SIRS, SEPSIS & MODS

Early Goal Directed Therapy

Ami Mayo MD
Director, Surgical Critical Care
Rambam Health Care Campus
Haifa, ISRAEL
<table>
<thead>
<tr>
<th>Era</th>
<th>Focus</th>
<th>Resuscitation</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>World war I</td>
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<td>↓ARF ARDS →MODS ↑MODS →Death</td>
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<td></td>
<td>Hemodynamics</td>
<td>resuscitation</td>
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<td>1980-1990</td>
<td>Physiology vs. Anatomy Specialized ICUs</td>
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<tr>
<td>1990-2012</td>
<td>Inflammatory response</td>
<td>EGDT for sepsis</td>
<td>↓MODS Death</td>
</tr>
</tbody>
</table>
Sepsis

• The worldwide incidence rate for Sepsis is 3/1000 population (18 million cases per year)

• The incidence rate for Sepsis is increasing by 1.5% / year

• Sepsis is the 10th leading cause of death in the USA

• There is an increase in the number of deaths despite a decline in case-fatality rates

• Sepsis accounts for more than 17 billion dollars in direct healthcare expenditures
Sepsis increasing incidence

Angus DC et al. Critical Care Medicine 2001
Sepsis

- Incidence of 1,000,000 cases/year (USA)
  - 2% of all hospital admissions
  - 75% of all ICU admissions
  - 40% of all ICU costs
SIRS, Sepsis & MODS:

- Clinical definitions
- Pathophysiology
- Treatment
SIRS, Sepsis & MODS:

- Clinical definitions
- Pathophysiology
- Treatment
The inflammatory response to stress

- Injury, Infection leads to an intense response
- Systemic Inflammatory Response Syndrome (SIRS)
- Compensatory Anti-inflammatory Response Synd. (CARS)
The inflammatory response to stress

• Clinical definitions:
  • SIRS
  • Sepsis
  • Severe Sepsis – Septic Shock
  • Multi-organ failure syndrome
Clinical definitions

- Systemic inflammatory response syndrome (SIRS):
  - Presence of two or more of the followings:
    - Temperature > 38°C or < 36°C
    - WBC > 12,000 or < 4,000 or > 10% stabs
    - Heart rate > 90 bpm
    - Respiration > 20/min or PaCO2 < 32mm Hg
Clinical definitions

• Sepsis:
  • SIRS plus a documented infection site
    • Blood cultures do **NOT** need to be positive

A primary site of infection cannot be established in 10% of patients with Sepsis/SIRS
Clinical definitions

• Severe sepsis – Septic shock:
  • Sepsis associated with:
    • At least one single organ dysfunction
    • Hypo-Perfusion abnormalities
      • Unaerobic metabolism with Lactic acidosis
      • Hypotension (may not be present after vasopressor support)
      • Oliguria

Malignant intravascular Inflammatory response
Clinical definitions

• Multi-Organ Dysfunction Syndrome:
  • More than two systems dysfunction:
    • Central nervous system
    • Respiratory
    • Hemodynamics
    • Nephrology
    • Liver
    • Host defenses (Immunology-Hematology)
Clinical definitions

- **Infection**: Microorganism invading sterile tissue
- **SIRS**
  - ≥2 of the following
  - T>38°C, <36°C
  - HR >90
  - RR >20/min
  - WBC >12,000/mm³ or <4,000/mm³ or >10% bands
- **Sepsis**: SIRS with a presumed or confirmed infectious process
- **Severe Sepsis**: Sepsis with organ failure
  - Vascular collapse
  - Renal
  - Hemostasis
  - Lung
- **Septic Shock**: Refractory hypotension

**Malignant** intravascular inflammatory response
Clinical definitions

- Mortality increases:
  - Number of SIRS symptoms
  - Severity of the inflammatory response
SIRS, Sepsis & MODS:

