (ED) patients with septic shock.
  - Secondary: determine whether the initial ScvO2 or the maximum ScvO2 achieved was associated with mortality.
- 619 patients from 4 hospitals; prospectively collected data

Multicenter Study of Central Venous Oxygen Saturation (ScvO2) as a Predictor of Mortality in Patients With Sepsis

Pope; et al

Maximun ScvO2 in 6 hours relates to mortality

Considering the maximum ScvO2 achieved in the ED, the presence of both hypoxia and hyperoxia was associated with a higher mortality rate compared with that of the normoxia group

Challenges to Adequate Fluid Resuscitation

- Does your institution still do 250 ml 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?
- Do you routinely measure lactate, and how?

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)

**Vasopressors**

- Recommend that MAP be maintain $>65$ mmHg (1C)
- Ideally adequate fluid resuscitation should be achieved before vasopressors and inotropes are used, but use early in septic shock may need to occur. When it does the goal should be to try and wean with continuing fluid resuscitation.
- Norepinephrine or dopamine as first choice. (1C)
- Epinephrine, phenylephrine or vasopression should not be used as the initial vasopressor. (2C) Vasopresion may be added to norepinephrine at 0.03 units/min.
- Suggest that epinephrine be the first chosen alternative. (2B)
- Low dose dopamine not be used for renal perfusion. (1A)

**Vasopressin vs Norepinephrine Infusion in Septic Shock VASST Study**

- **Design:** Multicenter, randomized, double-blinded
- **Population:** 778 patients with septic shock and were receiving a minimum of 5mcg/min of norepinephrine (or equivalent) for 6 hours (excluded pts with underlying heart disease)
- **Methods:** Received either low dose vasopressin (0.01-0.03U per minutes) or norepinephrine in addition to open-label vasopressors
- **End point:** 28 day mortality

**VASST Study Results**

- No significant difference in 28 day or 90 day mortality between the two groups
- Among patients who had less severe septic shock (on norepinephrine between 5-15 mcg/min) there was a trend toward improved mortality with vasopressin (hypothesis generating)
- No significant difference in rates of organ dysfunction between the two groups
- No significant difference in overall rates of serious adverse events between the two groups
- Trend toward higher rate of cardiac arrest in norepinephrine group
- Trend toward higher rate of digital ischemia in the vasopressin group

**Additional Findings**

- Vasopressin infusion allowed a rapid decrease in the total norepinephrine dose while maintaining mean arterial pressure
- Overall rates of serious adverse events were approximately 10% each in the vasopressin and norepinephrine groups.
- The MAP at baseline was 72-73mmHg—essentially making this a study of the effects of low dose vasopressin as a "catecholamine-sparing drug" not an evaluation of vasopressin in patients with catecholamine-unresponsive refractory shock

**EARLY MANAGEMENT**

- Early Recognition
- Early Antibiotics
- Prompt/Aggressive Resuscitation
- ICU/Additional Evidence Based Therapies
Case Study I: Early Identification and Intervention

- **Initial VS:**
  - Temp: 101.6°F
  - RR: 31
  - HR: 109, atrial fibr with occasional SVT
  - BP: 79/51
  - 2L of O2, O2 sat of 96%

- **Positive Screen for severe sepsis:**
  - SIRS: HR >90; RR> 20; Temp > 38
  - Organ dysfunction: SBP<90mmHg

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

Advanced Treatment Guidelines
Department of Emergency Services

**PURPOSE:** 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 all three of 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:
   - Hyperthermia: Temperature greater than 38°C (100.4°F)
   - Hypothermia: Temperature less than < 36°C (96.8°F)
   - Tachycardia: Pulse > 90 bpm
   - Tachypnea: RR > 20
3. SBP < 90

Patients who meet all three criteria will be placed in a room immediately after consultation with charge nurse and/or attending.

