Immunomodulation and Sepsis in Oncological Patients

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Objectives

• Immune dys-regulation in oncological septic patients

• Implementation of sepsis guidelines with special considerations to the pediatric oncologic patient
Shock in Oncology patient Population

- **Hypovolemia**
  - Hemorrhage
  - Pancreatitis
- **Cardiogenic**
  - Treatment-related
  - Myocarditis
  - Metabolic (Hyperkalemia, hypocalcemia)
- **Obstructive**
  - Cardiac tamponade
- **Distributive**
  - Anaphylaxis
  - Veno-occlusive disease
  - Sepsis

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Causes of Sepsis in oncology patients

• Defects in innate and adaptive host defense responses
  – Chemotherapy
  – Radiotherapy
  – Steroids
Host Defense
Innate Immunity

Wound

Skin barrier

Bacteria

Activation of serum complement

Phagocytosis and destruction of bacteria by macrophages and neutrophils

NK cells

Cytokines and Chemokines

Dendritic cells

Neutrophils

Macrophages

Blood vessel

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MICROBE RECOGNITION BY THE INNATE IMMUNE SYSTEM: TOLL-LIKE RECEPTORS
Host Defense
Adaptive Immunity

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Role of Neutrophils in Host Defense

Systemic Inflammation & Infection

Septic shock
Immunomodulation in the Oncologic Septic Patient

- Hold or decrease immuno-suppressive agents and chemotherapy drugs

- Pediatric use of G-CSF (ASCO 2006 Practice Guidelines)
  - Guided by clinical protocols
  - High risk patients with fever and neutropenia
    - Decreases the period of neutropenia
  - Potential risk is myeloid leukemia in children with ALL
Mortality Rates in Pediatric Septic Shock

**Design:**
- Retrospective review of septic shock patients 1 m-21 y.o. over 2 years period (1998-2000)
- 96 septic shock episodes
- 68 episodes (70.8%) were in patients with oncologic illness

**Results**
- Overall mortality was 13.5%; However,

*Kutko et al. Pediatr Critical Care 4:333-337, 2003*
PICU Outcome of Peds Oncology Patients in Septic Shock

• Rationale:
  – Cancer patients in septic shock thought to have poor outcome following PICU admission

• Design:
  – Single center retrospective review of 69 oncology patients and matched controls admitted to PICU with septic shock

• Results:
  – Mortality rate at PICU discharge were not different (15.9% vs. 11.6%; \( p = 0.61 \))
  – No difference in ventilator days and vasopressor use

• Conclusions:
  – PICU mortality in oncology patients in septic shock is not different than matched controls
  – Aggressive management is warranted


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Potential Reasons for Equal Survival in Oncologic vs. Non-Oncology Patients

• Early recognition
• Early removal of indwelling catheters when catheter-related sepsis was suspected
• Immunomodulation
  – Hold immuno-suppression
  – Use of G-CSF and GM-CSF
• Implementing surviving sepsis campaign guidelines and
• However, BMT patients continue to have a higher mortality
  – Related to the severe immunosuppressive regimen and immunologic dysregulation that patients experience following BMT
Resuscitation Bundle

1. Lactic acid
2. Blood culture
3. Antibiotics in 1 hr
4. Fluids 20 ml/kg as needed
5. Pressors
6. CVP > 8; ScvO$_2$ > 70%
## Outcome of Goal-Directed ScVO\(_2\) > 70%

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<tr>
<td><strong>CVP</strong></td>
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<td>Protocol</td>
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<tr>
<td><strong>ScVO(_2) &gt;70%</strong></td>
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<tr>
<td>Control</td>
<td>60%</td>
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<tr>
<td>Protocol</td>
<td>7.7</td>
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*Note: Diagram shows hospital mortality rates for severe sepsis and septic shock.*


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Pediatrics Outcomes Comparison With and Without monitoring ScVO$_2$

**Design:**
- Prospective randomized controlled study of pediatric septic shock treated with PALS guidelines (n=51) ± goal-directed ScVO$_2$ > 70% (n=51)
- 30-40% with heme-Onc underlying disease

