Oncologic Emergencies in the ICU

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Memorial Sloan Kettering Cancer Center
<table>
<thead>
<tr>
<th>Common</th>
<th>Uncommon (predicted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Neutropenic Septic Shock</td>
<td>• Pericardial Tamponade</td>
</tr>
<tr>
<td>• Cytokine Release Syndrome</td>
<td>• Acute Tumor Lysis</td>
</tr>
<tr>
<td>• Pulmonary Embolism</td>
<td>• SVC Syndrome</td>
</tr>
<tr>
<td>• Bleeding (hemoptysis, DIC, tumor invasion)</td>
<td>• Spinal Cord Compression</td>
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</tbody>
</table>

From my 10 yr experience at MSKCC
Neutropenic Septic Shock
What patient below meets criteria for sepsis?

- Neutropenic patient with a Sofa score of 4
- Neutropenic patient with 2 or more SIRS criteria
- Neutropenic pt with an elevated lactate level of 5.0
- Neutropenic pt with BP 70/40
The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.

### Flowchart

**Patient with suspected infection**
- **qSOFA ≥2?** (see A)
  - Yes → Assess for evidence of organ dysfunction
  - No → Sepsis still suspected? No → Monitor clinical condition; reevaluate for possible sepsis if clinically indicated
  - Yes → 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?
        - Yes → Septic shock
        - No → Monitor clinical condition; reevaluate for possible sepsis if clinically indicated

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

### SOFA Variables
- \( \text{PaO}_2/\text{FiO}_2 \) 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

*JAMA 2016;315(8):801-810*
...it was the host, not the germ, that drove the pathogenesis of sepsis.

Angus DC., & van der Poll, T. Critical Care Medicine, August 29, 2013
Management

Recognize & Act Quickly!

- IV antimicrobials within the **first hour** of recognition
- **Combination therapy** with **extended spectrum β-lactam** and either an aminoglycoside, fluoroquinolone or Azithromycin for **neutropenic pts** plus Vancomycin 1 g Q 12 hrs or Linezolid
- liposomal amphotericin B, voriconazole or micafungin with hx of HSCT and/or not responding to therapy (*fluconazole-abdominal surgery*)
- Antivirals (CMV, RSV) and Anti-PCP (steroids)
- Crystalloids/Colloids
- Norepinephrine or Epinephrine +/- Vasopressin
- GCSF
- Daily procalcitonin levels

Cytokine Release Syndrome & Neurotoxicity
Cancer Evolution Simplified

Normal Cell

Cancer cell

Killer T Cell

Normal Cell

Cancer cell

Normal Cell

Cancer cell
• Inflammation cascade
• Magnitude differs w/ each pt
• ↑ cytokines (IL-6)
GRADING ASSESSMENT

Grade 1 CRS
Fever, constitutional symptoms

Grade 2 CRS
Hypotension: responds to fluids or one low dose pressor
Hypoxia: responds to <40% O2
Organ toxicity: grade 2

Grade 3 CRS
Hypotension: requires multiple pressors or high dose pressors
Hypoxia: requires ≥ 40% O2
Organ toxicity: grade 3, grade 4 transaminitis

Grade 4 CRS
Mechanical ventilation
Organ toxicity: grade 4, excluding transaminitis
CRS

↑ tumor burden
↑ CAR-T cell proliferation
↑ dose of CAR-T infused

Severe CRS
Better outcomes
MSK Led trials

- Leukemia
- Lymphoma
- Ovarian
- Head and Neck
- Mesothelioma
- Gliomas (future?)

- Juno Rocket Trail - Phase II relapsed or refractory B cell acute lymphoblastic leukemia put on hold d/t severe CRS and neurotoxicity resulting in death
  - (removed Fludarabine as part of pretreatment and are only doing cyclophosphamide)
- Suicide gene
Cytokine Release Syndrome (CRS) Management Algorithm (for Grade ≥2)

- Hypotension SBP< 90 refractory to IVF challenge requiring vasopressors OR
- Respiratory distress/hypoxia requiring increasing supplemental oxygen or ventilatory support OR
- Acute coronary syndrome with positive troponin, clinically significant arrhythmia, and/or ECG changes

Tocilizumab 8mg/kg IV once

- Worsening CRS within 12 hours
  - Increasing vasopressors dose OR
  - Increasing oxygen requirement OR
  - Cardiac arrhythmia, evolving EKG

Dexamethasone 10-20mg IV q12h

- No clinical improvement ≥ 24 hours

- Clinical improvement < 24 hours
  - Decreasing vasopressor dose OR
  - Decreasing oxygen requirement

