Surviving Sepsis: Campaign Guidelines for Management of Severe Sepsis and Septic Shock

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Surviving Sepsis

Objectives:

- Discuss the epidemiology of severe sepsis & its implications.
- Explain the pathophysiology of severe sepsis.
- Describe the relationship of microcirculatory alterations to the risk of organ failure and death.
- Identify acute organ dysfunction as a marker of severe sepsis.
Surviving Sepsis

Objectives:

- Define systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock, multiple organ dysfunction syndrome (MODS).
- Explain the surviving sepsis campaign guidelines for the management of sepsis and septic shock.
- Discuss the sepsis bundles
- Review a case study
Severe Sepsis

- It is a disease of the microcirculation
- Patients in septic shock have persistent microcirculatory alterations which lead to associated organ failure and death
- Therefore, microvascular recruitment and not just global hemodynamic resuscitation should be targeted.

Severe Sepsis: A Significant Healthcare Challenge

- Major cause of morbidity and mortality worldwide
  - Leading cause of death in noncoronary ICU (US)*
  - 11th leading cause of death overall (US) †§

- More than 750,000 cases of severe sepsis in US annually‡

* Sands KE et al. *JAMA*. 1997;278:234-40; †Based on data for septicemia. §Murphy SL. National Vital Statistics Reports. ‡Angus DC et al. *Crit Care Med.* 2001; reflects hospital-wide cases of severe sepsis as defined by infection in the presence of organ failure.
Severe Sepsis

- In the US, more than 500 patients die of severe sepsis daily
- High mortality rate of 28% to 50%
- Costs an average of $22,000 per patient with a total cost of $16.7 billion to US hospitals
ACCP/SCCM Consensus Definitions

- **Infection**
  - Inflammatory response to microorganism, or
  - Invasion of normally sterile tissues

- **Systemic Inflammatory Response Syndrome (SIRS)**
  - Systemic response to a variety of processes

- **Sepsis**
  - Infection plus
  - 2 SIRS criteria

- **Severe Sepsis**
  - Sepsis
  - Organ dysfunction

- **Septic shock**
  - Sepsis
  - Hypotension despite fluid resuscitation

- **Multiple Organ Dysfunction Syndrome (MODS)**
  - Altered organ function in an acutely ill patient
  - Homeostasis cannot be maintained without intervention

SIRS: More Than Just a Systemic Inflammatory Response

SIRS: A clinical response arising from a nonspecific insult manifested by ≥2 of the following:

- Temperature ≥38°C or ≤36°C
- HR ≥90 beats/min
- Respirations ≥20/min
- WBC count ≥12,000/mL or ≤4,000/mL or >10% immature neutrophils

Sepsis: More Than Just Inflammation

- Sepsis:
  - Known or suspected infection
  - Two or more SIRS criteria
  - A significant link to disordered homeostasis

Severe Sepsis: Acute Organ Dysfunction and Disordered Homeostasis

Severe Sepsis: Sepsis with signs of organ dysfunction in $\geq 1$ of the following systems:
- Cardiovascular
- Renal
- Respiratory
- Hepatic
- Hematology
- CNS
- Unexplained metabolic acidosis

Identifying Acute Organ Dysfunction as a Marker of Severe Sepsis

- Tachycardia
- Hypotension
- CVP
- PAOP
- Jaundice
- Enzymes
- Albumin
- PT
- Altered Consciousness
- Confusion
- Psychosis
- Tachypnea
- PaO\(_2\) < 70 mm Hg
- SaO\(_2\) < 90%
- PaO\(_2\)/FiO\(_2\) ≤ 300
- Oliguria
- Anuria
- Creatinine
- Platelets
- PT/APTT
- Protein C
- D-dimer
Severe Sepsis: A Complex and Unpredictable Clinical Syndrome

- High mortality rate (28%-50%)
- Heterogeneous patient population
- Unpredictable disease progression
- Unclear etiology and pathogenesis

Coagulation and Impaired Fibrinolysis in Severe Sepsis

Inflammatory Response to Infection

Thrombotic Response to Infection

Fibrinolytic Response to Infection

The sublingual microcirculation during septic shock and resuscitation
A New Understanding of Sepsis Pathophysiology

Sepsis

↑ Inflammation

Endothelial Injury

↑ Coagulations
↓ Fibrinolysis

Organ Failure

Death
The Response: Surviving Sepsis Campaign

The Society of Critical Care Medicine (SCCM), European Society of Intensive Care Medicine (ESICM), & International Sepsis Forum (ISF) joined forces to develop a three phase SSC.
Surviving Sepsis Campaign Guidelines

A campaign developed by 11 organizations made up of international critical care and infectious disease experts.

