Pharmacotherapy Considerations in the Management of Shock

Core Therapeutic Module Series

Planned by the ASHP Section of Clinical Specialists and Scientists.

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Pharmacotherapy Considerations in the Management of Shock

ACTIVITY FACULTY

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Dr. Szumita earned a Doctor of Pharmacy degree at Northeastern University in Boston, and he is dual board certified in pharmacotherapy and critical care pharmacy. He also is a fellow in the American College of Critical Care Medicine.

At BWH, Dr. Szumita has helped develop and is responsible for managing clinical programs aimed at optimizing pharmacotherapy and improving patient outcomes. As a practicing clinical pharmacist in critical care, he has an active role in bedside education, clinical research, and guideline development and implementation with a focus on glucose management, pain management for critically ill patients, agitation and delirium, hemodynamics in shock states, and inpatient glycemic management.

Dr. Szumita is Adjunct Associate Professor of Pharmacy at three colleges and helps coordinate 15 clinical rotations, training more than 100 students each year. He has more than 50 peer-reviewed publications, and he serves on several committees focused on improving clinical practice at the local and national level, including the program advisory board for the ASHP Critical Care Pharmacy Specialty Examination Review Course and serves on the taskforce to revise the Society of Critical Care Medicine Guidelines for the Management of Pain, Agitation, and Delirium.
Pharmacotherapy Considerations in the Management of Shock

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METHODS AND FORMAT

This activity is one module in a series and can be completed consecutively or individually in any order. This online activity consists of audio and slides for one presentation and an activity evaluation. Participants must view the entire presentation and course evaluation to receive continuing pharmacy education credit. Participants may print their official statements of continuing pharmacy education credit immediately. The estimated time to complete this activity is 1 hour.

TARGET AUDIENCE

This activity is intended for Board Certified Specialists in need of recertification credit.
Pharmacotherapy Considerations in the Management of Shock

ACTIVITY OVERVIEW

The purpose of this activity is to help participants prepare for a Board of Pharmacy Specialty (BPS) examination by providing a review of pertinent topics, practice of required skills, and references to helpful study resources. Faculty will discuss therapeutic management of issues and provide resources on the disease state. The activity will assist the participant identify areas needed for in-depth review.

LEARNING OBJECTIVES

At the conclusion of this application-based educational activity, participants should be able to
• Interpret diagnostic and/or laboratory tests, vital signs, and clinical presentation in order to differentiate types of shock (hypovolemic, distributive, cardiogenic)
• Compare and contrast the pharmacologic agents utilized in shock
• Determine the most appropriate therapy and monitoring based on patient-specific information and the most current guidelines for the treatment of shock
Pharmacotherapy Considerations in the Management of Shock

SHOCK

I. What is shock?
   - Poor oxygen delivery caused by hypoperfusion
     - Signs/laboratory markers of poor oxygen delivery
       ▪ change in mental status
       ▪ decreased urine output
       ▪ lactic acid >4 mmol/L
       ▪ hemodynamic instability
       ▪ mottled skin

II. Consequences of shock
   - Poor oxygen delivery leads to cell death
   - Cell death leads to organ damage
   - Organ damage leads to organ failure
   - Organ failure leads to multi-organ failure
   - Multi-organ failure leads to death

III. Hemodynamic parameters “normal values” (not necessarily the “goal” values)
   - Systolic blood pressure (SBP): 100–130 mm Hg
   - Mean arterial pressure (MAP): 80-100 mm Hg
   - Central venous pressure (CVP): 2-6 mm Hg
   - Pulmonary capillary wedge pressure (PCWP): 18 mm Hg
   - Systemic vascular resistance (SVR): 800–1200 dynes.sec/cm^5
   - Cardiac output (CO): 4-7 L/min
   - Cardiac Index (CI): 2.8-3.8 L/min/m^2

IV. Types of shock
   - Cardiogenic (low cardiac index in setting of volume overload)
     o primary cardiac output and fluid overload
   - Obstructive
     o blood delivery (oxygen) is blocked by an obstruction (compartment syndrome)
       ▪ not discussed in this program due to time constraints
   - Hypovolemic
     o primary fluid loss leading to decreased cardiac output
   - Distributive (low volume and SVR)
     o primary vasodilatory shock often coupled with low volume state

V. Pharmacology
   - Vasopressin-1 receptors
     o When activated cause vasoconstriction
Pharmacotherapy Considerations in the Management of Shock

- Alpha-1 receptors
  - When activated cause vasoconstriction

- Beta-1 receptors
  - When activated cause increase in inotropy and chronotropy

- Vasopressin-1 receptors
  - When activated cause vasoconstriction

- Renal dopamine receptors (D1 & D2)
  - When activated cause vasodilatation of renal artery and vein

- Phosphodiesterase-3 inhibitors
  - Increase inotropy and vasodilatation

VI. Inotropes and vasoactive agents

- Vasopressin
  - Vasopressin-1 receptors

- Phenylephrine
  - Alpha-1 receptors

- Norepinephrine
  - Mostly alpha-1 and some beta-1 receptors

- Dopamine
  - Dose-dependent receptor activation
    - low doses = dopamine D1 & D2 receptors
    - moderate doses = beta-1 and dopamine receptors
    - high doses = alpha-1, beta-1, and dopamine receptors

- Dobutamine
  - Beta-1 receptors and minor vasodilatation

- Milrinone
  - Inhibits the action of phosphodiesterase-3 leading to increased contractility and vasodilatation

VII. Crystalloids versus colloids for fluid resuscitation

- A controversial issue
  - Large randomized trial of albumin vs. saline (SAFE trial)
    - no significant difference in primary endpoint of death at 28 days
    - controversy persists for certain subgroups
      - trauma
      - severe sepsis
      - traumatic brain injury

VIII. Management of shock

- Cardiogenic shock due to ST-Segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI)
Pharmacotherapy Considerations in the Management of Shock

- Percutaneous coronary intervention (PCI) or surgical revascularization
- Fibrinolytic therapy (STEMI)
- Intra-aortic balloon pump (IABP) counterpulsation for patients who do not quickly stabilize with pharmacologic therapy
- Alternative left ventricular assist devices may be considered in patients with refractory cardiogenic shock

- Cardiogenic (cold and wet)
  - If MAP > 100 mm Hg
    - nitroglycerin and diuretics
  - If MAP 70-100 mm Hg and no signs of shock (end organ damage)
    - vasodilators
    - dobutamine
    - diuretics
    - If signs of shock – norepinephrine or dopamine
  - If MAP <70 mm Hg
    - norepinephrine or dopamine
      - norepinephrine preferred due to increased alpha-1 effect

- Hypovolemic
  - Reverse cause ASAP (even before administration of fluids or blood)
  - Fluids
    - controversies surrounding how much fluid, choice of fluid, when to initiate fluid therapy and blood pressure goal
    - colloid (blood) if blood loss
      - massive transfusion protocol
    - crystalloid if dehydrated

- Distributive (sepsis)
  - First line therapy
    - fluid 30 mL/kg monitor for signs of dynamic improvements
      - the guideline no longer supports static goals of CVP
    - if refractory to fluid challenge
      - add norepinephrine to maintain MAP ≥65 mm Hg
    - if refractory to norepinephrine
      - add a second vasoactive agent
        - vasopressin
        - epinephrine
    - if refractory to multiple or high-dose vasopressors
      - consider corticosteroids for relative adrenal insufficiency
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Core Therapeutic Module Series

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Disclosure

• I have nothing to disclose related to the content of this presentation

Learning Objectives

• Interpret diagnostic and/or laboratory tests, vital signs, and clinical presentation in order to differentiate types of shock (hypovolemic, distributive, cardiogenic)

• Compare and contrast the pharmacologic agents utilized in shock

• Determine the most appropriate therapy and monitoring based on patient-specific information and the most current guidelines for the treatment of shock

Patient Case Scenario 1

DM is a 37 year old male (90 kg) admitted to your cardiac care unit with ST-Elevation Myocardial Infarction (STEMI)

• Traditional Acute Coronary Syndrome (ACS) management
  – Medical
    – Reperfusion strategies

• On day 2 of hospital admission, mean arterial pressure hypotensive and tachycardic

Patient Case - Scenario 1

DM is a 37 year old male s/p STEMI

• Scenario - DM is cold-dry by the Forrester’s Acute Heart Failure Classification with:
  – Pulmonary capillary wedge pressure (PCWP) = 12 mmHg,
  – Cardiac index (CI) = 1.2 L/min/m²,
  – Mean arterial pressure (MAP) = 55 mmHg,
  – Serum creatinine SCR increased from 0.7 to 1.2 mg/dL in the past 6 hours.