Observe

- Worsening CRS

Worsening Symptoms

- Start higher dose of corticosteroid
- Consider activating suicide gene if applicable

Clinical Improvement

- Taper over 3-5 days or longer if clinically indicated

Observe

- Worsening CRS

No clinical improvement ≥ 24 hours

- Clinical improvement < 24 hours

- Decreasing vasopressor dose OR
- Decreasing oxygen requirement

Observe
Neurological Toxicities Management Algorithm

- Neurological symptoms can range from confusion, altered level of consciousness, word finding difficulties, dysarthria, encephalopathy, and rarely to seizure.
- If the patient is experiencing CRS in addition to neurological symptoms, please refer to the CRS Management Algorithm to determine whether the patient will require additional measures to manage both symptoms.

Grade 1 or 2 Adverse Events, EXCEPT seizure

- Notify the PI or Co-PI immediately
- Consult with Neurology team
- Obtain MRI Brain or CT head
- Obtain diagnostic LP if feasible
- Consider EEG

Concomitant CRS of Grade ≥2 (Hypotension, hypoxia or dyspnea)

Please Refer to CRS Management Algorithm

Dexamethasone 20mg IV q24h or 10mg IV q12-24h

- Worsening Symptoms

Worsening Symptoms

- Consider higher dose of corticosteroid
- Consider high dose IVIG
- Consider activating suicide gene if applicable
Pulmonary Embolism
Pathophysiology of Major PE

BP = blood pressure; CO = cardiac output; LV = left ventricular; RV = right ventricular; TV = tricuspid valve.

Konstantinides et al. European Heart Journal, 2014
Presentation

Dyspnea (79%)

Tachypnea (57%)

Pleuritic pain (47%)

Leg edema, erythema, tenderness, palpable cord (47%)

Cough/ hemoptysis (43%)

Elevated Troponin?

In hemodynamically stable PE patients, elevated troponin levels increase mortality 6-fold.

Circulation 2007; 116: 427-433

Stein PD. Am J Med 2007; 120: 871-879
Treatment Algorithm for Suspected PE

1. Stabilize the patient
2. Anticoagulation contraindicated?
   - Yes
   - Diagnostic Eval (Echo)
     - IVC filter (consider AC)
   - No
Clinical suspicion for acute PE?

- High
  - Anticoagulation
- Moderate
  - Will diagnostic evaluation take longer than 4 hours?
    - Yes
      - Anticoagulation
    - No
      - No anticoagulation
- Low
  - Will diagnostic evaluation take longer than 24 hours?
    - Yes
      - Anticoagulation
    - No
      - No anticoagulation

Diagnostic evaluation

PE excluded
- Discontinue anticoagulants

PE confirmed
- Clinical severity warrant consideration of thrombolysis?
  - Yes
    - Thrombolytic therapy contraindicated?
      - No
        - Continue anticoagulants
      - Yes
        - Hold anticoagulation, administer thrombolytic agent, then resume anticoagulation
  - No
    - Clinical improvement?
      - Yes
        - Surgical or catheter embolectomy
      - No
        - Continue anticoagulants
Embolectomy

Surgical

- Operative mortality: 10-75%; 50-95% in pts who have had cardiopulmonary arrest
- Complications: ARDS, acute renal failure, mediastinitis, severe neurologic sequelae
- Critical to have an experienced and aggressive CT surgery team that can be rapidly mobilized

Catheter

- Transvenous insertion of embolectomy catheter → suction and pulverization by a high-speed rotor or fluid jet, and physical fragmentation with the catheter tip
- Limited studies, but survival rate ~70%-90%

Disseminated Intravascular Coagulation
DIC

- Persistent activation of the coagulation cascade
- Widespread (micro) vascular thrombosis
- Ongoing activation exhausts factors and platelets resulting in profuse bleeding

DX:
- Thrombocytopenia
- ↑ PT and APTT
- ↓ Fibrinogen
- ↑ Fibrin degradation products or (FDP) or fibrin split products

DIC: Cancer

• 10-15% of patients with metastasized tumors have evidence of DIC
  – Mucin-secreting adenocarcinomas; prostate, lung, breast, pancreas, stomach, bladder
• 15% of patients with acute leukemia have evidence of DIC (promyelocytic leukemia)
• Underreporting of DIC in cancer patients with sepsis
• DIC scoring systems not reliable in cancer patients

DIC: Management

• **Treat the cause**
  • PRBC (hgb >8d/dl), platelet transfusion (maintain platelet count > 20,000/ul (50,000 preferred))
  • Fibrinogen > 100
  • PT, APTT q 4-6 hrs
What is the difference between FFP and Cryoprecipitate?

