

BODY AS A WHOLE - CLINICAL MANAGEMENT

PRE-OPERATIVE PREDICTION OF PERI-OPERATIVE CARDIAC COMPLICATIONS

The single most important area in which preoperative evaluation and interventions may decrease peri-operative morbidity involves the patient's cardiac status because cardiac complications are the leading cause of death after most operations. Peri-operative cardiac complications include Myocardial Infarction, Congestive Heart Failure, and Death.

Pre-operative prediction of peri-operative cardiac complications depends on both patient-specific risk factors and surgery specific risks. The patient-specific risk factors are usually ascertained with a thorough history and physical examination and ECG. The American College of Cardiology has identified patient specific clinical predictors of increased peri-operative cardiac risk. They have grouped these clinical predictors into 3 major groups:

MAJOR:

?? Unstable coronary syndromes (recent MI >7days <1month and unstable or severe angina), decompensated CHF, Significant Arrhythmias (high grade AV block, symptomatic ventricular arrhythmias or uncontrolled SVTs), and severe Valvular Disease

INTERMEDIATE

?? Mild angina pectoris (Canadian Class I or II), Prior myocardial infarction by history or pathologic Q waves, Compensated or prior congestive heart failure, Diabetes Mellitus

MINOR

?? Advanced Age, Abnormal electrocardiogram (LVH, L BBB, ST-T abnormalities), Rhythm other than sinus (e.g. atrial fibrillation), Low functional capacity, History of Stroke, Uncontrolled Hypertension

The surgery specific cardiac risk for non-cardiac surgical procedures can be summarized as follows:

HIGH (reported cardiac risk often > 5%)

?? Emergency major operations, particularly in the elderly, aortic and other major vascular, peripheral vascular, or prolonged procedures associated with large fluid shifts +/- blood loss

INTERMEDIATE (reported cardiac risk often <5%)

?? Carotid Endarterectomy, Head and Neck, Intraperitoneal and Intrathoracic, Orthopedic, Prostate

LOW (reported cardiac risk often <1%)

?? Endoscopic Procedure, Superficial Procedure, Breast, Cataract

GENERAL RECOMMENDATIONS:

-For elective surgery, men or women older than 40 should receive a 12-lead electrocardiogram.

-Patients with an abnormal ECG, significant risk factors for CAD (e.g. previous MI or stroke, DM, HTN, Hypercholesterolemia, PVD), preoperative evidence of cardiac ischemia (e.g. angina), or functional heart disease should undergo a more formal cardiac evaluation depending on the clinical predictors and the inherent surgical risk of the operation.

?? Patients with major clinical predictors should be evaluated by a provocative cardiac examination (stress test) such as stress-ECG, thallium perfusion or dobutamine echocardiography irrespective of the inherent surgical risk of the operation they are planning to undergo and irrespective of their functional capacity. If the results of these tests are favorable, then the patient can proceed to the OR. If the results of these tests are unfavorable, then there must be some consideration of delaying or canceling the surgery and proceeding with coronary angiography with subsequent care dictated by the findings and treatment results.

?? Patients with intermediate clinical predictors planning to undergo a *low* risk surgical procedure may proceed to the OR. Those with intermediate clinical predictors and moderate to excellent functional capacity planning to undergo an *intermediate* surgical risk procedure may also proceed to the OR. However, patients with intermediate clinical predictors planning to undergo a *high* risk surgical procedure or those with a poor functional capacity should undergo further cardiac evaluation which can include echocardiography and provocative cardiac examination (stress ECG, adenosine-thallium, dobutamine echo) before proceeding to the OR.

?? Patients with minor or no clinical predictors can proceed to the OR without further evaluation for a *low* or *intermediate* surgical risk procedure. However, even patients with minor or no clinical predictors that have poor functional capacity should undergo non-invasive cardiac evaluation if they are planning to undergo a *high* surgical risk procedure.

1. Cameron JL Current Surgical Therapy p1266-75
2. Eagle KA ACC/AHA Task Force Report: Guidelines for perioperative cardiovascular evaluation for noncardiac surgery: *JACC* v27n.4 1996:910-48

Initial treatment of spinal shock

Central neurogenic hypotension (CNH) is treated by ameliorating vagal tone, ensuring adequate ventricular filling, and increasing vascular resistance. In spinal cord lesions rostral to T1, cardiac vagal influences dominate, and bradycardia is prominent. Hypotension (< 90 mm Hg systolic, or mean arterial pressure < 70 mm Hg) should first be treated with atropine to increase HR and prevent sudden death. Unopposed vagal innervation alters cardiac conduction and produces so-called dispersion of repolarization, manifested by a lengthened QTc, which can be the substrate of tachydysrhythmias. More often, vagal stimulation during intubation leads to sudden bradycystolic arrest from unopposed atrioventricular nodal suppression.

With CNH, atropine should be readily available in case it is needed during rapid sequence induction to block the vagal discharge triggered by tracheal intubation. Adequate intravascular volume expansion should be confirmed by CVP and BP measurements. With spinal cord injury, BP must be normalized, even if urine output indicates adequate renal perfusion.

Inadequate perfusion pressure can worsen ischemia in the region of a spinal cord contusion where vascular dysregulation exists. Consequently, pharmacologic vasoconstriction should be instituted promptly to increase spinal cord perfusion. The agents of choice are α_1 -adrenergic specific, including phenylephrine and ephedrine. In the setting of trauma resuscitation, ephedrine is especially useful; one 10-mg bolus will increase vascular resistance for 3 to 4 hours.

Diagnosis of liver lesion in a cirrhotic patient

Cirrhosis of the liver of any etiology may be followed by hepatocellular carcinoma (hepatoma). In fact, approximately 5% of patients with cirrhosis develop hepatocellular carcinoma and 60% of patients with hepatocellular carcinoma have cirrhosis.

Hepatocellular carcinoma is endemic to parts of Africa and Asian in areas where Aflatoxins of the mold *aspergillus flavus* are a contaminant in the diet or exposure to Hepatitis B and C are common. Other conditions associated with hepatocellular carcinoma are hemochromatosis, schistosomiasis, and environmental exposures.

Work up of a cirrhotic patient with a liver lesion should include:

- 1) Hep B and C ab panels
- 2) LFTS (although nonspecific)
- 3) Alpha Feto Protein (AFP) (elevated in approximately 80% of cases)
- 4) Imaging
 - a. Right Upper Quadrant Ultrasound
 - b. CT-scan
 - c. MRI if needed to determine resectability.

Diagnosis can be confirmed by biopsy usually image-guided techniques (e.g. CT or ultrasound).

Sabiston. 15th Edition. p.1070.

Schwartz. Principles of Surgery. 7th Edition. p.1409.

CNS EFFECTS OF HYPONATREMIA

Hyponatremia is defined as serum sodium of less than 136mEq/Liter and is a common electrolyte disorder encountered in clinical practice and is the most common electrolyte abnormality in surgical patients. Where as hypernatremia always denotes hypertonicity, hyponatremia can be associated with high, normal, or low tonicity.

Hypertonic hyponatremia occurs as a result of excess solute, such as glucose or BUN, which do not move freely across the cell membranes and induce a shift in water from the cell into the extracellular space. Isotonic hyponatremia, also known as spurious hyponatremia or pseudohyponatremia was a phenomenon noted in patients with hypertriglyceridemia and hyperproteinemia when sodium was measured by flame photometry and newer ion-specific electrodes have eliminated this artifact.

Hypotonic (or dilutional) hyponatremia is by far the most common form of hyponatremia and it may occur in patients who are hypovolemic, hypervolemic, or isovolemic. It essentially represents an excess of free water in relation to existing sodium stores, and is associated with conditions that impair the ability of the kidneys to excrete free water (such as in the post-operative state where there is a release of ADH attributable to the body's stress response).

- ?? Hypovolemic Hyponatremia- occurs when GI and renal losses of sodium-rich fluids are replaced by hypotonic fluid (e.g. overdiuresis with diuretics, adrenal insufficiency, vomiting, diarrhea, blood loss, fluid sequestration in bowel obstruction, pancreatitis, peritonitis, burns, and muscle trauma)
- ?? Euvolemic Hyponatremia- occurs in patients with SIADH, hypothyroidism, or excessive water intake.
- ?? Hypervolemic Hyponatremia- occurs in congestive heart failure, cirrhosis, nephrotic syndrome where there is a decrease in effective arterial circulating blood volume.

CLINICAL MANIFESTATIONS OF HYPONATREMIA ARE LARGELY EFFECTS ON THE CNS

Most patients with hyponatremia are asymptomatic unless their serum sodium concentrations are less than 125 mEq/L. Even then, it is the patient with a more rapid or profound decline in serum sodium who is more likely to experience central nervous system dysfunction, and this is related to water entry into the brain cells because of the osmotic gradient resulting in cerebral edema. Effects include:

- ?? Headache, Nausea and Vomiting
- ?? Muscle cramps, Lethargy, Restlessness, Disorientation, and Depressed Reflexes
- ?? Seizures (usually with Serum Na less than 120), Coma, Permanent brain damage
- ?? Brain stem herniation, respiratory arrest, and Death

TREATMENT

Primary objectives of treatment of hyponatremia are:

- ?? Correct the underlying causes and treat the associated conditions
- ?? Alleviate the symptoms by increasing the serum sodium
 - If the patient is symptomatic and the hyponatremia had developed rapidly, then emergency treatment with hypertonic saline (3%) is indicated. This can usually be combined with diuretic therapy to avoid cerebral edema. The patient's sodium deficit should be calculated and then no more than half of this deficit should be corrected in the first 24 hours.
 - If the patient is symptomatic and the hyponatremia is chronic, then urgent correction with 3% saline is indicated. Once the symptoms resolve or there is a 10% increase in serum sodium, then the hypertonic saline can be stopped and treatment switched to water restriction.
- ?? AVOID correcting hyponatremia too rapidly and precipitating shrinkage of the brain and osmotic demyelination (Central Pontine Myelinolysis), which can have as its neurologic sequelae quadriparesis, pseudobulbar palsy, seizures, coma, and death.
- ?? For asymptomatic hyponatremia:
 - Hypertonic Hyponatremia is primarily treated by reducing the excess solute.
 - Hypotonic Hyponatremia is usually treated with fluid restriction in the hypervolemic/euvolemic patient and isotonic saline in the hypovolemic patient.

