

MD SEMINAR

Management of severe sepsis

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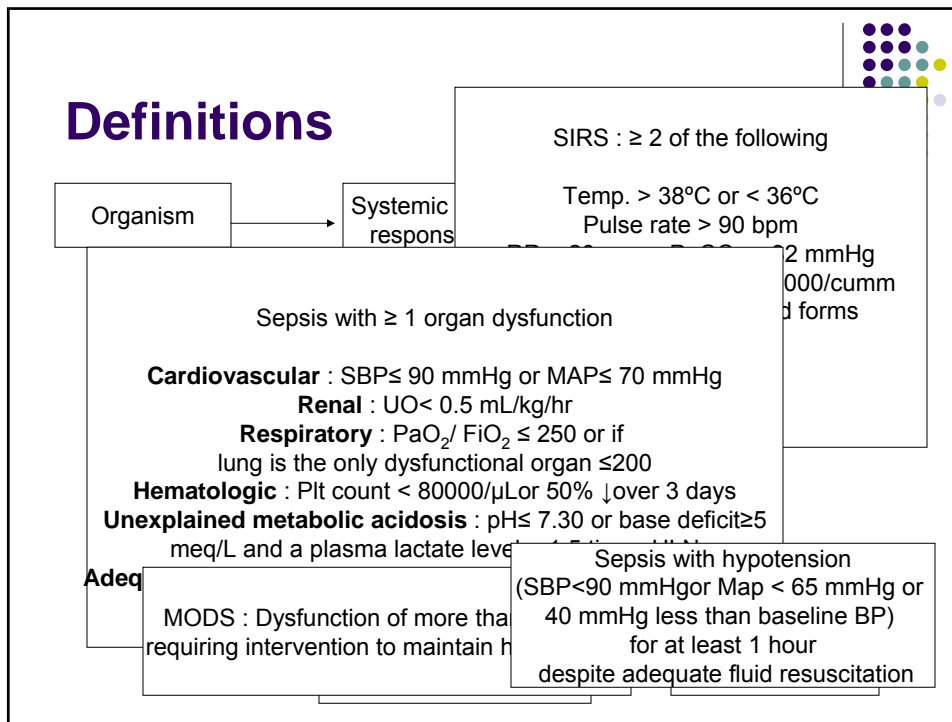


Introduction

- Incidence : 240/100000 (USA)
- Leading cause of death in non cardiac ICU
- Mortality : 20-50%
- Average expenditure per patient : 22000 \$
- Total annual cost :17 billion \$ (USA)
- **SURVIVING SEPSIS CAMPAIGN** (2002) launched through Barcelona declaration
- Aim: To reduce mortality due to sepsis by 25% by 2009



Definitions



Diagnosis

> History

- Epidemiological risk factors
- Patient risk factors – Immune status
 - Prosthetic devices
 - Occupation
 - Dietary proclivities
 - Addictions
- H/o fever (absent in extremes of age, MI, shock, immunocompromised state)
- Focal symptoms of infection
- H/o complications
- H/o medication

Diagnosis



➤ Examination

- Vital signs
- Temperature(oral/rectal)
- Physical examination
- Focal findings of infection

Diagnosis



➤ Investigations

- Leukocytosis, neutrophilia, bandemia, leukopenia, neutropenia
- Dohle bodies, toxic granulations, vacuoles
- Haemoconcentration
- Thrombocytopenia
- DIC w/u
- Hyperlactatemia
- Biological markers (CRP, IL-6, procalcitonin,protein C)
- Cultures
- Organ dysfunction parameters

