Objectives

• Review spinal anatomy and physiology
• Discuss spinal cord injuries and management
• Delineate between spinal/neurogenic shock and discuss management
• Cord compression (herniated disk, tumor, swelling, etc)

• Consider anatomy of spinal cord and how it relates to spinal motion restriction (SMR)
• Discuss current guidelines for implementation of SMR
• Identify pediatric considerations for SMR
Anatomy and Physiology
Vertebral Column

- Surrounds and protects spinal cord
  - 7 Cervical
  - 12 Thoracic
  - 5 Lumbar
  - 5 Sacral
  - Coccyx

(DynaMed Plus, 2016b)
Spinal Cord

- Transmits signals between central and peripheral nervous systems

(DynaMed Plus, 2016b)
Spinal Nerves

- Transmit signals between spinal cord and peripheral nerves
- Bilateral at each vertebral level

(DynaMed Plus, 2016b)
Transmission of Stimuli

Step 1: Arrival of stimulus and activation of receptor

Step 2: Activation of a sensory neuron

Step 3: Information processing in CNS

Step 4: Activation of a motor neuron

Step 5: Response by effector

Sensation relayed to the brain by collateral
Vascular Supply

- Provides O2 to spinal cord
  - 3 major arteries
    - 2 posterior spinal arteries
    - 1 anterior spinal artery
  - Metabolic demands more for gray matter than white

(DynaMed Plus, 2016b)
Spinal Assessment
Assessment

• Primary survey
  – Airway
    • Patent? Protected?
  – Breathing
    • Rate, Effort
  – Circulation
  – Disability
    • GCS, AVPU
  – Exposure (as appropriate)

• Vital Signs

(DynaMed Plus, 2016b)
Subjective Assessment

• Good history is key!
• May be difficult or impossible dependant on LOC
• SAMPLE
  – Signs/symptoms, Allergies, Medications, Past medical history, Last oral intake, Events leading to present situation
• OLD CARTS
  – Onset, Location, Duration, Character, Aggravating or Associated Symptoms, Reliving Factors, Timing, Severity
Trauma Specific History

- Speed, seat belt, helmet, etc.
- MOI
  - Not always a good predictor of spinal injury

(DynaMed Plus, 2016b)
Objective Assessment

- Neurologic exam
  - LOC
  - Cranial nerves (including PERLA) Examine/palpate spine
  - Motor strength x 4 extremities
  - Sensory testing
  - Reflexes
  - Coordination
  - Priapism
  - Gait

- Respiratory exam
  - Lung sounds, effort, rate, etc.

- Cardiac exam

- Other as appropriate
Spinal Cord Injury
Spinal Cord Injury (SCI) Incidence

- Rare
  - Just over 3 million traumas annually
  - 17,500 of those are SCI
  - Not inclusive of those who die on scene

(NSCISC, 2017; AAST, n.d.; DynaMed Plus)
Who's at Risk??

- Late teens and early twenties
- Predominantly men (3-4 X higher)
- MVA (48%), Falls (>60), Violence (GSW), Sports/Recreation (10%)
Spinal Cord Contusion

- Bruise
- Crushing of cord
- Can result in serious injury
- Outcome depends on ability of action potentials to pass through once healed

(DynaMed Plus, 2016a; DynaMed Plus 2016b)
Partial Tear of Spinal Cord

- Incomplete injury
  - Some preservation of motor and or sensory function below level of injury
  - Syndromes
    - Central cord, Brown-Sequard, Anterior cord, Posterior cord, etc.

(DynaMed Plus, 2016a; DynaMed Plus 2016b)
Transection

• Complete injury
  - Total muscle and sensory loss below level of injury

(DynaMed Plus, 2016a; DynaMed Plus 2016b)
Spinal Cord Injury With Out Radiographic Abnormality (SCIWORA)

- Can have injury without radiographic evidence
- More common in pediatrics
- Xray and CT will be negative
- MRI may or may not show contusion

(DynaMed Plus, 2016a; DynaMed Plus 2016b)
Spinal Shock

- Temporary deficits in motor or sensory function that occur immediately following injury

*Not to be confused with Neurogenic Shock*

(DynaMed Plus, 2016a; DynaMed Plus 2016b)
Secondary Injury

- Primary injury occurs immediately or within minutes of initial insult
- Secondary injury occurs hours to days after injury
  - Vascular insult, edema, electrolyte shifts, and necrosis at injury site
- Goal of initial management is to minimize this injury

(DynaMed Plus, 2016a; DynaMed Plus 2016b)
Management

• **Diagnostics**
  – Lab
    • ABG, CBC, CMP, Coags, Type and Screen, Lactate
  – Imaging
    • Plain films, CT, then potentially MRI

(DynaMed Plus, 2016a; DynaMed Plus 2016b)
Management

• Interventions
  – Early management of airway if needed
  – Spinal immobilization
  – IV access
  – Fluid bolus with NS/LR
  – Monitor for signs of neurogenic shock
    • Vasopressors may be needed
  – Pain management
    • Fentanyl often preferred due to shorter duration and less hemodynamic effects than morphine
  – Early surgical consult

(DynaMed Plus, 2016a; DynaMed Plus 2016b)
Steroids

• Not recommended
• American Association of Neurological Surgeon and the Congress of Neurological Surgeons
• Evidence suggests:
  – No improvement in outcomes
  – Increased incidence of harm and death

(National Guideline Clearinghouse, 2013)
Neurogenic Shock
Pathophysiology

- Occurs with SCI above T6
- Sudden loss of sympathetic tone and unopposed parasympathetic response driven by the Vagus nerve
  - Resulting hypotension worsens secondary injury
- Occurs in 19.3% of cervical spine injuries and 7% of thoracic spine injuries

