SEPSIS:

GUIDELINES FOR CURRENT MANAGEMENT

JONATHAN R. HIATT, MD
DEPARTMENT OF SURGERY
THE DAVID GEFFEN SCHOOL OF MEDICINE AT UCLA
SEPSIS MANAGEMENT

- Definitions
- Scoring systems
- Surviving Sepsis Campaign
- Evaluation of evidence
- Management guidelines
## Sepsis Management

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIRS</td>
<td>Systemic inflammatory response</td>
</tr>
<tr>
<td>MODS</td>
<td>Multiple organ dysfunction</td>
</tr>
</tbody>
</table>
## SEPSIS MANAGEMENT

### DEFINITIONS

<table>
<thead>
<tr>
<th>Inflammation</th>
<th>SIRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(fever, leukocytosis)</td>
<td>SIRS</td>
</tr>
<tr>
<td>SIRS + infection</td>
<td>Sepsis</td>
</tr>
<tr>
<td>Sepsis + multiorgan dysfunction</td>
<td>Severe sepsis</td>
</tr>
<tr>
<td>Severe sepsis + refractory hypotension</td>
<td>Septic shock</td>
</tr>
</tbody>
</table>
## SEPSIS MANAGEMENT

### SIRS: CLINICAL CRITERIA

*Any two or more:*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body temperature</td>
<td>&gt; 38 or &lt; 36</td>
</tr>
<tr>
<td>Heart rate</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>&gt; 20</td>
</tr>
<tr>
<td>Hyperventil. (PaCO$_2$)</td>
<td>&lt; 32</td>
</tr>
<tr>
<td>WBC</td>
<td>&gt; 12K or &lt; 4K</td>
</tr>
<tr>
<td>Immature polys</td>
<td>&gt; 10%</td>
</tr>
</tbody>
</table>

*Chest '92*
SEPSIS MANAGEMENT

SIRS: CAUSES

- Infection
- Intestinal endotoxin
- Ischemia
- Multisystem trauma
- Noxious substances
- Shock
- Thermal injury

Chest ’92
## SEPSIS MANAGEMENT

<table>
<thead>
<tr>
<th>MODS</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs</td>
<td>Acute respiratory distress synd.</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Acute tubular necrosis</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hyperdynamic hypotension</td>
</tr>
<tr>
<td>CNS</td>
<td>Metabolic encephalopathy</td>
</tr>
<tr>
<td>PNS</td>
<td>Polyneuropathy of crit. illness</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Disseminated intravasc. coag.</td>
</tr>
<tr>
<td>GI tract</td>
<td>Gastroparesis / ileus</td>
</tr>
<tr>
<td>Liver</td>
<td>Acute noninfectious hepatitis</td>
</tr>
<tr>
<td>Adrenals</td>
<td>Acute adrenal insufficiency</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>Rhabdomyolysis</td>
</tr>
<tr>
<td>Clinical Scoring Systems</td>
<td>Description</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>APACHE II</td>
<td>Acute Physiology &amp; Chronic Health Evaluation</td>
</tr>
<tr>
<td>MODS</td>
<td>Multiple Organ Dysfunction Score</td>
</tr>
<tr>
<td>GCS</td>
<td>Glasgow Coma Scale</td>
</tr>
</tbody>
</table>

ICU adm.: ICU admission
Daily: Daily
Dynamic: Dynamic
SEPSIS MANAGEMENT

SURVIVING SEPSIS CAMPAIGN

- Multinational expert committee
- Barcelona Declaration (2002)
- International Sepsis Forum (2001)
- 14 year MEDLINE review (1990-03)
- Grading
  - Evidence
  - Recommendations
- Total consensus in all but 2 recs.
  *(steroids, antibiotics)
<table>
<thead>
<tr>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
<tr>
<td>V</td>
</tr>
</tbody>
</table>
## SEPSIS MANAGEMENT

### GRADING OF RECOMMENDATIONS

<table>
<thead>
<tr>
<th>Grade</th>
<th>Support</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>At least 2 level I investigations</td>
</tr>
<tr>
<td>B</td>
<td>One level I investigation</td>
</tr>
<tr>
<td>C</td>
<td>Level II investigations only</td>
</tr>
<tr>
<td>D</td>
<td>At least 1 level III investigation</td>
</tr>
<tr>
<td>E</td>
<td>Level IV or V evidence</td>
</tr>
</tbody>
</table>