**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 500ml bolus of normal saline over 15 minutes.

Case Study 1: Early Identification and Intervention

- **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
  - U/A: positive for bacteria
  - Blood cultures X 2 drawn
Case Study 1: Early Identification and Intervention

- CXR: RLL consolidation
- Additional Interventions:
  - Broad spectrum antibiotics given within 3 hours of presentation
  - Lactic acid >4 mmol/L so CVP inserted
  - ScvO2: 49.1%
  - Fluid resuscitation continued
  - Foley inserted
- Received total of 3 Liters of NS during 3 hour ED stay
- ED diagnosis: Severe sepsis, Pneumonia, UTI, CHF
- Transferred to MICU

Case Study 1: Early identification and intervention—MICU

- Additional Interventions: Day 1
  - Hours 3-6
    - Continued fluid resuscitation—4L
    - Low dose vasopressor weaned off at 6 hours
  - Hours 6-24
    - VS: BP 96/50; HR 98; RR: 18 on 2 L; O2 Sat: 96%
    - WHAT ARE YOUR NEXT STEPS?
    - Need more information:
      - CVP: 6, ScvO2: 65%
      - Give fluids to increase CVP to get ScvO2 to > 70%
      - After 3L CVP now 10, ScvO2-72%
      - BP: 100/60 (73)
      - HR: 88
      - RR 16
      - O2 Sat: 98%
      - WHAT ARE YOUR NEXT STEPS??

Case Study 1: Early Identification and Intervention—MICU

- Additional Interventions: Day 1
  - Low dose steroids not indicated
  - Remained on 2 L nasal cannula
  - 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

Case Study II:

- 66 year old female; 99kg
- Hx: poorly controlled IDDM; rheumatoid arthritis on long term steroid therapy
- Presents to ED with 4 day history of pain and swelling of right foot. Indurated and tender with ascending inflammation involving her calf extending to her knee
- Assessment: lethargic, T: 38.6, 100/55, HR-120, RR-22
  - Probable diagnosis of necrotizing fasciitis

Case Study II

- Went to OR for emergency exploration and debridement
- Pt became hypotensive prior to induction and a fluid bolus was given
- Thirty minutes into surgery, pt VS deteriorated
  - BP decreased to 85/40, HR-135
- Despite fluid boluses with colloid and 1 unit of PRBC, patient’s VS remained unchanged
Case Study II: continued

- Radial arterial line placed and pulse contour device attached
- ScvO2 catheter placed
- Initial CO-3.0 CI-1.4, SV-45, SVV-15% and ScvO2 65%
- Additional 700cc of colloid was given and SVV decreased to 8%, SV to 60 and CO to 3.5
- SVR was calculated to be 550; levophed started and titrated up based on hemodynamics

- CO improved and remained at 4.8, while VS normalized: 110/60, HR-105; pt received antibiotics and went to the ICU post op
- Over next 24 hours the patient’s status was optimized with antibiotics, fluids and pressors
- Cultures grew out group A strep and staph
- CO increased to 5.0L, ScvO2 to 80% and SVR to 1300, pressors gradually weaned off over next day
- Patient was extubated on day 3 and transferred out of the ICU on day 4

EARLY MANAGEMENT

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

**Recombinant human Activated Protein C (2B)**

- Recombinant human Activated Protein C [Drotrecogin alfa (activated)] is recommended in patients at a high risk of death (APACHE II score ≥ 25, or Sepsis-induced multiple organ failure) if there are no contraindications.
- Within 30 days of surgery with the above indications (2C)
- Drotrecogin alfa (activated) is not indicated in adult patients with severe sepsis and lower risk of death. (1A)
- Relative contraindications/warnings should be considered

The Role Of Endogenous Activated Protein C In Severe Sepsis

- Adapted from Bernard G. Crit Care Med 2001;34:698-708
**Xigris® (Drotrecogin Alfa [Activated]) in Severe Sepsis: Indication**

- Xigris 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*).
- Xigris is not indicated in adult patients with severe sepsis and lower risk of death. Xigris is not indicated in pediatric patients with severe sepsis.
- Of measures used in the PROWESS** clinical trial, the APACHE II score was most effective in classifying patients by risk of death and by likelihood of benefit from Xigris.

* APACHE (Acute Physiology And Chronic Health Evaluation). For more information on using the APACHE II scoring system, please see http://www.sfar.org/scores2/scores2.html.
** Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis

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**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
- 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.

