Hemorrhage
Hematocrit, plasma & serum

Hematocrit = volume of red cells (~45%)
Plasma = fluid in fresh blood
Serum = fluid after blood has clotted
Plasma = serum + fibrinogen (such as other clotting factors)
Normal volumes:
  blood ~5.5L, plasma ~3L, rbc’s ~2.5L
<table>
<thead>
<tr>
<th>Specimen</th>
<th>+</th>
<th>-</th>
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<tbody>
<tr>
<td><strong>Serum</strong></td>
<td>more convenient sampling</td>
<td>activation of proteolytic</td>
</tr>
<tr>
<td></td>
<td>frequently used</td>
<td>processes</td>
</tr>
<tr>
<td></td>
<td>(retrospective samples)</td>
<td>cell lysis</td>
</tr>
<tr>
<td></td>
<td>clotting time required</td>
<td>time-dependent changes</td>
</tr>
<tr>
<td></td>
<td>(30-60 min)</td>
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<tr>
<td><strong>EDTA-Plasma</strong></td>
<td>less ex-vivo generated</td>
<td>complement 4 activation</td>
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<td></td>
<td>peptides</td>
<td></td>
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<tr>
<td></td>
<td>preserved cleavage sites</td>
<td>spontaneous clotting might</td>
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<td>occur (during storage or</td>
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<td></td>
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<td>free-thaw cycles)</td>
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<tr>
<td></td>
<td>cell free (&lt;10/nL)</td>
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</table>
The three pathways that makeup the classical blood coagulation pathway:

**Intrinsic**
- XII → XIIa
- XI → XIa
- IX → IXa
- surface contact

**Extrinsic**
- TF:VIIa → tissue damage

**Common**
- (V, PL, Ca++)
- (VIII, PL, Ca++)
- X → Xa
- prothrombin → thrombin (serine protease)
- fibrinogen → fibrin
- XIII → XIIIa
- stable fibrin clot

XII – Hageman factor, a serine protease
XI – Plasma thromboplastin, antecedent serine protease
IX – Christmas factor, serine protease
VII – Stable factor, serine protease
XIII – Fibrin stabilising factor, a transglutaminase
PL – Platelet membrane phospholipid
Ca++ – Calcium ions
TF – Tissue Factor (a = active form)
FIGURE 4–9 Schematic illustration of the conversion of factor X to factor Xa via the extrinsic pathway, which in turn converts factor II (prothrombin) to factor IIa (thrombin). The initial reaction complex consists of a proteolytic enzyme (factor VIIa), a substrate (factor X), and a reaction accelerator (tissue factor), all assembled on a platelet phospholipid surface. Calcium ions hold the assembled components together and are essential for the reaction. Activated factor Xa becomes the protease for the second adjacent complex in the coagulation cascade, converting prothrombin substrate (II) to thrombin (IIa) using factor Va as the reaction accelerator.
FIGURE 4–10 Role of thrombin in hemostasis and cellular activation. Thrombin plays a critical role in generating cross-linked fibrin (by cleaving fibrinogen to fibrin, and by activating factor XIII), as well as activating several other coagulation factors (see Fig. 4–8). Through protease-activated receptors (PARs), thrombin also modulates several cellular activities. It directly induces platelet aggregation and TxA₂ production, and activates ECs to express adhesion molecules, and a variety of fibrinolytic (t-PA), vasoactive (NO, PGI₂), and cytokine mediators (e.g., PDGF). Thrombin also directly activates leukocytes. ECM, extracellular matrix; NO, nitric oxide; PDGF, platelet-derived growth factor; PGI₂, prostacyclin; TxA₂, thromboxane A₂; t-PA, tissue plasminogen activator. See Figure 4–7 for additional anticoagulant activities mediated by thrombin, including via thrombomodulin.

(Courtesy of Shaun Coughlin, MD, PhD, Cardiovascular Research Institute, University of California at San Francisco; modified with permission.)
Intrinsic

surface contact

\[ \text{XII} \rightarrow \text{XII}_a \]
\[ \text{XI} \rightarrow \text{XI}_a \]
\[ \text{IX} \rightarrow \text{IX}_a \]
This test is done to evaluate the blood for its ability to clot. It is often done before surgery to evaluate how likely the patient is to have a bleeding or clotting problem during or after surgery.