1. Cameron JL **Current Surgical Therapy 7th Edition** p1253-1254, 1317-1318
2. Adroque HJ et al **Hyponatremia** *NEJM* v342no21:1581-1589 May 25,2000

Describe the treatment of Hyperkalemia causing abnormal QRS waveform

Treatment for hyperkalemia is divided into 3 categories:

1. Minimize cardiac effects of hyperkalemia.
2. Induce K⁺ uptake by cells resulting in decrease in plasma K⁺.
3. Remove K⁺ from the body.

Antagonize membrane effects and stabilize membrane potential:

1. **IV Calcium** is cardioprotective and the most rapid way to treat hyperkalemia (even in normocalcemic patients). It can be administered as calcium gluconate or calcium carbonate. When hyperkalemia is accompanied by evidence of circulatory compromise, calcium chloride is preferred; it may prove beneficial in maintaining peripheral vascular tone. Effects on the ECG are apparent in 1 – 3 minutes and last for 30 – 60 minutes; if no ECG changes are evident after 5 – 10 minutes an additional bolus of calcium should be administered.

Care should be taken for patients taking digoxin, as hypercalcemia can potentiate the cardiotoxicity of digitalis. Calcium should be administered over 30 minutes and not be used as liberally. Digitalis is a relative contraindication to calcium administration.

Accelerate Cellular Potassium Uptake:

1. **Insulin** rapidly stimulates hepatocytes and myocytes to take-up potassium. It works within 10 – 20 minutes. Insulin 10 Units should be administered with 1 Amp of D50.
2. **Beta₂-agonists** administered in nebulizer form has an *immediate* onset of action and is maximized at 90 – 120 minutes. The primary limitation of albuterol administration is tachycardia.
3. **Bicarbonate** administration is less effective than insulin and beta-agonists. It is most appropriate in those patients exhibiting acidosis associated with hyperkalemia. It is associated with a large sodium load, and thus should be used for patients with hyperkalemia and acidemia who do not have a history of congestive heart failure. Also, it should not be given after calcium is administered, as it binds calcium.

Enhance Potassium Removal:

1. **Potassium-wasting diuretics** include either loop or thiazide diuretics. These are usually *not* adequate for cases of acute hyperkalemia, especially in patients with underlying renal insufficiency. They may suffice as treatment for patients with chronic mild hyperkalemia.
2. **Sodium Polystyrene Resin (Kayexalate)** exchanges Na for K in the GI tract. It can be administered orally or per rectum as a retention enema. When given orally, coadministration of sorbitol can inhibit constipation; however, sorbitol should *not* be given in conjunction with the enema form, as this has been associated with rectal perforation.
3. **Dialysis** is the *most* efficient way to reduce K⁺. This may require a period of time to initiate, during which methods described above should be instituted.

Acute Management of Hyperkalemia

Condition	Treatment	Comment
EKG changes or serum K > 7 meq/L	Calcium Gluconate	Response lasts only 20 – 30 minutes; do NOT give bicarbonate after calcium.
EKG changes and circulatory compromise	Calcium Chloride	Calcium chloride has 3 x more Calcium than calcium gluconate.
AV block refractory to calcium treatment	1. Insulin 2. Glucose	This combination should drop the serum K by 1mEq/L for 1 – 2 hours.
Digitalis Cardiotoxicity	1. Magnesium sulfate 2. Digitalis-specific antibodies if necessary	Do NOT use calcium for hyperkalemia associated with digitalis toxicity.
After acute phase or when no EKG changes	Kayexalate with sorbitol.	Oral and / or rectal.

1. Brenner & Rector's: The Kidney, 6th edition., Copyright 2000. W.B. Saunders Company
2. The ICU Book. 2nd Edition. Paul Marino. Copyright 1998. Williams & Wilkens.

REFEEDING SYNDROME

The refeeding syndrome is an underappreciated entity characterized by acute electrolyte derangements--notably hypophosphatemia--that occur during nutritional repletion of patients with significant suboptimal caloric intake. Refeeding syndrome occurs when previously malnourished patients are fed with high carbohydrate loads. The result is a rapid fall in phosphate, magnesium and potassium, along with an increasing ECF volume, leading to a variety of complications.

Patients who are malnourished develop a total body depletion of phosphorous; serum phosphorous levels are maintained by redistribution from the intracellular space. The body uses endogenous fuel stores as it's main source of energy. Fat and protein (from muscle) are metabolized.

The delivery of glucose, either enterally or parenterally, as part of a feeding strategy, can cause a huge increase in the circulating insulin level. The patient struggles to cope with converting to exogenous fuel sources. There is rapid uptake of glucose, potassium, phosphate and magnesium into cells. The serum concentration of these agents falls dramatically. In addition, for an unexplained reason, the body swiftly begins to retain fluid, and the extracellular space expands.

The dramatic reduction in serum electrolytes and fluid retention leads to a number of systemic pathologies. There is an increase in cardiac workload, with increased stroke work, heart rate and oxygen consumption. This sudden increase in demand for nutrients and oxygen may outstrip supply. Moreover, in patients with cardiovascular disease, the sudden increase in cardiac work and circulating fluid can precipitate acute heart failure.

The sudden administration of carbohydrates exerts a considerable strain on the respiratory system, whose musculature may well be atrophied due to starvation. There is an increase in CO₂ production and O₂ consumption, and a resultant increase in the respiratory quotient (RQ). The consequence of this is an increase in minute ventilation, which may cause dyspnea and tachypnea, and make weaning difficult.

The gut atrophies with starvation and the production of digestive enzymes diminishes. With return of enteral nutrition, the gut may be initially intolerant, requiring time to adapt, and many patients complain of nausea and diarrhea.

The serum phosphorous level falls precipitously with refeeding, due to a shift of phosphate from the extracellular to the intracellular compartment, due to the huge demands for this ion for synthesis of phosphorylated compounds. The result of this sudden massive reduction in phosphorous levels is a multitude of life threatening complications involving multiple organs: respiratory failure, cardiac failure, cardiac arrhythmias, rhabdomyolysis, seizures, coma, red cell and leucocyte dysfunction.

The most effective way to treat refeeding is to be aware of it. One should start feeds slowly and aggressively supplement magnesium, phosphate and potassium.

Complications associated with cyclosporine use

Borel's discovery in 1972 of the immunosuppressive properties of cyclosporine, a fungal metabolite extracted from *Tolypocladium inflatum* Gams, contributed enormously to the rapid and successful growth of the field of clinical organ transplantation, especially of livers and hearts. It represented a completely new class of clinically important immunosuppressive agents. Many of its selective, suppressive effects on T cells appear to be related to its selective inhibition of TCR-mediated activation events. It inhibits cytokine production by T_H cells in vitro and impairs the development of mature CD4⁺ and CD8⁺ T cells in the thymus. Cyclosporine is a cyclic peptide (11 amino acids, molecular weight 1202 daltons).

Cyclosporine was discovered to be immunosuppressive by its ability to suppress antibody production in mice. Other in vivo properties include inhibition of antibody plaque-forming cell production, graft-versus-host disease, skin graft rejection, delayed solid organ allograft rejection, and delayed-type hypersensitivity reactions. Absence of myelosuppression was a major advance over other immunosuppressive agents and indicated that the mechanism of action was relatively specific for lymphocytes. Other inflammatory cells are much less sensitive to its inhibitory effects. Clinically, prophylactic administration of cyclosporine suppresses allograft rejection and GVH disease.

Analyses of the effect of cyclosporine on T lymphocytes have shown (1) inhibition of both IL-2-producing T lymphocytes and cytotoxic T lymphocytes, (2) inhibition of IL-2 gene expression by activated T lymphocytes, (3) no inhibition of activated T lymphocytes in response to exogenous IL-2, (4) inhibition of resting T-lymphocyte activation in response to alloantigen and exogenous lymphokine, (5) inhibition of IL-1 production, and (6) inhibition of mitogen (concanavalin A) activation of IL-2-producing T lymphocytes. These T-lymphocyte responses involve both CD4⁺ (T_H) and CD8⁺ (T-cytotoxic/suppressor) lymphocytes, and the inhibition appears to occur at the level of activation, and perhaps even maturation, of the resting cell. In mice, maturation of T cells that occurs in the thymus is significantly suppressed by cyclosporine, thus enriching a population of immature and less responsive T cells.

A number of kidney and other solid organ transplantation trials have shown that cyclosporine induces potent immunosuppression without myelosuppression. The addition of steroids to cyclosporine permitted a lowering of the cyclosporine dosage and decreased nephrotoxicity (the principal clinical side effect of the drug). The introduction of cyclosporine into widespread clinical use in 1983 led to a substantial improvement in the outcome of cadaveric renal transplantation and permitted the widespread practice of heart and liver grafting.