Assessment

- Must identify SCI
- Rule out hemorrhagic shock
  - Lack of response to fluid bolus
- Classic Signs
  - Persistent hypotension
  - Bradycardia (lack of reflex tachycardia)
  -Flushed warm skin
  - Temperature dysregulation
  - Orthostatic hypotension
- Note that neuro deficit is not required for diagnosis
- Autonomic Dysreflexia

Management

• **Diagnostics**
  – Lab
    • ABG, CBC, CMP, Coags, Type and Screen, Lactate
  – Imaging
    • CT/MRI

• **Management**
  – Airway management
  – Hemodynamic stabilization
    • IV fluid resuscitation
    • Vasopressors
      – Norepi generally 1\textsuperscript{st} choice
      – MAP 85-90 for 1\textsuperscript{st} 7 days to improve spinal cord perfusion
  – Continued spinal immobilization

Back Pain
Statistics

• 90% benign
• Leading cause of disability in the US
• 31 million Americans have back pain at any given time
• 10% can be related to serious problems which must be ruled out

When to Worry

- **Spinal Cord Compression**
  - Compression of the spinal cord that disrupts its normal function
- **Can be caused by most of above conditions**
- **Sudden or gradual onset**
  - Sudden: injury, hematoma, ruptured/herniated disk
  - Gradual: Abscesses or tumors, chronic infection, degenerative processes
- **Early diagnosis leads to better chance to reverse problem**

Spinal Disease/Back Pain Causes

- **Fractures**
  - Trauma, osteoporosis, cancer
- **Degenerative disease**
  - Spondylosis, arthritis
- **Ruptured or herniated disk**
- **Scoliosis**
- **Muscle or ligament injury**
- **Spinal Stenosis**

Causes Continued...

- **Hematoma**
  - Injury, AV malformations, tumors, anticoagulants

- **Tumors**
  - Malignant or benign
  - Always rule out metastatic disease if cancer already diagnosed and pt presenting with new back pain or neuro deficits

- **Infection**
  - Abscess in or near spinal cord, spinal TB, meningitis

Pearls...

• Symptoms can vary from mild to severe
  – Pain, weakness, sensation change, numbness, tingling, sexual dysfunction, bowel and bladder control issues, paralysis, complete loss of sensation

• Spinal percussion tenderness may indicate cancer, abscess, or hematomas

• Fractures can occur with little to no mechanism if patients have osteoporosis, metastatic disease, and some degenerative conditions

Diagnosis

• MRI if possible, CT if unavailable
• Lumbar Puncture if indicated
• Labs as appropriate to cause

Management of Spinal Cord Compression

• Pain management
  – NSAIDS (inflammation)
  – Opioids
• Physical Therapy
• Surgical treatment

Management of Benign Back Pain

• Interventions for benign causes
  – Pain management
    • 1st Line: Heat, massage, acupuncture, chiropractic care
    • 2nd Line: NSAIDS, muscle relaxants
    • 3rd Line: Opioids
      – Severely overused, risk of addiction and overdose may outweigh benefits, guidelines becoming more strict
  – Lifestyle changes
    • Weight loss, diet, exercise, avoid inactivity, stop smoking, maintain good posture
  – Most pain will resolve spontaneously

Spinal Immobilization
Spinal Immobilization

• Restriction/immobilization of movement of spine
  – Backboards, cervical collars, head blocks, straps, vacuum splints

• Concern for delayed paralysis and missed spinal fractures

• Standard and widespread since 1960s

(NREMT, 2016; Myer & Perina, 2016)
A Changing Practice...

• Minimal literature to support use
• Lots of literature detailing risks:
  – Prolonged time immobilized
  – Skin breakdown
  – Interference with resuscitation
  – Pain (increased imaging)
  – Anxiety
  – Aspiration
  – Respiratory compromise

(NREMT, 2016; Myer & Perina, 2016)
Damned if we do, damned if we don’t...

- Selected patients
- County of Sacramento EMSA 8044.13
- NREMT Recommendations

(Coastal Valleys EMS, 2014; NREMT, 2016)
Special Notes:

A. Moving the head into a neutral in-line position is contraindicated if:
   1. There is pain upon starting movement
   2. There’s muscle spasm or back pressure upon attempting movement
   3. Patient holds head angulated (tilted) to the side and patient cannot move head
   4. The head is rigidly held to one side
   5. The maneuver cannot be safely achieved due to space or other considerations
   6. In these cases the patient shall be immobilized in the position in which he/she is found

B. Spinal immobilization does not take precedence over airway, respiratory, and cardiovascular stabilization of the critical trauma patient.
Coastal Valley’s Spinal Injury Assessment

8002.2 SPINAL INJURY ASSESSMENT

Potential for Unstable Spinal Injury?

- Age ≥ 65
- Meets Coastal Valleys Trauma Triage Criteria
- Axial load to the head (e.g. diving injury)
- Numbness or tingling in extremities
  
  *If any one of the high-risk factors above are present, strongly consider SMR*

Reliable Patient?

- AND

Normal Spine Exam?

- AND

Normal Motor/Sensory?

A Reliable Patient is cooperative, alert and not intoxicated without:

- Significant Distracting Injuries
- Language Barrier

Palpate vertebral column thoroughly for SPINAL PAIN/TENDERNESS

Motor/Sensory Exam:

- Wrist or finger extension (both hands)
- Plantarflexion (both feet)
- Dorsiflexion (both feet)
- Check gross sensation in all extremities
- Check for abnormal sensations to extremities (e.g. paresthesia)

YES

OMIT SMR

NO

Possible Spine Injury Apply SMR

(Coastal Valleys EMS, 2014)
SMR

• Cervical collar
  – Traditional, X collar
• Backboard/head immobilizer/straps
  – Padding?
  – Strap location
• Vacuum splint
Special Considerations with SMR

- **Pediatrics**
  - Specific board?
  - Positioning on adult board
- **Pregnancy**
  - Tilt to side / SHS
- **Car seats**
  - Must have high back
- **Combative**
  - Avoid increasing agitation
- **Difficulty breathing**
  - Use with caution
Once Immobilized…Reassess!

