Surviving Sepsis: Helping Our Patients Survive

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The word “sepsis” was derived from the ancient Greek for rotten flesh and putrefaction. Sir William Osler was the first to recognize that “except on few occasions, the patient appears to die from the body’s response to infection rather than from the infection.”
In 1914, Schottmueller wrote, "Septicemia is a state of microbial invasion from a portal of entry into the blood stream which causes sign of illness."

The definition did not change significantly over the years because sepsis and septicemia were considered to refer to a number of ill-defined clinical conditions in addition to bacteriemia.

In practice, the terms were often used interchangeably; however, less than one half of the patients who have signs and symptoms of sepsis have positive blood culture results.
In the late 1960s, several reports appeared describing remote organ failure (e.g., pulmonary failure, liver failure) as a complication of severe sepsis. In 1975, a classic editorial by Baue was entitled "Multiple, progressive or sequential systems failure, a syndrome of the 1970s." This concept was formulated as the basis of a new clinical syndrome. Several terms were cloned thereafter, such as multiple organ failure, multiple system organ failure, and multiple organ system failure, to describe this evolving clinical syndrome of otherwise unexplained progressive physiological failure of several interdependent organ systems. More recently, the term multiple organ dysfunction syndrome (MODS) has been proposed as a more appropriate description.
Surviving Sepsis Campaign

- A global program to:
  - Reduce mortality rates
  - Improve standards of care

- European Society of Intensive Care Medicine
- International Sepsis Forum
- Society of Critical Care Medicine
SSC: Guidelines for Management

- *Crit Care Med* 2004;32:858–873
- www.survivingsepsis.org
Sponsoring Agencies

- American Association of Critical Care Nurses
- American College of Chest Physicians
- American College of Emergency Physicians
- American Thoracic Society
- International Sepsis Forum
- Society of Critical Care Medicine
- Surgical Infection Society
- Australian and New Zealand Intensive Care Society
- European Society of Clinical Microbiology and Infectious Diseases
- European Society of Intensive Care Medicine
- European Respiratory Society
Epidemiology

- ~ 50,000 people in the United States each year.
- ~ 1,100,000 individuals worldwide each year.
Launched in Fall 2002 as a collaborative effort of European Society of Intensive Care Medicine, the International Sepsis Forum, and the Society of Critical Care Medicine

Goal: reduce sepsis mortality by 25% in the next 5 years

Guidelines revealed at SCCM in Feb 2004
- Website: survivingsepsis.org
Key Components

- Fluid resuscitation
- Appropriate cultures prior to antibiotic administration
- Early targeted antibiotics and source control
- Use of vasopressors/inotropes when fluid resuscitation optimized
Key Components

- Evaluation for adrenal insufficiency
- Stress dose corticosteroid administration
- Recombinant human activated protein C (xigris) for severe sepsis
- Low tidal volume mechanical ventilation for ARDS
- Tight glucose control
Key Components: Prevent Complications of Critical Illness

- Prophylaxis for DVT
- Stress ulcer prophylaxis
- Prevention of nosocomial pneumonia by elevation of head to 45 degrees
- Facilitate extubation by daily interruption of sedation and early SBT
- Narrowing of antibiotic spectrum when appropriate
Key Components: Infection Control

- Appropriate cultures prior to antibiotic administration
- Early targeted antibiotics and source control
Goal Directed Therapy

Administration of fluids, pressors and transfusion based upon targets for CVP, blood pressure, urine output, mixed venous oxygen saturation and hematocrit
Pathogens bypass the first line defense, when broken skin and mucosal membranes are contaminated during injury and later by surgery and debridement.

- Surgical Drains, external fixators, IV catheters, ICP monitors, urinary catheters, wounds
- Nosocomial Infections
Caused by endogenous mediators
Overall inflammatory response that effects multiple organs with or without infection
SIRS can compromise the function of various organ systems resulting in MODS
SIRS with a confirmed infection is Sepsis
SIRS

- 2 or more of the following:
- Fever > 38 °C or < 36 °C
- HR > 90
- RR > 20 or CO2 < 32
- WBC > 12K or < 4K or > 10% bands
Definition of Sepsis

- A Documented or Suspected Infection With
- Two or More of the Following:
  - Fever (core temperature $>38.3^\circ$C)
  - Hypothermia (core temperature $<36^\circ$C)
  - Heart rate $>90$ min$^{-1}$ or $>2$ SD above the normal value for age
  - Tachypnea $>20$ bpm
  - Leukocytosis (WBC count $>12,000$ μL$^{-1}$)
  - Leukopenia (WBC count $<4000$ μL$^{-1}$)
  - Normal WBC count with $>10\%$ immature form
Sepsis