Cyclosporine is metabolized in the liver by cytochrome P-450 enzymes. Medications that increase or decrease cytochrome P-450 function can dramatically increase or decrease cyclosporine or tacrolimus levels. The narrow therapeutic windows of these immunosuppressants require care in prescribing practices. Antibiotics, seizure medications, and some calcium-channel blockers are major culprits, but interactions should be verified before prescribing any new medication to a transplant recipient.

The potential adverse effects of cyclosporine include nephrotoxicity, hypertension, hyperkalemia, hirsutism, gingival hyperplasia, tremor and other neurotoxicities, diabetogenicity, and hepatotoxicity. As with other immunosuppressive agents, cyclosporine therapy increases the risk of infection and malignancy but, by reducing steroid requirements, generally decreases infection rates.

From Sabiston Textbook of Surgery, The Biological Basis of Modern Surgical Practice, 16th Edition. 2003.

Electrolyte abnormalities associated with gastric outlet obstruction.

Differential Diagnosis of Gastric Outlet Obstruction

- ?? Complication of peptic ulcer disease—frequency is significantly decreased due to treatment of H. Pylori, anti-secretory medications (H2 blockers and proton pump inhibitors), and endoscopic dilation
- ?? Primary carcinoma of the gastric antrum
- ?? Pancreatic or biliary tract carcinoma

Symptoms of Gastric Outlet Obstruction

- ?? Delayed vomiting (more than one hour after meal ingestion)
- ?? Vomiting of partially digested food
- ?? Non-bilious vomiting (versus bilious vomiting which is characteristic of small bowel obstruction)
- ?? Epigastric pain/fullness, bloating, early satiety and post-prandial pain
- ?? Dehydration with electrolyte disturbances (hypokalemic, hypochloremic metabolic alkalosis)

Diagnosis of Gastric Outlet Obstruction

- ?? Physical Exam: succussion splash of gastric contents produced by shaking the patient's torso or presence of palpable mass (seen in 1/3 of cases)
- ?? Substantial quantities of retained gastric contents/fluid via aspiration by nasogastric tube
- ?? Confirmation of mechanical obstruction by endoscopy or barium contrast examination

Surgical Treatment of Gastric Outlet Obstruction

- ?? For peptic ulcer disease \approx pyloroplasty or antrectomy, with vagotomy
- ?? For obstructing primary gastric carcinomas \approx curative or palliative resection (subtotal vs. total gastrectomy) with reconstruction of GI continuity
- ?? For unresectable gastric neoplasm \approx G tube for decompress/vent of stomach; J tube for enteral feedings
- ?? For unresectable pancreatic or biliary tract neoplasm \approx creation of gastrojejunostomy to bypass the obstruction

Electrolyte Abnormalities Associated with Gastric Outlet Obstruction

- ?? Hypokalemic hypochloremic metabolic alkalosis is caused by loss of HCl containing gastric secretions
- ?? Hypokalemia is exacerbated by exchange of sodium for potassium in the renal tubule in an attempt to conserve sodium losses via secondary hyperaldosteronism (aldosterone = absorbs Na⁺, and excretes K⁺)
- ?? Alkalosis is exacerbated by contraction of extracellular fluid (volume contraction causes decrease in renal GFR which leads to absorption of Na and HCO₃⁻), and hydrogen secretion in the distal tubule to offset potassium deficiency
- ?? May see paradoxical aciduria because HCO₃⁻ is the available anion which is reabsorbed in the proximal tubule to offset the gastrointestinal losses of chloride via HCl
- ?? Treatment: resuscitation with normal saline and potassium

Differential Diagnosis of Causes of Metabolic Alkalosis

- ?? Diuretics, posthypercapnia alkalosis (see when chronic respiratory acidosis is rapidly corrected with mechanical ventilation which causes 2-3 day lag in renal bicarbonate excretion), vomiting, NGT suction, exogenous alkali (antacids, lactate/citrate/acetate—precursors of bicarbonate; these are common ingredients in TPN), contraction alkalosis, excess mineralocorticoids (primary hyperaldo via adrenal adenoma—Conn's syndrome)

References:

1. Quigley EM, Hasler WL, and Parkman HP. American Gastroenterological Association Technical Review on Nausea and Vomiting. *Gastroenterology*. 120(1), 2001.
2. Townsend. Sabiston Textbook of Surgery, 16th edition, 2001.
3. Abeloff. *Clinical Oncology*, 2nd edition, 2000.
4. Adrogué HJ, and Madias NE. Management of Life-Threatening Acid-Base Disorders. *NEJM*. 1998, 338:26-33, 107-110

Treatment of post-transplant cytomegaloviral (CMV) infection

Organ transplant recipients are susceptible to postoperative viral infections as a result of immunosuppression. The most important of these infections is caused by Cytomegalovirus (CMV), a DNA Herpes virus that is thought to afflict nearly one-third of solid-organ transplant recipients. Patients are especially susceptible during the most intense period of immunosuppression, usually 30-180 days after transplant. CMV is a ubiquitous agent which infects most people during their lives, and as with other herpesviruses, becomes latent in donor and recipient tissues (e.g., lymphocytes). Post-transplant infection can range from an asymptomatic rise in anti-CMV titers to severe systemic disease with fever, leukopenia, lethargy, hypotension, respiratory failure, hepatitis, pancreatitis, GI ulceration with hemorrhage, retinitis, multi-system organ failure, and death. A common presentation of post-transplant CMV infection is fever, leukopenia, cough, hypoxia, and diffuse interstitial pulmonary infiltrates on chest x-ray. CMV seropositive recipients can experience reactivation disease with immunosuppression, and this form tends to be of mild to moderate severity. Patients at increased risk for severe disease are those seronegative recipients who receive organs from seropositive donors. Others at high risk are those who receive anti-rejection therapy (esp. antilymphocyte tx), elderly patients, and those who receive cadaveric organs. Diagnosis of CMV infection can be clinical, but confirmatory evidence consists of CMV inclusion bodies in body fluid or tissue specimens. Prophylactic therapy with intravenous ganciclovir, an acyclic guanosine analog that requires triphosphorylation for activation prior to inhibiting CMV DNA polymerase, has been shown to decrease the incidence of symptomatic post-transplant CMV disease. Ayclovir, anti-CMV immunoglobulin, or various combinations of all three agents have also been effective prophylactically. Established CMV disease is most effectively treated with intravenous ganciclovir. Foscarnet, an inorganic pyrophosphate compound that inhibits viral DNA and RNA polymerases, is another agent that can be used to treat CMV, although it can cause considerable neuro- and nephrotoxicity.

References: Greenfield LJ. *Surgery: Scientific Principles and Practice*, 3rd Ed. pp 543-544.

Adrenal Insufficiency/Shock

Etiology

- primary insufficiency (due to loss of adrenal function)
 - in general, autoimmune disorders are most common cause
 - in ICU, hemorrhage is most common cause
 - other causes:
 - Waterhouse-Friedrichsen syndrome: adrenal hemorrhage, meningococcal sepsis
 - tuberculous infection of adrenal glands
 - metastatic disease
- secondary insufficiency (secondary to disease or suppression of hypothalamic-pituitary axis)
 - surgery or trauma in setting of adrenal suppression is most common cause
 - Sheehan syndrome (postpartum pituitary infarction)

Presentation:

- two main flavors:
 - low cardiac output with high vascular resistance (if patient dry)
 - high cardiac output with low vascular resistance (if patient tanked)
- fluid/electrolyte abnormalities: primarily related to mineralocorticoid deficiency
 - hyponatremia, hypochloremia, hyperkalemia, hypoglycemic, metabolic acidosis, excessive volume requirement
- other:
 - fever, hypotension, lethargy, vomiting

Diagnosis

- ACTH stimulation test:
 - look at baseline cortisol levels (usually 7 - 24 µg/dl); in a stressed patient, levels should be 20 µg/dl or greater at baseline
 - Administer 0.25 mg (250 mcg) of cosyntropin (synthetic ACTH) IV/IM
 - repeat cortisol levels 30,60 minutes and 6 hours after ACTH
 - value should increase by at least 25-50% after ACTH stimulation (some say should double, but that likely is not feasible in a stressed patient with amplified adrenal activity)

Management

- fluid resuscitation: normal saline, glucose
- options for adrenal replacement
 - hydrocortisone (100-300 mg/day)
 - maximally stimulated adrenal gland produces about this much
 - interacts with cortisol assays
 - hydrocortisone has mineralocorticoid effect
 - may need additional mineralocorticoid once dose tapered < 50 mg/day
 - taper dose based on clinical judgement
 - dexamethasone 4 mg q2-6 hours
 - does not interact with cortisol assays (can be used during stim test)
 - no mineralocorticoid activity; will need IV hydrocortisone
 - mineralocorticoids can be given later
 - fludrocortisone acetate (mineralocorticoid) 0.1 mg qd
 - pure mineralocorticoid
 - adjunct to either hydrocortisone or dexamethasone
- check ACTH level before steroids to confirm diagnosis
- peri-operative stress regime:
 - hydrocortisone (Solu-Cortef) 100 mgs evening before surgery, 100 mgs morning of, 100 mgs q8h for 24 hours, then taper to regular dose

References:

Gold et al General Surgery Board Review
Cameron's Seventh Edition
Emedicine (<http://www.emedicine.com/emerg/topic16.htm>)

Neurologic findings associated with brain death

- Widespread cortical destruction
 - Unresponsiveness to the environment
- Midbrain damage
 - Absent pupillary light reaction
- Pontine Damage
 - Absent oculovestibular
 - Absent corneal reflexes
- Medullary dysfunction
 - Complete Apnea

Other signs/SX

- Pulse rate is invariable and unresponsive to atropine
- Many have diabetes insipidus
- Pupils dilated
- Absence of spinal reflexes not required

Tests

- EEG
- Radionuclide brain scanning, Cerebral angio,
Transcranial dopplers – all able to demonstrate
the absence of cerebral blood flow

R/o drug induced or hypothermic CNS depression

Timing of initial dose of prophylactic antibiotics (pre-operatively)

Administration of the initial prophylactic dose of antibiotics should be timed such that a bactericidal concentration of the drug is established in serum and tissues when the incision is made. Then therapeutic levels of the agent in serum and tissues should be maintained for the duration of the operation. And only until, at most, a few hours after the incision is closed.