**Results:**
- 28 day mortality decreased from 39.2% to 11.8%

**Limitations:**
- Patients in intervention group were significantly older (6.5 vs. 4.5 y.o.)
- High mortality rate of control group

Continuous ScVO₂ Monitoring

- If ScVO₂ < 70% despite CVP >8-12 and pressors:
  - Transfuse pRBCs to achieve a hematocrit of ≥30%
  - Administer an inotropic agent (milrinone or dobutamine)
Special Considerations in Oncologic Patients: ScVO$_2$ >70%

- Patients may have pre-existing drug-induced cardiomyopathy or chronic lung disease
  - Daunorubicin, 5-fluorouracil, cyclophosphamide → Cardiac toxicity
  - Busulfan, Bleomycin → Lung injury

- Transfuse with irradiated, CMV-ve pRBCs in the immuno-suppressed
Special Considerations in Oncologic Patients: Fever and Neutropenia

• Neutropenic patients with fever $>39.5^\circ$ and prolonged capillary refill time $>3$ sec. are at very high risk of developing life-threatening illnesses (*Ped Emergency Care* 20:79-84, 2004)

• Management of febrile neutropenic patients (2002 IDSA Guidelines)
  – Empiric antibiotics in first 30 min: mono- or combination therapy
  – Add antifungal $\pm$ change antibiotics if fever/neutropenia persists
  – G-CSF indicated if conditions worsens and neutropenia persists
Maintenance Bundle

1. Low dose steroids
2. Recombinant human activated protein C
3. Glucose control
4. ARDSnet recommendations

24 hrs.

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GUIDELINE: Steroids

• Use should be reserved to children with:
  – Catecholamine resistant shock
  – Proven or suspected adrenal insufficiency

• Oncologic patients are frequently on or have recently received steroids, and therefore, frequently need stress dosing of hydrocortisone during severe sepsis (4X physiological dose)
GUIDELINE: Recombinant human Activated Protein C (rhAPC)

- Pediatric studies were halted because of lack of efficacy and increased incidence of ICH in infants with severe sepsis

- Oncologic patients frequently have coagulopathy and low platelet counts → rhAPC is contraindicated
GUIDELINE: Glucose Control

• Hyperglycemia is associated with poor outcome in pediatric patients in septic shock (Ped Crit Care Med 9:636-640, 2007)
• Emerging evidence that tight glycemic control using exogenous insulin is helpful in PICUs (Lancet 373:520, 2009)
• Any such benefit will have to be balanced against the risk of hypoglycemia
• Glucose should be monitored closely if continuous infusion of insulin is used

• Oncologic patients are at increased risk of hyperglycemia because of use of exogenous steroids and risk of chemo-induced pancreatitis
GUIDELINE: Sepsis-Induced ARDS

• Low tidal volume; Maintain median inspiratory plateau pressure < 30 cm H₂O. Prophylactic high PEEP does not improve outcome

• Broncho-alveolar lavage procedure is recommended in immune deficient patients with lung infiltrates
Have Changes in Ventilation Practice Improved Outcome in Children with ALI?

- Retrospective study comparing MV practice between 1988-1992 (past) vs. 2000-2004 (Recent Group)
- During first 3 days: TV, PIP, & PaO\textsubscript{2} were significantly lower, while mean PEEP & PaCO\textsubscript{2} were significantly higher in Recent vs. Past group
- Multi-variate regression analyses immune deficiency, and TV associated with increased mortality

Conclusions:
- Change in ventilatory practice
- Relationship between TV & mortality in Pediatric ALI patients

Limitations:
- Other time-related modifications of care not accounted for

Albuali et al. Ped Crit Care Med 8:324, 2007
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Conclusions

• Oncological patients are immunosuppressed and have impaired innate and adaptive immunity that make them susceptible to infections

• Aggressive treatment in oncological septic patients is justified

• Treatment should be in accordance with Surviving sepsis campaign guidelines with special considerations