• Recheck ABCs
• Regularly check motor and sensory function
• Consider Sp02/EtCO2 Monitoring
• Remember ABCs trump immobilization
• Do not delay transport
Questions???
References

- All images retrieved from Google images
Objectives

• Learn about the pathophysiology of sepsis and the inflammatory response

• Focused assessment and early recognition of SIRS and sepsis will be emphasized

• Nursing management, interventions, and treatments will be discussed

• Case scenarios included to enhance learning
Why Sepsis is so Important

• >2,000,000 cases a year occur in the US
• Mortality rate is up to 50%
• 27,000,000 globally develop sepsis and 8 million die that’s 66% worldwide!
• Half of all patients that die in the hospital are septic
More failed systems = increased mortality

Figure 1. Mortality related to the number of systems with failure (MOF)
Mortality related to the system affected

Figure 2. Mortality (%) related to the type of system failure

<table>
<thead>
<tr>
<th>System</th>
<th>Mortality%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>60</td>
</tr>
<tr>
<td>Renal</td>
<td>80</td>
</tr>
<tr>
<td>Hepatic</td>
<td>60</td>
</tr>
<tr>
<td>Cardiovasc.</td>
<td>80</td>
</tr>
<tr>
<td>CNS</td>
<td>120</td>
</tr>
<tr>
<td>Coagulation</td>
<td>100</td>
</tr>
<tr>
<td>Gastric</td>
<td>60</td>
</tr>
<tr>
<td>Metabolic</td>
<td>40</td>
</tr>
</tbody>
</table>
Find and Treat Fast!

Similar to MI, stroke, and polytrauma, early identification and appropriate management in the initial hours after sepsis develops improves outcomes.
Sepsis and septic shock are true medical emergencies and treatment and resuscitation should begin immediately !!!!!!!
What is the “Surviving Sepsis Campaign (SSC)”? 

- A consensus committee of 55 international experts representing 25 international organizations
  - They reviewed millions of data points and developed a list of questions for the committee based on
    - Population, Intervention, Comparison, Outcomes (PICO)

Background: To provide an update to the Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock, first published in 2004.

Methods: A consensus committee of international experts representing 35 international organizations was convened. National groups were assembled at a key international meeting for these committees. Members attended the conference, which formed a list of initial policies developed at the time in the presence and at the time of the process and at the time of the time for the process and at the time of the time for the process. The primary purpose of the guidelines was to provide recommendations for the management of severe sepsis and septic shock.

Results: Key recommendations and suggestions, based on evidence, include: daily quantitative resuscitation of the septic patient during the first 24 hours after recognition, and early goal-directed therapy with cancer patients in severe sepsis and septic shock.

Special Articles

This is a must read!
Criteria for Best Practice Statements

1. Is the statement clear and actionable?
2. Is the message necessary?
3. Is the net benefit unequivocal?
4. Is the net harm unequivocal?
5. Is the evidence difficult to collect or summarize?
6. Is the rationale explicit?
7. Is this better to be formally GRADEd?
Assessing Quality of the Evidence: GRADE

We assess the body of evidence available for each outcome using the GRADE (Grading of Recommendations, Assessment, Development & Evaluation) system.

For each body of evidence we make assessments across 5 domains:

<table>
<thead>
<tr>
<th>Risk of Bias</th>
<th>Consistency</th>
<th>Directness</th>
<th>Precision</th>
<th>Reporting Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any methodological limitations or flaws?</td>
<td>How much variation between studies (direction and size of estimates)?</td>
<td>How well does it match the PICO statement?</td>
<td>Enough participants or events? How wide is the confidence interval?</td>
<td>Any indications of publication bias?</td>
</tr>
</tbody>
</table>

These evaluations result in one of 4 quality ratings that reflect the degree of confidence that the available evidence correctly reflects the theoretical true effect of the intervention, service or practice:

- **High**: true effect lies close to estimate; further research unlikely to change this
- **Moderate**: true effect lies close to estimate but possibility it is substantially different; further research may change estimate
- **Low**: true effect may be substantially different from estimate; further research very likely to have important impact on confidence and to change estimate
- **Very Low**: estimate of effect is very uncertain; further research very likely to have important impact on confidence and to change estimate

Each body of evidence begins with a high rating which is downgraded one level for every domain judged to have serious concerns (2 levels if concerns are very serious).
SSC Has Now Defined Sepsis As:

A life-threatening organ dysfunction caused by a dysregulated host response to infection.
• **SIRS**: A clinical response to a nonspecific insult of either an infectious or noninfectious origin

• SIRS can be caused by ischemia, inflammation, trauma, infection or metabolic insults

• **Defined as 2 or more variables:**
  – Fever > 38 or < 36
  – Heart rate > 90
  – RR > 20 or PaC02 < 32
  – count > 12,000 or < 4,000
Think dysregulated inflammatory response

Anaphylaxis

SIRS
### Table 1: Examples of Inciting Factors of SIRS

<table>
<thead>
<tr>
<th>STERILE INFLAMMATORY DISEASES</th>
<th>INFECTIONOUS INSULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonseptic SIRS</strong></td>
<td><strong>Septic SIRS</strong></td>
</tr>
<tr>
<td>Burns</td>
<td>Anaerobic bacteria</td>
</tr>
<tr>
<td>Chemical aspiration</td>
<td>Fungi</td>
</tr>
<tr>
<td>Heatstroke</td>
<td>Products of gram-negative bacteria</td>
</tr>
<tr>
<td>Immune-mediated disease</td>
<td>Products of gram-positive bacteria</td>
</tr>
<tr>
<td>Ischemic organ necrosis (eg, splenic torsion)</td>
<td>Protozoa</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>Viruses</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
</tr>
</tbody>
</table>
The Complexity of SIRS and Sepsis
Neutrophil Activation is Primary Mediator

Nature Reviews | Immunology
1. Bacteria and other pathogens enter wound

2. Platelets from blood release blood-clotting proteins at wound site

3. Mast cells secrete factors that mediate vasodilation and vascular constriction. Delivery of blood, plasma, and cells to injured area increases

4. Neutrophils secrete factors that kill and degrade pathogens

5. Neutrophils and macrophages remove pathogens by phagocytosis

6. Macrophages secrete hormones called cytokines that attract immune system cells to the site and activate cells involved in tissue repair

7. Inflammatory response continues until the foreign material is eliminated and the wound is repaired
So what does all that mean for us?