- High Mortality Rates: 40% for uncomplicated sepsis...80% for cases of septic shock and MODS
- Severe Sepsis: Sepsis with organ hypoperfusion
- Septic Shock: Severe sepsis with hypotension...requires fluids, vasopressors
Sepsis

- Early, Goal Directed Therapy
- Oxygenate
- Central Venous Oximetry monitor and A-line
- CVP <8 Crystalloid, Colloid
- MAP <65 or >90 Vasoactive agents
- ScVO2 <70% Transfuse PRBC’s to Hct >30
- ScVO2 still <70% start Dobutamine
- Antibiotics within one hour
**CVP**: central venous pressure

**MAP**: mean arterial pressure

**ScvO₂**: central venous oxygen saturation
MODS: Multi-Organ Dysfunction Syndrome

- MODS is the presence of altered organ function in a patient who is acutely ill such that homeostasis cannot be maintained without intervention.
- Primary MODS is the direct result of a well-defined insult in which organ dysfunction occurs early and can be directly attributable to the insult itself.
- Secondary MODS develops as a consequence of a host response and is identified within the context of SIRS. The inflammatory response of the body to toxins and other components of microorganisms causes the clinical manifestations of sepsis.
Definition of Severe Sepsis

- Is Defined As Sepsis Associated With Organ Dysfunction, Hypoperfusion or Hypotension:
- Organ dysfunction variables:
  - Acute alteration in mental status
  - Arterial hypoxemia (PaO2/FIO2 < 300)
  - Acute oliguria (UOP < 0.5 mL·kg⁻¹·hr⁻¹ or 45 mmol/L for 2 hrs.)
  - Creatinine > 2.0 mg/dL
  - Coagulation abnormalities (INR > 1.5 or aPTT > 60 secs)
  - Thrombocytopenia (platelet count < 100,000 µL⁻¹)
  - Hyperbilirubinemia (total bilirubin > 2.0 mg/dL or 35 mmol/L)
  - Hyperlactatemia (> 2 mmol/L)
- Hemodynamic variables:
  - Arterial hypotension (SBP < 90 mm Hg, MAP < 65)
The SEPSIS CASCADE

Balk, adapted from R Bone
Identifying Acute Organ Dysfunction as a Marker of Severe Sepsis

- Altered Consciousness
- Confusion
- Psychosis

- Tachypnea
  \( \text{PaO}_2 < 70 \text{ mm Hg} \)
  \( \text{SaO}_2 < 90\% \)
  \( \text{PaO}_2/\text{FiO}_2 < 300 \)

- Jaundice
  \( \uparrow \) Enzymes
  \( \downarrow \) Albumin
  \( \uparrow \) PT

- Tachycardia
- Hypotension
- Altered CVP
- Altered PAOP

- Oliguria
- Anuria
  \( \uparrow \) Creatinine

- Platelets
  \( \downarrow \)
- PT/APTT
  \( \downarrow \)
- Protein C
  \( \uparrow \)
- D-dimer
Gram positive organisms have surpassed gram negatives as the most common source of sepsis.

Therapy targeted to the suspected site (eg, CAP, intra-abdominal source).

Drainage, debridement and device removal as indicated.
Goal Directed Therapy

Administration of fluids, pressors and transfusion based upon targets for CVP, blood pressure, urine output, mixed venous oxygen saturation and hematocrit
Study purpose: to evaluate the efficacy of early goal-directed therapy in patients presenting to an emergency department with severe sepsis or septic shock (prior to ICU admission)

Study design: prospective, randomized controlled, partially blinded, single center trial
Patient randomized
N=263

Early goal directed therapy N=130

- CVP $\geq$ 8-12 mm Hg
- MAP $\geq$ 65 mm Hg
- Urine Output $\geq$ 0.5 ml/kg/hr
- ScvO$_2$ $\geq$ 70%
- SaO$_2$ $\geq$ 93%
- Hct $\geq$ 30%

Antibiotics given at discretion of treating clinicians

At least 6 hours of EGDT
Mean 8hrs

Transfer to ICU
ICU MDs blinded to study treatment

Standard therapy N=133

- CVP $\geq$ 8-12 mm Hg
- MAP $\geq$ 65 mm Hg
- Urine Output $\geq$ 0.5 ml/kg/hr

As soon as possible
Mean 6.2hrs

*NEJM* 2001;345:1368-77.
Algorithm of EGDT. Hct = hematocrit.