Antibiotic prophylaxis is most effective when the antibiotic is present in tissue before the skin incision is made. Antibiotics are ineffective when administration is delayed for 3 h and intermediately effective when administered within that interval.

The half-life of Ancef(Cefazolin) is sufficiently long that bactericidal tissue levels are still present at incision when drug is given up to 1 hour beforehand, affording greater flexibility in scheduling. Current trends are toward a limited duration of prophylaxis. A regimen consisting of only a single preoperative dose of antibiotics appear to be as effective as a longer regimen. A second dose may be beneficial after 3-4 hours (1-2 half-lives of the drug used) if the operation lasts longer. No data support prophylactic use beyond that point, although many surgeons prefer to continue the regimen for 24 hr. **Prophylactic antibiotic regimens beyond 24 hrs are unsupportable.**

- 1) Timed to allow adequate wound antibiotic levels before contamination
- 2) administer only for short period during perioperative period
- 3) specific for the likely infecting organism
- 4) safe. minimal additional hazard to patient.

1. Surgery: Basic Science and Clinical Evidence. Norton et al; 2001. p375-378
2. Principles of Surgery. Schwartz et al; 1999. 7th edition. p328.

Interpretation of Pulmonary Arterial Catheter (PAC) Tracings

When “floating a swan” through a right internal jugular vein puncture site, the PAC tip should reach the right atrium at approximately 20 to 25cm (CVP tracing still), the right ventricle at 30 to 35cm, the pulmonary artery at 40 to 45cm, and wedge position at 45 to 55 cm. When using the left IJ or right/left subclavian veins or in a larger than average patient, the distances may be slightly greater, but if the expected waveform is not seen as the PAC is advanced, the PAC may be coiled and the PAC should be withdrawn and refloat. For detailed guidelines of PAC insertion, please see reference.¹

CVP/RA waveform- low mean pressure value (normally 0-8mm Hg)

RV waveform- seen when systolic pressure increases, but diastolic pressure is low (approx. same as RA pressure); ventricular arrhythmias can occur.

PA waveform-higher diastolic pressure than RV diastolic (decreased difference between systolic and diastolic pressure); systolic PAP approximates systolic RV pressure if no pulmonic valve disease

PAP Wedge- dampening of PA waveform seen; reflects pressure of pulmonary vascular bed and thus Left atrial pressure.

TABLE 1-10 – Data collection and interpretation²

Hemodynamic Measurement	Normal Value	Clinical Significance	Abnormalities
Right atrial pressure (RAP)	0–8 mm Hg	Equivalent to central venous pressure (CVP)	? Right ventricular failure, pulmonary embolism, tricuspid valve abnormalities, pericardial tamponade, right ventricular infarction ? Hypovolemia
Pulmonary artery pressure (PAP)	Systolic 15–30 mm Hg	PAP is equal to RV pressure during systole while the pulmonary valve is open. If the pulmonary vascular resistance is normal, the pulmonary artery diastolic pressure (PADP) is 1–4 mm Hg greater than PCWP and can be substituted for it in following the patient’s hemodynamic measurements.	? Pulmonary embolism, chronic lung disease, VSD, cardiogenic shock, right ventricular infarction
	Diastolic 5–12 mm Hg		If the PADP is 5 mm Hg > PCWP, consider: ARDS, pulmonary emboli, or COPD
	Mean 10–20 mm Hg		
Pulmonary capillary wedge pressure (PCWP)	5–12 mm Hg	PCWP is normally equal to left atrial pressure; it is therefore a sensitive indicator of the presence of pulmonary congestion and left-sided CHF. PCWP is not equal to left ventricular end diastolic pressure (LVEDP) in the following situations: PCWP > LVEDP:	? Left ventricular failure with resultant pulmonary congestion, acute mitral insufficiency, tamponade, decreased left ventricular compliance (hypertrophy, infarction)
		Mitral stenosis Patient receiving PEEP Left atrial myxoma Pulmonary venous obstruction PCWP < LVEDP: “Stiff” left ventricle ? LVEDP (>25 mm Hg)	
Cardiac output (CO)	3.5–7 L/min	CO = stroke volume multiplied by heart rate	? Cardiac dysrhythmias, ? contracting muscle mass (myocardial ischemia, MI), mitral insufficiency, VSD
Cardiac index (CI)	2.5–4 L/m ²	CI relates CO to body surface area (BSA), CI = CO/BSA	? High output failure secondary to fluid overload, hepatocellular failure, renal disease, septic shock
			? Hypovolemia, cardiogenic shock, pulmonary embolism, hypothyroidism, CHF with failing ventricle
Systemic vascular resistance (SVR)	900–1300 dyne/sec/cm ⁻⁵	Resistance against which the left ventricle must work to eject its stroke volume	? Hypervolemic vasoconstrictive states (hypertension, cardiogenic shock, traumatic shock)
			? Septic shock, acute renal failure, pregnancy
Pulmonary vascular resistance (PVR)	155–255 dyne/sec/cm ⁻⁵		? Cor pulmonale, pulmonary embolism, valvular heart disease, CHF
			? Hypervolemic states, pregnancy

Box 1-2. Hemodynamic Measurements in Specific Disease States²

Septic shock

Early: ? PCWP, ? SVR, ? CO

Late: ? PCWP, ? SVR, ? CO

Neurogenic shock: ? PCWP, ? SVR, N/? CO

Cardiac tamponade: ? PCWP, ? SVR, ? CO, ? CI

CVP = PADP = PCWP

Pulmonary embolism: Normal PCWP, ? PADP, ? CI

Cardiogenic shock: ? PCWP, ? PADP, ? CO, ? CI, ? SVR

Hypovolemic shock: ? PCWP, ? CO, ? SVR, ? CI

Right ventricular infarct: RAP/PCWP =0.8

* ?, Increases; ?, decreases, *CI*, cardiac index; *CO*, cardiac output; *N*, no effect; *PADP*, pulmonary artery diastolic pressure; *PCWP*, pulmonary capillary wedge pressure; *RAP*, right atrial pressure; *SVR*, systemic vascular resistance.

TABLE 1-11 -- Effects of therapeutic measures on hemodynamic measurements²

Therapeutic Measure	CO	SVR	PCWP
IV fluids	N/?	N/?	?
Diuretics	N/??	?/Secondary ?	?
Nitrates	N?/?	?	?
Nitroprusside	?	??	N/?
Catecholamines	N/??	???	N/?
Dopamine	N/?	??	N/??
Dobutamine	??	?	N/?

?, Increases; ?, decreases; *CO*, cardiac output; *N*, no effect; *PCWP*, pulmonary capillary wedge pressure; *SVR*, systemic vascular resistance.

¹Miller: Anesthesia, 5th ed., Churchill Livingstone, Inc: 2000, pp. 1159, 1165-1166.

²Ferri: Practical Guide to the Care of the Medical Patient, 5th ed., Mosby: 2001, p. 25.

Grade is most important in which types of neoplasms

Most neoplasms are staged using the TNM classification: T (Tumor Characteristics – i.e. Depth of Invasion; N (Nodal Status); and M (Metastatic Status).

Sarcomas arise from mesodermal tissues and they are unique for two reasons: 1) histologic grade is the best indicator of the biologic behavior of soft tissue sarcomas and plays a much greater role than size and 2) dissemination occurs predominantly via the hematogenous route and not the lymphatic system.

Histologic grading is mostly based on a three stage classification scheme:

Grade I / III (Low Histologic Grade)
Grade II / III (Intermediate Histologic Grade)
Grade III / III (High Histologic Grade)

Criteria used to determine grades include 1) degree of differentiation, 2) cellularity, 3) mitotic index, and 4) amount of spontaneous necrosis.

As sarcomas tend to disseminate via the hematogenous route, the lung is the principle site of metastasis for extremity sarcomas and the liver is the principle site of metastasis for intraabdominal sarcomas. Lymph node metastases are rare. Preoperative evaluation for extremity sarcomas includes CXR for low grade lesions and chest CT for high-grade lesions. CT-scan of the abdomen (liver) should be performed for intraabdominal sarcomas to r/o metastases.

Staging (AJCC GTNM Classification)

Stage	Grade	Tumor	Nodes	Metastasis
Stage I	G1	T1,2	N0	M0
Stage II	G2	T1,2	N0	M0
Stage III	G3	T1,2	N0	M0
Stage IVA	GX	TX	N1	M0
Stage IVB	GX	TX	N0	M0

(T1 - <5cm size; T2 - >5cm size)

Cameron. Current Surgical Therapy. Seventh Edition. p.1213-1214.
Greenfield. 2nd Edition. P2242-2252.

CHARACTERISTICS OF CALCITONIN

Structure: Human Calcitonin is a 32 amino-acid hypocalcemic peptide hormone produced by the para-follicular (a.k.a. clear or C) cells of the thyroid gland, which in several mammalian species serves as the physiologic antagonist of PTH (parathyroid hormone).