- Clinical definitions
- Pathophysiology
- Treatment
Pathophysiology

- **Bacterial/Viral/Fungal factors**
  - Endotoxins
  - Exotoxins

- **Cellular response**
  - PMN
  - Monocytes
  - Macrophages
  - Endothelial cells
  - Inflammatory cytokines
    - TNFα, IL-1β, IL-6, IL-8
    - Platelet activating factor (PAF)

**Malignant intravascular inflammatory response**
The response to stress

Mitochondrial damage & cellular death
Sepsis & Immune-suppression

- Anti inflammatory mediators (IL-4, IL-10)
- Compensatory anti-Inflammatory response system
Sepsis & Immune-suppression

Relative lymphopenenia
Sepsis physiologic failure rate

<table>
<thead>
<tr>
<th>System</th>
<th>Failure rate</th>
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<tbody>
<tr>
<td>Pulmonary</td>
<td>45.8%</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>24.4%</td>
</tr>
<tr>
<td>Renal</td>
<td>22.0%</td>
</tr>
<tr>
<td>Hematology</td>
<td>20.6%</td>
</tr>
<tr>
<td>Neurology</td>
<td>9.3%</td>
</tr>
<tr>
<td>Liver</td>
<td>1.3%</td>
</tr>
</tbody>
</table>
Respiratory failure

- Direct damage – Tissue lysis - ARDS
- Respiratory muscles catabolism
Respiratory failure

Acute Respiratory Distress Syndrome
Cardio-Vascular failure

- Vascular damage
  - Vaso-plegia
  - Capillary leak syndrome
  - Tissue hypoxia

- Cardiac dysfunction
  - High cardiac output failure
  - Low effective blood volume
  - Cardiac depression
    - Troponin I
    - BNP
Cardio-Vascular failure

- Cardiac muscle damage

Troponin I

BNP
## Physiologic Systemic Failure

### Multi-Organ Dysfunction Syndrome – 50% mortality

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<tr>
<td>Renal</td>
<td>AKI-ATN-ARF</td>
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<tr>
<td>Hematology</td>
<td>DIC</td>
</tr>
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<td>Neurology</td>
<td>Neuropathy</td>
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<tr>
<td>Liver</td>
<td>“Shock liver”</td>
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SIRS, Sepsis & MODS:

- Clinical definitions
- Pathophysiology
- Treatment
50 year old, MVC, Unstable hemodynamics

Pelvic fracture, Spleen laceration (5% mortality)
60 year old, crushing chest pain

ST elevation MI (10% mortality)
70 years old, Cough, Fever, Tachychardic, BP 80/50

Pneumonia & Sepsis (30% mortality)
ICU – Severe Sepsis Support

- Physiologic monitoring & supportive treatment
  - Source control
  - Resuscitation
  - Fixing the physiology – “Fixing the numbers”
  - Keeping the organism alive
  - Avoiding further systemic deterioration
  - Waiting for organ recovery

No tools for Inflammatory modulation
ICU - Sepsis treatment

Too late & Not enough
“Hectic Fevers at its inception is difficult to recognize but easy to treat.

Left untreated, it becomes easy to recognize, but difficult to treat”

Machiavelli - 1513
Sepsis interventions

- “Over 13,000 patients have been enrolled in 23 multi-center, placebo-controlled, clinical trials”
- “Results have been generally disappointing with… some spectacular failures…”
Proven interventions in Sepsis

- Early, Appropriate antibiotics
  - Numerous (no randomized trials)
- Intensive insulin therapy
  - Van Den Berghe et al. NEJM 345(19), NOV 8, 2001
- Activated protein C
- Steroids in adrenal suppression
  - Annane et al. JAMA 288(7), August 21, 2002
- Early Goal Directed Therapy
“Proven” interventions in Sepsis
Proven interventions in Sepsis

- **Early, Appropriate antibiotics (10-40%)**
  - Numerous (no randomized trials)

- **Intensive insulin therapy (3%)**
  - Van Den Berghe et al. NEJM 345(19), NOV 8, 2001