Developed guidelines to assist the bedside clinician on improving the outcomes in severe sepsis and septic shock. Initial 2004.

Updated in 2008

Critical Care Med 2008, 36(1)
Surviving Sepsis Campaign Recommendations

Initial Resuscitation

- Early goal directed therapy within the 1st 6 hours of diagnosis of severe sepsis
  - Fluids, fluids, and more fluids
    - CVP 8-12 mm Hg or 12-15 mm Hg if on vent
    - MAP ≥ 65 mm Hg
    - UOP ≥ 0.5 mL/kg/hr
    - ScVO₂ ≥ 70% or SVO₂ ≥ 65%
  - If fluid is inadequate, transfuse with PRBCs to a hematocrit of ≥30%, and/or administer dobutamine (up to a max. of 20 mcg/kg/min)
Diagnosis

- Appropriate cultures should always be obtained before antimicrobial therapy is initiated.
  - Two blood cultures
- Cultures of other sites based on clinical manifestations
  - Urine, sputum, CSF, wounds, other bodily fluids
- Perform imaging studies promptly to confirm & sample any source of infection
Surviving Sepsis Campaign Recommendations

抗生素治疗

- 应在严重败血症的首次识别后1小时内开始，且在适当培养物之后。
- 初始经验性广谱抗生素治疗
- 重新评估并缩小谱系
- 限制持续时间为7-10天
- 如非感染源引起，应停用抗生素

源控制
Fluid Therapy

Fluid resuscitation may consist of natural or artificial colloids or crystalloids.

- Initial resuscitation – require aggressive large volume over a short period of time based on clinical response
- Maintenance
Surviving Sepsis Campaign Recommendations

**Vasopressors**

- When an appropriate fluid challenge fails to restore adequate blood pressure and organ perfusion, vasopressors should be started.
- Target MAP $\geq 65$ mm Hg

Vasopressor as a Marker for Severe Sepsis with High Risk of Death
Which Vasopressors?

Dopamine and Norepinephrine are first choice given through a central line.

- Dopamine $↑$ MAP and cardiac output, primarily due to $↑$ in stroke volume and heart rate
- Norepinephrine $↑$ MAP due to its vasoconstrictive effects with little change in heart rate and less increase in stroke volume compared to Dopamine
Surviving Sepsis Campaign Recommendations

**Inotropic Therapy**

- Dobutamine may be used in patients with a low cardiac output despite adequate fluid resuscitation. May be combined with a vasopressor if hypotension is present.
- Do not use to increase cardiac index to predetermined supranormal levels.
Surviving Sepsis Campaign Recommendations

Relative Adrenal Insufficiency

Steroids

- Consider for adult septic shock when hypotension responds poorly to adequate fluid resuscitation & vasopressors
- ACTH stimulation test not be used to identify the subset of adults with septic shock
- Intravenous corticosteroids (hydrocortisone) 200-300 mg/day
- Wean steroids when vasopressors no longer required
Recombinant Human Activated Protein C (Drotrecogin Alfa Activated – Xigris)

- Should be considered for patients with APACHE II ≥ 25 or with multiple organ failure
- Used to decrease inflammation, decrease coagulation, and improve fibrinolytic activity associated with severe sepsis
The Multiple Mechanisms of Action of Drotrecogin Alfa (Activated) in Severe Sepsis
Surviving Sepsis Campaign Recommendations

Mechanical Ventilation of Sepsis-Induced Acute Lung Injury (ALI/ARDS).

- Use of low tidal volume 6 ml/kg of predicted body weight with the goal of maintaining a plateau pressure of <30 cm $H_2O$
- Permissive hypercapnia be allowed to minimize plateau pressures & tidal volumes
- PEEP be set to avoid extensive lung collapse at end expiration
Surviving Sepsis Campaign Recommendations

Mechanical Ventilation of Sepsis-Induced Acute Lung Injury (ALI/ARDS).
- Prone positioning in patients requiring potentially injurious levels of $\text{FiO}_2$ or plateau pressure
- HOB elevated 30-45°
- Noninvasive ventilation be considered only in patients with mild-moderate hypoxemia
Mechanical Ventilation of Sepsis-Induced Acute Lung Injury (ALI/ARDS).