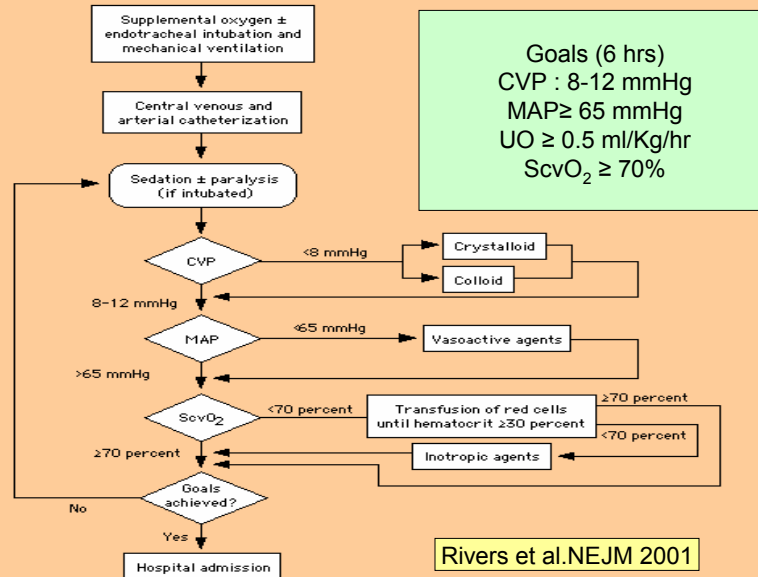
Diagnosis

Evaluation of Common Sources of Sepsis*

Suspected site	Symptoms/signs	Microbiologic evaluation
Upper respiratory tract	Pharyngeal inflammation plus exudate ± swelling and lymphadenopathy	Throat swab for aerobic culture
Lower respiratory tract	Productive cough, pleuritic chest pain, consolidative auscultatory findings	Sputum of good quality, quantitative culture of protected brush or bronchoalveolar lavage
Urinary tract	Fever, urgency, dysuria, loin pain	Urine microscopy >50 WBC/hpf plus: - midstream urine >100,000 cfu/mL - catheter urine >100,000 cfu/mL - Suprapubic aspirate >1000 cfu/mL
Wound or burn	Inflammation, edema, erythema, discharge of pus	Gram stain and culture of draining pus, wound culture not reliable
Skin/soft tissue	Erythema, edema, lymphangitis	Culture blister fluid or draining pus; role of tissue aspirates not proven
Central nervous system	Signs of meningeal irritation	CSF microscopy, protein, glucose, culture, bacterial antigen test
Gastrointestinal	Abdominal pain, distension, diarrhea, and vomiting	Stool culture for Salmonella, Shigella, and Campylobacter
Intra-abdominal	Specific abdominal symptoms/signs	Aerobic and anaerobic culture of percutaneously or surgically drained abdominal fluid collections
Peritoneal dialysis (PD) infections	Cloudy PD fluid, abdominal pain, fever	Cell count and culture of PD fluid
Genital tract	Low abdominal pain, vaginal discharge	Endocervical and high vaginal swabs onto selective media

*Adapted from Cohen, J, Microbiologic requirements for studies of sepsis. In: Sibbald, W.J, Vincent, J.L (eds), Clinical Trials for the Treatment of Sepsis, Springer-Verlag, Berlin, 1995, p 73.

Early goal directed therapy



Resuscitation bundle-EGDT



➤ Fluid therapy

- Targets- CVP: 8-12 mmHg; PAOP: 12-15mmHg
- Isotonic crystalloids or iso-oncotic colloids equally effective when titrated to the same hemodynamic end points
SAFE TRIAL, NEJM 2004
- Crystalloids: 0.9%NaCl, Ringers lactate
- Colloids : 5% albumin, 6% HES solution
- Crystalloids: 2-4 times more volume required and longer time to achieve goals but cheaper

Resuscitation bundle-EGDT



➤ Complications of fluid therapy

- Pulmonary edema: Colloids mitigate fluid efflux at higher filling pressures
- Systemic edema
- HES : Tubular injury, bleeding

➤ Resuscitation end points

- Clinical : BP, HR ,UO,skin perfusion, mental status
- Indices of tissue perfusion : Blood lactate, ScvO₂

Resuscitation bundle-EGDT



- Vasopressor therapy
- Patients should be adequately fluid resuscitated
- Dopamine and norepinephrine equally effective
- Dopamine \uparrow CO more than NE but use limited by tachycardia
- NE \uparrow BP without affecting cardiac index and organ perfusion
- Phenylepinephrine useful in tachyarrhythmias
- Epinephrine can be used in refractory hypotension but \downarrow mesenteric perfusion

Vasopressor therapy (contd.)



- Administration of low doses of dopamine to \uparrow renal perfusion not recommended
- Low dose of vasopressin used in refractory hypotension
- Refractory hypotension may respond to replacement dose steroids
- Intraarterial pressure monitoring preferred, femoral site being recommended

Vasopressors



Vasoactive Agents in Septic Shock

Drug	Effect on heart rate	Effect on contractility	Arterial constriction effects
Dobutamine	+	+++	-(dilates)
Dopamine	++	++	++
Epinephrine	+++	+++	++
Norepinephrine	++	++	+++
Phenylephrine	0	0	+++
Amrinone	+	+++	--(dilates)

Inotropic therapy



- Dobutamine first choice for patients with low cardiac index and/or low ScvO₂ and an adequate MAP following fluid resuscitation
- In presence of tissue hypoperfusion, it may increase cardiac output and organ perfusion
- Can be titrated independent of vasopressors

Blood product administration



- Optimal MAP + ScvO₂ < 70% + hct < 30% → Transfuse packed RBC to achieve a hct > 30%
- Erythropoietin not recommended as a treatment
- Use of FFP to correct clotting abnormalities in the absence of bleeding or planned invasive procedure not recommended
- Platelet count in severe sepsis
 - < 5000 – Transfuse
 - 5000-30000 - Transfuse if risk of bleed
 - 50000 – Optimal for surgery