• Initial management of the poor perfusion should be:

Patient Case - Scenario 2

DM is a 37 year old male s/p STEMI

• Scenario – DM is cold-wet by the Forrester’s Acute Heart Failure Classification with:
  – PCWP = 25 mmHg,
  – CI = 1.2 L/min/m²,
  – MAP = 85 mmHg with relatively cool extremities.

• Initial management of the poor perfusion with no signs of acute shock should be:
Patient Case - Scenario 3
DM is a 37 year old male s/p STEMI

- Scenario – DM is cold-wet by the Forrester’s Acute Heart Failure Classification with
  - PCWP = 25 mmHg,
  - CI = 1.2 L/min/m²,
  - MAP = 55 mmHg.

- Initial management of the poor perfusion should be:

Patient Case - Scenario 4

- AL is a 73 year old female (70kg) who presents to the ED complaining of “tearing stomach and back pain.” In the ED she became unresponsive and was intubated. CT scan revealed a ruptured thoracic aortic aneurysm w/ large left hemothorax. In the OR, chest tubes were placed to relieve the hemothorax resulting in 12 L of fluid loss:
  - Vital signs - HR 101 bpm,
  - BP 80/45 mmHg,
  - MAP 56 mmHg,
  - Urine output ~ 30 mL/hr,
  - Temp 96.9 °F.

- Initial management of the poor perfusion should be (after the intervention to stop the blood loss):

Patient Case - Scenario 5

- SB is a 36 year old male; mechanically ventilated (pressure support ventilation PEEP = 10) with an open abdomen secondary to compartment syndrome. On post-op day 3, SB is showing signs of shock:
  - HR 110 bpm,
  - Temp 102.3 °F,
  - WBC 6.63 to 0.75 x 10⁹/L (later peak @ 13.93 x 10⁹/L ),
  - BP 73/40 mmHg,
  - MAP 51 mmHg,
  - CVP 6 mmHg,
  - Urine output ~ 20mL/hr,
  - Micro – Gram stain positive for gram negative rods.

- Initial management of the poor perfusion should be:

Classification of Shock

- Cardiogenic
  - Pump failure
- Obstructive
  - Flow stopped or largely reduced
    - Clot or cardiac tamponade
- Hypovolemic
  - Decreased circulating volume
- Distributive
  - Vascular dysfunction/vasodilation

Differential Diagnosis of Shock Based on Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Pump Function</th>
<th>Preload</th>
<th>Afterload</th>
<th>Tissue Perfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Index</td>
<td>PCWP (8-12 mm Hg)</td>
<td>SVR (800-1400 dynes/sec/cm²)</td>
<td>Mixed SVO₂</td>
</tr>
</tbody>
</table>

- Hyperkinetic Shock
  - Normal
  - Low
  - Normal
  - Low

- Cardiogenic Shock
  - Low
  - High
  - High
  - Low

- Hypovolemic Shock
  - Normal
  - Low

- Vascular Dysfunction/ Vasodilation

Frank Starling Curves

Cardiac Output

At rest: Preload = Afterload

"Cardiac Function"
1. Preload
2. Inotropy
3. Afterload
4. Heart rate

CO = HR X SV

Agents Utilized in Shock Management

- Few controlled clinical trials have directly compared these agents or documented improved outcomes due to their use.

Potential Catecholamine Receptors

- Alpha-1
  - Vascular smooth muscle
- Alpha-2
  - Centrally located
- Beta-1
  - Heart
- Beta-2
  - Lungs

Vasopressor and Inotropic Support in Septic Shock: An Evidence-Based Review


Vasopressin

- MOA:
  - Antidiuretic hormone (ADH) - V2 receptor
  - Vasoconstriction - V1 receptor agonist
- Increases SVR through V1-mediated vasoconstriction
- May potentiate effects of norepinephrine
- Caution: doses > 0.03 units/min can cause tissue ischemia

**Vasopressin in Action**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Serum Level</th>
<th>Location</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1 (V1a)</td>
<td>10-200 pmol/L</td>
<td>Vascular smooth muscle</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>V2</td>
<td>&lt; 10 pmol/L</td>
<td>Renal collecting ducts</td>
<td>Fluid retention</td>
</tr>
<tr>
<td>V3 (V1b)</td>
<td>?</td>
<td>Anterior pituitary gland</td>
<td>Adrenocorticotropic hormone (ACTH) release</td>
</tr>
</tbody>
</table>

**Milrinone**

- Phosphodiesterase III inhibitor
- Inotropic & vasodilatory properties
- Dosage adjustment for renal dysfunction
- Caution: ventricular arrhythmias (less than dobutamine), hypotension

**Complications of Vasopressor Therapy**

- Tachycardia/ tachyarrhythmias
- Tachyphylaxis
- Reflex bradycardia (phenylephrine)
- ↓ myocardial oxygen supply
- ↑ myocardial oxygen consumption
- ↓ CO/CI
- Limb ischemia
- ↓ splanchnic blood flow
- Dopamine
  - Prolactin suppression
  - ↑ glucose
  - ↑ TSH
  - ↑ risk of ARF with low-dose

**Patient 1**

- DM is a 37 year old male admitted to your cardiac care unit with STEMI
- Traditional ACS management
  - Medical
  - Reperfusion strategies
- On day 2 of hospitalization, hypotensive and tachycardic

**Cardiogenic Shock**

- Decreased systemic CO in presence of adequate intravascular volume leading to tissue hypoxia
- Caused by
  - Left ventricular failure (typically MI and to a lesser extent advanced heart failure)
  - Right ventricular failure (pulmonary hypertension)
  - No ventricular dysfunction
    - Severe mitral regurgitation
    - Ventricular septal rupture
    - Pericardial tamponade
    - Cardiomyopathy

**ASHP Critical Care Pharmacy Specialty Examination Review Course**

- In depth coverage of acute coronary syndrome and acute heart failure
  - Complex Case: Acute Coronary Syndrome
Differential Diagnosis of Shock Based on Hemodynamic Parameters

<table>
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<tbody>
<tr>
<td>Cardiac Index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2.5-4.7 L/min/m²)</td>
<td>(8.12 mm Hg)</td>
<td>SVR (800-1400 dynes/s/cm²)</td>
<td>Mixed So₂</td>
<td></td>
</tr>
<tr>
<td>Distributive Shock</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Hypovolemic Shock</td>
<td>Normal</td>
<td>Low</td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td>Cardiogenic Shock</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>