- Weaning protocols
- Against the routine use of pulmonary artery catheters
- Use a conservative fluid strategy for patients with established ALI who do not have evidence of tissue hypoperfusion
Surviving Sepsis Campaign
Recommendations

**Blood Product Administration.**

- Target hemoglobin of 7 to 9 g/dl.
- Use of fresh frozen plasma to correct clotting abnormalities in the absence of bleeding or planned invasive procedures is not recommended.
- Do not administer antithrombin for the treatment of severe sepsis & septic shock
- Platelets should be administered if <5,000, between 5,000-30,000 & significant risk of bleeding, or ≤ 50,000 for surgery or invasive procedure
Surviving Sepsis Campaign
Recommendations

+Sedation and Analgesia in Sepsis.
  + Use sedation protocols
  + Bolus or continuous. If continuous, do daily interruption or lightening

+Neuromuscular Blockade in Sepsis.
  + Avoided if possible
  + Use train of four to monitor depth of block
Surviving Sepsis Campaign Recommendations

Glucose Control.

- Use protocols to maintain glucose $< 150\text{mg/dl}$
- When using IV insulin patients should receive a glucose calorie source & blood glucose be monitored q1-2 hrs until stable & then q 4 hrs
- Low glucose levels obtained with point of care testing be interpreted with caution
Surviving Sepsis Campaign Recommendations

Renal Replacement

- Continuous renal replacement therapies & intermittent hemodialysis are equivalent in patients with severe sepsis & acute renal failure
- Use continuous therapies to facilitate management of fluid balance in hemodynamically unstable septic patient
Surviving Sepsis Campaign Recommendations

**Bicarbonate Therapy.**
- Bicarbonate use for the purpose of improving hemodynamics or reducing vasopressor requirements is not recommended for treatment of hypoperfusion induced lactic acidemia with pH ≥ 7.15

**Deep Venous Thrombosis Prophylaxis.**
- Use LMWH or low dose unfractionated heparin. If high risk for bleeding use a mechanical prophylactic device
- Combination of pharmacologic & mechanical be used for very high risk patients
Surviving Sepsis Campaign Recommendations

- Stress Ulcer Prophylaxis.
  - H$_2$ receptor inhibitor or proton pump inhibitor
- Selective Digestive Tract Decontamination (SDD)
Surviving Sepsis Campaign Recommendations

- Consideration for Limitation of Support
- Advanced Directives
Sepsis Bundles - Resuscitation

+ Serum lactate measured
  + All patients with elevated lactate >4mmol/L should be treated with the sepsis bundles regardless of blood pressure

+ Blood cultures obtained prior to antibiotics
  + Fevers, chills, hypothermia, leukocytosis, bandemia, neutropenia, development of otherwise unexplained organ dysfunction

+ Broad spectrum antibiotics within 3 hours of ED or 1 hour for non ER ICU admissions
  + Use broad spectrum antibiotics until causative organism & its sensitivities are identified
Sepsis Bundles - Resuscitation

- Hypotension and/or lactate > 4
  - Deliver an initial minimum of 20 ml/kg of crystalloid or colloid equivalent
  - Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain MAP $\geq 65$ mm Hg
In the event of persistent hypotension despite fluid resuscitation and/or lactate >4

- Achieve CVP > 8 mm Hg or 12 to 15 mm Hg for ventilator patients
- Achieve ScVO$_2$ >70%

If patient is both hypovolemic and the hematocrit is <30%, it is appropriate to transfuse PRBCs provided fluid resuscitation has achieved a CVP ≥8

If cardiac output is diminished, consider Dobutamine
Sepsis Bundles - Maintenance

- Low dose steroids for septic shock
- Drotrecogin Alfa (Activated)
- Maintain adequate glycemic control
- Inspiratory plateau pressure < 30cm H$_2$O for mechanical ventilated patients
The Surviving Sepsis Campaign: Results of an international guideline based performance targeting severe sepsis

N=15,022 subjects at 165 sites in the United States, Europe, and South America.

Elements of the guidelines were “bundled” into two sets of targets to be completed within 6 and 24 hours.

