

**PART I – Shock, Hemorrhage & Thrombosis – Dr. Lefkowitz**

**PART II – Shock – Dr. Marcantonio**

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*Thanks to adobe acrobat most of this was copied from last year's transcript which was verbatim.*

**PART I**

**SHOCK:** Low perfusion circulatory insufficiency that results in an imbalance between the **metabolic needs** of vital organs and **available blood flow**.

Features: decreased O<sub>2</sub> delivery to cells, decreased removal of wastes.

Key organs affected: brain, heart, lungs, kidneys (i.e. those receiving greatest portion of the cardiac output)

Shock Types: **hypovolemic** (low blood volume): may follow rupture of aortic aneurism, GI hemorrhage or colon carcinoma

**cardiogenic\*** (pump failure): may follow acute or longstanding MI

**septic\*** (pathogenic organisms or their toxins in blood): circulation of bacterial organism generating **endotoxin** (bacteria = gram neg) or exotoxin (bacteria = gram pos) that causes changes in peripheral vasculature

**neurogenic:** may follow spinal cord injury. less common than other three types

\* *high mortality*

Clinical signs: hypotension; weak, thready pulse; cool, clammy skin (vasoconstriction in periphery as blood is diverted to vital organs); tachycardia (HR>100); altered respirations and sensorium (due to low perfusion to brain and lung); peripheral cyanosis (turn purple due to vasoconstriction); oliguria in the early stages (scant urine output due to kidney effects).

**3 Phases of Shock**

	Lefkowitz	Robbins
1	early (hours) – <b>immediate</b> problems due to medical, surgical or obstetric catastrophe (electrolytes, acidosis due to anaerobic respiration in muscle groups, respiratory difficulties). eg: placenta praevia in which low-lying position of placenta → rupture	<b>nonprogressive</b> – reflex compensatory mechanisms are activated and perfusion of vital organs is maintained
2	2-6 days – <b>renal</b> dysfunction (acute tubular necrosis (ATN) due to O <sub>2</sub> deprivation → decreased urine → fluid overload, hyperkalemia, acidosis/uremia) – measures of clearance will be altered in blood	<b>progressive</b> – tissue hypoperfusion and worse circulatory and metabolic imbalance
3	10-14 days –during <b>diuretic</b> phase see increase in urine volume (3L/day) due to capacity renal tubular epithelium to be reverting post-mitotic cells	<b>irreversible</b> – severe cellular and tissue injury. phase try to get patients through, but has high mortality.

## **HEMORRHAGE Nomenclature:**

**Hematoma:** massive clot (several cm): extravasated blood in extravascular space (as opposed to congestion in which the blood remains in the vasculature)

**Hemothorax:** hemotoma in thoracic cavity

**Hemopericardium:** in pericardium

**Hemoperitoneum:** in peritoneum

**Petechiae:** pinpoint hemorrhages (1-2 mm) [are not blanched with pressure] – associated with disseminated intravascular condition (DIC) because of widespread clotting and fibrinolysis that goes on in small vessels

**Purpura:** larger (1 cm)

**Ecchymoses:** larger (a few cm) and blotchy (eg: what third year med students produce when they first attempt to draw blood)

## **Significance of hemorrhage determined by volume and time course**

1)  $\leq 10-20\%$  of blood volume or slow loss of blood → no clinical findings. eg: occult carcinoma of colon oozing blood which is discovered during routine examination

2) larger or more rapid blood loss → shock syndrome

**CONGESTION** (hyperemia) – increased volume of blood in affected tissue but (in comparison to hemorrhage) the blood is still contained within the tissue's blood vessels.

**Congestion mechanism:** arterial/arteriolar dilation due to vasoactive substances and neural inputs → dilation/dilatation and increased blood flow into capillaries.

**slide of “nutmeg” liver:** dark/purple/red areas = centralobular regions engorged with blood indicate liver congestion and problem with venous outflow. May be due to a number of conditions: left sided failure leading to right sided heart failure; constrictive pericarditis; primary pulmonary hypertension.