Cardiogenic Shock: Definition and Diagnosis

- Systolic blood pressure of < 90 mmHg for > 1 hr that is:
  - Not responsive to fluid administration alone
  - Secondary to cardiac dysfunction
  - Associated w/ signs of hypoperfusion OR CI < 2.2 L/min/m² and PCWP > 18 mmHg

Treatment Strategies - Reperfusion

- PCI or surgical revascularization (class I evidence B)
  - SHOCK trial
- Fibrinolytic therapy (in absence of contraindication and not able to receive PCI or CABG) (class I evidence B)
- Intra-aortic balloon pump counterpulsation (IABP) for patients who do not quickly stabilize with pharmacological therapy (class IIa evidence B)
  - Was a class I recommendation in cardiogenic shock (2004); downgraded based on no improvement in survival in Intraaortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial
- Alternative left ventricular assist devices may be considered in patients with refractory cardiogenic shock (class IIb evidence B)

2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction

- Medical support with inotropes and vasopressor agents should be individualized and guided by invasive hemodynamic monitoring (ungraded)
- Use of dopamine may be associated with excess hazard (ungraded)

2016 European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure

- Fluid challenge is recommended as first-line treatment if no signs of overt fluid overload (I, LOE C)
- Dobutamine may be considered to increase cardiac output (IIb, LOE C)
- A vasopressor (norepinephrine preferably over dopamine) may be considered in patients who have cardiogenic shock, despite treatment with another inotrope, to increase blood pressure and organ perfusion (IIb, LOE B)
- Recommend to monitor ECG and blood pressure when using inotropic agents and vasopressors, as they can cause arrhythmia, myocardial ischemia, and in the case of levosimendan and PDE III inhibitors also hypotension. (I, LOE C)

ASHP Pharmacy Specialty Examination Review Course: BCPS and BCCCP

- In depth coverage of ACS for BCCCP review
  - Complex Case: Acute Coronary Syndrome
- In depth coverage of cardiovascular disease for BCPS review
  - Cardiovascular Disease modules
    - Primary prevention
    - Secondary prevention case #1 and #2

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2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction

- Intra-aortic balloon pump (IABP) may be useful for patients who do not quickly stabilize with pharmacological therapy (class IIa evidence B)

- LV assist devices may be considered in patients with refractory cardiogenic shock (class IIb evidence C)
  - Left ventricular assist device (LVAD)
  - Venoarterial extracorporeal membrane oxygenation (VA ECMO)

2016 European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure

- IABP is not routinely recommended in cardiogenic shock (III, LOE B)

- Short-term mechanical circulatory support may be considered in refractory cardiogenic shock depending on patient age, comorbidities and neurological function (IIb, LOE C)

Modality

- Venovenous (VV)
  - Drainage and return occur in the venae cavae/femoral vein
  - Provides oxygenation and removal of CO₂
  - Provides NO cardiac support

- Venoarterial (VA)
  - Drainage occurs in the venae cavae/right atrium and return occurs in the proximal ascending aorta or femoral artery
  - Provides oxygenation and removal of CO₂
  - Provides cardiac support

Forrester’s Acute Heart Failure Classification

<table>
<thead>
<tr>
<th>PCWP (mm Hg)</th>
<th>≤ 19 (Dry)</th>
<th>≥ 19 (Wet)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3. Hypovolemic (Cold-Dry)</td>
<td>4. Cardiogenic (Cold-Wet)</td>
</tr>
<tr>
<td></td>
<td>1. Stable (Warm-Dry)</td>
<td>2. Pulmonary Edema (Warm-Wet)</td>
</tr>
</tbody>
</table>

Indication by Modality

- Respiratory Support
  - VV ECMO

- Hemodynamic Support
  - VA ECMO

- Hypoxic Respiratory Failure
- Hypercapnic Respiratory Failure
- Cardiac Arrest
- Cardiogenic Shock
- Acute RV Failure
- Failure to wean CPB after surgery
- Bridge to transplant

Forrester’s Acute Heart Failure Classification

- Subset 1. Warm-Dry
  - Stable
  - No immediate hemodynamic management
  - Maximize HF regimen

- Subset 2. Warm-Wet
  - Pulmonary edema/congestion
  - Initial treatment diuretics, vasodilators, and oxygen

- Subset 3. Cold-Dry
  - Inadequate perfusion and hypovolemic
  - PCWP less than 15 mmHg – IV fluid volume warranted
  - PCWP 15-18 mmHg – depends on patient status and MAP

- Subset 4. Cold-Wet
  - Cardiogenic Shock
  - Treatment depends on MAP
Cardiogenic Shock Management by MAP

- MAP > 100 mmHg
  - Vasodilators (nitroglycerin) +/- Diuretics
- MAP 70-100 mmHg
  - Vasodilators +/- Inotropes (dobutamine) +/- Diuretics
  - If signs of shock
    - Pressors
- MAP < 70 mmHg
  - Norepinephrine is favored over epinephrine and dopamine

Comparison of Norepinephrine + Dobutamine (NE-D) with Epinephrine (E) in Cardiogenic Shock

Endpoints/Results
- HR ↑ transiently in epinephrine group
- Oliguria reversed in 10 vs 13 patients in epi vs NE-D (p = 0.05)
- Lactate ↑ in epi and ↓ in NE-D

10 patients survived in the epi group,
11 in the NE-D group

Comparison of Dopamine with Norepinephrine in the Treatment of Shock

- 8 centers in Europe
- MAP < 70 mmHg or SBP < 100 mmHg after “adequate volume resuscitation”
  - 1000 mL crystalloid
  - 500 mL colloid
- Signs of tissue hypoperfusion
- Excluded if received vasopressors for more than 4 hours
- Types of shock
  - 62% sepsis
  - 17% cardiogenic
  - 16% hypovolemic

Mortality Rates

<table>
<thead>
<tr>
<th>Setting/Time Frame</th>
<th>Dopamine (%)</th>
<th>Norepinephrine (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU</td>
<td>50.2</td>
<td>45.9</td>
<td>0.07</td>
</tr>
<tr>
<td>Hospital</td>
<td>59.4</td>
<td>56.6</td>
<td>0.24</td>
</tr>
<tr>
<td>28-day</td>
<td>52.5</td>
<td>48.5</td>
<td>0.1</td>
</tr>
<tr>
<td>6 month</td>
<td>63.8</td>
<td>62.9</td>
<td>0.71</td>
</tr>
<tr>
<td>12 month</td>
<td>65.9</td>
<td>63.0</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Predefined Subgroups

- Predefined Subgroup Analysis According to Type of Shock - Kaplan–Meier analyses 28-day mortality
  - No significant difference
    - septic shock (P = 0.19)
    - hypovolemic shock (P = 0.84)
    - Increased mortality in dopamine arm
      - cardiogenic shock (P = 0.03)
- Incidence (%) of arrhythmias
  - Dopamine 24.1% vs. NE 12.4%
    - P < 0.001

Predefined Subgroups

Hazard Ratio (95% CI)

- Type of shock
  - Cardiogenic
  - Hypovolemic
  - Septic
  - All patients
- Norepinephrine Better
- Dopamine Better

End of Document
Treatment Strategies - Hemodynamics

- Inotropes
  - Dobutamine
  - Milrinone
  - Levosimendan

- Inotrope/Vasopressor
  - Dopamine
  - Norepinephrine

- Vasodilators and Diuretics

“Assist functionality of the heart and vasculature”


Patient Case - Scenario 1
DM is a 37 year old male s/p STEMI

- DM is cold-dry by the Forrester’s Acute Heart Failure Classification
  - PCWP = 12 mmHg
  - CI = 1.2 L/min/m²
  - MAP = 55 mmHg,
  - SCr increased from 0.7 to 1.2 in the past 6 hours.