Secretion & Metabolism: Secretion of calcitonin is increased when the thyroid gland is perfused with solutions containing a high Ca^{2+} concentration; i.e. secretion is under direct control of blood calcium. Measurement of circulating calcitonin by immunoassay indicates that it is not secreted until the plasma calcium level reaches approximately 9.5mg/dL and that above this calcium level, plasma calcitonin is directly proportional to plasma calcium.

Other stimulators of calcitonin secretion include β -Adrenergic agonists, dopamine, and estrogen. Gastrin, CCK, glucagons, and secretin have all been reported to stimulate calcitonin secretion.

Mechanism of Action: The main action of calcitonin is that it is a calcium-lowering hormone. Serpentine receptors for calcitonin are found in bones and the kidneys. Calcitonin lowers the circulating calcium and phosphate levels and its calcium lowering effect is exerted via two distinct mechanisms:

- ?? The hypocalcemic effect of calcitonin is accounted for primarily by its direct inhibition of osteoclast-mediated bone resorption. This action is direct, and calcitonin inhibits the activity of osteoclasts in vivo.
- ?? Also, calcitonin has the secondary effect of stimulating renal excretion of calcium.
- ?? Calcitonin also exerts additional effects through receptors present in brain, gastrointestinal tract, and immune system. For example, it exerts analgesic effects directly on cells in the hypothalamus and related structures, possibly by interacting with receptors for related peptide hormones, such as calcitonin gene-related peptide (CGRP) or amylin.

Physiological Significance of Calcitonin: The exact physiologic role of calcitonin is uncertain, but it seems to be of limited physiologic significance in humans, at least in calcium homeostasis, as contrasted with a clearly definable role in calcium metabolism in many other mammalian species. In humans, changes in calcium and phosphate metabolism are not seen despite extreme variations in calcitonin production. The calcitonin content of the human thyroid is low, and after thyroidectomy, bone density and plasma Ca^{2+} levels are normal as long as the parathyroid glands are intact.

Furthermore, no definite effects are attributable to either calcitonin deficiency (as seen in totally thyroidectomized patients receiving only replacement thyroxine) or excess (as seen in patients with medullary carcinoma of the thyroid, a calcitonin-secreting tumor).

Clinical Significance of Calcitonin: Despite the fact that calcitonin does not seem to play any physiologically significant role in calcium metabolism in humans, it does have some clinical significance and uses:

- ?? Calcitonin is useful in the treatment of Paget's disease, a condition in which increased osteoclastic activity triggers compensatory formation of disorganized new bone.
- ?? Calcitonin has also been useful as an adjunctive treatment of severe hypercalcemia seen in such diseases as humoral hypercalcemia of malignancy (HHM) and local osteolytic hypercalcemia (LOH), conditions where serum calcium levels become extremely elevated secondary to osteoclast mediated bone resorption.
- ?? Calcitonin also has medical significance because of its role as a tumor marker in sporadic and hereditary cases of medullary carcinoma of the thyroid.

¹ Ganong, WF **Review of Medical Physiology- 21st Ed (2003)** Section IV: Endocrinology, Metabolism, & Reproductive Function 21. Hormonal Control of Calcium Metabolism & the physiology of bone

² Harrison's On-Line, Chapter 341: Diseases of the Parathyroid Gland and other Hyper- and Hypocalcemic Disorders

List the characteristics of cyclosporine

Cyclosporine (FDA Approved 1983 Nov):

Indications: Arthritis, rheumatoid; Keratoconjunctivitis sicca; Psoriasis; Rejection, heart transplant, prophylaxis; Rejection, liver transplant, prophylaxis; Rejection, renal transplant, prophylaxis

Pregnancy Category C (Cyclosporine was not teratogenic in appropriate test systems)

The effectiveness of cyclosporine results from specific and reversible inhibition of immunocompetent lymphocytes in the G₀- and G₁-phase of the cell cycle. T-lymphocytes are preferentially inhibited. The T-helper cell is the main target, although the T-suppressor cell may also be suppressed. Cyclosporine also inhibits lymphokine production and release including interleukin-2. No effects on phagocytic function (changes in enzyme secretions, chemotactic migration of granulocytes, macrophage migration, carbon clearance *in vivo*) have been detected in animals. Cyclosporine does not cause bone marrow suppression in animal models or man. The immunosuppressive activity of cyclosporine is primarily due to parent drug. Following oral administration, absorption of cyclosporine is incomplete. The extent of absorption of cyclosporine is dependent on the individual patient, the patient population, and the formulation.

Cyclosporine is extensively metabolized by the cytochrome P-450 3A enzyme system in the liver, and to a lesser degree in the gastrointestinal tract, and the kidney. Elimination of cyclosporine is primarily biliary with only 6% of the dose (parent drug and metabolites) excreted in urine. The disposition of cyclosporine from blood is generally biphasic, with a terminal half-life of approximately 8.4 hours (range 5-18 hours). Following intravenous (IV) administration, the blood clearance of cyclosporine (assay: HPLC) is approximately 5-7 ml/min/kg in adult recipients of renal or liver allografts. Blood cyclosporine clearance appears to be slightly slower in cardiac transplant patients.

Cyclosporine is distributed largely outside the blood volume. The steady state volume of distribution during IV dosing has been reported as 3-5 L/kg in solid organ transplant recipients. In blood, the distribution is concentration dependent. Approximately 33-47% is in plasma, 4-9% in lymphocytes, 5-12% in granulocytes, and 41-58% in erythrocytes. At high concentrations, the binding capacity of leukocytes and erythrocytes becomes saturated. In plasma, approximately 90% is bound to proteins, primarily lipoproteins. Cyclosporine is excreted in human milk.

The principal adverse reactions of cyclosporine therapy are renal dysfunction, tremor, hirsutism, hypertension, and gum hyperplasia. Cyclosporine can cause nephrotoxicity and hepatotoxicity when used in high doses, and it is not unusual for serum creatinine and BUN levels to be elevated during cyclosporine therapy. These elevations in renal transplant patients do not necessarily indicate rejection, and each patient must be fully evaluated before dosage adjustment is initiated. Occasionally patients have developed a syndrome of thrombocytopenia and microangiopathic hemolytic anemia, which may result in graft failure. Hypertension is a common side effect of cyclosporine therapy which may persist. Significant hyperkalemia (sometimes associated with hyperchloremic metabolic acidosis) and hyperuricemia have been seen occasionally in individual patients. Those patients receiving cyclosporine are at increased risk for development of lymphomas and other malignancies, particularly those of the skin. Encephalopathy has been described both in post-marketing reports and in the literature. Manifestations include impaired consciousness, convulsions, visual disturbances (including blindness), loss of motor function, movement disorders and psychiatric disturbances.

Laboratory

Nephrotoxicity	Rejection
CyA serum trough level >200 ng/ml. Gradual rise in Cr (<0.15 mg/dl/day) †. Cr plateau <25% above baseline. BUN/Cr =20	CyA serum trough level <150 ng/ml. Rapid rise in Cr (>0.3 mg/dl/day) ‡. Cr >25% above baseline. BUN/Cr <20

Mosby's Drug Consult

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List the inhibitors of platelet aggregation

Primary hemostasis: process of platelet plug formation at sites of injury

Secondary hemostasis: the reactions of the plasma coagulation system which result in fibrin formation

There are 3 major events in primary hemostasis:

- 1) Platelet adhesion: the interaction of platelets with nonplatelet surface such as vascular endothelium
- 2) Platelet activation and secretion: the secretion of a variety of factors such as ADP, Factor Va, Thrombospondin, von Willebrands Factor, etc.
- 3) Platelet aggregation: the binding of activated platelets to the adherent monolayer

PLETAL (cilostazol): mechanism not fully understood. PLETAL and several of its metabolites are cyclic AMP (cAMP) phosphodiesterase III inhibitors, inhibiting phosphodiesterase activity and suppressing cAMP degradation with a resultant increase in cAMP in platelets and blood vessels, leading to inhibition of platelet aggregation and vasodilation (mainly in the femoral vascular bed), respectively.

PLAVIX (clopidogrel): An inhibitor of ADP-induced platelet aggregation acting by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. Irreversibly modifies the platelet ADP receptor.

TRENTAL (pentoxifylline): Pentoxifylline and its metabolites improve the flow properties of blood by decreasing its viscosity. The precise mode of action still to be defined. Pentoxifylline administration has been shown to produce dose-related hemorrheologic effects, lowering blood viscosity, improving erythrocyte flexibility, increase leukocyte deformability, and to inhibit neutrophil adhesion and activation. Tissue oxygen levels have been shown to be significantly increased by therapeutic doses of pentoxifylline in patients with peripheral arterial disease

ASPIRIN: irreversibly acetylates and inactivates the enzyme cyclooxygenase and thereby inhibits platelet production of thromboxane A₂.

DIPYRIDAMOLE: mechanisms not fully understood, but increase adenosine (coronary vasodilator and inhibitor of platelet aggregation), intraplatelet cAMP, and cGMP to inhibit platelet aggregation

AGGRENOX (aspirin/extended-release dipyridamole)

TICLID (ticlopidine): mechanism not fully understood, but inhibits adenosine diphosphate (ADP)-induced binding of fibrinogen to the platelet membrane at a specific receptor site (the glycoprotein IIb-IIIa complex). Release of platelet granule constituents, platelet-platelet interactions, and platelet adhesion to the endothelium and to atheromatous plaque are inhibited.