- **Activated protein C (6% absolute mortality reduction)**
  - Bernard et.al. NEJM. March 8, 2001:344:10:699-709

- **Steroids in adrenal suppression (10%)**
  - Annane et al. JAMA 288(7), August 21, 2002

- **Early Goal Directed Therapy (16%)**
Activated Protein C - Xigris

• First inflammatory modulation agent effective in sepsis
• Anticoagulant agent
  – Takes part in the Inflammatory response, Thrombotic response & Fibrinolytic response to sepsis
  – Prevents micro-thrombi formation & capillary obstruction
  – Avoids hypo-perfusion
• Major risk - hemorrhage
Activated Protein C

PROWESS study (2001)

The New England Journal of Medicine

Efficacy and Safety of Recombinant Human Activated Protein C for Severe Sepsis

Gordon R. Bernard, M.D., Jean-Louis Vincent, M.D., Ph.D., Pierre-Francois Laterre, M.D., Steven P. LaRosa, M.D., Jean-Francois Dhainaut, M.D., Ph.D., Angel Lopez-Rodriguez, M.D., Jay S. Steingrub, M.D., Gary E. Garber, M.D., Jeffrey D. Helterbrand, Ph.D., E. Wesley Ely, M.D., M.P.H., and Charles J. Fisher, Jr., M.D., for the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) Study Group*
Activated Protein c

PROWESS study (2001)

![Graph showing survival rates with activated protein c and placebo. The graph indicates a statistically significant difference (P=0.006) in survival rates between the two groups at 28 days after the start of the infusion. The activated protein c group shows a higher survival rate compared to the placebo group.](image)
Activated Protein c

ADDRESS study (2005)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Drotrecogin Alfa (Activated) for Adults with Severe Sepsis and a Low Risk of Death

CONCLUSIONS

The absence of a beneficial treatment effect, coupled with an increased incidence of serious bleeding complications, indicates that DrotAA should not be used in patients with severe sepsis who are at low risk for death, such as those with single-organ failure or an APACHE II score less than 25.
Activated Protein C - Xigris

- The failed study “PROWESS-SHOCK” study (2008-2011)
- 1,696-patient with septic shock
- Xigris did not meet the goal of a statistically significant reduction in 28-day mortality rate (p value - 0.31)

- The risk of severe bleeding was also similar
Activated Protein C - Xigris

- **Xigris Recall Issued by Eli Lilly** (October 26th, 2011)

  - Eli Lilly and Co has withdrawn its sepsis drug *Xigris* from the world market after the product failed to improve survival in a clinical trial.

  - *Xigris* increased the risk of serious bleeding in earlier studies, although no significant higher risk was found in the latest study.

  - Patients currently receiving Xigris treatment should stop, while doctors should not start any new patients on the drug.
Activated Protein C - Xigris

- **FDA Drug Safety Communication:**

  The Food and Drug Administration (FDA) is informing healthcare professionals and the public that on October 25, 2011, Eli Lilly and Company announced a worldwide voluntary market withdrawal of Xigris. In a recent study, Xigris failed to show a survival benefit for patients with severe sepsis and septic shock.

  - Xigris treatment should not be started in new patients. Xigris treatment should be stopped in patients being treated with Xigris.

  - All remaining Xigris product should be returned to the supplier from whom it was purchased.
Proven interventions in Sepsis

- Early, Appropriate antibiotics (10-40%)
  - Numerous (no randomized trials)
- Intensive insulin therapy (3%)
  - Van Den Berghe et al. NEJM 345(19), NOV 8, 2001
- **Activated protein C (6% absolute mortality reduction)**
- Steroids in adrenal suppression (10%)
  - Annane et al. JAMA 288(7), August 21, 2002
- **Early Goal Directed Therapy (16%)**
Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock

Emanuel Rivers, M.D., M.P.H., Bryant Nguyen, M.D., Suzanne Havstad, M.A., Julie Ressler, B.S., Alexandria Muzzin, B.S., Bernhard Knoblich, M.D., Edward Peterson, Ph.D., Michael Tomlanovich, M.D., for the Early Goal-Directed Therapy Collaborative Group
Early Goal Directed Therapy

- 233 patients
  - 130 EGDT vs 33 standard therapy
- Prospective, double blinded, randomized study
- Inclusion criteria:
  - SIRS + septic shock (after 20cc/kg fluid)
  - SIRS + lactate >4 mmol/L
- Treatment Protocol (6 hour ED optimization)

Early Goal Directed Therapy

Treatment Protocol – “6 hours window”

Supplemental oxygen ± endotracheal intubation and mechanical ventilation

Central venous and arterial catheterization

Sedation, paralysis (if intubated), or both

**CVP**
- <8 mm Hg: Crystalloid
- 8–12 mm Hg
- ≥65 mm Hg

**MAP**
- <65 mm Hg: Vasoactive agents

**ScvO₂**
- <70%: Transfusion of red cells until hematocrit ≥30%
- ≥70%

Goals achieved

No

Yes

Hospital admission

# Early Goal Directed Therapy

## Study results

<table>
<thead>
<tr>
<th></th>
<th>EGDT</th>
<th>Standard</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fluids</td>
<td>$5.0L \pm 3.0L$</td>
<td>$3.5L \pm 2.4L$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>RBC Transfusion</td>
<td>64%</td>
<td>19%</td>
<td>$&lt;0.001$</td>
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<tr>
<td>Dubotamine</td>
<td>13.7%</td>
<td>0.8%</td>
<td>$&lt;0.001$</td>
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<tr>
<td>ScvO$_2$&gt;70%</td>
<td>95%</td>
<td>60%</td>
<td>$&lt;0.001$</td>
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<tr>
<td>Research Team</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>30.5%</td>
<td>46.5%</td>
<td>$&lt;0.001$</td>
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Early Goal Directed Therapy

What’s the Magic?
Preventing Tissue Hypoxia

• Preload
  – Maintain adequate filling pressures (PAWP/CVP)

• Perfusion Pressure
  – MAP > 60

• Match Delivery with Consumption
  – Optimize Oxygen Delivery (Sao₂ > 95%)
  – Monitor Oxygen extraction rate (Svo₂ > 70%)
  – Increase oxygen carrying capacity (Hct > 30)
  – Match cardiac output

Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008

R. Phillip Dellinger
Mitchell M. Levy
Jean M. Carlet
Julian Bion
Margaret M. Parker
Roman Jaeschke
Konrad Reinhart
Derek C. Angus
Christian Brun-Buisson
Richard Beale
Thierry Calandra
Jean-Francois Dhainaut
Herwig Gerlach
Maurene Harvey
John J. Marini
John Marshall
Marco Ranieri
Graham Ramsay
Jonathan Sevransky
B. Taylor Thompson
Sean Townsend
Jeffrey S. Vender
Janice L. Zimmerman
Jean-Louis Vincent

Sepsis bundle
Surviving Sepsis Campaign

Identify patient → Activate Sepsis Team

Early antibiotics

Rapid central venous access (with continuous central venous SaO2 monitoring)

Early Goal-Directed Therapy

CVP?

MAP?

Hct?

Central venous O2 saturations?