Mrs. K is a 64 year old female, that arrives to our ER by ambulance, with the chief complaint of an upper respiratory infection for four days.
Physical Assessment

Subjective assessment
• She has had a productive cough for 4 days with dark green sputum. She has had increasing difficulty breathing and lethargy. She is communicative but has difficulty following directions.

Objective assessment
• Temp – 38.5
• HR -92 sinus w/o ectopy
• Respirations – 24
• BP 97/62
• SpO2 – 92% room air
• A&O x 2. Disoriented to time and events.
### Old and New Clinical Criteria for Sepsis

<table>
<thead>
<tr>
<th></th>
<th>OLD</th>
<th>NEW</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SEPSIS</strong></td>
<td>SIRS</td>
<td>SUSPECTED/DOCUMENTED INFECTION</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>2 or 3 on qSOFA (HAT):</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Hypotension (SBP ≤100 mmHg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- AMS (GCS ≤13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Tachypnea (≥22/min)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rise in SOFA score by 2 or more</td>
</tr>
<tr>
<td><strong>SEVERE SEPSIS</strong></td>
<td>Sepsis +</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SBP &lt;90 mmHg or MAP &lt; 65 mmHg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>lactate &gt; 2.0 mmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>INR &gt;1.5 or a PTT &gt;60 s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bilirubin &gt;34 µmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urine output &lt;0.5 mL/kg/h for 2 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Creatinine &gt;177 µmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Platelets &lt;100 ×10^9/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SpO2 &lt;90% on room air</td>
<td></td>
</tr>
<tr>
<td><strong>SEPTIC SHOCK</strong></td>
<td>SEPSIS + HYPOTENSION</td>
<td>SEPSIS</td>
</tr>
<tr>
<td></td>
<td>after adequate fluid resuscitation</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VASOPRESSORS needed for MAP &gt;65 mmHg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LACTATE &gt;2 mmol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>after adequate fluid resuscitation</td>
</tr>
</tbody>
</table>
SIRS OUT! (sort of)  (quick)SOFA IN!

- SIRS
- Any two or more of the following:
  - Body Temperature > 38°C or <36°C
  - Heart Rate > 90bpm
  - Respiratory rate > 20
  - Hyperventilation (PaCO2 <32mmHg)
  - WBC >12,000/mm³ or <4,000/mm³
  - Immature neutrophils > 10%

- Plus **INFECTION**, confirmed or suspected
Chain of Infection Will Give Index of Suspicion
What is qSOFA

- It is an effective “screening tool” to determine if a patient will, depending on clinical picture, have a higher risk of dying in the hospital or get admitted to the ICU

- Risk stratification
Benefits of Using qSOFA

• It is very easy for clinicians to master the assessment tool

• It can be done at the bedside with no extra equipment

• It is as statistically accurate and as reliable for predicting “badness” as the more tech intensive assessment tools

• Who has end-tidal CO2 easily accessible?

• How long does it take to get a STAT CBC & count ordered, drawn and read?

• Labs statistically wont tell you more than the thermometer will in the first 15 minutes of your assessment
What Are The New (SSC) Guidelines

1. Patient with suspected infection
   - qSOFA ≥2? (see A)
     - Yes: Assess for evidence of organ dysfunction
       - SOFA ≥2? (see B)
         - Yes: Sepsis
           - Despite adequate fluid resuscitation, 1. vasopressors required to maintain MAP ≥ 65 mm Hg
             - AND
             - 2. serum lactate level > 2 mmol/L?
               - Yes: Septic shock
               - No: Monitor clinical condition; reevaluate for possible sepsis if clinically indicated
         - No: Monitor clinical condition; reevaluate for possible sepsis if clinically indicated
   - No: Sepsis still suspected?
     - Yes: Monitor clinical condition; reevaluate for possible sepsis if clinically indicated

A qSOFA Variables
- Respiratory rate
- Mental status
- Systolic blood pressure

B SOFA Variables
- PaO₂/FiO₂ ratio
- Glasgow Coma Scale score
- Mean arterial pressure
- Administration of vasopressors with type and dose rate of infusion
- Serum creatinine or urine output
- Bilirubin
- Platelet count
Assess for Organ Dysfunction

**Sequential [Sepsis-Related] Organ Failure Assessment (SOFA) Score**

<table>
<thead>
<tr>
<th>System</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3 with respiratory support</th>
<th>4 with respiratory support</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiration PaO2/FiO2, mmHg (kPa)</td>
<td>2400 (53.3)</td>
<td>&lt;400 (53.3)</td>
<td>&lt;300 (40)</td>
<td>&lt;200 (26.7)</td>
<td>&lt;100 (13.3)</td>
</tr>
<tr>
<td>Coagulation Platelets, x10^9/μL</td>
<td>2150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Liver Billirubin, mg/dL (umol/L)</td>
<td>&lt;1.2 (20)</td>
<td>1.2 - 1.9 (20 - 32)</td>
<td>2.0 - 6.9 (33 - 101)</td>
<td>6.0 - 11.9 (102 - 204)</td>
<td>&gt;12.0 (204)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>MAP &gt;70mmHg</td>
<td>MAP &gt;70mmHg</td>
<td>Dopamine &lt;5 or Dobutamine (any dose)</td>
<td>Dopamine 5.1 - 15 or Epinephrine 0.1 or Norepinephrine 0.1</td>
<td>Dopamine &gt;15 or Epinephrine &gt;0.1 or Norepinephrine &gt;0.1</td>
</tr>
<tr>
<td>CNS</td>
<td>15</td>
<td>13 - 14</td>
<td>10 -12</td>
<td>6 - 9</td>
<td>&lt;6</td>
</tr>
<tr>
<td>Renal</td>
<td>&lt;1.2 (110)</td>
<td>1.2 - 1.9 (110 - 170)</td>
<td>2.0 - 3.4 (171 - 299)</td>
<td>3.5 - 4.9 (300 - 440)</td>
<td>&gt;6.0 (440)</td>
</tr>
<tr>
<td>Creatinine, mg/dL (umol/L)</td>
<td>Urine Output, mL/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: Catecholamine Doses = μg/kg/min for at least 1hr*
How Bad is “BAD”