Otero R M et al. Chest 2006;130:1579-1595
**CVP**: central venous pressure

**MAP**: mean arterial pressure

**ScvO₂**: central venous oxygen saturation
Early Goal-Directed Therapy Results: 28 Day Mortality

*Key difference was in sudden CV collapse, not MODS

- **Standard Therapy**
  - N = 133
  - Mortality: 49.2%
  - Sudden CV Collapse: 21% vs 10%
    - P = 0.02
  - MODS: 22% vs 16%
    - P = 0.27

- **EGDT**
  - N = 130
  - Mortality: 33.3%

*NEJM 2001;345:1368-77.*
Fluid Resuscitation

Crystalloids and colloids are equally effective in restoring intravascular volume
SAFE Study

- In a randomized, controlled trial conducted in 16 ICUs in Australia and New Zealand, 6997 patients were randomized to receive either saline or 4% albumin for fluid resuscitation.
- The albumin group received less fluid volume, but required more transfusion in the first 48h.

NEJM 2004; 350:2247
There were also no differences in duration of mechanical ventilation or ICU stay, development of single or multiple organ failure or duration of hospitalization.
Several non-randomized studies and one small prospective randomized study of dopamine vs norepinephrine for septic shock suggest that survival may be improved with the use of norepinephrine.
Norepinephrine vs Dopamine+/− Epinephrine in Septic Shock

Claude, Critical Care Med 2000;28:2758
Pressors

- If cardiac output is inadequate with norepinephrine, as indicated by a reduced mixed venous oxygen saturation, dobutamine may be added.
- Vasopressin is emerging as a valuable addition to therapy for septic shock in patients with catecholamine refractory hypotension.
Why Vasopressin?

There is vasopressin deficiency in vasodilatory shock.
VASOPRESSIN DEFICIENCY OCCURS IN SHOCK

A. Normal

B. After one hour of hemorrhagic shock
Why Vasopressin?

- Patients with septic shock have increased sensitivity to its pressor effects.
- Vasopressin restores vascular tone in catecholamine resistant shock by several mechanisms including potentiation of adrenergic agents.
- Low dose vasopressin increases urine output in septic patients, and increases creatinine clearance.
Whoopee!! Hey honey, I did it!
I finally got this darned meter over 400!!
Wow! I wonder how high this baby can go!

A sure sign someone is unclear on the concept of tight blood glucose control.
Glucose Control: Mechanisms

- Stress hyperglycemia is common in sepsis
- Glucose has pro-inflammatory effects
- Insulin resistance is common in sepsis
- Insulin has an anti-inflammatory effect, possibly via NOS.
- Benefit is likely related to both insulin itself and lowering of blood glucose
Tight Glucose Control

- In a Belgian study, 1548 SICU patients on mechanical ventilation were prospectively randomized to tight glucose control (80–110) vs standard control (180–200)
- Tight glucose control had a dramatic effect on morbidity in mortality, especially for patients in the ICU for >5 days

Van den Burghe, NEJM 2001; 345: 1359
Intensive Insulin Therapy in Critically Ill Patients: Mortality

ICU Mortality was reduced by 42%  
\[ p < 0.04 \text{ (adjusted)} \]

In-Hospital Mortality was reduced by 34%  
\[ p = 0.01 \]

Mortality (%)

\[
\begin{array}{c|c|c|c}
\text{Mortality} & \text{Conventional} & \text{Intensive} \\
\hline
\text{N=783} & 8.0\% & 4.6\% \\
\text{N=765} & 10.9\% & 7.2\% \\
\end{array}
\]

NEJM 2001;345:1359-1367.
Other dramatic effects: 46% decrease in bacteremias, 41% in acute renal failure requiring dialysis, 50% reduction in blood transfusion and a 44% decrease in critical illness polyneuropathy

Patients with bacteremia had a mortality of 12.5% vs 29.5% and a decreased risk of MSOF
CGM systems are more expensive than conventional glucose monitoring, but they may enable better glucose control. CGM devices produced by Abbott, DexCom, and Medtronic have been approved by the FDA.

- These devices provide real-time measurements of glucose levels, with glucose levels displayed at 5-minute or 1-minute intervals.
- Users can set alarms to alert them when glucose levels are too low or too high.
- Special software is available to download data from the devices to a computer for tracking and analysis of patterns and trends, and the systems can display trend graphs on the monitor screen.
There is insufficient information from randomized controlled trials to determine the optimal target range of blood glucose in the severely septic patient.