Question 1
Initial management of the poor perfusion should be:

a) Sodium chloride 500 mL IV X1, monitor MAP, and reassess signs of perfusion
b) Low “renal dose” dopamine to help the kidneys and reassess signs of perfusion
c) Treatment dose dopamine, monitor MAP and reassess signs of perfusion
d) Treatment dose dobutamine, monitor MAP and reassess signs of perfusion

Patient Case - Scenario 2
DM is a 37 year old male s/p STEMI

- DM is cold-wet by the Forrester’s Acute Heart Failure Classification with PCWP = 25 mmHg,
  CI = 1.2 L/min/m², MAP = 85 mmHg with relatively cool extremities.

Patient Case - Scenario 3
DM is a 37 year old male s/p STEMI

- DM is cold-wet by the Forrester’s Acute Heart Failure Classification with PCWP = 25 mmHg,
  CI = 1.2 L/min/m², MAP = 55 mmHg.
Question 3
Initial management of the poor perfusion should be:

a) Sodium chloride 500 mL IV X1, monitor MAP, and reassess signs of perfusion
b) Low "renal dose" dopamine to help the kidneys and reassess signs of perfusion
c) Treatment dose norepinephrine, monitor MAP and reassess signs of perfusion
d) Treatment dose dobutamine, monitor MAP and reassess signs of perfusion

Patient Case - Scenario 4

- AL is a 73 year old female (70kg) who presents to the emergency department (ED) complaining of “tearing stomach and back pain”

- In the ED she became unresponsive and was intubated

- A CT scan revealed a ruptured thoracic aortic aneurysm w/ large left hemothorax

Patient Case - Scenario 4

- In the operating room, chest tubes were placed to relieve the hemothorax, resulting in loss of 12 L (mostly blood)

- Vital signs
  - HR 101 bpm
  - BP 80/45 mmHg
  - MAP 56 mmHg
  - Urine output ~ 30 mL/hr
  - Temp 96.9 °F

Differential Diagnosis of Shock Based on Hemodynamic Parameters

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<th>Pump Function</th>
<th>Preload</th>
<th>Afterload</th>
<th>Tissue Perfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Index</td>
<td>PCWP (8-12 mm Hg)</td>
<td>SVR (800-1400 dynes.sec/cm²)</td>
<td>Mixed ( \text{O}_2 )</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>Normal</td>
<td>Low</td>
</tr>
</tbody>
</table>

Hypovolemic Shock

- Normal
- Low
- Normal
- Low

Hypovolemic Shock Management

- Rapid & significant loss of intravascular volume
  - Trauma
  - Dehydration (vomiting, diarrhea)
  - Burns
  - Surgery

Hypovolemic Shock

- Treatment
  - The goals of improving physiology
    - Restoring or maintaining normothermia
    - Minimizing coagulopathy
    - Stop bleeding!!
    - Establish blood pressure goal (penetrating wound, blunt trauma, brain injury)
    - Fluid challenge (controversies = type of fluid, timing, and amount)
      - More is not always better
  - First-line treatment – fluid resuscitation
  - Second-line treatment – vasopressor therapy

Blood Pressure Goals in Trauma Hypovolemic Shock

• Penetrating Trauma
  – Initial systolic blood pressure 50–70 mmHg
  – Once hemorrhage is controlled higher goal are accepted

• Blunt Trauma
  – Initial systolic blood pressure 80–90 mmHg
  – Once hemorrhage is controlled higher goal are accepted

• Brain injury
  – Initial systolic blood pressure 100–110 mmHg, MAP > 70 mmHg

![Image](Image 1)

Classes of Hemorrhagic Shock

<table>
<thead>
<tr>
<th>Class</th>
<th>Blood loss %</th>
<th>Heart rate – beats per minute</th>
<th>Blood pressure mmHg</th>
<th>Pulse pressure</th>
<th>Respiratory rate – breaths per minute</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;15</td>
<td>&lt;100</td>
<td>Normal</td>
<td>Normal</td>
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<tr>
<td>2</td>
<td>15–30</td>
<td>&gt;100</td>
<td>Decreased</td>
<td>Decreased</td>
<td>20–30</td>
</tr>
<tr>
<td>3</td>
<td>30–40</td>
<td>&gt;120</td>
<td>Decreased</td>
<td>Decreased</td>
<td>30–40</td>
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<tr>
<td>4</td>
<td>&gt;40</td>
<td>&gt;140</td>
<td>Decreased</td>
<td></td>
<td>&gt;40</td>
</tr>
</tbody>
</table>

![Image](Image 2)

Strategies for IV Fluid Resuscitation in Trauma Patient

- Major Trauma
  - 1–2 L of crystalloid or clear colloid fluid resuscitation

- Non-responders
  - No source control
  - Acidoic Low temperature
  - Poor response
  - Massive Transfusion Protocol

- Responders
  - Source control
  - Acidotic Low temperature
  - Transfuse Red blood Cells
  - Good response

- Judicious crystallized

![Image](Image 3)

Choice of Fluid

• Crystalloids
  – Sodium chloride 0.9%
  – Lactated Ringers
  – Hypertonic saline

• Colloids
  – Modified gelatins
  – Dextran
  – Albumin
  – Hydroxyethyl starches
  – Red blood cells

![Image](Image 4)

Crystalloids vs. Colloids

• Systematic reviews and meta-analysis
• No evidence that colloids are better than crystalloids for fluid resuscitation in all comers to ICU, trauma, burns or following surgery
  – Mortality
  – Pulmonary edema
  – Length of stay
  – Crystalloid resuscitation may associated with lower mortality than colloids in trauma patients.
• Larger well-designed randomized trials are needed to achieve sufficient power to detect potentially small differences in treatment effects if they truly exist

![Image](Image 5)

Massive Transfusion Protocol

• Typically 1:1:1 ratio (controversial)
  – Red blood cells
  – Platelets
  – Fresh frozen plasma

• Additional management patient-specific
  – Blood factors
  – Antifibrinolitics
  – Calcium
  – Blood warmers
  – Electrolyte management

![Image](Image 6)
A Comparison of Albumin and Normal Saline for Fluid Resuscitation in the Intensive Care Unit – SAFE Trial (not necessarily hypovolemic shock)

- Multicenter, randomized, double-blind trial to compare the effects of albumin vs. normal saline in a heterogeneous population of patients in the ICU
  - Albumin 4% or Normal Saline
- Use of either fluid for resuscitation resulted in similar outcomes:
  - 28-day mortality
  - ICU length of stay
  - Hospital length of stay
  - Length of mechanical ventilation
  - Days of renal replacement therapy


SAFE Trial Predefined Subgroups - 2004

- No significant difference in any of the predefined subgroups
- Controversy persists for certain subgroups
  - trauma
  - severe sepsis
  - traumatic brain injury

Hydroxyethyl Starch (HES) or Saline for Fluid Resuscitation in Intensive Care (CHEST trial)

- 7000 patients
- 6% HES (130/0.4) or normal saline:
  - No significant difference in 90-day mortality RR 1.06; P=0.26
- 6% HES 130/0.4 group had a significantly greater need for renal-replacement therapy than normal saline group


Cumulative Incidence of Death Within 28 days- 2013 CRISTAL Trial

- The CRISTAL – Hypovolemic shock
  - 2857 patients received colloids versus crystalloids (any/4L, unblinded)
  - RR for 28-day mortality was 0.96 with P=0.26.
- However, 90-day mortality was significantly lower among patients receiving colloids
- These findings are theory building at this time


Volume liberal or restrictive in hypovolemic shock during trauma?