Antibiotic therapy



- **Principle : In early, hit hard, out early**
- **Start antimicrobials as soon as possible**
- **Give correct therapy**
 - Broad spectrum: cover gram +ve & gram -ve
 - Consider resistance, consult local antibiogram
 - Consider NLF gram -ve if late onset (>5 days)
 - Consider non bacterial microbes
- **Give correct dose at correct interval**
- **All antimicrobials to be given parenterally**
- **Only bactericidal antibiotics**
- **Narrow antimicrobial spectrum as soon as results available**
- **Stop antimicrobials as soon as possible**

Antibiotic therapy



> Risk factors for infection with resistant organisms

- Prolonged hospital stay (>5 days)
- Previous hospitalization of >2 days within past 90 days
- Broad spectrum antibiotics within past 90 days,
- Antibiotic resistance in the area
- Admission from long-term care institution
- Chronic renal dialysis within past 30 days
- Home chronic wound care
- Poor underlying condition
- Immunocompromised state
- Presence of invasive hardware, e.g. central lines

Antibiotic therapy



● Community acquired bacteremia

- Sites of infection**
- Lung (21%)
 - Abdomen (20%)
 - Urinary tract (20%)
 - Endocarditis (4%)
 - Other (10%)
 - No primary source (25%)

Valles, Chest 2003

- Pathogens**
- E.Coli (25%)
 - S.Pneumoniae (16%)
 - S.Aureus (14%)

Valles, Chest 2003

Antibiotic therapy



- Hospital acquired bacteremia

Site of infection
Lung(35%)
Abdomen(21%)
Urinary tract(13%)
Skin and soft tissue(7%)
Other site(8%)
Unknown primary site(16%)
<i>JAMA 1997</i>

Organisms
MRSA(30%)
Ps. Aeuroginosa(21%)
E.Coli(18%)
Acinetobacter(6%)
Enterobacter(5%)
K. pneumoniae(8%)
<i>JAMA 1997</i>

Emperical antibiotic regimens in severe sepsis



Sepsis source	Recommended antibiotic regimen
Unknown source	Vancomycin 1gm Q 12h and levofloxacin 750 mg Q 12 h and gentamycin 7 mg/Kg Q 24 h
CAP	Vancomycin 1gm Q 12h and levofloxacin 750 mg Q 12 h (and gentamycin 7 mg/Kg Q 24 h if recent nursing home residence, recent antibiotic residence or bronchiectasis)
Meningitis	Vancomycin 1gm Q 12h and ceftriaxone 2 gm Q 12h (and ampicillin 2gm Q 4h if elderly or immunocompromised) after dexta 10 mg Q 6 h
UTI	Pip-Tazo 3.375 gm Q 6h and gentamycin 7 mg/Kg Q 24 h
Intraabdominal/ pelvic infection	Pip-Tazo 3.375 gm Q 6h and gentamycin 7 mg/Kg Q 24 h
Skin & soft tissue infection	Vancomycin 1gm Q 12h and Pip-Tazo 3.375 gm Q 6h and Clindamycin 900 mg Q 8h

Source control



Source Control Methods for Common ICU Infections[†]

Site	Interventions
Sinusitis	Surgical decompression of the sinuses
Pneumonia	Chest physiotherapy, suctioning
Empyema thoracis	Drainage, decortication
Mediastinitis	Drainage, debridement, diversion
Peritonitis	Resection, repair, or diversion of ongoing sources of contamination, drainage of abscesses, debridement of necrotic tissue
Cholangitis	Bile duct decompression
Pancreatic infection	Drainage or debridement
Urinary tract	Drainage of abscesses, relief of obstruction, removal or changing of infected catheters
Catheter-related bacteremia	Removal of catheter
Endocarditis	Valve replacement
Septic arthritis	Joint drainage and debridement
Soft tissue infection	Debridement of necrotic tissue and drainage of discrete abscesses
Prosthetic device infection	Device removal

[†]Adapted from Marshall, JC, Lowry, SF. Evaluation of the adequacy of source control. In: Sibbald, WJ, Vincent, JL, Clinical Trials for the Treatment of Sepsis. Springer-Verlag, Berlin, 1995 p 329.