- Cryoprecipitate is 10 times more concentrated than FFP
- Cryoprecipitate contains additional factors including fibrinogen and Von Wilbrand
- There is no difference except for manufacturer
- FFP does not include Factors II and X; Cryoprecipitate does
### FFP vs Cryoprecipitate

- **Primary indication for Cryo is Fibrinogen < 100**
- **Transfused in pools of 6-10 units which will increase fibrinogen 30-80 mg/dL**

<table>
<thead>
<tr>
<th></th>
<th>FFP</th>
<th>Cryo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factors</td>
<td>II, V, VII, VIII (70%), X, XII, XIII</td>
<td>II, V, VII, VIII, X, XII, XIII</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>vWB</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Pericardial Tamponade
Pericardial Tamponade

• A pericardial effusion occurs when the production of fluid exceeds the rate of resorption
• Tamponade: rapid accumulation of fluid in the pericardial space causing compression of the heart faster than the pericardium can distend
  • Rapid increase of only a very small volume
  • Slow increase over weeks may never lead to tamponade
• Malignant - 13-23%
  • Lung cancer #1 cause of malignant effusions
• Physical Signs: Increased JVD, peripheral edema, pulses paradoxus (Drop of 10-12 mmHg in SBP on inspiration), tachycardia, hypotension, respiratory failure, hemodynamic collapse

Pericardial Tamponade

- Echo Findings
  - Right atrial systolic collapse (RASC)
    - Right atrial inversion
    - About 100% sensitive, but low specificity (33-94% in some series)
  - Right ventricular diastolic collapse (RVDC)
    - 75-93% sensitive and 85-100% specific
Pericardial Tamponade: Surgical Management

- Pericardiocentesis
  - Remove 10-50 cc of fluid to see improvement
  - Should be ultrasound guided unless emergency
  - Low risk
- Pericardial Window (subxiphoid, transthoracic)
  - Pericardial drain

Pericardial Tamponade: Post-op

- Rapid improvement in hemodynamics
- Decrease O2 requirements
- Lasix (due to increase RA and RV filling pressures)
- Mild symptoms of right heart failure initially after surgery
  - Improves with diureses
  - Lasix often given in the OR to reduce this risk

- But some get worse...

Pericardial Tamponade

- **Paradoxical hemodynamic Instability**
  - Instead of improving, patients worsen after tamponade is released
  - Unknown etiology
  - Poor prognosis

- Review of MSKCC data on pericardial effusions over 5 years
  - Evaluated survival, predictive factors and incidence of paradoxical hemodynamic instability (PHI)
Paradoxical Hemodynamic Instability

- Occurred in 11% of all patients
  - 84% of patients in tamponade
  - Only 4% of those not in tamponade
- Acute cardiogenic pulmonary edema
- Hemodynamic instability
- Often normal findings on echo
  - Biventricular function is usually preserved
- Respiratory failure
- Median survival is 35 days
  - Majority do not survive their hospital stay
### TABLE 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>PHI (n = 19)</th>
<th>No PHI (n = 160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>54.0 ± 13.8</td>
<td>55.8 ± 15.3</td>
<td>.6</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (31.6%)</td>
<td>59 (36.9%)</td>
<td>.8</td>
</tr>
<tr>
<td>Female</td>
<td>13 (68.4%)</td>
<td>101 (63.1%)</td>
<td></td>
</tr>
<tr>
<td>Primary malignant disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>8 (42.1%)</td>
<td>70 (43.8%)</td>
<td>.9</td>
</tr>
<tr>
<td>Breast</td>
<td>5 (26.3%)</td>
<td>30 (18.8%)</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>2 (10.5%)</td>
<td>15 (9.4%)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>2 (10.5%)</td>
<td>11 (6.9%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (10.5%)</td>
<td>34 (21.2%)</td>
<td></td>
</tr>
<tr>
<td>Malignant cells identified, cytology or pathology</td>
<td>13 (68.4%)</td>
<td>65 (40.6%)</td>
<td>.03</td>
</tr>
<tr>
<td>Volume of pericardial fluid drained, mean ± SD, mL</td>
<td>674 ± 217</td>
<td>495 ± 231</td>
<td>.003</td>
</tr>
<tr>
<td>Preoperative atrial fibrillation</td>
<td>2 (10.5%)</td>
<td>9 (5.6%)</td>
<td>.3</td>
</tr>
<tr>
<td>Concurrent pulmonary embolism</td>
<td>2 (10.5%)</td>
<td>8 (5.0%)</td>
<td>.3</td>
</tr>
</tbody>
</table>