- Systematic reviews and meta-analysis
  - 3 RCT
  - 7 observational trials
- Initial liberal fluid resuscitation strategies may be associated with higher mortality than restrictive strategies
- Larger well-designed randomized trials are needed to achieve sufficient power to detect potentially small differences in treatment effects if they truly exist


Timing and Volume of Fluid Resuscitation in Bleeding Trauma Patients

- No RCTs to make any real recommendation
  - Cochrane Database
- Liberal use of isotonic crystalloid to correct hypotension
  - The Advanced Trauma Life Support (ATLS) protocol of the American College of Surgeons
    – Based on no RCTs

Vasopressor Options in Hypovolemic Shock – to Increase SVR

- Would depend on patient factors
- Guidelines do not have a specific recommendation

Patient Case - Scenario 4

AL is a 73-year-old female (70 kg) who presented to the emergency department (ED) complaining of "tearing stomach and back pain." In the ED she became unresponsive and was intubated. A CT scan revealed a ruptured thoracic aortic aneurysm with a large left hemothorax. In the operating room chest tubes were placed to relieve the hemothorax, resulting in a loss of 12 L of fluid. Vital signs included HR 101 bpm, BP 80/45 mmHg, MAP 56 mm Hg. Urine output was ~ 30 mL/hr. Temp = 96.9°F.

Question 4

Initial management of the poor perfusion should be (after the intervention to stop the blood loss):

a) Sodium chloride 500 mL IV X1, monitor MAP and Hgb, and reassess for signs of perfusion, repeat fluid challenge as needed, and consider blood transfusion
b) Low "renal dose" dopamine to help the kidneys and reassess signs of perfusion
c) Treatment dose dopamine, monitor MAP and reassess signs of perfusion
d) Treatment dose dobutamine, monitor MAP and reassess signs of perfusion

Patient Case - Scenario 5

SB is 36 year old male (85 kg) with an open abdomen secondary to compartment syndrome

- On day 3 of hospital stay SB is again showing signs of shock

Patient Case - Scenario 5

- HR 110 bpm
- Temp 102.3°F
- WBC 6.63 to 0.75 x10⁹/L (later peak @ 13.93 x10⁹/L)
- BP 73/40 mmHg
- MAP 51 mmHg
- CVP 6 mmHg
- Urine output ~ 20mL/min
- Micro – Gram stain positive for gram negative rods

Distributive Shock

- Sepsis
- Activation of systemic inflammatory response
- Toxic shock syndrome
- Drug/toxin reactions
- Addisonian crisis
- Myxedema coma
- Neurogenic shock
Differential Diagnosis of Shock Based on Hemodynamic Parameters

<table>
<thead>
<tr>
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<th>Preload</th>
<th>Afterload</th>
<th>Tissue Perfusion</th>
</tr>
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<tbody>
<tr>
<td>Cardiac Index (2.5-4.7 L/min/m²)</td>
<td>PCWP (8-12 mm Hg)</td>
<td>SVR (800-1400 dynes.sec/cm²)</td>
<td>Mixed SVO₂</td>
</tr>
</tbody>
</table>

- **Distributive Shock**: High Low Low Low
- **Hypovolemic Shock**: Normal Low Normal Low
- **Cardiogenic Shock**: Low High High Low

---

ASHP Critical Care Pharmacy Specialty Examination Review Course

- In depth coverage of Sepsis
  - Complex Case: Sepsis

---

Sepsis Definitions

1. **Surviving Sepsis Campaign**
   - 2012
   - Refined in 2016
2. The Third International Consensus Definitions for Sepsis and Septic Shock “Sepsis-3”
3. **SEP-1**: CMS Core Measure

---

Surviving Sepsis Campaign Definitions - 2012

<table>
<thead>
<tr>
<th>Inflammatory variables</th>
<th>Hemodynamic variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature &gt;38.5°C or &lt;36°C</td>
<td>Arterial hypotension (SBP &lt; 90, MAP &lt; 70)</td>
</tr>
<tr>
<td>Heart rate &gt; 90/min</td>
<td>Organ dysfunction variables</td>
</tr>
<tr>
<td>Respiratory rate &gt;20 breaths/min</td>
<td>Arterial hypoxemia</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>Acute oliguria</td>
</tr>
<tr>
<td>Significant clinical or biochemical abnormality</td>
<td>Creatinine increase</td>
</tr>
<tr>
<td>Hyperglycemia in absence of diabetes</td>
<td>Coagulation abnormalities</td>
</tr>
<tr>
<td>Inflammatory variables</td>
<td>Hyperbilirubinemia</td>
</tr>
<tr>
<td>Lactate &gt;2 mmol/L</td>
<td>Tissue Perfusion Variables</td>
</tr>
<tr>
<td>Mixed venous blood gas &lt;70% oxygen saturation</td>
<td>Hypervolemic/hypertensive</td>
</tr>
<tr>
<td></td>
<td>Sepsis-associated organ dysfunction or shock</td>
</tr>
<tr>
<td></td>
<td>Septic shock – Sepsis-induced hypotension persisting despite adequate fluid resuscitation</td>
</tr>
</tbody>
</table>

---

The Third International Consensus Definitions for Sepsis and Septic Shock “Sepsis-3” and also the Surviving Sepsis Campaign Definition - 2016

- **Sepsis**
  - Life-threatening organ dysfunction due to a dysregulated host response to infection
    - Organ dysfunction can be identified as an acute change in total Sequential Organ Failure Assessment (SOFA) score ≥ 2 points consequent to the infection.
    - The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction.
    - A SOFA score ≥ 2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection.
  - **Severe sepsis**
    - No longer used

---

The Third International Consensus Definitions for Sepsis and Septic Shock “Sepsis-3” and also the Surviving Sepsis Campaign Definition - 2016

- **Septic shock**
  - Subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities substantially increase mortality
  - Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasoressors to maintain MAP 65 mm Hg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation
  - With these criteria, hospital mortality is in excess of 40%

- **Important note**: quick sequential organ failure assessment (qSOFA) is NOT a part of the definition
Sequential Organ Failure Assessment Score

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<tr>
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<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td>PaO2/FiO2 mmHg</td>
<td>≥ 400</td>
<td>≥ 300</td>
<td>≥ 200</td>
<td>≥ 100</td>
</tr>
<tr>
<td>Platelets x 10^9/µL</td>
<td>≥ 150</td>
<td>≥ 100</td>
<td>≤ 50</td>
<td>≤ 20</td>
</tr>
<tr>
<td>Bilirubin mg/dL</td>
<td>&lt; 1.2</td>
<td>1.2-1.9</td>
<td>2-5.9</td>
<td>&gt;12</td>
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</tbody>
</table>

Cardiovascular (simplified)

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Arterial Pressure</td>
<td>&gt; 70 mmHg</td>
<td>&lt; 70 mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose pressors</td>
<td>Medium dose pressors</td>
<td>High dose pressors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Scale score</td>
<td>15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
</tr>
<tr>
<td>Creatinine mg/dL/Urine output mL/day</td>
<td>&lt;1.2/ NA</td>
<td>1.2-1.9/ NA</td>
<td>2-3.4/ NA</td>
<td>3.5-4.9/ NA</td>
</tr>
</tbody>
</table>