*Dellinger, CCM ’04*
## Grades in Guidelines (n=52)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At least 2 level I investigations</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>B</td>
<td>One level I investigation</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>C</td>
<td>Level II investigations only</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>D</td>
<td>At least 1 level III investigation</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>E</td>
<td>Level IV or V evidence</td>
<td>27</td>
<td>52</td>
</tr>
</tbody>
</table>

*Dellinger, CCM ’04*
SEPSIS MANAGEMENT

- Definitions
- Scoring systems
- Surviving Sepsis Campaign
- Evaluation of evidence
- Management guidelines
SEPSIS MANAGEMENT

INITIAL RESUSCITATION

- For severe sepsis or hypoperfusion (hypotension or lactic acidosis)
- Normotensive: Elevated lactate identifies hypoperfusion
- Begin immediately
- Do not delay for ICU admission
- 1st 6 hours: Goals and interventions
SEPSIS MANAGEMENT

INITIAL RESUSCITATION

- First 6-hour goals:
  - CVP 8-12
  - MAP ≥ 65
  - Urine ≥ 0.5 ml/kg/hr
  - $O_2$ sat (CV or MV) ≥ 70%
- If $O_2$ sat < 70% with CVP 8-12:
  - PRBC to Hct ≥ 30 and/or
  - Dobutamine (up to 20 ? g/kg/min)
Cultures before antibiotics
At least two blood cultures
  - Percutaneous
  - Each vasc access device unless inserted within 48 hrs.
Diagnostic studies
  - Unless unstable for transport
  - Consider bedside tests (sono)
SEPSIS MANAGEMENT

ANTIBIOTIC THERAPY

- Initiation
- Regimen
  - Empiric
  - Specific (focused)
- Cessation
ANTIBIOTIC THERAPY

- **Initiation**: within one hour
- **Empiric regimen**
  - *Initial broad spectrum*
  - *Active ag. likely pathogens*
  - *Penetrate likely site*
  - *Consider local susceptibility patterns*
  - *Hepatic, renal function affect dosing*
- **Cessation** if noninfectious cause
FOCUSED ANTIBIOTIC REGIMEN

- Reassess after 48 – 72 hrs
- Cultures guide therapy
- Narrow spectrum agent
  - Resistance, toxicity, costs
- Course: 7 – 10 days
- Monotherapy, not combination
  - *Possible exception: Pseudomonas
  - *Definite exception: Neutropenia
# SEPSIS MANAGEMENT

## NOSOCOMIAL SEPTICEMIA

<table>
<thead>
<tr>
<th>Organism</th>
<th>%</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram neg. enterics</td>
<td>38</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Coag. neg. staph</td>
<td>18</td>
<td>Vasc. catheters</td>
</tr>
<tr>
<td><em>Staph aureus</em></td>
<td>11</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Enterococci</td>
<td>10</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Streptococci</td>
<td>7</td>
<td>Unknown</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>5</td>
<td>Pneumonia</td>
</tr>
<tr>
<td><em>Candida</em> species</td>
<td>5</td>
<td>Vasc. catheters</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>Mult. sources</td>
</tr>
</tbody>
</table>

*Pittet, JAMA ’94*
SEPSIS MANAGEMENT

SOURCE CONTROL

- Search for treatable focus
- Multidisciplinary approach
- Interventions: Consider risks / benefits
- Intervene early after resuscitation
- Vascular access devices:
  - Common sources of bacteremia
  - If potential source: Establish alternate access, remove early
### CATHETER SEPTICEMIA

<table>
<thead>
<tr>
<th>Organism</th>
<th>%</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. epi.</td>
<td>27</td>
<td><strong>Guidewire exchange</strong></td>
</tr>
<tr>
<td>S. aureus</td>
<td>26</td>
<td>Suspected infection</td>
</tr>
<tr>
<td>Candida</td>
<td>17</td>
<td>Aseptic placement</td>
</tr>
<tr>
<td>Klebs.</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Serratia</td>
<td>5</td>
<td><strong>New site</strong></td>
</tr>
<tr>
<td>Pseud.</td>
<td>3</td>
<td>Infected site (red, pus)</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>Infected tip (&gt; 15 cfu)</td>
</tr>
</tbody>
</table>