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**Low Tidal Volume Ventilation: SSC Recommendations**

- Target tidal volumes to < 6 mL/kg (predicted body weight) in patients with ALI/ARDS (1B)
- Initial upper limit goal for plateau pressures in a passively inflated patient be ≤ 30 cm H₂O (1C)
- Hypercapnia can be tolerated in patients with ALI/ARDS if required to minimize plateau pressures and tidal volumes (1C)
- Recommend that positive end expiratory pressure be set as to avoid extensive lung collapse at end-expiration (1C)
- Suggest prone positioning in ARDS patients requiring potentially injurious levels of FiO₂ or plateau pressures in facilities that have experience with the practice (2C)


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**ARDS Network ALI/ARDS Ventilator Study**

**Methodology:**

- Inclusion criteria: p/f ratio < 300, bilateral infiltrates, no cardiac cause, receiving mechanical ventilation
- Outcomes: mortality/VFD
- 841 patients randomized
- 12 ml/kg TV group – Plat < 50 cm H₂O
- 6 ml/kg TV group - Plat < 30 cm H₂O

**Results:**

- PEEP: no difference in average amount used
- Mortality: 31% (6 ml/kg TV) vs. 40% (12 ml/kg TV) p=0.007
- VFD: 12+11 vs. 10+11 (p=0.007)
- Greater organ failure free days in protective group
- Reduction in IL-6 levels by day 3
- Difficulty with agitation/high rates in the 6 ml/kg group

**Additional Mechanical Ventilation Recommendations**

- Unless contraindicated, maintain HOB elevated to limit aspiration and prevent VAP (1B).
  - Elevation should be 30 to 45 degrees (2C).
- Non-invasive mask ventilation only be considered in that minority of mild to moderate hypoxemic respiratory failure patients who are able to protect their airway & are hemodynamically stable. A low threshold for intubation should be maintain (2B).

**Corticosteroids In Septic Shock: SSC Recommendations (2C)**

- Intravenous corticosteroids should only be given to adult septic shock patients after it has been confirmed that their blood pressure is poorly responsive to fluid resuscitation and vasopressor therapy.
- Suggest that the ACTH stimulation test should not be used to identify the subset of adult with septic shock who should receive hydrocortisone. (2B)
- We suggest that patients with septic shock should not receive dexamethasone if hydrocortisone is available. (2B)
  - Administer intravenous hydrocortisone <300 mg daily (1A)
  - Fludrocortisone is optional if hydrocortisone is used (2C)

**Glucose Control: SSC Recommendations**

- Initial stabilization of patients with severe sepsis and hyperglycemia who are admitted to the ICU receive IV insulin therapy to reduce blood glucose levels. (1B)
- Use of a validated protocol and target glucose levels to <150 mg/dL range. (2C)
- All patients receiving IV insulin should receive a glucose calorie source and blood glucose values should be initially assessed every 1-2 hrs, then q 4 hours after stabilization. (1C)
- Low glucose levels obtained by Point of Care testing should be interpreted with caution (1B)

**Intensive versus Conventional Glucose Control**

**Methodology:**

- Randomized, controlled, prospective
- 42 hospitals in Australia, New Zealand and Canada
- 6,104 patients
- Inclusion criteria: expected ICU stay > 3 days; adult in medical or surgical ICU
- Exclusion: admission to ICU > 24 hrs prior to assessment, imminent death or expected to eat within 24 hrs
- Primary endpoint is death from any cause within 90 days

**Intensive Glucose Control**

- n=3054
- Target blood glucose: 81-108 mg/dL
- Insulin gtt titrated using study treatment algorithm
  - Avg BG: 115 +/- 18
  - Avg insulin dose: 50.2 units/day
  - Avg # days on insulin: 4.2
  - % with hypoglycemic event (BG<40 mg/dL): 6.8%

**Conventional Glucose Control**

- N=3050
- Target blood glucose: <180
- Insulin gtt started if BG >180, then turned off if glucose < 144
- Insulin gtt titrated using study treatment algorithm
  - Avg BG: 144 +/- 23
  - Avg insulin dose: 16.9 u/day
  - Avg # days on insulin: 4.3
  - % with hypoglycemic event (BG<40 mg/dL): 0.5%
Intensive versus Conventional Glucose Control in Critically Ill Patients