Sepsis Screening

- Suspected/documented infection plus:
  - Acute increase of ≥ 2 Sequential [Sepsis-Related] Organ Failure Assessment (SOFA) score points
- Quick SOFA (qSOFA):
  - RR ≥ 22 breaths/min
  - Altered mentation
  - SBP ≤ 100 mmHg
  - If ≥ 2 qSOFA points present, evaluate for organ failure

qSOFA vs. SIRS

- qSOFA provides simple bedside criteria to identify adult patients who are likely to have poor outcomes without the need for laboratory data
- qSOFA trying to capture the deleterious response to an infection
- SIRS probably not sufficiently specific
  - Many ICU patients have 2 SIRS criteria

qSOFA Utility

- qSOFA is screening criteria for patients at risk of sepsis
- Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside with qSOFA
  - Inpatient hospital wards
  - Emergency department
- Two of three qSOFA criteria for risk of sepsis
  - Altered mental status
  - Glasgow Coma Scale < 15
  - Fast Respiratory Rate
  - ≥ 22 breaths per minute
  - Low blood pressure
  - Systolic blood pressure ≤ 100 mmHg

Septic Shock Screening

- Sepsis plus:
  - Persisting hypotension requiring vasopressors to maintain MAP ≥ 65 mm Hg
  - AND
  - Blood lactate >2 mmol/L despite adequate volume resuscitation

SEP-1: CMS Core Measure

- CMS Core Measure
  - More complicated/controversial than many traditional measures
- Sepsis definition according to SEP-1:
  - Suspected source of infection, 2 SIRS criteria, and evidence of end-organ dysfunction
- Septic shock definition according to SEP-1:
  - Initial lactate ≥ 4 mmol/L OR evidence of hypotension documented in the first hour following the completion of a 30 mL/kg IV fluid bolus

Page 22 of 32
SEP 1 Requirement
- To be completed within 3 hours after time of presentation:
  1. Measure lactate level
  2. Obtain blood cultures prior to administration of antibiotics
  3. Administer broad-spectrum antibiotics
  4. Administer 30 ml/kg crystallized for hypotension or lactate ≥4 mmol/L.
     - “Time of presentation” is defined as the time of earliest chart annotation consistent with all elements of severe sepsis or septic shock ascertained through chart review.
- To be completed within 6 hours after time of presentation:
  5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a MAP ≥ 65 mmHg
  6. In the event of persistent hypotension after initial fluid administration (MAP < 65 mmHg) or if initial lactate was ≥4 mmol/L, reassess volume status and tissue perfusion and document findings according to next slide
  7. Repeat measurement of lactate if initial lactate elevated

60-day mortality
N (%) | Risk Ratio | 95% CI | P Value
--- | --- | --- | ---
56.9 | 0.67 (0.46-0.96) | 0.03

28-day mortality
N (%) | Risk Ratio | 95% CI | P Value
--- | --- | --- | ---
49.2 | 0.60 (0.46-0.98) | 0.04

In-hospital mortality
N (%) | Risk Ratio | 95% CI | P Value
--- | --- | --- | ---
30.5 | 0.58 (0.38-0.87) | 0.009

SEP 1: Fluid Resuscitation: Post-assessment
- Either
  - Documented repeat focused exam (after fluids) by licensed independent practitioner, including vital signs, cardiopulmonary exam, capillary refill, pulse and skin findings
  - Or documentation of two of the following:
    - CVP measurement
    - Central venous oxygen saturation (ScvO2) measurement
    - Bedside cardiovascular ultrasound
    - Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge

Early Goal Directed Therapy
(landmark Trial)
- Population: 263 patients entering ED w/ severe sepsis or septic shock
- Intervention: Received either (for 6 hr):
  - Standard therapy
  - Early goal-directed therapy
- Endpoints:
  - In-hospital, 28- and 60-day mortality
  - Hemodynamic variables
  - Lab values

Early Goal Directed Therapy
<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard</th>
<th>EGDT</th>
<th>Relative Risk</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td>59 (46.5)</td>
<td>38 (30.5)</td>
<td>0.58 (0.38-0.87)</td>
<td>0.009</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>19 (30.0)</td>
<td>9 (14.9)</td>
<td>0.46 (0.21-1.03)</td>
<td>0.06</td>
</tr>
<tr>
<td>Septic shock</td>
<td>40 (56.8)</td>
<td>29 (42.3)</td>
<td>0.60 (0.36-0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>Sepsis syndrome</td>
<td>44 (63.0)</td>
<td>35 (51.5)</td>
<td>0.66 (0.42-1.04)</td>
<td>0.07</td>
</tr>
<tr>
<td>28-day mortality</td>
<td>61 (49.2)</td>
<td>40 (33.3)</td>
<td>0.58 (0.39-0.87)</td>
<td>0.01</td>
</tr>
<tr>
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<td>70 (56.9)</td>
<td>50 (44.3)</td>
<td>0.67 (0.46-0.96)</td>
<td>0.03</td>
</tr>
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</table>

Landmark EGDT Trials
<table>
<thead>
<tr>
<th>Rivers</th>
<th>ProCESS</th>
<th>ARISE</th>
<th>ProMISe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year Published</td>
<td>2005</td>
<td>2013</td>
<td>2014</td>
</tr>
<tr>
<td>Design</td>
<td>Single-center, USA</td>
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<td>Multicenter, AUS</td>
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<tr>
<td>Patients</td>
<td>1813</td>
<td>1305</td>
<td>1305</td>
</tr>
<tr>
<td>Hospital length of stay (days)</td>
<td>18.1 - 18.9</td>
<td>17.9 - 18.1</td>
<td>18.0 - 19.0</td>
</tr>
<tr>
<td>Sepsis severity score</td>
<td>6.8 - 7.7</td>
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<td>APACHE II score</td>
<td>19.4 - 21.6</td>
<td>20.2 - 20.6</td>
<td>21.5 - 21.9</td>
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<tr>
<td>ICU in hospital</td>
<td>51 - 59</td>
<td>18.1 - 18.7</td>
<td>16.1 - 18.6</td>
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</table>

Early Goal Directed Therapy
<table>
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<tr>
<th>Variable</th>
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<td>0.03</td>
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</table>
### Landmark EGDT Trials

<table>
<thead>
<tr>
<th>Name</th>
<th>ProCESS</th>
<th>ASSE</th>
<th>ProMISe</th>
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<tr>
<td><strong>Intravenous</strong></td>
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<td><strong>Resuscitation Goal</strong></td>
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<td>Heart rate</td>
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<td><strong>Additional</strong></td>
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<td>Vasopressors</td>
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<tr>
<td><strong>Blood Products</strong></td>
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<td>Red cell transfusion</td>
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<td>Platelet transfusion</td>
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<tr>
<td><strong>Infection</strong></td>
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<td>Antibiotic</td>
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<tr>
<td>Ciprofloxacin</td>
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<td>Metronidazole</td>
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### Sepsis Management

- **Hemodynamics**
  - Fluids
  - Vasopressors & inotropic therapy
  - Monitoring for target resuscitation goals
- **Infection**
  - Timing of Antibiotic therapy
- **Empiric**
  - Combination
- **Targeted (if known source)**

### Fluid Therapy

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystalloids (sodium chloride, lactated rings, etc)</td>
<td></td>
</tr>
<tr>
<td>Inexpensive</td>
<td>Ease of administration</td>
</tr>
<tr>
<td>May increase risk for pulmonary edema</td>
<td>Acid base disorder</td>
</tr>
<tr>
<td>Colloids (albumin, starches, blood, etc)</td>
<td></td>
</tr>
<tr>
<td>Less volume</td>
<td>May have advantages in outcomes is certain subpopulations</td>
</tr>
<tr>
<td>Expensive</td>
<td>Side effect profile specific to product/agent</td>
</tr>
</tbody>
</table>