**Normal PT Values:** 10-12 seconds (this can vary slightly from lab to lab)

Common causes of a prolonged PT include vitamin K deficiency, hormones drugs including hormone replacements and oral contraceptives, disseminated intravascular coagulation (a serious clotting problem that requires immediate intervention), liver disease, and the use of the anti-coagulant drug warfarin. Additionally, the PT result can be altered by a diet high in vitamin K, liver, green tea, dark green vegetables and soybeans.

http://www.intechopen.com/source/html/42171/media/image3_w.jpg  
http://surgery.about.com/od/beforesurgery/qt/PTPTTINRtests.htm
Partial Thromboplastin Time Blood Test-PTT
This test is performed primarily to determine if heparin (blood thinning) therapy is effective. It can also be used to detect the presence of a clotting disorder. It does not show the effects of drugs called “low molecular weight heparin” or most commonly by the brand name Lovenox.

**Normal PTT Values:** 30 to 45 seconds (this can value slightly from lab to lab)
Extended PTT times can be a result of anticoagulation therapy, liver problems, lupus and other diseases that result in poor clotting.

http://www.intechopen.com/source/html/42171/media/image3_w.jpg
http://surgery.about.com/od/beforesurgery/qt/PTPTTINRtests.htm
International Normalized Ratio Blood Test-INR

Normal INR Values: 1 to 2
The INR is used to make sure the results from a PT test is the same at one lab as it is at another lab. In the 1980’s the World Health Organization determined that patients may be at risk because the results of a PT test would vary from one lab to another, based upon the way the test was done. The “normal” range for one lab would be different than a “normal” value from another lab, creating problems for patients who were being treated in several locations. In order to standardize the results between labs, the INR was created. The INR result should be the same, regardless of the location where the tests are performed.

http://surgery.about.com/od/beforesurgery/qt/PTPTTINRtests.htm

INR=(PT patient/PT normal)^{ISI}

PT patient = patient's measure PT (seconds)

PT normal = laboratory's geometric mean value for normal patients (seconds)

ISI = International Sensitivity Index

http://easycalculation.com/medical/inr.php
**Figure 3** Action of LMWHs on the traditional coagulation cascades, showing coagulation factors PKK and HMWK

D-dimer is the degradation product of crosslinked (by factor XIII) fibrin.

It reflects ongoing activation of the hemostatic system.

FIGURE 4-11 The fibrinolytic system, illustrating various plasminogen activators and inhibitors.

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Hemostatic clot resolution

• tPA, tissue plasminogen activator, cleaves plasminogen to plasmin
• Plasmin digests fibrin clot
• Tightly regulated yin-yang of hemostasis
Primary hemostatic clot formation

- Platelets are activated by contact with Extra Cellular Matrix
- Circulating von Willebrand Factor tethers platelet glycoprotein receptors to ECM collagen
- Thrombin is released to cleave fibrinogen creating fibrin nets that capture more platelets as well as RBCs and WBCs
- Platelets contract with microtubular contractile proteins, consolidating plug
Hemorrhage

Extravasation of blood into the extravascular space.

Capillary bleeding can occur under conditions of chronic congestion.

Rupture of a large artery or vein results in severe hemorrhage and is almost always due to vascular injury, including trauma, atherosclerosis, or inflammatory or neoplastic erosion of the vessel wall.
Capillary Bleeding

http://www.glowm.com/resources/glowm/graphics/figures/v2/1080/15.jpg

http://www.sciencephoto.com/image/303985/350wm/P2120043-Ruptured_capillary,_SEM-SPL.jpg
Hemorrhage

- Extravasation of blood due to ruptured vessels
  - From *hemo* = blood, *rrhagia* = to burst forth
- Hemorrhage may be external or internal
- Hemorrhage may be obvious (gross) or hidden (occult)
- This is whole blood with RBCs, not just edemic transudates or exudates
Hemorrhage may be external or contained within a tissue.

Any accumulation is called a hematoma.

Hematomas may be relatively insignificant or so massive that death ensues.
The Ocular Pathology of Terson's Syndrome

Hematoma--subdural
Subcapsular Hematoma

http://www.daviddarling.info/images/spleen_cross-section.jpg


Minute 1- to 2-mm hemorrhages into skin, mucous membranes, or serosal surfaces are called **petechiae**

These are most commonly associated with locally increased intravascular pressure, low platelet counts (thrombocytopenia), or defective platelet function (as in uremia).

**FIGURE 4–4A** A, Punctate petechial hemorrhages of the colonic mucosa, a consequence of thrombocytopenia. B, Fatal intracerebral bleed.

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**FIGURE 4–4B** A, Punctate petechial hemorrhages of the colonic mucosa, a consequence of thrombocytopenia. B, Fatal intracerebral bleed.

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Figure 3 Kinetics of inflammatory bleeding in thrombocytopenic mice during reverse passive Arthus reaction.