The NICE-SUGAR Study Investigators

**Results:**
- Mortality rate: 27.5% in Intensive control group vs 24.9% in Conventional control group (p=0.02)
- Baseline characteristics for both groups similar, except Intensive control group had more pts with severe sepsis and on corticosteroids

Limitations
- Use of subjective criterion (expected LOS in ICU) for inclusion
- Lack of blinding
- Glucose levels in Intensive group substantially above target range
- Significant number of patients in which study was discontinued prematurely—data still included
- Was the study treatment algorithm flawed—resulting in more hypoglycemia?

Questions:
- Why no difference in LOS or organ dysfunction in intensive group with higher mortality?
- Was the increased mortality simply related to hypoglycemia? Need further exploration of the precise causes of death in pts

Post hoc analysis needs to be done to help answer these questions

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.

Surviving Sepsis Campaign
- 252 hospitals in 18 countries
- Data from January 2005-March 2008
- Observational; time series
- Baseline is first quarter data was collected
- Use of standardized screening tool
- Excluded site if less than 20 patients or less than 3 months of results
Surviving Sepsis Campaign Results

- Final Sample Size: 15,022 patients from 166 sites (95% of total)
  - North America: 58%
  - Europe: 31%
  - South America: 10%

<table>
<thead>
<tr>
<th>Entry Point</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED</td>
<td>52%</td>
</tr>
<tr>
<td>ICU</td>
<td>12.8%</td>
</tr>
<tr>
<td>Ward</td>
<td>34.8%</td>
</tr>
</tbody>
</table>

Hospital mortality went from 37% to 30% 7% ARR; 19% RRR; p< 0.007

Surviving Sepsis Campaign Bundle Compliance

<table>
<thead>
<tr>
<th>Bundle</th>
<th>Baseline</th>
<th>2 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resuscitation</td>
<td>10.9 %</td>
<td>31.3 %</td>
</tr>
<tr>
<td>Management</td>
<td>18 %</td>
<td>36 %</td>
</tr>
</tbody>
</table>

Risk Adjusted Hospital Mortality decreased by 5.4%
20% improvement in compliance with bundles

Bundle Implementation: Decreased Mortality

Methodology
- 2-year prospective study in academic tertiary care facility, with majority of care delivered in the ED
- 330 patients enrolled
- Measured 5 quality indicators related to management of severe sepsis & septic shock population. CVP/ScvO2 by 2 hrs, antibiotics by 4 hours, EGDT completed at 6 hours, appropriate steroids, lactate clearance

Results:
- In hospital mortality in patients who completed the bundle was significantly lower than those who did not complete the bundle (20.8 vs. 38.5; p<0.01)
- 14% of patients that completed the bundle received Xigris® (drotrecog alfa [activated])
- Completing EGDT in 6 hours was the only quality indicator with a significant odds ratio for decreased mortality using multivariate regression analysis
- After 2 years, achieved 51% compliance with all five indicators

Bundle Component Compliance and Impact on Mortality

<table>
<thead>
<tr>
<th>In-Hospital Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

* Number of patients (out of 330 total patients) completing vs. not completing the quality indicator

Sepsis Bundles: Significant Impact on Hospital Outcomes

- Two acute National Health Service Trust Teaching Hospitals in England performed a prospective observational study with 101 adult patients with severe sepsis or septic shock.

Outcomes measures:
- Rate of compliance with 6-hour and 24-hour bundles adapted from 2004 SSC guidelines
- Mortality between compliant and noncompliant groups

Compliance with bundles
- 6-hour bundle 52%
- 24-hour bundle 30%

Bundle Mortality
- Noncompliant: 49% (p=.001)
- Compliant: 23% (p=.001)

More than two-fold increase in hospital mortality associated with noncompliant group

Assessed compliance as “all or none” for the bundle elements

Is a two-fold mortality improvement a possibility in your institution?