The NICE–SUGAR trial is the largest most compelling study to date on glucose control in ICU patients given its inclusion of multiple ICUs and hospitals, and a more general patient population.
NICE Sugar Trial

- Based on the results of this trial, we recommend against intravenous insulin therapy titrated to keep blood glucose in the normal range (80–110 mg/dl) in patients with severe sepsis.

- It is clear that attempts to normalize blood glucose with IV insulin during critical illness results in higher rates of hypoglycemia.
Until additional information is available, teams seeking to implement glucose control should consider initiating insulin therapy when blood glucose levels exceed 180 mg/dL with a goal blood glucose approximating 150 mg/dL as was observed in the beneficial arm of the NICE–SUGAR trial.
Sepsis

SIRS

Severe Sepsis

Septic Shock

Early Goal Directed Therapy

Antibiotics and Source Control

Insulin and tight glucose control

Xigris (Drotrecogin)

Activated Protein C in Sepsis

Protein C:
1. Inactivates clotting factors limiting the generation of thrombin
2. Inhibits prodn of inflammatory cytokines
1690 Patients:
- Known or suspected infection
- $\geq 3$ of the SIRS criteria
- $\geq 1$ acute (< 24hr in duration) organ failures

**Primary Endpoint:** All-Cause Mortality at 28 days

**Randomized**

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**Placebo**
- 96 hr infusion
- + standard treatment

**Drotrecogin (xigris)**
- 24 mcg/kg/hr
- 96 hour infusion
- + standard treatment

*NEJM 2001;344:699-709.*
PROWESS Results

Primary Stratified Intention-to-Treat Analysis

- 6.1% ↓ in absolute mortality
- 19.4% ↓ in RR of death

28 Day All-Cause Mortality

Placebo: 30.8% (n=850)
Drotrecogin alfa (activated): 24.7% (n=840)

p=0.0054
### Table 5. Incidence of Serious Adverse Events.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>Placebo Group (N=840)</th>
<th>Drotrecogin Alfa Activated Group (N=850)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one serious adverse event</td>
<td>102 (12.1)</td>
<td>106 (12.5)</td>
<td>0.84</td>
</tr>
<tr>
<td>Serious bleeding event*</td>
<td>17 (2.0)</td>
<td>30 (3.5)</td>
<td>0.06</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>9 (1.1)</td>
<td>9 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Intraabdominal</td>
<td>4 (0.5)</td>
<td>3 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Intrathoracic</td>
<td>1 (0.1)</td>
<td>6 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>0</td>
<td>4 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Intracranial</td>
<td>1 (0.1)</td>
<td>2 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Skin or soft tissue</td>
<td>0</td>
<td>2 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Genitourinary</td>
<td>0</td>
<td>2 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Source unidentified†</td>
<td>2 (0.2)</td>
<td>2 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Thrombotic events</td>
<td>25 (3.0)</td>
<td>17 (2.0)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

* A serious bleeding event was defined as any intracranial hemorrhage, any life-threatening bleeding, any bleeding event classified as serious by the investigator, or any bleeding that required the administration of 3 units of packed red cells on two consecutive days.

† These patients received 3 units of packed red cells on two consecutive days but had no identifiable source of bleeding.
Xigris (Drotrecogin)

- Mortality increased in patients with one organ failure who underwent surgery within the previous 30 days, and is contraindicated in this group.
Xigris: Increases Bleeding: Contraindications

- 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
Xigris: Contraindications

- Concurrent therapeutic dosing of heparin to treat an active thrombotic or embolic event
- Platelet count <30,000 x 10^6/L, even if the platelet count is increased after transfusions
- Prothrombin time–INR >3.0
- Recent (within 6 weeks) gastrointestinal bleeding
- Recent administration (within 3 days) of thrombolytic therapy
- Recent administration (within 7 days) of oral anticoagulants or glycoprotein IIb/IIIa inhibitors
- Recent administration (within 7 days) of aspirin >650 mg per day or other platelet inhibitors
- Recent (within 3 months) ischemic stroke
- Intracranial arteriovenous malformation or aneurysm
- Known bleeding diathesis
- Chronic severe hepatic disease
- Any other condition in which bleeding constitutes a significant hazard
There is significant disagreement about how to best evaluate adrenal function in critical illness.

General agreement that a random cortisol of less than 25 is abnormal in this population.

Some screen with random cortisol and reserve ACTH stim test for those with low levels.

Use of total rather than free cortisol in those with hypoalbuminemia may overestimate the incidence of adrenal insufficiency.
In a double–blind, placebo controlled study in France, 300 patients were randomized to receive stress dose steroids (hydrocortisone 50 mg q6h) and fludrocortisone (50 mcg daily) or placebo for 7 days.