**13 prosp. studies**  
S.Clin.N.Am 1988

*Marino, The ICU Book*
# SEPSIS MANAGEMENT

## SOURCE CONTROL

<table>
<thead>
<tr>
<th>Technique</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drainage</td>
<td>Intra-abd. abscess; empyema; septic arthritis; pyelo; cholangitis</td>
</tr>
<tr>
<td>Debridement</td>
<td>Necrotizing fasciitis; pancreatic necrosis/abscess; mediastinitis</td>
</tr>
<tr>
<td>Device removal</td>
<td>Infected vascular catheter; urinary catheter; ET tube; IUD</td>
</tr>
<tr>
<td>Definitive control</td>
<td>Sigmoid resection (diverticulitis); cholecystectomy; amputation for clostridial myonecrosis</td>
</tr>
</tbody>
</table>
SEPSIS MANAGEMENT

FLUID THERAPY

- Colloid or crystalloid
  - *Crystal*: ↑ volumes, edema; ↓ cost
- Fluid challenge
  - *Crystal*: 500 – 1000 mL
  - *Colloid*: 300 – 500 mL
  - Infuse over 30 min
  - Repeat based on response, tolerance
SEPSIS MANAGEMENT

VASOPRESSORS

- Indication: ↓BP, perfusion despite fluids
- Route: through central line
- Agent: norepinephrine or dopamine
- No low-dose dopa for renal protection
- Arterial catheter for monitoring
- Refractory shock: vasopressin .01-.04 u/m
SEPSIS MANAGEMENT

INOTROPIC THERAPY

- Indication: Low CO despite fluids
- Agent: Dobutamine
- Low BP: combine with vasopressors
- Goals:
  - *Arbitrary elevated level not advised* (**A**)
  - Adequate oxygen delivery
  - Avoid flow-dependence
SEPSIS MANAGEMENT

$O_2$ EXTRACTION - DELIVERY

Graph showing the relationship between $\dot{V}O_2$ (mL/kg/min) and $D_O_2$ (mL/kg/min)
ARTERIAL OXYGEN CONTENT

\[ \text{CaO}_2 = (1.34 \times \text{Hb} \times \text{SaO}_2) + (0.003 \times \text{PaO}_2) \]

= 1.34 x 15 x 0.98

= 19.7 mL/100 ml
SEPSIS MANAGEMENT

OXYHEMOGLOBIN DISSOCIATION CURVE
**SEPSIS MANAGEMENT**

**OXYGEN DELIVERY**

\[
\text{DO}_2 = Q \times \text{CaO}_2 \\
= Q \times (1.34 \times \text{Hb} \times \text{SaO}_2) \times 10 \\
= 5 \times 19.7 \times 10 \\
= 985 \text{ mL/min} \\
= 520 - 570 \text{ mL/min/m}^2
\]
**SEPSIS MANAGEMENT**

**OXYGEN EXTRACTION**

\[ \text{VO}_2 = Q \times 13.4 \times \text{Hb} \times (\text{SaO}_2 - \text{SvO}_2) \]

\[ = 5 \times 13.4 \times 15 \times (0.98 - 0.73) \]

\[ = 229 \text{ ml/min} \]

\[ = 110 - 160 \text{ mL/min/m}^2 \]
OXYGEN EXTRACTION RATIO

\[ \text{O}_2\text{ER} = \frac{\text{VO}_2}{\text{DO}_2} \]

\[ = \frac{110}{520} \]

\[ = 0.2 - 0.3 \]
SEPSIS MANAGEMENT

$O_2$ EXTRACTION - DELIVERY

![Graph showing the relationship between $\dot{V}O_2$ (mL/kg/min) and $D_O_2$ (mL/kg/min).]
Indication: septic shock requiring pressors despite adequate fluids

Agent: Hydocortisone IV
- 200-300 mg/day
- 3 or 4 divided doses
- 7-day course

* Consider: ACTH stimulation test
- ACTH 250 \( ? \) g IV
- Measure cortisol 30-60 min
- Responder: increase 9 \( ? \) g/dl
STEPRIDS FOR SEPTIC SHOCK

- Consider taper at end of therapy
- Consider fludrocortisone (50 ? g PO qid)
- Hydrocortisone > 300 mg/day not indicated (A)
- No shock: steroids not indicated
- Maintenance or stress dose steroids: no contraindication
SEPSIS MANAGEMENT