Compliance with 24-Hour Bundle


Impact of Utilization with a Severe Sepsis Protocol

Retrospective cohort study
- 60 patients (30 consecutive receiving SOP severe sepsis management compared to historical controls)
- Treatment Cohort
  - Implementation of Standard Operating Procedure
  - September 2002 to December 2003
- Historical Control
  - Prior to Implementation of SOP
  - January 2002 to August 2002
- Resultsa
  - In SOP group: ↑ use of dobutamine, glucose control, steroids, and drotrecogin α (activated).
- Mortalitya
  - Control vs. SOP (57% vs. 27% p < .05)

* Study conclusions limited by small sample size


Standardized Order Set- Sepsis Bundles

- 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 goals for septic 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; 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 patient age and not receiving >20 mL/kg of IV fluid prior to vasopressors

**Economic Implications of an Evidence-based Sepsis Protocol: Can We Improve Outcomes and Lower Costs?**

**Objective**
- To determine financial impact of a sepsis protocol designed for use in the ED

**Design**
- Analysis of results from recent prospective study comparing outcomes in patients with septic shock before and after initiation of sepsis protocol

**Setting**
- Academic, tertiary care hospital in US

**Subjects**
- Adults (n=120) who sequentially presented to ED with septic shock, specifically:
  - At least two systemic inflammatory response syndrome (SIRS) criteria
  - Known or suspected infection (based on radiologic imaging and clinical suspicion)
  - Shock requiring both fluid resuscitation and vasopressor administration

**Median Costs per Patient for Treating Sepsis**

<table>
<thead>
<tr>
<th></th>
<th>Median per-patient cost</th>
<th>Range</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before protocol initiation</td>
<td>$21,985</td>
<td>$3,610–99,795</td>
<td>0.008</td>
</tr>
<tr>
<td>After protocol initiation</td>
<td>$16,103</td>
<td>$3,445–102,440</td>
<td></td>
</tr>
</tbody>
</table>

- Median saving of $5,882
- 18.3% more survivors following protocol initiation
- Receipt of care under the protocol associated with decreased costs (adjusted HR: 1.70; 95% CI, 1.03–2.80)

**Overall LOS in Hospital**
- Following protocol initiation there was a median reduction in overall hospital LOS of 5 days (p=0.023)
- The likelihood of remaining hospitalized separated early between the two groups
  - Pre-protocol, 36.7% were hospitalized for >2 weeks vs. 13.3% post-protocol (p=0.003)
- A difference was seen in the frequency of extreme hospitalization:
  - Pre-protocol, 20% were hospitalized for ≥20 days vs. 8.3% post-protocol (p=0.071)

**Costs Among Survivors**
- Survivors
  - Pre-protocol 51.7%, post-protocol 70.0% (p=0.04)

<table>
<thead>
<tr>
<th></th>
<th>Pre-protocol Range</th>
<th>Post-protocol Range</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median total costs</td>
<td>$21,985 5</td>
<td>$3,610–99,795</td>
<td></td>
</tr>
<tr>
<td>Hospital LOS</td>
<td>3–37 days</td>
<td>3–41 days</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Summary of Results**
- Post-protocol, savings of ~$6,000/patient observed
  - Translated into total cost difference of $573,000 between the two groups
- Post-protocol, ICU costs reduced by ~35% (p=0.026) and ward costs fell by 30% (p=0.033)
- Protocol resulted in a reduction in overall hospital LOS of 5 days (p=0.023)
- Pre-protocol, 28-day mortality rate was 48.3% vs. 30.0% following protocol initiation (p=0.040)
Keys to Success

- Team in place with key stakeholders overseeing implementation
- Project coordinator with lead clinical staff on each unit
- Sepsis resource/coordinator rounds frequently on units
- Strong physician leadership on team
- Reminders to staff through use of bedside sepsis tools/checklist
- Empowerment of nursing staff to prevent errors
- Administrative support to help manage barriers
- Review data monthly to identify opportunities for improvement
- Support from state-wide collaborative/surviving sepsis campaign

EDUCATION, EDUCATION, EDUCATION

A Healthcare Imperative

“In medicine, as in any profession, we must grapple with systems, resources, circumstances, people-and our own shortcomings, as well. We face obstacles of seemingly endless variety. Yet somehow we must advance, we must refine, we must improve.”


Seize the Opportunity

Begin the Campaign Today