Patients first underwent a cortrosyn stimulation test to determine relative adrenal insufficiency.
Low Dose Steroid Treatment in Septic Shock: Study Design

Onset of shock

Randomization

Time 0

Cortrosyn stimulation

Within 8 Hours

Hydrocortisone IV 50mg every 6 hours x 7 days

+ Fludrocortisone 50mcg NG daily x 7 days

Placebo X 7 days

Primary Outcome: 28-day survival

Relative adrenal insufficiency was defined as a failure to increase serum cortisol by greater than 9mcg/dl after a 250 mcg ACTH stimulation test.

Using this criteria, 77% of patients in this study were adrenally insufficient.
Low Dose Steroid Treatment in Septic Shock: 28 Day Mortality (Non–responders vs. Responders)

Patients with Relative Adrenal Insufficiency (ACTH Test Non-responders) (77%)

- Low-dose Steroids: 53%
- Placebo: 63%
- \( p = 0.04 \)

Patients Without Relative Adrenal Insufficiency (ACTH Test Responders) (23%)

- Low-dose Steroids: 61%
- Placebo: 53%
- \( p = 0.96 \)

\( N = 114 \) vs. \( N = 36 \)

Corticosteroids in Sepsis

- Obtain a baseline cortisol or ACTH stimulation
- Start stress dose steroids (hydrocortisone 200–300mg +/- fludrocortisone 50 mcg)
- Discontinue if levels are adequate
Prevention of Infection

- Urinary Catheters out early
- Central Lines out early
How do we as NP’s Help?

- First order of business: create a template/protocol that will work in your institution. (see handout)
  - Get buy in from 1 Doc, 1 RN, 1 ICU.
  - Describe the plan for your first test of change
  - Know in advance how you will detect failure
  - Team meets weekly (?). Redesign protocol
Creating a Multidisciplinary Sepsis Protocol

- CRITICALCARENURSE Vol 26, No. 3, JUNE 2006 43
- Samples of documents
- Surviving Sepsis Website
An implementation model of EGDT.

Otero R M et al. Chest 2006;130:1579-1595
The goal is to perform all indicated tasks 100% of the time within the first 6 hours of identification of severe sepsis.

The tasks are:
1. Measure serum lactate
2. Obtain blood cultures prior to antibiotic administration
3. Administer broad-spectrum antibiotic, within 3 hrs of ED admission and within 1 hour of non-ED admission
4. In the event of hypotension and/or a serum lactate > 4 mmol/L
   a. Deliver an initial minimum of 20 ml/kg of crystalloid or an 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
   a. Achieve a central venous pressure (CVP) of > 8 mm Hg
   b. Achieve a central venous oxygen saturation (ScvO2) > 70 % or mixed venous oxygen saturation (SvO2) > 65 %

SEPSIS RESUSCITATION BUNDLE
Efforts to accomplish these goals should begin immediately, but these items may be completed within 24 hours of presentation for patients with severe sepsis or septic shock.
1. Administer low-dose steroids for septic shock in accordance with a standardized ICU policy. If not administered, document why the patient did not qualify for low-dose steroids based upon the standardized protocol.
2. Administer drotrecogin alfa (activated) in accordance with a standardized ICU policy. If not administered, document why the patient did not qualify for drotrecogin alfa (activated).
3. Maintain glucose control > 70, but < 150 mg/dl
4. Maintain a median inspiratory plateau pressure (IPP)* < 30 cm H2O for mechanically ventilated patients

For questions or concerns, please contact the Critical Care
Pocket Guide: Downloadable

- Surviving Sepsis Website
- Podcasts, Posters, ID badge
- Lots of resources available for education
SURVIVING SEPSIS: We are the ones at the bedside treating patients

- Implementation of Evidence Based Practice
- Fluid resuscitation, goal-directed
- Appropriate cultures prior to antibiotic administration
- Early targeted antibiotics and source control
- Use of vasopressors/inotropes when fluid resuscitation optimized
SURVIVING SEPSIS

- Evaluation for adrenal insufficiency
- Stress dose corticosteroid administration
- Recombinant human activated protein C (xigris) for severe sepsis
- Insulin drip for tight glucose control
- Low tidal volumes (6cc/kg) for mechanical ventilation in ARDS
PREVENT COMPLICATIONS

- Stress ulcer and DVT prophylaxis
- Narrow antibiotic spectrum
- Prevent VAP: 45 degree elevation
- Facilitate early discontinuation of mechanical ventilation: sedation interruption, early SBT


References


References

- CHEST November 2006 vol. 130 no. 5 1579–1595