RECOMBINANT HUMAN ACTIVATED PROTEIN C (rhAPC)

- Endog. anticoagulant, anti-inflammatory
- Rationale: coagulation, endothelial activation in septic inflam. response
- Improved survival (Bernard, NEJM 2001)
- Recommended:
  - APACHE II ≥ 25
  - Sepsis-induced MOF, shock, or ARDS
  - No contraindications
28% of 850 PROWESS patients

Mortality risk reduction:
- All surgical pts.: 3.2%
- Intra-abdominal procedures: 9.1%

Bleeding:

Barie, Am J Surg 04
SEPSIS MANAGEMENT

rhAPC: CONTRAINDICATIONS

- Active internal bleeding
- Recent (3 mos) hemorrhagic stroke
- Recent (2 mos):
  - Intracranial operation
  - Intraspinal operation
  - Severe head trauma
- Trauma with increased bleeding risk
- Epidural catheter
- Intracranial neoplasm, mass, herniation
**SEPSIS MANAGEMENT**

**BLOOD PRODUCTS**

- **PRBC** for Hgb < 7 g/dl
- Erythropoietin not indicated
- **FFP**: bleeding, invasive procedures
- Antithrombin not indicated
- **Platelet transfusion:**
  - *Counts < 5000*
  - 5-30,000 w significant risk of bleeding
  - > 50,000 for surgery / invasive proced.
SEPSIS MANAGEMENT

ALI / ARDS: MECHANICAL VENT.

- Reduced tidal volumes (6 mL/kg)
- Plateau pressure < 30 cm H$_2$O
- Permissive hypercapnia acceptable
- PEEP to prevent end-expir. collapse
- Consider prone positioning
- Elevate HOB 45$^\circ$ (prevents pneumonia)
- Use weaning protocol
• $P_{plat}$: small airways pressure in PPV
• Cause of ventilator-induced lung injury
SEPSIS MANAGEMENT

WEANING CRITERIA

- Arousable
- Stable hemodynamics off pressors
- No new potentially-serious conditions
- Low vent., PEEP requirements
- $F_iO_2$ deliverable by mask or prongs
- Spontaneous breathing trial (A) (CPAP or T-piece)
## SPECIFIC WEANING CRITERIA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nl. adult range</th>
<th>Wean. threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO$_2$/FiO$_2$</td>
<td>&gt; 400</td>
<td>200</td>
</tr>
<tr>
<td>Tidal volume</td>
<td>5-7 mL/kg</td>
<td>5 mL / kg</td>
</tr>
<tr>
<td>Resp. rate</td>
<td>14-18 / min</td>
<td>&lt; 40 / min</td>
</tr>
<tr>
<td>Vital capacity</td>
<td>65-75 mL / kg</td>
<td>10 mL / kg</td>
</tr>
<tr>
<td>Min. ventilation</td>
<td>5-7 L / min</td>
<td>&lt; 10 L / min</td>
</tr>
<tr>
<td></td>
<td><strong>Greater predictive value</strong></td>
<td></td>
</tr>
<tr>
<td>Max. insp. press.</td>
<td>&gt;=-90 cm H$_2$O (F)</td>
<td>- 25 cm H$_2$O</td>
</tr>
<tr>
<td></td>
<td>&gt;=-120 cm H$_2$O (M)</td>
<td></td>
</tr>
<tr>
<td>Rate / tidal vol.</td>
<td>&lt; 50 / min / L</td>
<td>&lt; 100 / min / L</td>
</tr>
</tbody>
</table>

*Marino, The ICU Book*
## CLINICAL CRITERIA FOR ARDS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ARDS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Acute</td>
</tr>
<tr>
<td><strong>Clinical setting</strong></td>
<td>Predisposing condition</td>
</tr>
<tr>
<td><strong>Gas exchange</strong></td>
<td>$\text{PaO}_2 / \text{FiO}_2 &lt; 200$</td>
</tr>
<tr>
<td></td>
<td>regardless of PEEP level</td>
</tr>
<tr>
<td><strong>Chest x-ray</strong></td>
<td>Bilateral infiltrates</td>
</tr>
<tr>
<td><strong>Wedge pressure</strong></td>
<td>$\leq 18 \text{ mm Hg}$</td>
</tr>
</tbody>
</table>
Original illness resolving; no new illness
Off vasopressors and continuous sedatives
  Cough during suctioning
  \( \text{PaO}_2/\text{FiO}_2 > 200 \text{ mm Hg} \)
  PEEP < 5 cm H2O
  Minute ventilation < 15 L/min
  F/TV ratio ≤ 105 during 2-min spontaneous breathing trial