Conclusions:

- Compliance with the resuscitation bundled increased linearly from 10.9% in the first quarter to 31.3% by the end of 2 years ($p<.0001$).
- Compliance with the management bundle started at 18.4% in the first quarter & increased to 36.1% by the end of 2 years ($p=.008$)
- Unadjusted hospital mortality rate decreased from 37% to 30.8% over 2 years ($p=.001$)
- Adjusted odds ratio for mortality improved the longer a site was on the campaign, adjusted absolute drop of 0.8% per quarter & 5.4% over 2 years (95% CI, 2.5-8.4)

What’s in the Future?
References

History of present illness:

- 50 y.o. Caucasian male seen in the ER
- C.C.: several day history of hematemesis & melena.
- Other associated manifestations included weakness, dizziness, & anorexia.
- Three days ago, he saw his PCP with a C.C. of bilateral leg pain. He was given narcotics for presumptive peripheral neuropathy
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<th>Past Surgical History</th>
<th>Medications</th>
<th>Social History</th>
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<td>Married with 2 children, Ages 14 &amp; 21</td>
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<td>Past Medical History</td>
<td>Claritin</td>
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<tr>
<td>Right Rib Fracture</td>
<td>Roxicet</td>
<td>Occupation: Unemployed</td>
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<td>Seasonal Allergies</td>
<td>ASA</td>
<td>(recently laid off)</td>
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<td>Hepatitis C</td>
<td>Advil</td>
<td>ETOH: a bottle of wine &amp;</td>
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<tr>
<td>Liver Cirrhosis</td>
<td>Codeine</td>
<td>Several beers</td>
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<tr>
<td>ETOH Abuse</td>
<td>Tylenol</td>
<td>Tobacco: Neg</td>
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</tbody>
</table>

Medical History

Married with 2 children, Ages 14 & 21
Occupation: Unemployed
ETOH: a bottle of wine & Several beers
Tobacco: Neg
Drugs: Neg
On admission:

**Vital Signs** – T 36.5 C, P 104, RR 22, B/P 91/57

**General** – 71 kg, Moderate distress, A&O x3

**HEENT** – Scleral icterus

**Musculoskeletal** – 2+ edema bil. Lower extremities. Sl. Erythema, warm & tender to palpation esp. both feet

**Skin** – spider angioma, mild jaundice

**Abdomen** – Mildly distended, nontender, normoactive bowel sounds
## Laboratory Data

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### Results
- **AST**: 103
- **AØ**: 66
- **TP**: 6.1
- **Mg**: 1
- **Ca**: 8.1
- **ALT**: 96
- **BT**: 1.8
- **Alb**: 2.5
- **Amylase**: 37
- **Lipase**: 150
- **Ammonia**: 5
- **Acetaminophen**: neg
- **ETOH**: neg

### Neutrophils
- **83%**

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<td>10/12 - 1616</td>
<td>7.33/19.3/79.2/9.8</td>
<td>BE -14.6</td>
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**On 3 L NC**

### Neutrophils
- **33%**

### Bands
- **34%**
Admitted to the Medical Unit at 1700 with UGIB
Orders:
Normal saline 125ml/hr
Protonix 40 mg IV daily
MVI, Thiamine, Folate
Magnesium sulfate 2 gm
Ativan
ETOH withdrawal observation
US abdomen to R/O ascites
H&H q4h
GI Consult
10/12 - 2300

Vitals: T37.4 HR 120 RR 60 B/P 76/32

Patient ‘s condition begins to deteriorate. Neuro: more confused & disoriented.

Lungs: good breath sounds w/rapid kussmaul breathing

Abdomen: Hypoactive

Extremities: edematous, mottled, only dopplerable post. Tibialis pulses
Laboratory Data

10/12 - 2300

<table>
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<tr>
<th></th>
<th>133</th>
<th>104</th>
<th>59</th>
<th>93</th>
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<tr>
<td></td>
<td>3.9</td>
<td>9</td>
<td>2.8</td>
<td>93</td>
</tr>
</tbody>
</table>

1.6  9.9  82

7.13/20/171/6.6 BE -19.9

Neutrophils 20%
Bands 28%
Lactate 13

He was transferred to ICU and admitted to the Critical Care Service at 2315.
ICU Orders

- Intubated and placed on pressure controlled ventilation: Rate 18, ΔP 25, PEEP 5*
- Ventilation with lower tidal volumes
ICU Orders

- Femoral CVC and intra-arterial lines were inserted
- D5W with 3 amps NaHCO$_3$ @ 999ml/hr x 6*
- Normal saline @ 999ml/hr
- Magnesium 4 gm IV over 4 hours
- Norepinephrine to titrate MAP >65 mm Hg*
ICU Orders

- Diprivan drip*
- Fentanyl drip*
- Urine & blood cultures were sent*
- Pipercillin/Tazobactam 4.5 gm q6h*
- Gentamycin 350 mg q 24h*
- Protonix 40 mg IV q 12h*
- Activated Protein C (Xigris) was ordered & then d/c’d due to UGIB history*
10/13 - 0600
Sedated.  VSS T38.6 HR 120 MAP 65-75 Minimal UOP
Norepinephrine 18 mcg/min
Propofol 15 mcg/kg/min
Fentanyl 50 mcg/h
D5W with 3 amps NaHCO3 @ 999cc/hr