### TABLE 2. Echocardiographic findings

<table>
<thead>
<tr>
<th></th>
<th>PHI (n = 19)</th>
<th>No PHI (n = 160)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative echocardiogram</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tamponade present</td>
<td>16/19 (84%)</td>
<td>87/155 (56%)</td>
<td>.01</td>
</tr>
<tr>
<td>LV dysfunction, moderate-to-severe (EF &lt; 40%)</td>
<td>0/19 (0%)</td>
<td>2/115 (2%)</td>
<td>.7</td>
</tr>
<tr>
<td>Postoperative echocardiogram</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV dysfunction, moderate-to-severe (EF &lt; 40%)</td>
<td>2/18 (11%)</td>
<td>3/90 (3%)</td>
<td>.16</td>
</tr>
<tr>
<td>RV dysfunction, moderate-to-severe</td>
<td>4/17 (24%)</td>
<td>9/75 (12%)</td>
<td>.25</td>
</tr>
<tr>
<td>RV dilatation, moderate-to-severe</td>
<td>2/18 (11%)</td>
<td>3/83 (4%)</td>
<td>.22</td>
</tr>
</tbody>
</table>

PHI, Paradoxical hemodynamic instability; LV, left ventricular; EF, ejection fraction; RV, right ventricular.

### TABLE 3. Multivariate analysis of factors associated with PHI

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Malignant cells identified, cytology or pathology</td>
<td>5.8</td>
<td>1.2–28.3</td>
<td>.029</td>
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<tr>
<td>Volume of pericardial fluid drained, per mL</td>
<td>1.003</td>
<td>1.0001–1.005</td>
<td>.043</td>
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<tr>
<td>Presence of tamponade</td>
<td>4.1</td>
<td>0.8–20.3</td>
<td>.082</td>
</tr>
</tbody>
</table>

PHI, Paradoxical hemodynamic instability; OR, odds ratio; CI, confidence interval.

- Malignant cells
- Larger effusion
- Pre-op tamponade (did not reach significance)
Paradoxical Hemodynamic Instability

• Prevention of PHI
  – Slow drainage of fluid
    • Similar to re-expansion pulmonary edema phenomenon
  – Early prophylactic drainage of effusions
    • Only 4% of non-tamponade patients developed PHI
  – Massive hemodynamic support in the first 24-48 hrs
    • If no early improvement, unlikely to every recover
    • Must explain this all to the family

Wagner et al. JTCVS 2011
Acute Tumor Lysis
Acute Tumor Lysis

• Destruction of tumor cells with treatment → Metabolic derangements (Hyperkalemic, Hyperphosphatemic, Hyperuricemia and Hypocalcemic) and release of intracellular debris or spontaneous d/t rapid growth

• High Risk - Tumors with high growth fraction, bulky disease (leukemias, lymphomas, solid tumors (small cell lung, breast)

• Can occur 24-72 hrs after initiation of therapy

• Treatment (prevent AKI)
  – HYDRATION, HYDRATION, HYDRATION (200 ml/hr)
  – DIURESIS (urine output 150-200ml/hr)
  – Allopurinol (prophylaxis only) (inhibits production)
  – Rasburicase – catabolizes uric acid
    • Cannot use if pt has glucose-6-phosphate dehydrogenase (G6PD) deficiency (hemolytic anemia or methemoglobinemia)
  – Sodium bicarb - Urine alkalization - less favorable d/t nephropathy
  – Phosphate binding aluminum antacids - Sevelamer
Laboratory Tests
(serum potassium, phosphorus, calcium, creatinine, uric acid)

One abnormal test result

Estimate tumor burden and lysis risk

Small tumor burden

Low risk for lysis

Patient condition

No abnormalities

Minimal risk

No prophylaxis indicated

Low risk

Prophylaxis:
Hydration
± allopurinol
Close monitoring

Intermediate risk

Prophylaxis:
Hydration
Allopurinol or rasburicase
Cardiac monitoring
Lab tests every 8-12 hours

High risk

Prophylaxis:
Hydration
Rasburicase
Cardiac monitoring
Lab tests every 6-8 hours

Clinical TLS

Prophylaxis:
Hydration
Rasburicase
Cardiac monitoring/ICU
Lab tests every 4-6 hours

Two or more abnormal test results (Laboratory TLS)