### 2016 Surviving Sepsis Campaign: Initial Resuscitation

- Sepsis and septic shock are medical emergencies and treatment beings immediately - best practice statement - BPS
- 30 mL/kg of IV crystalloid fluid be given with first 3 hours of sepsis-induced hypoperfusion - strong recommendation, low quality of evidence (QOE)
- Additional fluids guided by frequent assessment - BPS
- Further hemodynamic assessment to determine type of shock if not clear - BPS
- Dynamic variables be used in lieu of static variables to predict fluid responsiveness when available – weak recommendation, low QOE
- Initial target MAP of 65 mmHg in septic shock requiring vasopressors – strong recommendation, moderate QOE
- Guiding resuscitation to normalize lactate when lactate is elevated - weak recommendation, low QOE

### 2016 Surviving Sepsis Campaign: No Longer Support “Static” Goals from 2012 Guideline

- Goals no longer used:
  - CVP 8 – 12 mmHg
  - Urine output > 0.5 mL/kg/hr
  - ScvO2 70% or SVO2 65%

### 6 % Hydroxyethyl Starch 130/0.4 versus Ringer’s Acetate in Severe Sepsis

- Compared with Ringer’s acetate, 6% HES 130/0.4 associated with significantly:
  - Higher risk of death (90-day)
  - Greater need for renal replacement therapy

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**6% Hydroxyethyl Starch 130/0.4 versus Ringer’s Acetate in Severe Sepsis**

SAFE Trial Predefined Subgroups - 2004

- No significant difference in any of the predefined subgroups
- Controversy still exists for certain subgroups
  - trauma
  - severe sepsis
  - traumatic brain injury

Impact of Albumin Compared to Normal Saline on Organ Function and Mortality of Patients with Severe Sepsis

- Predefined subgroup of original SAFE trial – severe sepsis
  - 1,218 patients
- Unadjusted RR of death for albumin vs. normal saline
  - 0.87 (0.74–1.02)
- Multivariate logistic regression analysis: adjusted odds ratio for death for albumin versus normal saline (75% of the 1,218 patients):
  - 0.71 (95% CI: 0.52–0.97; p = 0.03)

Fluid Recommendations in Severe Sepsis and Septic Shock

- Fluid challenge technique be applied where fluid administration is continued as long as hemodynamic factors continue to improve – BPS
- Crystalloids as the initial fluid of choice and subsequent intravascular volume replacement in patients with sepsis and septic shock - strong recommendation, moderate QOE
- Either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock - weak recommendation, low QOE
- Albumin in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock, when patients require substantial amounts of crystalloids: weak recommendation, low quality of evidence
- Recommend against the use of hydroxyethyl starches - strong recommendation, high QOE
- Crystalloids over gelatins - weak recommendation, low QOE
- Conservative fluid strategy with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion – strong recommendation, moderate QOE

Question 5

Dopamine vs. NE

Compared with norepinephrine in patients with shock, dopamine was associated with:

a) Significantly increased mortality in all comers
b) Significantly decreased mortality in all comers
c) No significant difference in mortality in all comers, but a lower incidence of new-onset cardiac arrhythmias
d) No significant difference in mortality in all comers, but a higher incidence of new-onset cardiac arrhythmias

Norepinephrine vs. Dopamine in Septic Shock

- Few data available to support the use of one vasopressor versus another
- Both NE and Dopamine have properties that increase CO as well as SVR
  - Dopamine has greater effect than NE on β1-receptors (thus CO)
  - NE has greater effect than dopamine on α1-receptors (thus SVR)
- Dopamine effects not predictable, associated with greater side effects than NE

Norepinephrine or Dopamine for the Treatment of Hyperdynamic Septic Shock

Hyperdynamic Septic Shock (n=32)

DA 2.5 to 25 mcg/kg/min (n=16)
- Responders 9/16 patients
- 9/10 "responders" to NE

NE 0.5 to 5 mcg/kg/min (n=16)
- Responders 10/16 patients

Does dopamine administration in shock influence outcomes?

**Population**
1,058 adult ICU patients with shock
- 50% medical
- 50% surgical

**Intervention**
- Catecholamine use
  - NE 80%
  - Dopamine 35.4%
  - Both 11.6%
  - Epinephrine 23.3%
  - Dobutamine 33.9%

**Endpoint**
ICU, Hospital, & 30-day Mortality


Dopamine vs. NE

- No significant difference in the rate of death when used as the first-line vasopressor agent
- Dopamine is associated with a greater risk of adverse events


Predefined Subgroups

- Predefined Subgroup Analysis According to Type of Shock - Kaplan–Meier analyses 28 day mortality
  - No difference
    - septic shock (P = 0.19)
    - hypovolemic shock (P = 0.84)
  - Increased mortality in dopamine arm
    - cardiogenic shock (P = 0.03)
- Incidence of (%) Arrhythmias
  - Dopamine 24.1% vs. NE 12.4%
  - P < 0.001


Vasopressin deficiency?

- Low fixed-dose vasopressin infusion (0.01–0.04 units/min) in septic shock:
  - Restores depleted physiologic levels
    - 0.04 units/min ~150–290 pg/mL
  - Spares high dose catecholamine
  - ↑ MAP
  - ↑ SVR
  - ↑ Urine output in most studies


Vasopressin and Septic Shock Trial (VASST)
- Multicenter, randomized, double-blind trial
- Septic shock receiving norepinephrine 5 mcg/min
  - receive either low-dose vasopressin (0.01 to 0.03 units/min) or norepinephrine (5 to 15) mcg per min
- The primary end point was the mortality rate 28 days after the start of infusions

Vasopressin Levels in the VASST (29.8 % of patients)

<table>
<thead>
<tr>
<th>Time</th>
<th>Norepinephrine group (pg/mL)</th>
<th>Vasopressin group (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3.2</td>
<td>3.2</td>
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<tr>
<td>6 hours</td>
<td>&quot;no change&quot;</td>
<td>73.6</td>
</tr>
<tr>
<td>24 hours</td>
<td>&quot;no change&quot;</td>
<td>98.0</td>
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</table>

Survival – All Patients

<table>
<thead>
<tr>
<th>Time</th>
<th>Norepinephrine group (%)</th>
<th>Vasopressin group (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-day mortality</td>
<td>39.3</td>
<td>35.4</td>
<td>0.26</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>49.6</td>
<td>43.9</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Survival – Severity of Shock

<table>
<thead>
<tr>
<th>Time</th>
<th>Norepinephrine group (%)</th>
<th>Vasopressin group (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-day mortality</td>
<td>35.7</td>
<td>26.5</td>
<td>0.05</td>
</tr>
<tr>
<td>90-day mortality</td>
<td>46.1</td>
<td>35.8</td>
<td>0.04</td>
</tr>
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Vasopressors and Inotropes in Septic Shock
- First line agent = Norepinephrine (NE) – strong recommendation, moderate QOE
- When an additional agent is needed to maintain adequate MAP
  - Vasopressin (up to 0.03 units/min) – weak recommendation, moderate QOE
  - Epinephrine – weak recommendation, low QOE
- Vasopressin 0.03 units/min can be added to norepinephrine with intent of decreasing NE dosage – weak recommendation, moderate QOE

Vasopressors and Inotropes in Septic Shock (cont.)
- Dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients; low risk of tachyarrhythmias and absolute or relative bradycardia – weak recommendation, low QOE
- Low-dose dopamine should not be used for renal protection – strong recommendation, high QOE
- Dobutamine with persistent hypoperfusion despite adequate fluid loading and use of vasopressor – weak recommendation, low QOE
Patient Case - Scenario 5

• SB is a 36-year-old male; mechanically ventilated (pressure support ventilation with positive end expiratory pressure [PEEP] = 10 mm Hg) with an open abdomen secondary to compartment syndrome. On postop day 3, SB is showing signs of shock: HR 110 bpm, Temp 102.3°F, WBC 6.63 x 10⁹/L (later peak @ 13.93 x 10⁹/L), BP 73/40 mm Hg, MAP 51 mm Hg, central venous pressure (CVP) 6 mm Hg, urine output ~ 20 mL/hr, Micro – Gram stain positive for gram negative rods.