NSAIDs (NONSTEROIDAL ANTI-INFLAMMATORY DRUGS: ibuprofen, naproxen, indomethacin, etc.): though not used as platelet aggregation inhibitors, do have reversible inhibition of platelet aggregation. Inhibits activity of enzyme cyclooxygenase and result in decreased formation of precursors of prostaglandins and thromboxanes.

References:

- 1) Harrison's Principles of Internal Medicine. Isselbacher, et al., 13th edition; Chapter 57.
- 2) Drug Information for the Health Care Professional. 17th edition; p. 1230-1231, 2867.
- 3) Drug prescribing information Plavix:
http://www.sanofi-synthelab.com/products/pi_plavix/pi_plavix.html
- 4) Drug prescribing information Pletal:
http://www.pletal.com/Mechanism_of_Action_of_PLETAL-305.asp#flash.
- 5) Drug prescribing information Trental: http://www.aventis-us.com/Pis/trental_TXT.html.

List the mechanism of leukocyte adhesion to endothelial cells

It is now clear that leukocyte adhesion and transmigration are determined largely by the binding of complementary adhesion molecules on the leukocyte and endothelial surfaces and that chemical mediators--chemoattractants and certain cytokines-- affect these processes by modulating the surface expression or avidity of such adhesion molecules. The adhesion receptors involved belong to four molecular families--the selectins, the immunoglobulins, the integrins, and mucin-like glycoproteins. The most important of these are shown in [Table 3-1](#).

Selectins consist of E-selectin (CD62E, previously known as ELAM-1), which is confined to endothelium; P-selectin (CD62P, previously called GMP140 or PADGEM), present in endothelium and platelets; and L-selectin (CD62L, previously known by many names, including LAM-1), which decorates most leukocyte types. Selectins bind, through their lectin domain, to sialylated forms of oligosaccharides (e.g., sialylated Lewis X), which themselves are covalently bound to various mucin-like glycoproteins (GlyCAM-1, PSGL-1, ESL-1, and CD34).

The immunoglobulin family molecules include two endothelial adhesion molecules: ICAM-1 (intercellular adhesion molecule 1) and VCAM-1 (vascular cell adhesion molecule 1). Both of these molecules interact with integrins found on leukocytes.

Integrins are transmembrane-adhesive heterodimeric glycoproteins, made up of alpha and beta chains that also function as receptors for the extracellular matrix. The principal integrin receptors for ICAM-1 are the beta integrins LFA-1 and MAC-1 (CD11a/CD18 and CD11b/CD18), and those for VCAM-1 are the integrins alpha₄beta₁ (VLA-4) and alpha₄beta₇.

How are these molecules modulated to induce leukocyte adhesion in inflammation? There are a number of mechanisms, dependent on the duration of inflammation, the type of inflammatory stimulus, and blood flow conditions.

TABLE 3-1 – ENDOTHELIAL/LEUKOCYTE ADHESION MOLECULES

Endothelial Molecule	Leukocyte Receptor	Major Role
P-selectin	Sialyl-Lewis X PSGL-1	Rolling (neutrophils, monocytes, lymphocytes)
E-selectin	Sialyl-Lewis X ESL-1, PSGL-1	Rolling, adhesion to activated endothelium (neutrophils, monocytes, T cells)
ICAM-1	CD11/CD18 (integrins) (LFA-1, Mac-1)	Adhesion, arrest, transmigration (all leukocytes)
VCAM-1	alpha ₄ beta ₁ (VLA4) (integrins) alpha ₄ beta ₇ (LPAM-1)	Adhesion (eosinophils, monocytes, lymphocytes)
GlyCam-1 CD34	L-selectin	Lymphocyte homing to high endothelial venules Neutrophil, monocyte rolling

ICAM-1 and VCAM-1 belong to the immunoglobulin family of proteins; ESL-1, E-selectin ligand 1; PSGL-1, P-selectin glycoprotein ligand 1.

Redistribution of adhesion molecules to the cell surface: P-selectin, for example, is normally present in the membrane of specific intracytoplasmic endothelial granules, called *Weibel-Palade bodies*. On stimulation by mediators such as histamine, thrombin, and platelet-activating factor (PAF), P-selectin is rapidly redistributed to the cell surface, where it can bind the leukocytes. ^[15] This process occurs within minutes in flowing blood and serves to deliver preformed adhesion molecules in short order to the surface. Studies suggest that this process may be particularly important in early leukocyte *rolling* on endothelium.

Induction of adhesion molecules on endothelium: Some inflammatory mediators, particularly cytokines (IL-1 and TNF), induce the synthesis and surface expression of endothelial adhesion molecules. This process requires new protein synthesis and begins usually after a delay of some 1 or 2 hours. E-selectin, for example, which is not present on normal endothelium, is induced by IL-1 and TNF and mediates the adhesion of neutrophils,

monocytes, and certain lymphocytes by binding to its receptors. The same cytokines also increase the expression of ICAM-1 and VCAM-1, which are present at low levels in normal endothelium.

Increased avidity of binding: This mechanism is most relevant to the binding of integrins. For example, LFA-1 is present on leukocytes--neutrophils, monocytes, and lymphocytes--but does not adhere to its ligand ICAM-1 on endothelium. To become firmly adherent, the neutrophils need to be activated such that LFA-1 is converted from a state of low-affinity binding to high-affinity binding toward ICAM-1, owing to a conformational change in the integrin molecule. The principal agents causing such leukocyte activation are chemotactic agents (including the chemokines, discussed later) made by endothelium or other cells emanating from the site of injury. During inflammation, the increased affinity of LFA-1 on the activated leukocyte, coupled with the increased ICAM-1 expression on endothelium induced by cytokines, sets the stage for strong LFA-1/ICAM-1 binding. The LFA-1/ICAM-1 interaction causes *firm adhesion* to the endothelium and appears also to be necessary for the subsequent *transmigration across* the endothelium.

Cotran: Robbins Pathologic Basis of Disease, 6th ed. , Copyright © 1999 W. B. Saunders Company

List the nondepolarizing anesthetic agent whose metabolism is unaffected by hepatic or renal disease.

Background Information on Metabolism of Anesthetic Agents

Systemic clearance of anesthetic drugs is usually via hepatic metabolism. The liver metabolizes drugs through oxidation and reduction (via the cytochrome P450 system), hydrolysis, and conjugation (transformation of hydrophobic molecules into water-soluble molecules through addition of polar groups \rightleftharpoons renders the metabolite easier to excrete via the kidneys).

Renal clearance of anesthetic agents occurs via filtration at the level of the glomerulus with direct transport into the renal tubules. Both renal blood flow and creatinine clearance are inversely correlated with age, so anesthetic agents must be dosed appropriately in elderly patients despite presence of normal creatinine level. It is also important to note that inhalational anesthetics also decrease renal blood flow and therefore delay renal excretion. For example, pancuronium is 85% eliminated via renal clearance.

Tissue clearance (i.e. blood, muscle and lungs) is another important mechanism of metabolism.

- ?? Remifentanyl is cleared by nonspecific esterases located primarily in muscle and intestines.
- ?? Succinylcholine (depolarizing muscle relaxant) and mivacurium are all metabolized by plasma butyrylcholinesterases (also known as pseudocholinesterases).
- ?? Cisatracurium (an isomer of atracurium) is metabolized completely by Hofmann degradation (a spontaneous process in plasma at normal pH and temperature; this process does NOT depend on circulating esterases); therefore cisatracurium metabolism is NOT affected by disease or genetic variants of cholinesterase metabolism.

Comparison of Metabolism of Commonly Used Neuromuscular Blocking Drugs

DRUG	DURATION	METABOLISM (%)
Succinylcholine (depolarizing muscle relaxant)	Ultrashort	Plasma cholinesterase (98-99%) **synthesized by liver
Mivacurium	Short	Plasma cholinesterase (95-99%) **synthesized by liver
Atracurium	Intermediate	Hofmann elimination and nonspecific ester hydrolysis (60-90%)
Vecuronium	Intermediate	Liver (30-40%)
Pancuronium	Long	Liver (10-20%)

Conclusions

- ?? ATRACURIUM metabolism is NOT affected by hepatic or renal dysfunction because it undergoes spontaneous chemical degradation (Hofmann elimination) and ester hydrolysis.

References:

1. Miller. Anesthesia. 5th edition, 2000.
2. Katzung, BG and Trevor AJ. Examination and Board Review: Pharmacology, 5th edition, 1998

Characterize an immunologic chimera

Chimerism is the existence in an individual of two or more cell lines, each of which has a different genetic origin.

The most robust form of donor-specific tolerance is that associated with hematopoietic stem cell chimerism. TLI plus donor bone marrow infusion of adult mice can cause tolerance induction. The first association between chimerism and tolerance was observed in the 1940s when Dr. Owen reported that Freemartin cattle were red blood cell chimeras. The common placenta that they shared allowed exchange with hematopoietic stem cells. Although genetically disparate, these cattle accepted skin grafts from the other twin. Billingham and colleagues demonstrated that this active transfer of tolerance to donor antigens was due to bone marrow hematopoietic stem cells from the donor. Subsequently, chimerism was demonstrated to be associated with tolerance in mice, pigs, rats, primates, and humans. Until recently, the risk of conventional bone marrow transplantation was too great to tolerate in clinical attempts to induce tolerance. However, a number of advances have been made in the clinical application of hematopoietic stem cell chimerism to induce tolerance approach as clinical reality. Reconstitution of mice with mixtures of T-cell-depleted syngeneic and allogeneic bone marrow (pioneered by Ildstad and Sachs) produces mixed hematopoietic bone marrow chimerism and donor-specific tolerance to skin grafts. Most importantly, 1% donor chimerism is sufficient to provide robust deletional tolerance, opening the door to partial conditioning strategies to establish mixed chimerism. Nonlethal preparative regimens, using anti-T-cell monoclonal antibodies, cyclophosphamide, ALG, and tacrolimus, in addition to sublethal total body irradiation plus donor bone marrow, have more recently been shown to induce tolerance in mice. Recent improvements in marrow processing and graft engineering to decrease problems with GVH disease have increased interest in this approach.