Recombinant human activated Protein C



- **PROWESS** : Multicenter, international placebo controlled study, 1690 patients
aPC reduces 28 day mortality from sepsis/septic shock (30.8% → 24.7%), RR-19.8%, p-0.005
- **ADDRESS**: DrotAA should not be used in patients with single organ failure or an APACHE 2 score of 25
- **ENHANCE**: DrotAA given within 24 hrs of severe sepsis associated with better outcome.

aProtein C



- **Recommended** in patients with high risk of death (APACHE 2 \geq 25, sepsis induced multi-organ failure, sepsis induced ARDS).
- **Absolute contraindications**
 - Active internal bleeding
 - Hemorrhagic stroke within 3 months
 - Intracranial/intraspinal surgery
 - Severe head trauma within 2 months
 - Trauma with \uparrow risk of life threatening bleed
 - Presence of intradural catheter
 - Intracranial neoplasm/mass lesion
 - Known hypersensitivity

Corticosteroids



- **Annane et al JAMA, 2002** : Administration of corticosteroids \downarrow 28 day mortality 63% \rightarrow 53%, RR \downarrow 16%, $p=0.04$
- Time receiving vasopressors were also significantly shortened
- **Annane JAMA 2000, Cooper NEJM 2003**: Relative adrenal insufficiency present in 56%-77% of mechanically ventilated patients with fluid refractory septic shock
- **CORTICUS trial** underway

Corticosteroids



- **Recommendations**
- Intravenous corticosteroids(**hydrocortisone 200-300 mg/day for 7 days in 3-4 divided daily doses**) are recommended in patients with septic shock who despite adequate fluid replacement require vasopressor therapy to maintain BP
- Before starting corticosteroid treatment,ACTH stimulation test should be performed and corticosteroids continued only in patients with **inadequate adrenal response**(< 9µg ↑in ser. Cortisol after 250 µg ACTH)

Mechanical ventilation



- High tidal volumes that are coupled to high plateau pressure should be avoided in ALI/ARDS
- **Goal** : TV- 4-6 mL/Kg IBW; $P_{plat} < 30 \text{ cm H}_2\text{O}$
ARDS Net trial, NEJM2000
- **Permissive hypercapnia** allowed to minimize TV & P_{plat}
- **Minimum PEEP** adjusted based on oxygenation defect and guided by FiO_2 should be used
- **Semirecumbent position** with elevation of the head end of the bed to 45% should be used to prevent VAP
- **Weaning** : SBT → Extubation

Glucose control



- **Van der Berghe, NEJM 2001:** Significant improvement in survival when continuous insulin infusion used to maintain blood glucose between 80-110 mg%
- Maintain blood glucose < 150 mg%
- Monitor glucose every 30-60 min till glycemic goals met then 4 hrly
- Enteral feeding to be preferred

Sedation, analgesia, NM blockade



- Either intermittent bolus sedation or continuous infusion sedation to predetermined end points (sedation scales) with daily interruption of sedation with awakening and reinitiation are recommended
- Neuromuscular agents should be avoided if at all possible in the septic patient
- If used longer than the first hour of MV, either intermittent bolus or continuous infusion with monitoring of depth of block should be used

Renal replacement



- In ARF and in the absence of hemodynamic instability, CVVH and intermittent hemodialysis are considered equivalent
- Continuous hemofiltration offers easier management of fluid balance in hemodynamic unstable patients

DVT prophylaxis



- Severe sepsis patients should receive DVT prophylaxis with either low dose UFH or LMWH
- For septic patients who have a contradiction for heparin use, use of a mechanically prophylactic device (graduated compression stockings/ intermittent compression device) is recommended unless c/I by PVD
- In very high risk patients, combination of mechanical and pharmacologic therapy is recommended

SU prophylaxis



- It should be given to all patients with severe sepsis
- H₂ receptor blockers are more efficacious than sucralfate

Failed therapies



Cytokines

- Anti- TNF therapy
 - NORACEPT 1
 - INTERCEPT
 - NORACEPT 2
 - RAMCES
 - MONARCS
- IL-1R atagonists - No benefit

No benefit

Failed therapies



➤ **Anti inflammatory agents**

- Ibuprofen
- Prostaglandin E
- Pentoxifylline

➤ **Oxygen scavengers**

- N- acetyl cysteine
- Selenium

➤ **Drugs enhancing host defences**

- Immunoglobulins
- Granulocyte stimulating factor

Others

- GH
- Ketoconazole
- Polymyxin B
- Antithrombin III
- Tifagocin

New Therapies



- **Statins**- 19% RR reduction of risk of sepsis in patients with cardiovascular disease

Lancet Jan 2006

- **LPS vaccine** : Phase 2 trials
- **E5564**: Toll receptor antagonist ; Phase 2 trials
- **ATL 146e** : Synthetic adenosine ; Phase 1 trials

Future strategies

- HDL
- Anti- CD14 antibodies
- Extra-corporeal endotoxin removal
- Lipid A analogues
- MIF
- HMBG1
- Coupled plasma filtration and adsorption



THANK YOU