Treatment of Relative Adrenal Insufficiency

• Physiologic “stress-dose” glucocorticoid therapy (hydrocortisone 150-200 mg daily x 5-7 days) compared to placebo has been associated with:
  – Fewer days of vasopressor support
  – Increased risk of secondary infection

2016 Red Blood Cell Transfusion in Septic Shock

• Red blood cell transfusions only when hemoglobin concentrations decrease to less than 7 g/dL in adults in the absence of extenuating circumstances – strong recommendation, high QOE
  – Myocardial ischemia
  – Severe hypoxemia
  – Acute hemorrhage

2016 Corticosteroids in Septic Shock

• IV hydrocortisone to treat septic shock in patients if adequate fluid resuscitation and vasopressor therapy are not able to restore hemodynamic stability at a dose of 200 mg per day – weak recommendation, low QOE

Summary

• Cardiogenic shock
  – Poor perfusion due to pump failure
  – Management - improve CO and maintain MAP > 70 mmHg

• Hypovolemic shock
  – Poor perfusion due to lack of intravascular volume
  – Management with volume (crystalloids or colloids)

• Distributive shock
  – Poor perfusion - systemic
  – Initial Management
    – Fluids
    – Vaspressors

Question 6

Initial management of the poor perfusion should be:

a) Sodium chloride 500 mL IV X1; until 30 mg/kg and monitor MAP and reassess signs of perfusion. If MAP persistently low (<65 mmHg) norepinephrine infusion to maintain MAP ≥ 65 mmHg

b) Initiate norepinephrine infusion to maintain MAP ≥ 65 mmHg. Consider fluid challenge with sodium chloride 500 mL IV X1 and repeat to goal CVP > 12 mmHg when stabilized

c) Treatment dose dopamine, monitor MAP and reassess signs of perfusion

d) Initiate dobutamine, monitor MAP, and reassess signs of perfusion
Pharmacotherapy Considerations in the Management of Shock

REFERENCES

QUESTIONS IN PRESENTATION

Patient Case - Scenario 1 (DM is a 37-year-old male s/p ST-elevation myocardial infarction [STEMI])

DM is cold-dry by the Forrester’s Acute Heart Failure Classification with pulmonary capillary wedge pressure (PCWP) = 12 mm Hg, cardiac index (CI) = 1.2 L/min/m², mean arterial pressure (MAP) = 55 mmHg, and serum creatinine (SCr) increased from 0.7 mg/dL to 1.2 mg/dL in the past 6 hours.

1. Initial management of the poor perfusion should be:
   a) Sodium chloride 500 mL IV X 1, monitor MAP, and reassess signs of perfusion
   b) Low “renal dose” dopamine to help the kidneys and reassess signs of perfusion
   c) Treatment dose dopamine, monitor MAP, and reassess signs of perfusion
   d) Treatment dose dobutamine, monitor MAP, and reassess signs of perfusion

Patient Case - Scenario 2 (DM is a 37-year-old male s/p STEMI)

DM is cold-wet by the Forrester’s Acute Heart Failure Classification with PCWP = 25 mmHg, CI = 1.2 L/min/m², MAP = 85 mmHg with relatively cool extremities.

2. Initial management of the poor perfusion with no signs of acute shock should be:
   1. Sodium chloride 500 mL IV X 1, monitor MAP, and reassess signs of perfusion
   2. Low “renal dose” dopamine to help the kidneys and reassess signs of perfusion
   3. Treatment dose dopamine, monitor MAP, and reassess signs of perfusion
   4. Treatment dose dobutamine, monitor MAP, and reassess signs of perfusion

Patient Case - Scenario 3 (DM is a 37-year-old male s/p STEMI)

DM is cold-wet by the Forrester’s Acute Heart Failure Classification with PCWP = 25 mmHg, CI = 1.2 L/min/m², MAP = 55 mmHg.

3. Initial management of the poor perfusion should be:
   A. Sodium chloride 500 mL IV X 1, monitor MAP, and reassess signs of perfusion
   B. Low “renal dose” dopamine to help the kidneys and reassess signs of perfusion
   C. Treatment dose norepinephrine, monitor MAP, and reassess signs of perfusion
   D. Treatment dose dobutamine, monitor MAP, and reassess signs of perfusion
Pharmacotherapy Considerations in the Management of Shock

Patient Case - Scenario 4 (AL is a 73-year-old female)

AL is a 73-year-old female (70 kg) who presents to the emergency department (ED) complaining of “tearing stomach and back pain.” In the ED she became unresponsive and was intubated. A CT scan revealed a ruptured thoracic aortic aneurysm with a large left hemothorax. In the operating room, chest tubes were placed to relieve the hemothorax, resulting in a loss of 12 L of fluid. Vital signs included HR 101 bpm, BP 80/45 mmHg, MAP 56 mmHg. Urine output was ~ 30 mL/hr. Temp = 96.9°F.

4. Initial management of the poor perfusion should be (after intervention to stop the blood loss):
   a) Sodium chloride 500 mL IV X 1, monitor MAP and Hgb, and reassess signs of perfusion, repeat fluid challenge as needed, and consider blood transfusion
   b) Low “renal dose” dopamine to help the kidneys and reassess signs of perfusion
   c) Treatment dose dopamine, monitor MAP, and reassess signs of perfusion
   d) Treatment dose dobutamine, monitor MAP, and reassess signs of perfusion

Dopamine versus Norepinephrine

5. Compared with norepinephrine in patients with shock, dopamine was associated with:
   A. Significantly increased mortality in all comers
   B. Significantly decreased mortality in all comers
   C. No significant difference in mortality in all comers, but a lower incidence of new-onset cardiac arrhythmias
   D. No significant difference in mortality in all comers, but a higher incidence of new-onset cardiac arrhythmias

Patient Case - Scenario 5 (SB is a 36-year-old male)

SB is a 36-year-old male; mechanically ventilated (pressure support ventilation with positive end expiratory pressure [PEEP] = 10 mm Hg) with an open abdomen secondary to compartment syndrome. On postop day 3, SB is showing signs of shock: HR 110 bpm, Temp 102.3°F, WBC 6.63 to 0.75 x 10⁹/L (later peak @ 13.93 x 10⁹/L), BP 73/40 mm Hg, MAP 51 mm Hg, central venous pressure (CVP) 6 mm Hg, urine output ~ 20 mL/hr, Micro – Gram stain positive for gram negative rods.

6. Initial management of the poor perfusion should be:
   a) Sodium chloride 500 mL IV X1; until 30 mg/kg and monitor MAP and reassess signs of perfusion. If MAP persistently low (<65 mmHg) norepinephrine infusion to maintain MAP ≥ 65 mmHg
   b) Initiate norepinephrine infusion to maintain MAP ≥ 65 mmHg; Consider fluid challenge with sodium chloride 500 mL IV x1 and repeat to goal CVP > 12 mmHg when stabilized
   c) Treatment dose dopamine, monitor MAP and reassess signs of perfusion
   d) Initiate dobutamine, monitor MAP, and reassess signs of perfusion
Pharmacotherapy Considerations in the Management of Shock

ANSWERS

1. A.
2. D.
3. C.
4. A.
5. D.
6. A.