Immunoglobulin A

- major role: mucosal immunity.
- humans produce more IgA than any other class (20% of total serum immunoglobulins)
- IgA found in serum and external secretions such as saliva, tracheobronchial secretions, colostrum, milk, and genitourinary secretions
- there are two IgA subclasses and these differ only in 22 of 365 amino acids
- IgA exists both in monomeric (80% of total) and polymeric forms $[(\alpha_2\gamma_2)_n]$ or $(\alpha_2\gamma_2)_n$ where n is 2–5]
- monomeric IgA is synthesized by plasma cells located in the interstitial space of exocrine glands
- the major polymeric form is the IgA dimer (monomers combine with the J chain, which is also synthesized by IgA plasma cells, to form $(\text{IgA})_2$ -J dimers)
 - IgAs are too large to cross tight junctions, they are transported across the epithelium by an active transport system

Secretory IgA

- appear to be locally derived and not from serum, consists of four components:
 - 1/2. dimer of two monomeric molecules
 3. secretory component (70-kd protein) which binds noncovalently to the IgA dimer
 4. J chain (15-kd protein)

Mechanism of secretion

- epithelial cells synthesize secretory component in the form of a six-domain precursor
- the sixth domain functions as the transmembrane segment of the polypeptide receptor.
- the membrane form of secretory component is located at the basolateral surface of the epithelial cells, which are exposed to locally produced IgA dimers
- membrane secretory component acts as a specific receptor for the J chain of IgA dimers
- after binding to dimeric IgA, the noncovalently associated secretory component-IgA dimer complex is endocytosed into intracellular vesicles that transport the entire complex to the apical plasma membrane
- at some point, the dimeric IgA becomes covalently linked to the secretory component through a disulfide bond
- the newly formed dimeric IgA-secretory component complex is cleaved from the membrane-anchoring domain of membrane secretory component
- secretory IgA can then be released into exocrine secretions by exocytosis.

Middleton: Allergy: Principles and Practice, 5th ed., Copyright © 1998 Mosby-Year Book, Inc.

Hoffman: Hematology: Basic Principles and Practice, 3rd ed., Copyright © 2000 Churchill Livingstone, Inc.

Characterize confidence intervals

When a variable has a bell-shaped distribution, the sample mean $\pm 1.96 \times \text{SEM}$ represents the 95% confidence interval for the mean. The length of this confidence interval describes the precision of the mean estimate. For example, if a study reports that mean systolic blood pressure is 123mm Hg, SD = 10 mm Hg, and SEM = 2 mm Hg, then 95% of the population represented by this study should have a systolic blood pressure between 103 and 143 mm Hg, and if 100 similar studies were performed, 95 of them would be expected to yield a mean systolic blood pressure within the confidence interval from 119 to 125 mm Hg. In other words, 95% probability that the reported interval contains the true value.

Source: Goldman: Cecil Textbook of Medicine, 21st ed,pg 85

The effect of xanthine oxidase in ischemia-reperfusion injury

Cells lacking adequate vascular supply of nutrient oxygen are ischemic and will progress to cellular death unless blood flow is efficiently restored to these tissues. Reperfusion of viable ischemic tissue, however, can actually amplify cellular injury through a complex cascade of cellular and tissue changes. Reperfusion injury is often far more severe than the damage incurred during the period of ischemia, and it is characterized by cellular edema, intracellular calcium overload with activation of calcium-dependent autolytic enzymes, disruption of lipid-laden membranes, and alteration of mitochondrial structure and function. The first organ discovered to exhibit reperfusion dysfunction was the heart, which experiences arrhythmias and impaired ventricular contractile function (“myocardial stunning”) with reperfusion after acute coronary events. Reperfusion injury centers around the re-introduction of oxygen to ischemic cells, and highly reactive, unstable oxygen metabolites [superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl anion (OH^-)] are its major mediators. These toxic oxygen-derived metabolites subsequently produce peroxidation of lipid membranes, protein degradation, nucleic acid damage, hemoprotein/cytochrome inactivation, and neutralization of nitric oxide. A major source of these reactive oxygen species in reperfusion injury is the enzyme xanthine oxidase, which is converted from xanthine dehydrogenase in ischemic endothelial and parenchymal cells. Xanthine oxidase utilizes oxygen and hypoxanthine as substrates, and it is responsible for the majority of superoxide anion and hydrogen peroxide produced in reperfusion injury. Experimentally, oxygen free radical scavengers and antioxidants have been shown to decrease the severity of reperfusion injury. In addition to reactive oxygen metabolites, other mediators and cytokines from resident PMN’s and endothelial cells combine to produce severe reperfusion injury, consisting of vasoconstriction, platelet aggregation, PMN-plugging of capillaries, and increased microvascular permeability (i.e., the “no re-flow” stage of reperfusion injury).

References:

- O’Leary JP. *The Physiologic Basis of Surgery*, 3rd Ed. pp 398-99.
Greenfield LJ. *Surgery: Scientific Principles and Practice*, 3rd Ed. pp 172-173.

List the most common side effects of pancuronium

PANCURONIUM

A nondepolarizing neuromuscular blocking agent

Action is usually antagonized by anticholinesterase agents

Has vagolytic activity

Side Effects:

- histamine release (less likely than most other neuromuscular blocking agents)
- itching of skin (less frequent, may be cause by histamine release)
- bronchospasm (rare, may be cause by histamine release)
- circulatory depression or collapse (rare, may be cause by histamine release)
- decreased blood pressure (rare, may be cause by histamine release)
- edema (rare, may be cause by histamine release)
- erythema (rare, may be cause by histamine release)
- skin flushing (rare, may be cause by histamine release)
- increased blood pressure
- tachycardia* (less frequent, may be cause by histamine release or vagolytic activity)
- excessive salivation
- skin rash (less frequent, may be cause by histamine release)
- apnea, respiratory insufficiency

References:

- 1) Drug Information for the Health Care Professional. 17th edition; p. 2121, 2131-2.
- 2) Clinical Pharmacology Made Ridiculously Simple, Olsen 1997, p 82.

Malignant Hyperthermia

Malignant hyperthermia is characterized by paroxysmal fulminant hypermetabolic crisis in skeletal and heart muscle. Massive heat generation overwhelms body's ability to dissipate heat. Any anesthetic agent and muscle relaxants may trigger this condition. Halothane and succinylcholine are the most common offenders. Of note, malignant hyperthermia is a condition that can occur at any time perioperatively.

Malignant hyperthermia is genetically predisposed syndrome transmitted in autosomal dominant fashion with reduced penetrance and variable expressivity. This condition results from sudden increase in intracellular calcium in skeletal muscle (and possibly also cardiac muscle) triggered by causative agents.

Excessive myoplasmic calcium activates ATPase and phosphorylase and cause muscle contracture. This results in massive increase in oxygen consumption, carbon dioxide production and heat generation. Calcium within mitochondria at toxic concentration cause uncoupling of oxidative phosphorylation and lead to increased anaerobic metabolism. This results in accelerated generation of lactic acid, carbon dioxide and heat. Membrane permeability increases when ATP level eventually falls, leading to leakage of potassium, magnesium and phosphates from myoplasm and flow of calcium into myoplasm. Severe respiratory and metabolic acidosis develops and dysrhythmias and cardiac arrest may ensue. Muscle damage manifest as rhabdomyolysis, myoglobinuria and hyperkalemia.

Patients with malignant hyperthermia present with unexplained tachycardia (96%) and tachypnea (85%). They may also present with profuse sweating, flushed skin, mottling and cyanosis, arrhythmias, hyper or hypotension. Marked fasciculations or sustained rigidity may also be present. Rapid rise in body temperature (1 degree celcius per 5 minutes) is classic finding, but this is a relatively late sign. Diagnosis of malignant hyperthermia is made based on clinical findings: most commonly, clinical triad of history of exposure to causative agent, muscle rigidity and signs of hypermetabolic activity with hyperthermia. 20% of patients may not have any of these signs. They may present instead with pulmonary edema, myoglobinuria, DIC or cardiovascular collapse.

ABG analysis classically reveals respiratory and metabolic acidosis in association with hypercapnia. Sudden, marked increase in end-tidal CO₂ is best early clue to the diagnosis. Hypoxemia, hyperkalemia, hypermagnesemia, myoglobinemia, hemoglobinemia, increase in lactate, pyruvate and creatine kinase may also be observed.

Early diagnosis, prompt dantrolene treatment and supportive and cooling measures are key to management of patients with malignant hyperthermia. Clinician must promptly discontinue use of causative agent, intubate and hyperventilate the patient with 100% oxygen, cool down the patient with iv refrigerated saline, iced saline lavage of GI tract and surface cooling with ice/alcohol/fans. IV dantrolene sodium should be administered promptly at 1-2mg/kg and same dose should be repeated Q15-30 minutes up to 10-20mg/kg as needed and continue treatment for up to 48 hours to prevent retriggering event. Fluid resuscitation, diuretic, procainamide and bicarbonate may be used as needed. Patient needs to be closely monitored. Mortality is in excess of 30%

References:

1. Tomarken JL, Britt BA: Malignant hyperthermia *Ann Emerg Med* 1987;16:1253-65
2. Ellis FR, Smith G: Symposium on malignant hyperthermia. *Br J Anaesth* 1988; 60:251-319
3. Sabiston, 15th edition, p343

Describe the compensation of isovolemic anemia

Isovolemic anemia is also known as acute hemodilution. This is sometimes used as a method to reduce autologous pRBC transfusion in the perioperative period. The patient will undergo the removal of blood and replacement with cell-free fluid (colloid or crystalloid). The intent is that operative blood loss will be dilute and the patient can be transfused autogenous blood instead of autologous blood, ideally after operative blood loss has occurred. There are conflicting reports of the physiologic response of isovolemic anemia. Please see the abstract below.