Spontaneous breathing trial** (30–120 mins)
  Respiratory rate > 35/min
  Oxygen saturation < 90%
  Pulse > 140/min or change ≥ 20%
  SBP > 180 mm Hg or < 90 mm Hg
  Agitation, diaphoresis, or anxiety
  F/TV ratio > 105

Note: Achieving any of these criteria for a sustained period at any time during the trial represents a weaning failure and the need to return to maintenance MV.

- Cough adequate to clear secretions
- Able to protect airway

- Yes → Extubate
- No → Return to maintenance MV
SEPSIS MANAGEMENT

ARDNET PROTOCOL

- Assist control mode—volume ventilation
- Reduce tidal volume to 6 mL/kg predicted body weight
- Keep Pplat <30 cm H₂O
  —Reduce Tv as low as 4 mL/kg predicted body weight* to limit Pplat
- Maintain Sao₂/Spo₂ 88–95%
- Anticipated PEEP settings at various Fio₂ requirements

| Fio₂ | 0.3 | 0.4 | 0.4 | 0.5 | 0.5 | 0.6 | 0.7 | 0.7 | 0.8 | 0.9 | 0.9 | 0.9 | 1.0 |
| PEEP | 5   | 5   | 8   | 8   | 10  | 10  | 10  | 12  | 14  | 14  | 14  | 16  | 18  | 20–24 |

*Predicted Body Weight Calculation

- Male—50 + 2.3 [height (inches) – 60] or 50 + 0.91 [height (cm) – 152.4]
- Female—45.5 + 2.3 [height (inches) – 60] or 45.5 + 0.91 [height (cm) – 152.4]

Tv, tidal volume; Sao₂, arterial oxygen saturation; PEEP, positive end-expiratory pressure.
SEPSIS MANAGEMENT

SEDATION PROTOCOLS

- Required in critical illness
- Sedation goals
  - Set end-points
  - Measured by standard subjective scales
- Bolus or continuous infusion
- Daily awakening / retitration
- Reduce vent. duration, LOS, trach rate
SEPSIS MANAGEMENT

NEUROMUSCULAR BLOCKERS

- Avoid if possible
- Bolus or continuous infusion
- Train of four monitoring
- Risk: prolonged muscle weakness
Maintain blood glucose < 150 mg/dL
Continuous insulin / glucose
Glucose monitoring
  • Initiation: q 30-60 min
  • Maintenance: q 4 hr
Enteral nutrition preferred
SEPSIS MANAGEMENT

RENAL REPLACEMENT

- Hemodialysis, continuous venovenous hemofiltration (CVVH) equivalent
- Unstable hemodynamics: CVVH
BICARBONATE THERAPY

- Not recommended for treatment of hypoperfusion-induced lactic acidemia with pH ≥ 7.15
**SEPSIS MANAGEMENT**

<table>
<thead>
<tr>
<th>DVT PROPHYLAXIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Recommended for severe sepsis (A)</td>
</tr>
<tr>
<td>• Agent: Low-dose unfractionated heparin or LMWH</td>
</tr>
<tr>
<td>• Compression stockings if heparin contraindicated</td>
</tr>
<tr>
<td>• Very high risk (DVT hx): combination</td>
</tr>
</tbody>
</table>
Recommended for severe sepsis (A)

• H$_2$ receptor antagonists preferred

• H$_2$ RA better than sucralfate

• PPI: equivalent gastric pH effects but not assessed vs. H$_2$ RI
SEPSIS MANAGEMENT

LIMITATION OF SUPPORT

- Advance care planning advised
- Discussion with patient and family
  - Likely outcomes
  - Realistic goals of treatment
- Consider patient’s best interest:
  - Less aggressive therapy
  - Withdrawal of support
SUMMARY

- Practice guidelines
- Evidence-based
- Source control
- Physiologic basis