**slide of nutmeg liver/higher resolution:** centralobular regions with prominent vascular congestion in veins and immediate perivenular sinusoids.

**EDEMA:** abnormal accumulation of fluid in the intercellular tissue spaces or body cavities – can be **localized** to an organ/cavity or **systemic** (generally seen in patients with low oncotic pressure/ low albumin).

Types: **ascites:** edema in abdomen

**pleural effusion/ pleural hydrothorax:** in pleura

**pericardial effusion:** in pericardium

**edema fluid content** (important to distinguish inflammatory vs increased pressure)

**transudate:** fluid transfer due to increased pressure. protein poor, non-inflammatory (seen in pleural effusions due to congestive heart failure) specific gravity lower than...

**exudates:** protein rich, yellow, inflammatory exudates (tb in abdomen).

### **edema mechanisms:**

1. Decreased plasma colloid oncotic pressure (e.g. GI, renal and liver disease)
2. Increased hydrostatic pressure (e.g. congestive heart failure)
3. Increased endothelium permeability (e.g. acute inflammatory process)
4. Lymphatic blockage (e.g. invasive carcinoma or surgical removal of lymph nodes during mastectomy. *Not* expected in patients with lymphoma)

**slide w/ edema localized to abdomen:** ascites (looks like a huge pot belly) – in end-stage cirrhosis

**slide w/ edema in lower extremities:** extracellular spaces so filled with fluid that lower legs and feet are bloated and may exhibit **pitting edema** i.e. applied pressure leaves indent. Again this may be due to left-sided heart failure → blood back-up into pulmonary circulation → right-sided failure → back pressure in venous circulation.

### **Congestion vs. Edema**

**Congestion:** Patient presents complaining of shortness of breathe and having to raise him/herself with a pillow to sleep at night. Clinician hears diminished breath sounds, rales, and fluid sounds. Chest X-ray shows increased whiteness in lungs or vasculature.

**slide w/ simple congestion in lung:** alveoli walls with prominent, dilated, blood filled capillaries.

**Edema:** Patient hospitalized with acute MI, developed extreme respiratory embarrassment, was intubated but did not survive. Autopsy revealed pink fluid.

**slide w/ edema in lung:** alveoli filled with amorphous pink material with few cells/protein poor/non-inflammatory. Pink froth = transudate when pressure exceeds what vessel can hold. (If seen in post-mortem section, you can infer that left heart was affected)

**THROMBOSIS:** After activation of coagulation cascade by either intrinsic or extrinsic pathway, you may generate **thrombus**. Vessel contraction → platelet adhesion → fibrin accumulation → white cells → red blood cells accumulate (red thrombus) (DON'T NEED TO DISTINGUISH WHITE FROM RED THROMBUS ON EXAM)

**slide w/ pulmonary thromboembolus:** Thrombus from deep leg veins lodged in pulmonary artery. Rings of fibrin strands (pink strands), RBCs (interspersed), and platelets (pink dots), collectively referred to as the **lines of Zahn**, indicate that this clot was formed while patient was alive b/c coagulation cascade was triggered. Lines will be apparent upon gross and microscopic inspection.

**slide w/ RCA atherosclerosis:** thrombi in coronary arteries begin with atherosclerosis. white blockages indicates **calcium** deposits (gritty and hard). Pathogenesis of acute **myocardial infarct** usually linked to rupture of plaque leading to thrombosis.

## **Thrombi Nomenclature:**

**White thrombi:** platelets, fibrin, scant RBCs

**Red thrombi:** RBCs, tangled fibrin, attached to endothelium (bread and butter type)

**Occlusive:** These are clinically threatening. May appear in coronary/cerebral/iliac/femoral (e.g. leg pain after relatively little exertion, a syndrome called **intermittent claudication**, may be due to thrombus in fem or iliac)

**Mural** (“the wall of”): generally refers to heart ventricle, forms when a portion of wall is less kinetic (i.e. from scarring due to previous infarct.)