**SOFA Score**
The European Society of Intensive Care Medicine

<table>
<thead>
<tr>
<th>SOFA score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>&lt;10%</td>
<td>0-6</td>
<td>&lt;300</td>
<td>142-220</td>
<td>&lt;100</td>
</tr>
<tr>
<td></td>
<td>15-20%</td>
<td>7-9</td>
<td>&lt;200</td>
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<th>Mortality</th>
<th>Score trend (First 48 hrs)</th>
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<tr>
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<tr>
<td>&lt;27%</td>
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</table>


dr. wire output (ml/hr)
# Pulmonary Failure Secondary to ARDS

<table>
<thead>
<tr>
<th>ARDS Severity</th>
<th>PaO2/FiO2</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>MILD</td>
<td>200-300</td>
<td>27%</td>
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<tr>
<td>Moderate</td>
<td>100-200</td>
<td>32%</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 100</td>
<td>45%</td>
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</table>
PaO2/ FiO2 Ratio

• Divide PaO2 by the FiO2.
• Example:
  – PaO2-120/ FiO2 21%
  – Ratio = 571  Healthy.
  – PaO2-89/ FiO2 100%
  – Ratio = 89
  VERY BAD!!!!!
Thrombocytopenia: Decreased Platelets

- Independent risk factor associated with an increased 28 day mortality if not corrected
- DIC, bleeding and medications contribute to decreased platelet count
Liver Failure; Increased Billirubin

- Billirubin level > 2 is indicative of injury to the liver
- Coags can be evaluated and a PTT greater that 1.5 times the control and an INR >1.5
Hemodynamic Flow Pattern in Septic Shock

- Decreased CVP
- Low cardiac filling pressures
- Increased cardiac output
- Low systemic vascular resistance
- Low SVR due to leaky capillaries
Vasodilation is the Principal Problem

- The vascular changes are attributed to the enhanced production of nitric-oxide in vascular endothelial cells
- Oxidant injury in the vascular endothelium leads to fluid extravasation
Cardiac Dysfunction in Septic Shock

- Proinflammatory cytokines promote cardiac dysfunction
The GCS is an indicator of cerebral perfusion and the brain is the most sensitive organ to any metabolic, circulatory aberrancies.
Renal Failure in Sepsis

- Increased creatinine is an indicator of renal failure. The kidneys are particularly prone to the micro vascular insults that occur during SIRS and septic shock pathophysiology.

- SSC has determined that there was no statistical benefit to renal replacement therapy but they do recommend its use.
Lactate in Septic Shock

- Lactate >2 is associated with a higher mortality rate in the setting of sepsis.

- It is more of a statistical indicator rather than a direct causal factor for mortality.

- It is not a direct measure of tissue perfusion but increases in serum lactate represent tissue hypoxia.

- The causes are multifactorial.
Why Measure It?

Five RCTs have evaluated lactate-guided resuscitation of patients in septic shock.

A significant reduction in Mortality has been observed in lactate-guided resuscitation compared to resuscitations without lactate monitoring.
## Mortality Between Groups With 3 Variables

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>+ Vasopressors</th>
<th>Lactate &gt; 2</th>
<th>Prevalence</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Hypotensive after fluids + vasopressors Lactate &gt; 2</td>
<td></td>
<td></td>
<td>45%</td>
<td>42%</td>
</tr>
<tr>
<td>Group 2</td>
<td>Hypotensive after fluids + vasopressors Lactate &lt; 2</td>
<td></td>
<td></td>
<td>21%</td>
<td>30%</td>
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<tr>
<td>Group 3</td>
<td>MAP &gt; 65 - vasopressors Lactate &gt; 2</td>
<td></td>
<td></td>
<td>17%</td>
<td>25%</td>
</tr>
<tr>
<td>Group 4</td>
<td>Map &gt;65 after fluids - vasopressors Lactate &gt; 2</td>
<td></td>
<td></td>
<td>14%</td>
<td>29%</td>
</tr>
</tbody>
</table>
Mrs. K SOFA Score

- Respiratory rate 24.
- PO2 110 / 40% FiO2
- Platelets – 181
- Bilirubin – 2.1
- BP 98/71 (83)
- GCS -14
- Creatinine – 1.3
- Lactate - 3

qSOFA + 1
- Score + 2
- Score + 0
- Score + 2
- qSOFA + 1
- Score + 1 /qSOFA +1
- Score + 1
- > 2 + higher mortality