(A) Photographs of progressing rpA in the dorsal skinfold chamber. In the absence of platelets, petechial bleeding was clearly visible after 2 hours and increased with time. In nondepleted animals there were virtually no petechial spots. Window diameter was 12 mm. (B) Microscopic view of the progressing rpA in a thrombocytopenic mouse. Petechial bleeding was detected at 20 minutes, with further growth of the spot at 40 minutes. Bar = 200 μm. (C) Petechial spots visible to the eye (∼ 100 μm) were counted during rpA in thrombocytopenic and control animals. The difference in incidence of petechiae became statistically significant within 1 hour (P < .01; n = 4). At t = 4 hours, the petechiae became confluent, impairing quantification. Error bars represent SEM.
Slightly larger (≥3 mm) hemorrhages are called purpura. These may be associated with many of the same disorders that cause petechiae or can be secondary to trauma, vascular inflammation (vasculitis), or increased vascular fragility (e.g., in amyloidosis).

Figure 2: Microscopic examination of palpable purpura. Severe pandermal leucocytoclastic vasculitis without granulation (HE, original magnification ×40; inset: ×400).
Larger (>1 to 2 cm) subcutaneous hematomas (i.e., bruises) are called ecchymoses.

The red cells in these lesions are degraded and phagocytized by macrophages; the hemoglobin (red-blue color) is then enzymatically converted into bilirubin (blue-green color) and eventually into hemosiderin (gold-brown color), accounting for the characteristic color changes in a bruise.

**fig-002:** Continuing hemorrhagic drainage and a massive ecchymosis on right side in spite of primary surgical hemostatis.

**Mentions:** The patient developed a large right lumbar ecchymosis while daily drainage volume remained 150-200 ml (Figure 2). Hemoglobin level dropped to 8.9 g and hematocrit to 26.6%. He was still complaining of considerable pain in spite of medications. A re-exploration was decided on day-5. Previous incision was re-opened with local anesthetic infiltration. A pulsatile hemorrhage was seen from an approximately 1-mm vessel. Despite this vessel was ligated the hemorrhage kept continuing. The operating team concluded to try hemostatic matrix [FloSeal®, Baxter] for definitive hemostasis. After applying this novel hemostatic agent the bleeding stopped (Figure 3).
EPIDEMIOLOGY — In one United States survey of 500 healthy, ethnically-diverse adults, 18 percent of individuals reported easy bruising. This finding is consistent with many other studies in which the frequency of easy bruising in healthy individuals ranged from 12 to 55 percent. Women are more likely than men to report easy bruising.

PATHOPHYSIOLOGY — A bruise (ecchymosis) is a collection of blood beneath the skin, resulting from extravasation of blood from surrounding vessels. Easy bruising can result from abnormalities affecting the blood vessels themselves, the surrounding skin and subcutaneous structures, platelet number and function, or coagulation cascade function.

Physical injury to a blood vessel normally triggers a vigorous physiologic response. Damage to endothelial tissue causes activation and adhesion of circulating platelets with the assistance of von Willebrand factor. This in turn results in the rapid formation of a platelet plug at the site of injury. Stabilization of the plug via fibrin deposition subsequently results from activation of the coagulation cascade. A problem or defect at any step of this process will increase the risk of abnormal bruising and bleeding, regardless of the degree of trauma.

ETIOLOGY — The etiology of bruising can be broadly classified by the anatomic/physiologic defenses against bleeding. The following list includes the main categories with their most commonly-associated etiologies: Disorders of blood vessels and surrounding tissue (eg, physical abuse, vitamin C deficiency, connective tissue disease). Platelet abnormalities (eg, drugs, systemic illness including infections, von Willebrand disease). Coagulation disorders (eg, coagulation factor deficiency, liver disease, vitamin K deficiency).

EVALUATION — As bruising is a common complaint, the clinician should be familiar with important signs and symptoms that require further workup. The history and physical examination are more useful than laboratory testing in this assessment. The principal goal of the clinical history and examination is to distinguish easy bruising from normal bruising, from other skin lesions that can be mistaken for bruising, and from physical abuse. Laboratory testing is used in selected cases for further evaluation.

http://www.uptodate.com/contents/easy-bruising?source=search_result&search=ecchymosis&selectedTitle=1~150
Ecchymoses or contusions
Depending on the location, a large accumulation of blood in a body cavity is denoted as a **hemothorax**, hemopericardium, hemoperitoneum, or hemarthrosis (in joints).