**Venous:** 90% in leg veins (deep calf/femoral/popliteal/iliac) – may be source of pulmonary embolism

**slide w/ coronary thrombus:** Occlusion. Intima and media hard to distinguish and replaced by grey lipid material with cleft-like formations of cholesterol. Cholesterol looks like lens-like empty spaces with surrounding grey material from other plaque material. Also see fibrosis.

**slide w/ MI:** gross appearance of heart with acute myocardial infarct – **coagulative necrosis**. Color looks like “tiger skin” – pale and yellow (necrotic) areas juxtaposed to normal “beefy” red areas. Under high power: myocytes with absent nuclei and deep red color, surrounded by neutrophils.

**slide w/ splenic infarct:** result of arterial thrombotic occlusion (e.g. thromboembolus from a **mitral valve**, or local thrombosis due to **sickle cell disease**). Yellow portion typical of necrotic tissue.

**slide w/ pulmonary embolus:** in pulmonary artery, total infarction of upper lobe evident compared to other lobes.

**DISSEMINATED INTRAVASCULAR COAGULATION (DIC):** Widespread thrombosis in the microcirculation with platelets and fibrin (few RBC) in capillaries. Activation of intrinsic pathway of coagulation. (Think sepsis or cancer)

**DIC mechanism:** activation of intrinsic pathway

**Clinical findings:** **shock**, respiratory distress, CNS depression, heart/renal failure

**Pathophysiology:** rapid consumption of fibrinogen, platelets, prothombin, factors V, VIII, X, and at same time generation of **fibrin split products D-DIMERS** (important diagnostic entity produced by plasmin.

**slide w/ DIC:** capillary with platelets and fibrin

Enter Dr. Marcantonio: PART II

**SEPTIC SHOCK (often see DIC in this setting):** characterized by **normal cardiac output** and a markedly **decreased systemic vascular resistance** (eventually cardiac output goes down, but initial response is increased CO)→drop in blood pressure. Can measure with swan-ganz catheter.

Clinical presentation: sudden drop of BP

Major initiator: **Gram-negative endotoxin** (esp. Lipid A)

Minor initiators: Exotoxins (staph aureus) / Gram-positive cell wall products / Yeast, viral and fungal antigens

**Septic Shock mechanism:** endotoxin binds monocytes and macrophages → cytokines → turn on acute inflammatory response at high level with local or systemic effects (systemic effects in the case of DIC). **Amplified** signal causes systemic response: fever, DIC, cardiovascular depression. Can lead to death very quickly.

Basic **steps:** (1) bacterial lysis (2) formation of **LPS-LPB** (LPS binding protein complex) in blood (3) monocyte/macrophage binding of complex at **CD 14** receptor (4) trigger cytokine secretion (**TNF $\alpha$ , IL-1**) (5) endothelial cell secretion of cytokines, can lead to endothelial injury which leads to DIC

Time course of cytokine induction (hrs) (fig 4-19)

LPS in bloodstream – then TNF – then IL-1 – then IL6, IL8

note: drugs that target TNF have not succeeded in part due to the quick rate of events.

Pathogenesis of shock – **LPS Signaling:**

- target cells are macrophages and monocytes
- CD 14 on cells and in the plasma binds LPS
- Other cell surface receptors, such as **CCR chemokine receptors** and **integrins** may also bind LPS
- Toll-like receptors (**TLR**) are the actual signaling receptors -> activate **Nf kappaB** to initiate massive cytokine synthesis (positive feedback loop) \*potential therapeutic target\*
- TLR4 gram negative shock, TLR2 gram positive sepsis – highly specific. (TLR4 KO mice do not develop shock even when injected with high levels of endotoxins)

**slide w/ nutmeg liver:** massive amount of congestion

**Main culprit for low bp: NITRIC OXIDE**

1. produced by endothelium and macrophages
2. **NO Synthetase** is induced in macrophages by numerous cytokines (iNOS)
3. deletion of cNOS (constitutive) from mice leads to systemic hypertension

**Mechanism:** NO made by endothelial cells/macrophages → diffuses through basement membrane due to gaseous properties → relaxes vascular smooth muscle → hypotension