Laboratory TLS plus one or more:
Serum creatinine ≥1.5 ULN
Cardiac arrhythmia
Seizure

Large tumor burden

High risk for lysis

Abnormalities:
Renal dysfunction
Dehydration
Low blood pressure
Acidosis
SVC Syndrome
Pathophysiology

• Occlusion of the SVC resulting in an increase in venous pressure which leads to venous stasis and engorgement

• Causes - Lung Cancer (Small Cell- 65-80%)
  – Catheters, thrombosis, aneurysm, vasculitis, sarcoidosis

• Symptoms: periorbital edema, facial fullness, dyspnea, cough, arm swelling, chest pain, dysphagia

• Late signs: Dysphagia and hoarseness due to the entrapment of the laryngeal nerve and laryngeal edema, Increasing intercranial pressure, cerebral edema, heart failure

• Treatment: chemotherapy, radiation, stenting, thrombosis

• Adjunct management: diuretics, steroids, avoid CVC insertion
Spinal Cord Compression
High Risk for SCC

• High Risk: Primary Intramedullary Tumors (Ependymoma, Astrocytoma, Glioma, Hemangioblastoma), Metastatic Intramedullary Tumors (Lymphoma, Neuroblastoma) Metastatic Bone/Epidural Tumors (Breast, Lung, Prostate, Renal, Myeloma, Thyroid, Sarcoma), vertebral fractures or intraspinal abscesses

• Symptoms: Pain $\rightarrow$ parethesias $\rightarrow$ motor loss $\rightarrow$ loss of proprioception

• Treatment: High dose corticosterioids, laminectomy, radiation, chemo
Case Study
Case Study - DAY 3

• 61 y/o man with CAD s/p MI, hyperlipidemia, HTN, Type II DM and AML s/p allo-BMT (September). Post transplant course significant for neutropenic sepsis, CMV viremia, with multiple hospital admissions- last admission d/c 3/3.
• Recently admitted to local hospital for c/o diarrhea . Found to have elevated LFTs. Concerned for C diff- treated him with metronidazole and transferred care to MSKCC on 3/24 where he was admitted to the BMT ward.
• Admission data: 38.3 C, 132/74, HR 110 bpm, 98% on RA
• ANC 1.3 1.8 18
• LFTs: AST- 275 , ALT 114, t bili 1.0
Case Study - DAY 2

- Doing OK
- Ongoing diarrhea
- Afebrile next day
- BP 98/60, HR 70, RR 18, 97% RA
- Imipenem, Linezolid (VRE surveillance rectal swab was +)
- Micafungin, posaconazole and acyclovir for fungal and viral prophylaxis
- D/C posaconazole d/t increased LFTs
- MRI to evaluate liver lesions

- ANC 1.4 × 10.2 × 18 × 31.9
  136 112 33 192
  3.6 12 1.9 3.12
  35.0
  58.7

LFTs: AST - 753, ALT 261, t bili 1.8, LDH 1041
Case Study - Day 3

• Continued to be febrile
• Ongoing nausea → vomited bile
• Started to become lethargic
• ICU consulted - BP 84/50, HR 116, SpO2 82%
  – Admitted
  – Intubated shortly after arrival
• MRI → periportal edema, lesions → ?fungal etiology

• LA - 7.5       1.8       18
  31.9
• 10.2

<table>
<thead>
<tr>
<th>146</th>
<th>121</th>
<th>31</th>
<th>149</th>
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<tbody>
<tr>
<td>4.3</td>
<td>11</td>
<td>2.3</td>
<td></td>
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</table>

LFTs: AST - 4400, ALT 741, t bili 4.2
ABG: 7.19/6/181/10
Case Study: Day 3 - ICU

• Admitted to ICU for...
  – 1. Hepatic failure
  – 2. Respiratory Failure
  – 3. Renal failure
  – 4. Coagulopathy

• Why?

• **Severe Neutropenic Sepsis**
  • Fluids but continued to drop his BP
  • Levophed->quickly titrated up
  • Attempted radial a-line but too hypotensive- femoral a line
  • Hematuria
• This is 2 hours after we attempted the right radial line...
Case Study: Day 3- ICU

- Upgraded his antibiotics
- Overnight need massive transfusion
- BP started to drop despite being on Levophed
- Bleeding now from everywhere!
Case Study: Day 3 - ICU

- 10.1 → (2 hrs) 8.0 → (30 mins) 6.9 → (5 hrs) → 3.7

- Looking back...
- Severe neutropenic septic shock with MSOF
- Fungal hepatitis (despite being on prophylaxis)
- DIC
Thank you!