130 | 95 | 52 ↓ 358↑ 6.7 ↓ 45 ↓
3.6 | 20 | 2    1.2 18.8 ↓

7.43/34/102/22.5 BE-1.2

Neutrophil 11% ↓
Bands 13% ↓
PT/INR 22.5/3.8 ↑ PTT 66
AST 132 ↑ ALT 63
Lactate 12.4
CXR: bilateral interstitial infiltrates
Extremities: pitting edema, mottled, cold below knees, hot around thighs, only dopplerable pulses, small bullous skin lesions bilaterally.
Asked wife if he had taken any meds or eaten anything different lately
wife replied he had eaten escargot and been in a hot springs recently.
Transfuse 4 units of PRBCs & 4 units of leuko-poor Fresh Frozen Plasma
Stop the NaHCO$_3$
Started Insulin Protocol*
Obtained a general surgery & vascular consult
10/13 - 0900

Blood cultures came back positive for gram negative rods in all 4 bottles

Urinalysis had a few bacteria & WBC but nonspecific

Bullous skin lesions were more pronounced
Dr. DeFlice, the Gastroenterologist, came in. He was told of the patient physical findings and deteriorating condition.

Did the patient eat any raw oysters recently?

Vibrio Vulnificus
Vibrio Vulnificus

**Epidemiology**

- First identified in late 1970s, is a gram. Neg bacterium.
- It exists as a free living bacterium inhabiting marine environment.
- Filter feeding shellfish, such as oysters, concentrate the bacteria.
Epidemiology

Certain populations are at highest risk for serious infection.

- Alcoholic cirrhosis – 31 to 43%
- Underlying liver disease including cirrhosis & chronic hepatitis – 24 to 31%
- Alcohol abuse without documented liver disease – 12 to 27%
- Hereditary hemochromatosis – 12%
- Chronic diseases such as diabetes mellitus, rheumatoid arthritis, thalassemia major, chronic renal failure, preleukemia, lymphoma – 7 to 8%
Clinical Manifestations

Most serious are wound infections and bacteremia

Wound infections

V. vulnificus may contaminate wounds exposed to estuarine waters or shellfish
Clinical Manifestations

- Primary bacteremia – Associated with ingestion of raw or undercooked shellfish, particularly raw oysters. Generally occurs with patient who are high risk.
  - One-third will present in shock or become hypotensive within 12 hours of hospital admissions.
  - Three-fourths will have distinctive bullous skin lesions
  - Thrombocytopenia is common with evidence of DIC
  - Leukopenia rather than leukocytosis will occur
  - GI bleed
Mortality

More then 50% overall with primary bacteremia and more than 90% in those who become hypotensive.

Persons who survive the acute shock often require prolonged hospitalization in the ICU with complications resulting from multiorgan system failure.
Vibrio Vulnificus

**Diagnosis**
- Blood or stool cultures

**Treatment**
- No definitive trials of therapy
- Tetracycline and Ciprofloxacin (based on clinical observations & limited animal studies)
Vibrio Vulnificus

**Prevention**

- Persons in high risk groups should avoid eating raw or undercooked shellfish, esp. raw oysters and should avoid situations in which estuarine associated wounds are likely to occur.
ID consult was obtained. Zosyn & Gentamycin were d/c’d. Changed to Levaquin, Fortaz, Doxycycline, Flagyl

10/13 - 1030
Wife arrived with son. She confirmed patient had eaten raw oysters at a local restaurant one week ago. After discussing patient’s extremely grave condition and poor prognosis, wife decided to make him a *DNR.*
10/13 - 1200
Chem. BG ↓ 54. Insulin off. 1 amp glucose given. UOP ↓

10/13 - 1600
Bullous skin lesions worsen (see photos)
10/13 - 1800

Oliguria

Hypotension despite ↑ Norepinephrine to 25 µg/min.

*Vasopressin started @ 0.04 unit/min.*

*Cortrosyn stimulation test was done to R/O relative adrenal insufficiency*

10/13 - 2014

7.06/58/56/16.4 BE -12.2 NaHCO3 drip started
PEEP ↑ 16
10/13 - 2107
SpO2 ↓ 64%

10/13 - 2200
Daughter arrived from out of town

10/13 - 2400
Peak inspiratory pressures ↑ suddenly 77
SpO2 35%

10/14 - 0115
Family made decision to withdraw life support. Expired at 0120
Final blood cultures were V. Vulnificus