Patients with extensive bleeding can develop jaundice from the massive breakdown of red cells and hemoglobin.
Hemorrhage into cavities

• Pleural hemorrhage—hemothorax
  ▪ Build-up of pressure prevents lung expansion
    • Prevents gas exchange
    • May lead to lung collapse
  ▪ Instigates coughing or hiccups, which exacerbates bleeding

• Pericardial hemorrhage—hemopericardium
  ▪ Build-up of external pressure inhibits filling
  ▪ Cardiac *tamponade* = compression

• Intracranial hemorrhage
  ▪ Always bad because of the rigid cranium
  ▪ CSF pressure increases rapidly if bleeding rate is greater than rate of fluid resorption
Hemopericardium

This is hemopericardium as demonstrated by the dark blood in the pericardial sac opened at autopsy. Penetrating trauma or massive blunt force trauma to the chest (often from the steering wheel) causes a rupture of the myocardium and/or coronary arteries with bleeding into the pericardial cavity. The extensive collection of blood in this closed space leads to cardiac tamponade. A pericardiocentesis, with needle inserted into the pericardial cavity, can be a diagnostic procedure.
The clinical significance of hemorrhage depends on the volume and rate of bleeding.

**Rapid loss of up to 20% of the blood volume or slow losses of even larger amounts may have little impact in healthy adults**; greater losses, however, can cause *hemorrhagic (hypovolemic) shock*.

The site of hemorrhage is also important. For example, bleeding that is trivial in the subcutaneous tissues can cause death if located in the brain; because the skull is unyielding, intracranial hemorrhage can result in an increase in pressure that is sufficient to compromise the blood supply or to cause the herniation of the brainstem.

Finally, chronic or recurrent external blood loss (e.g., peptic ulcer or menstrual bleeding) causes a net loss in iron and can lead to an iron deficiency anemia. In contrast, when red cells are retained (e.g., hemorrhage into body cavities or tissues), iron is recovered and recycled for use in the synthesis of hemoglobin.
Shock is the final common pathway for several potentially lethal clinical events, including severe hemorrhage, extensive trauma or burns, large myocardial infarction, massive pulmonary embolism, and microbial sepsis.

Shock is characterized by systemic hypotension due either to reduced cardiac output or to reduced effective circulating blood volume.

The consequences are impaired tissue perfusion and cellular hypoxia. At the outset the cellular injury is reversible; however, prolonged shock eventually leads to irreversible tissue injury that often proves fatal.
<table>
<thead>
<tr>
<th>Type of Shock</th>
<th>Clinical Example</th>
<th>Principal Mechanisms</th>
</tr>
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<tbody>
<tr>
<td><strong>CARDIOGENIC</strong></td>
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<tr>
<td></td>
<td>Myocardial infarction</td>
<td>Failure of myocardial pump resulting from intrinsic myocardial damage, extrinsic pressure, or obstruction to outflow</td>
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<tr>
<td></td>
<td>Ventricular rupture</td>
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<td></td>
<td>Arrhythmia</td>
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<tr>
<td></td>
<td>Cardiac tamponade</td>
<td></td>
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<tr>
<td></td>
<td>Pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td><strong>HYPOVOLEMIC</strong></td>
<td>Fluid loss (e.g., hemorrhage, vomiting, diarrhea, burns, or trauma)</td>
<td>Inadequate blood or plasma volume</td>
</tr>
<tr>
<td><strong>SEPTIC</strong></td>
<td>Overwhelming microbial infections (bacterial and fungal)</td>
<td>Peripheral vasodilation and pooling of blood; endothelial activation/injury; leukocyte-induced damage, disseminated intravascular coagulation; activation of cytokine cascades</td>
</tr>
<tr>
<td></td>
<td>Superantigens (e.g., toxic shock syndrome)</td>
<td></td>
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</tbody>
</table>
- Place the victim in shock position
- Keep the person warm and comfortable
- Turn the victim's head to one side if neck injury is not suspected

Decreased Intravascular volume

Decreased Cardiac output
S/Sx: Decreased BP

Shift of interstitial fluid
Aldosterone, ADH
Spleenic Discharge

Increased Volume

Increased HR, contractility
Catecholamine release

Increased Cardiac Output

More volume loss
Decreased Cardiac output
Decreased Tissue perfusion
Impaired cellular metabolism

Decreased Systemic and pulmonic pressures

Nurseonlineph

Inadequate perfusion

Cell hypoxia

Energy deficit

Lactic acid accumulation and fall in pH → Anaerobic metabolism

Vasoconstriction

Metabolic acidosis

Failure of pre-capillary sphincters

Peripheral pooling of blood

Cell membrane dysfunction and failure of 'sodium pump'

Intracellular lysosomes release digestive enzymes

Efflux of potassium

Influx of sodium and water

Toxic substances enter circulation

Capillary endothelium damaged

Destruction, dysfunction, and cell death