SOFA = 6
## Sequential [Sepsis-Related] Organ Failure Assessment (SOFA) Score

<table>
<thead>
<tr>
<th>System</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO₂/FiO₂, mmHg (kPa)</td>
<td>2400 (53.3)</td>
<td>&lt;400 (53.3)</td>
<td>&lt;300 (40)</td>
<td>&lt;200 (26.7) with respiratory support</td>
<td>&lt;100 (13.3) with respiratory support</td>
</tr>
<tr>
<td>Coagulation Platelets, x10³/μL</td>
<td>2150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin, mg/dL (umol/L)</td>
<td>&lt;1.2 (20)</td>
<td>1.2 - 1.9 (20 - 32)</td>
<td>2.0 - 6.9 (33 - 101)</td>
<td>6.0 - 11.9 (102 - 204)</td>
<td>&gt;12.0 (204)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
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<tr>
<td>MAP</td>
<td>70 mmHg</td>
<td>70 mmHg</td>
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<tr>
<td>Renal</td>
<td></td>
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<tr>
<td>Creatinine, mg/dL (umol/L)</td>
<td>&lt;1.2 (110)</td>
<td>1.2 - 1.9 (110 - 170)</td>
<td>2.0 - 3.4 (171 - 299)</td>
<td>3.5 - 4.9 (300 - 440)</td>
<td>&gt;6.0 (440)</td>
</tr>
<tr>
<td>Urine Output, mL/d</td>
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</tbody>
</table>

*Catecholamine Doses = ug/kg/min for at least 1hr*
## How Bad is “BAD”

### SOFA Score

The European Society of Intensive Care Medicine

<table>
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<tr>
<th>SOFA score</th>
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<td></td>
<td></td>
<td>&lt;300</td>
<td>&lt;200</td>
<td>&lt;100</td>
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<td>142-220</td>
<td>67-141</td>
<td>&lt;67</td>
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</tbody>
</table>
What Are The New (SSC) Guidelines?

Patient with suspected infection

- qSOFA ≥2? *(see A)*
  - No: Sepsis still suspected?
    - No: Monitor clinical condition; reevaluate for possible sepsis if clinically indicated
    - Yes: Assess for evidence of organ dysfunction
      - SOFA ≥2? *(see B)*
        - No: Monitor clinical condition; reevaluate for possible sepsis if clinically indicated
        - Yes: Sepsis
          - Despite adequate fluid resuscitation, 1. vasopressors required to maintain MAP ≥65 mm Hg AND 2. serum lactate level >2 mmol/L?
            - No: Septic shock
            - Yes: Sepsis
When Are We in Septic Shock?

• Despite adequate fluid resuscitation 30ml/kg bolus the patient remains hypotensive and a vasopressor is needed to maintain MAP >65mmHg

• And the serum lactate level is > 2

• These patients have a 42% mortality
<table>
<thead>
<tr>
<th>SURVIVING SEPSIS CAMPAIGN RECOMMENDATION HIGHLIGHTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SEPSIS DEFINITION</strong></td>
</tr>
<tr>
<td>Systemic manifestation of infection + suspected</td>
</tr>
<tr>
<td>infection</td>
</tr>
<tr>
<td>Severe sepsis: sepsis + organ dysfunction</td>
</tr>
<tr>
<td>Life threatening organ dysfunction caused by</td>
</tr>
<tr>
<td>dysregulated response to infection</td>
</tr>
<tr>
<td>No severe sepsis category</td>
</tr>
<tr>
<td><strong>INITIAL RESUSCITATION</strong></td>
</tr>
<tr>
<td>at least 30 cc/kg in first 3 hours</td>
</tr>
<tr>
<td>Crystalloid fluid (no recommendations on 0.9% NaCl vs balanced solution)</td>
</tr>
<tr>
<td>Albumin if patients require “substantial” fluids (weak)</td>
</tr>
<tr>
<td>Protocolized care including</td>
</tr>
<tr>
<td>CVP</td>
</tr>
<tr>
<td>ScVO2</td>
</tr>
<tr>
<td>Normalize lactate</td>
</tr>
<tr>
<td>Use dynamic resuscitation markers (passive leg raise)</td>
</tr>
<tr>
<td>Target MAP of 65mmHg</td>
</tr>
<tr>
<td>Reassess hemodynamic status to guide resuscitation</td>
</tr>
<tr>
<td>Normalize lactate</td>
</tr>
<tr>
<td><strong>VASOPRESSORS</strong></td>
</tr>
<tr>
<td>target MAP of 65 mmHg</td>
</tr>
<tr>
<td>1. Norepinephrine</td>
</tr>
<tr>
<td>2. Epinephrine if not at target MAP OR vasopressin to reduce norepinephrine requirement</td>
</tr>
<tr>
<td>3. Avoid dopamine in most patients</td>
</tr>
<tr>
<td><strong>STEROIDS</strong></td>
</tr>
<tr>
<td>Only indicated for patients with septic shock refractory to adequate fluids and vasopressors</td>
</tr>
<tr>
<td><strong>ANTIBIOTICS</strong></td>
</tr>
<tr>
<td>One or more antibiotics active against presumed pathogen</td>
</tr>
<tr>
<td>Combination therapy (double coverage) for neutropenic patients and pseudomonas</td>
</tr>
<tr>
<td>Initial broad spectrum antibiotics (ex: vancomycin + piperacillin-tazobactam)</td>
</tr>
<tr>
<td>Against combined therapy (i.e. do not double cover pseudomonas)</td>
</tr>
<tr>
<td>May use procalcitonin to guide de-escalation</td>
</tr>
<tr>
<td><strong>SOURCE CONTROL</strong></td>
</tr>
<tr>
<td>Achieve within 12 hours, if feasible</td>
</tr>
<tr>
<td>Achieve as soon as medically and logically feasible</td>
</tr>
<tr>
<td><strong>VENTILATOR</strong></td>
</tr>
<tr>
<td>6 cc/kg tidal volume</td>
</tr>
<tr>
<td>prone patients with severe ARDS (P/F &lt;150 in 2017 guidelines)</td>
</tr>
<tr>
<td>no recommendation</td>
</tr>
<tr>
<td>Against high frequency oscillatory ventilation (HFOV)</td>
</tr>
<tr>
<td>weak recommendation for noninvasive ventilation in select patients with sepsis induced ARDS</td>
</tr>
<tr>
<td>Unable to make recommendation on noninvasive ventilation</td>
</tr>
</tbody>
</table>