< 8 - 12

≥ 8 - 12

< 65

≥ 65

< 70%

≥ 70%

< 30%

≥ 30%

500 cc crystalloid bolus

Tritrate vasopressors

Norepinephrine preferred as initial pressor

Transfuse

Activated protein C if criteria met

ACTH stim test; steroids if criteria met

Intensive insulin for normoglycemia

Semi-recumbent position

Lung-protective ventilation for pts with ALI/ARDS

Titrate dobutamine
Surviving Sepsis Campaign

1. Identify patient
2. Activate Sepsis Team

Early Goal-Directed Therapy

- Early antibiotics
- Rapid central venous access (with continuous central venous SaO2 monitoring)

**CVP?**
- < 8 - 12
  - 500 cc crystalloid bolus
- ≥ 8 - 12
  - MAP?
    - < 65
      - Titrate vasopressors
    - ≥ 65
      - Central venous O2 sat?
        - < 70%
          - Hct?
            - < 30%
              - Transfuse
            - ≥ 30%
              - Titrate dobutamine

**ACTH stim test; steroids if criteria met**
**Intensive insulin for normoglycemia**
**Semi-recumbent position**
**Lung-protective ventilation for pts with ALI/ARDS**
Sepsis Team Implementation

Trauma team

Cath. team

Sepsis team
## Sepsis Team Implementation

### 6 Steps program

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Admit</td>
</tr>
<tr>
<td>2</td>
<td>Collaboration</td>
</tr>
<tr>
<td>3</td>
<td>Organization</td>
</tr>
<tr>
<td>4</td>
<td>Implementation</td>
</tr>
<tr>
<td>5</td>
<td>Education</td>
</tr>
<tr>
<td>6</td>
<td>Evaluation</td>
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</table>
Step 1: Admit

Admit that you have a problem
Step 2: Collaboration

- Emergency medicine
- All Medical critical care units
- All Surgical critical care units
Step 3: Organization

- Protocol - Handbook
- Protocol - Quick guide
- Bedside posters
- Nursing flow sheets
Step 3: Organization

The MUST Protocol

Multiple Urgent Sepsis Therapies

Why?
Sepsis is common and lethal — it kills as many people as acute MI. Recent research proves that new sepsis treatments save lives — to save one life you only need to treat 6 people (or, maybe, less).

Who?
Only 3 things are needed to qualify for the protocol:

1) suspected infection
2) Two out of four:
   - Fever (>100.4) ... or hypothermia (T<96.8)
   - Fast heart rate (>90)
   - Fast respiratory rate (>20) ... or PaCO2 < 32
   - High white count (>12,000)
     ... or WBC < 4,000
     ... or > 10% bands
3) SBP<90 after a 20-30 cc/kg fluid bolus, or
   Lactate > 4.0

How?
1) Page the Sepsis Team (online paging system)
2) Follow the protocol.
Step 3: Organization

Treatment flow sheet
Step 4: Education, Education…

- Nursing Education
  - Basic sepsis education
  - Theory behind EGDT

- Physician Education
  - Grand rounds
  - Handbook
  - Online tutorial
  - Continuous bedside education
  - Feedback
Step 5: Implementation

- Adopting mentally the “Sepsis Team” concept
- Line placement
- Treatment zone
- Nursing driven protocol
- ED-ICU interaction
Step 6: Evaluation

- Multidisciplinary quality assurance committee
- Quality assurance measures
- Provide feedback
In our busy Emergency Department:

<table>
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<tr>
<th>Diagnosis</th>
<th>Activate</th>
<th>Treat. Zone</th>
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<tr>
<td>Crushing chest pain</td>
<td>Acute STEMI</td>
<td>ICCU team</td>
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<tr>
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<td>Cath. Lab.</td>
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<tr>
<td>Major car crush</td>
<td>Multiple trauma</td>
<td>Trauma team</td>
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<td>ED-Op. theater</td>
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<tr>
<td>Fever, Cough, Shock</td>
<td>Pneumonia Severe Sepsis</td>
<td>Sepsis team</td>
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SIRS, Sepsis & MODS:

- Malignant intravascular inflammation
- Yet, there is no inflammatory modulation tool
- Treatment – Early intervention
  - EGDT concept
  - Sepsis team
## SIRS, Sepsis in the perspective of time

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<tr>
<td>The future</td>
<td>Molecular biology Molecular genetics</td>
<td>Inflammatory modulation</td>
<td>↓Mortality rate</td>
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</table>
Thanks for your attention