The Surviving Sepsis Campaign Resuscitation Bundle

- Serum lactate measured
- Blood cultures obtained prior to antibiotic administration.
- From the time of presentation, broad-spectrum antibiotics administered within 1 hour for all admissions
- In the event of hypotension and/or lactate >4 mmol/L (36 mg/dL):
  - Deliver an initial minimum of 20 ml/kg of crystalloid (or colloid equivalent)
  - Give vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) ≥ 65 mm Hg.
- In the event of persistent arterial hypotension despite volume resuscitation (septic shock) and/or initial lactate >4 mmol/L (36 mg/dL):
  - Achieve central venous pressure (CVP) of ≥ 8 mm Hg
  - Achieve central venous oxygen saturation (ScvO2) ≥ 70%

... within 6 hours of onset!
Blood Cultures

• It is recommended that routine microbiologic cultures be obtained before starting antimicrobial therapy if it doesn’t substantially delay the start of antimicrobials

• TWO sets!!!
Fluid Resuscitation in Septic Shock

- Crystalloids are the fluid of choice
- Balanced crystalloids LR/ Plasma-Lyte or NS for resuscitation
- Balanced fluids have shown better outcomes secondary to decreased chloride
- Albumin is suggested in addition to crystalloids when large volumes are given
- Recommend against using hydroxyethyl starches for IV volume replacement
- Additional fluid resus be guided by frequent reassessment of hemodynamic status
- Dynamic over static variables be used to predict fluid responsiveness
- Remember septic shock is distributive

<table>
<thead>
<tr>
<th>Hypovolemic</th>
<th>Cardiogenic</th>
<th>Distributive</th>
<th>Obstructive</th>
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</thead>
<tbody>
<tr>
<td>- Intravascular vol loss</td>
<td>- Arrhythmia</td>
<td>- Vasodilatory-↓↓ SVR</td>
<td>- Tension PTX</td>
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<tr>
<td>- hemorrhagic</td>
<td>- AMI, valve failure</td>
<td>- septic shock/SIRS/TSS</td>
<td>- Tamponade</td>
</tr>
<tr>
<td>- fluid loss</td>
<td>- cardiomyopathy</td>
<td>- Anaphylaxis</td>
<td>- PE</td>
</tr>
</tbody>
</table>

- Lab abnormalities - consider other causes - low CI, CVP by choice of fluids - lab workup - fluids and additional labs - DPL, BUN, protein - IV catheters and other lines
Vasopressors in Septic Shock

Norepinephrine is the first choice of vasopressor

Vasopressin or Epinephrine can be added to Norepinephrine to increase MAP
Vasopressin can be added to decrease Norepinephrine.

Dopamine as an alternative to Norepinephrine in highly select patients

Low dose (renal) Dopamine is not recommended

Dobutamine for hypotension in spite of adequate fluid and vasopressor use
Corticoid Steroids in Sepsis

- IV hydrocortisone is not recommended in sepsis and septic shock if adequate fluid resuscitation and vasopressor therapy are available to restore hemodynamic stability.

- If this is not achievable, IV hydrocortisone at a dose of 200mg per day.
Time to Antibiotic Therapy is CRUCIAL!

Sepsis is a medical emergency

Patient survival rate (%)

0% 100%

Time to antibiotics

0 hours 1 2 3 4 5 6 9 12 24 36

Patients with effective antibiotic therapy

Made for World Sepsis Day by lingruen-gmbh.com
Complexity of Sepsis and Septic Shock

Factors that affect choice of antimicrobial regime:

• The anatomic site of infection with respect to the typical pathogen profile and the properties of the antimicrobial to penetrate the site
• Prevalent pathogens in the community, hospital, ward
• The resistance patterns of offending pathogens
• The presence of specific immune defects: splenectomy, HIV, neutropenia
• Age and patient comorbidities including chronic illness and organ dysfunction, acute illness and injury, and the presence of invasive devices (e.g., central venous catheters, Foley, IV’s)
### TABLE 6. Important Terminology for Antimicrobial Recommendations

<table>
<thead>
<tr>
<th><strong>Empiric therapy</strong></th>
<th>Initial therapy started in the absence of definitive microbiologic pathogen identification. Empiric therapy may be mono-, combination, or broad-spectrum, and/or multidrug in nature.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Targeted/definitive therapy</strong></td>
<td>Therapy targeted to a specific pathogen (usually after microbiologic identification). Targeted/definitive therapy may be mono- or combination, but is not intended to be broad-spectrum.</td>
</tr>
<tr>
<td><strong>Broad-spectrum therapy</strong></td>
<td>The use of one or more antimicrobial agents with the specific intent of broadening the range of potential pathogens covered, usually during empiric therapy (e.g., piperacillin/tazobactam, vancomycin, and anidulafungin; each is used to cover a different group of pathogens). Broad-spectrum therapy is typically empiric since the usual purpose is to ensure antimicrobial coverage with at least one drug when there is uncertainty about the possible pathogen. On occasion, broad-spectrum therapy may be continued into the targeted/definitive therapy phase if multiple pathogens are isolated.</td>
</tr>
<tr>
<td><strong>Multidrug therapy</strong></td>
<td>Therapy with multiple antimicrobials to deliver broad-spectrum therapy (i.e., to broaden coverage) for empiric therapy (i.e., where pathogen is unknown) or to potentially accelerate pathogen clearance (combination therapy) with respect to a specific pathogen(s) where the pathogen(s) is known or suspected (i.e., for both targeted or empiric therapy). This term therefore includes combination therapy.</td>
</tr>
<tr>
<td><strong>Combination therapy</strong></td>
<td>The use of multiple antibiotics (usually of different mechanistic classes) with the specific intent of covering the known or suspected pathogen(s) with more than one antibiotic (e.g., piperacillin/tazobactam and an aminoglycoside or fluoroquinolone for gram-negative pathogens) to accelerate pathogen clearance rather than to broaden antimicrobial coverage. Other proposed applications of combination therapy include inhibition of bacterial toxin production (e.g., clindamycin with β-lactams for streptococcal toxic shock) or potential immune modulatory effects (macrolides with a β-lactam for pneumococcal pneumonia).</td>
</tr>
</tbody>
</table>
## Antibiotics for the Treatment of Sepsis

### Possible empiric antibiotic choice in severe sepsis

<table>
<thead>
<tr>
<th>Suspected site of infection</th>
<th>Antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>Cefotaxime + erythromycin</td>
</tr>
<tr>
<td>Community acquired</td>
<td>Cefotaxime/cefazidime alone or</td>
</tr>
<tr>
<td>Hospital acquired</td>
<td>Ureidopenicillin + aminoglycoside</td>
</tr>
<tr>
<td>VAP</td>
<td>Carbapenem, quinolone</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>Quinolone</td>
</tr>
<tr>
<td>Community acquired</td>
<td>Amoxicillin + clavulanic acid (co-amoxiclav)</td>
</tr>
<tr>
<td>Hospital acquired</td>
<td>Ceftazidime alone or</td>
</tr>
<tr>
<td></td>
<td>Ureidopenicillin + aminoglycoside</td>
</tr>
<tr>
<td>Skin and soft tissue</td>
<td>Benzyl-penicillin + nafcillin (flucloxacillin)</td>
</tr>
<tr>
<td>Community acquired</td>
<td>Cefotaxime + nafcillin or</td>
</tr>
<tr>
<td>Hospital acquired</td>
<td>Cefotaxime + vancomycin</td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>Cefotaxime + metronidazole or</td>
</tr>
<tr>
<td></td>
<td>Ureidopenicillin + aminoglycoside or</td>
</tr>
<tr>
<td></td>
<td>Carbapenem (monotherapy), quinolone</td>
</tr>
<tr>
<td>Biliary tract</td>
<td>Ureidopenicillin + aminoglycoside</td>
</tr>
<tr>
<td>Neutropenic</td>
<td>Ureidopenicillin + aminoglycoside or</td>
</tr>
<tr>
<td></td>
<td>Ceftazidime monotherapy</td>
</tr>
</tbody>
</table>

**Nosocomial severe sepsis and septic shock without a clear site of infection:**

Beta lactam + vancomycin + aminoglycoside or quinolone
SSC Recommendations for Antimicrobial Therapy

- Antimicrobials should be given as soon as possible.
- Empiric broad-spectrum therapy to cover all likely pathogens.
- Antimicrobial therapy be narrowed once pathogen identification and sensitivities are established.
- Refrain from sustained systemic antimicrobial prophylaxis in patients with severe inflammatory states of non-infectious etiology.
- Dosing strategies of antimicrobials be optimized based on accepted pharmacokinetic/ pharmacodynamic principals and specific drug properties.
- Empiric combination therapy aimed at the most likely pathogen for initial management.
- Combination therapy should not be routinely used for ongoing treatment of other serious infections not associated with shock. Neutropenic included.
- If combination therapy is used for septic shock, de-escalation is recommended with discontinuation of combination therapy within the first few days in response to clinical improvement/ or resolution of infection. Targeted and empiric.
- Antimicrobial treatment for 7-10 days is adequate for most serious infections
- Longer courses are appropriate for some patients.
- Shorter courses are appropriate for some patients.
- Daily assessment is recommended for de-escalation of therapy.
- The measurement of procalcitonin levels can be used to support shortening the duration of therapy.
- Procalcitonin levels can be used to support the discontinuation of empiric therapy in patient who subsequently have limited evidence of infection.
Procalcitonin

- PCT has been shown to be the most useful laboratory study in differentiating patients with an inflammatory response from those with an infection

- Procalcitonin is a propeptide of calcitonin that is responsible for calcium homeostasis
Find out what is making the patient sick

- Indwelling catheters
- Abscesses that can be seen (cutaneous) and those that can’t
- Necrotic tissue
- Foreign bodies in the body
- Teeth
- Post-operative procedures
ARDS and Mechanical Ventilation

• Use the protective mode of ventilation to avoid and treat ARDS

• The prone position is recommended

• NO (HFOV) high frequency

• Neuromuscular blocking agents recommended first 48 hours of ARDS

• Conservative fluid strategy

• No B-agonist without bronchospasm
Protective Strategy

Is a protocol established by the ARDSnet network to protect patients from Ventilator induced lung injury during mechanical ventilations
Patients That Need Protecting

• Trauma patients

• CVA, cardiovascular, septic patients

• Patients that have no underlying pulmonary or respiratory disease

• Patients that have pulmonary injury that can easily progress to ARDS
Objectives of Protective Strategy

- Maintain ETCO: 35-45cm H2O
- Maintain SpO2: > 92%
- Tidal volumes: 6ml – 8ml/kg
- PEEP: 5cm H2O to maintain recruitment
- Pplat: < 30cm H2O

Monitoring the Pplat is the critical element of the protective strategy. This reduces lung and alveolar distention and injury. PEEP decreases “shear” injury secondary to alveoli collapse.
What’s on the Horizon???

Vitamin-C

- Three studies have shown the benefit.
  - Fowler et al (2014)
  - Zabet et al (2014)
  - Dr. Marik soon to be released

- In an anecdotal treatment for 3 terminal “fulminant” cases of sepsis, a cocktail of vit-c, hydrocortisone were used out of desperation. These patients quickly recovered

- 47 patients enrolled and treated with vit-c hydrocortisone and Thiamine
  - The mortality was 8.5% compared to 40% mortality in a group that was not treated with the cocktail.
Another look at inflammatory injury

Inflammation as source

• The problem with inflammatory injury is not the inflammation but the host's inability to protect itself from the inflammation.

Oxidative injury as source

• The inflammatory injury is a manifestation of oxidative stress. Therefore, inflammatory injury can be the result of inadequate antioxidant protection.
QUESTIONS???
Thank You!!!