Transfusion

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Heart rate increases linearly in response to acute isovolemic anemia

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BACKGROUND: The cardiovascular response to acute isovolemic anemia in humans is thought to differ from that of other species. Studies of anesthetized humans have found either no change or a decreased heart rate. A previous study showed that in 32 healthy unmedicated humans, heart rate increased during acute isovolemic anemia. The hypothesis that heart rate in humans increases in response to acute isovolemic anemia and that the increase is affected by gender was tested.

STUDY DESIGN AND METHODS: Acute isovolemic anemia to a Hb concentration of approximately 5 g per dL in 95 unmedicated healthy humans was produced by simultaneous withdrawal of blood and IV replacement with 5-percent HSA and autologous platelet-rich plasma. The relationship between heart rate and Hb concentration was examined using a mixed-effects linear regression model that allowed each person to have a fitted line with its own slope and intercept. Cubic and quadratic terms were added to determine if these improved the goodness of fit. The effect of gender was tested by including it and its interactions with Hb in the mixed model.

RESULTS: The relationship between heart rate and Hb concentration was linear ($p < 0.001$) and consistent among the population studied: heart rate = $116.0 - 4.0 [\text{Hb}]$ (slope 95% CI: -4.2 to -3.8 beats/min/g Hb). Adding a cubic or quadratic term did not significantly improve the goodness of fit of the mathematical expression to the data, confirming the linear nature of the relationship between heart rate and Hb concentration. For women, the slope of the heart rate response was significantly greater than it was for males (difference \pm SE: 0.70 ± 0.23 , $p < 0.005$).

CONCLUSION: In 95 unmedicated, healthy humans, heart rate was a linear function of Hb during acute isovolemic anemia. Females had a significantly greater slope of increase in heart rate with decreasing Hb concentration than did males. The relationship is consistent among individuals, is similar to that reported for conscious dogs, and differs from that found previously in anesthetized humans.

Determine the significance of randomized trials

Randomization is a process in which patients are assigned to different arms of a trial without bias. Randomization allows for removal of selection bias—treatment groups will be similar with respect to all variables (e.g. Age, sex, race, comorbidities, etc.) except for the one being tested (e.g. drug vs. placebo). This effect of eliminating confounding variables increases with sample size. Without randomization one could choose to put those more likely to respond to treatment in the intervention group, and those less likely in the placebo group. Decisions regarding who will receive treatment are not made by a person in randomized studies. By removing all other variables one can be certain that differences between groups are due to treatment.

In studies that are not randomized, for example case control studies, great effort is required to ensure that comparisons are made between individuals that are as similar as possible. It is however, impossible to eliminate all variation. These efforts are not necessary with randomized trials. All that is required is a system for randomization and a large enough group. Randomization does not eliminate all forms of bias. Blinding is required to eliminate observer bias and measurement bias.

Randomized trials allow for causality to be determined. While other study types may be able to determine that a relationship exists, only randomized controlled trials allow for determining the nature of that relationship.

Sources

Fletcher RH, Fletcher SW, Wagner EH. *Clinical Epidemiology The Essentials*. 3rd ed. Williams and Wilkins, 1996, p145.

Describe the increased collagen content during wound healing

There are 3 phases to wound healing: *Inflammatory Phase*, *Proliferative Phase*, and *Maturational Phase*.

Inflammatory Phase (0–3 days): Neutrophils arrive on the scene and attain large numbers by 24 hours after wound healing begins. Next, macrophages have the *dominant* role in the inflammatory phase; they are recruited and secrete many growth factors and cytokines which induce fibroblast proliferation (source of collagen), endothelial cell proliferation, and extracellular matrix production.

Proliferative Phase (3 days–3 weeks): The formation of a fibrin-fibronectin matrix initiates the proliferative phase; this becomes saturated with fibroblasts approximately 3 days after the insult. Fibroblasts are the *dominant* cell involved in the proliferative phase. Collagen accumulation in the wound reaches a maximum by the end of this phase (3 weeks). Type III collagen is predominant. The amount of collagen synthesized dictates the *initial* wound strength. At approximately 3–4 weeks, collagen synthesis declines and remodeling takes place. Collagen crosslinking is dependent on hydroxylation of lysine and proline. Oxygen, Vitamin C, and Iron enhance hydroxylation. Corticosteroids inhibit hydroxylation; their effect can be counterbalanced by Vitamin A. (However, steroid inhibition on wound contraction—a process dependent on myofibroblasts—is not reversed with Vit. A).

Maturational / Remodeling Phase: Type I collagen replaces Type III collagen; the usual 4:1 ratio as in a normal adult is restored. *Tensile* strength is increased as random collagen fibrils are replaced with organized fibrils with more intermolecular bonds. Collagen is in a state of equilibrium: collagen degradation by collagenase (and other MMPs) is balanced by new production of collagen. At equilibrium, collagen fibrils align themselves in a longitudinal manner as dictated by the stress on the wound. Scars increase in *tensile* strength for approximately 6 months after the initial insult and reach approximately 70% of normal skin tensile strength. Ultimate wound strength is determined by the degree of collagen organization and crosslinking.

List the mechanism of skin necrosis during coumadin administration

Coumadin induced skin necrosis, associated with a diffuse thrombosis in small vessels usually involves full thickness sloughing over fatty areas such as buttocks, abdomen, and breasts but can occur anywhere.

Coumadin blocks the essential vitamin K-dependent carboxylation of coagulation factors II, VII, IX, and X resulting in the formation of biologically inactive proteins and a decrease in the coagulation activity of these factors in plasma. Half-life of Vit K dependent factors ranges from 6-60hours therefore the full effect of the therapy is delayed for 2-3 days. Also, full restoration of normal coagulation after stopping coumadin requires at least 3-5 days.

The tissue necrosis is **associated with a protein C deficiency**. **Protein C is normally an anticoagulant** by inactivating Factor Va and Factor VIIIc. **Protein C and S are also Vitamin K dependent factors**. Therefore, the relatively rapid decay in already low protein C levels at a time when levels of coagulation factors are still normal, results in a net procoagulant state. Treatment includes stopping Coumadin and starting Heparin.

INR: International Normalized Ratio corrects for the differences of the various thromboplastins used in the prothrombin assays.

1. Surgery: Basic Science and Clinical Evidence. Norton et al; 2001. p123-150
2. Greenfield, 2nd Edition. p97-98.

Characterize radiation injury to soft tissues

Radiotherapy works by releasing free radicals and peroxidases into cells. These intermediaries cause destruction of rapidly dividing cells, such as neoplastic cells, by fracturing DNA molecules. These ionizing rays also cause a nonspecific injury and therefore can damage surrounding normal tissue. Endothelial cells in blood vessels are particularly susceptible to injury, leading to arteritis and ischemic fibrosis. Hence, poorly vascularized tissues such as bone and cartilage are very susceptible to radiation injury. A wide spectrum of injuries has been reported, ranging from erythema of the skin (radiodermatitis) to soft tissue ulceration with osteoradionecrosis and chondroradionecrosis. Although the severity of the injuries is dose-dependent, standard doses of 4500 to 5000 cGy given over 4 to 6 weeks appear to limit complications.

TABLE 198-1 -- TOLERANCE OF NORMAL TISSUES TO IRRADIATION

TISSUE	TOXIC EFFECT	LIMITING DOSE (Gy) *
Bone marrow	Aplasia	2.5
Lung	Pneumonitis, fibrosis	15.0
Kidney	Nephrosclerosis	20.0
Liver	Hepatitis	25.0
Spinal cord	Infarction, necrosis	45.0
Intestine	Ulceration, fibrosis	45.0
Heart	Pericarditis, myocarditis	45.0
Brain	Infarction, necrosis	50.0
Skin	Dermatitis, sclerosis	55.0

*Radiation in 2.0-Gy fractions to the whole organ for 5 days weekly produces a 5% incidence of the listed toxicities at the limiting doses listed.

Source: Townsend: Sabiston Textbook of Surgery, 16th ed., Copyright ©
Goldman: Cecil Textbook of Medicine, 21st ed., Copyright © 2000
W. B. Saunders Company pgs1061-1062

List the statistical definition of Median

The median is the number that divides the total distribution of ordered observations in half. If the number of observations (n) is even, then the median is the mean of the $n/2$ and $(n/2)+1$ observations. It is considered more robust than the mean because it is less influenced by outliers.

The mean is defined as the sum of all observations divided by the number of observations.

The mode is the value of the variable that occurs most frequently.

Dunn and Clark. Basic Statistics: a primer for the biomedical sciences. 3rd ed. Copyright ? 2001 John Wiley and Sons, Inc.

Characterize staph epiderm exoslime

Staphylococcus epidermis exoslime is a polysaccharide composed of glycosaminoglycans which allows for strong intercellular adhesion between bacterial cells and the formation of biofilms. The ability to form biofilms allows *S. epidermidis* to cause resistant infections particularly when foreign object are present. This is due to inability of antibiotics to penetrate the mucopolysaccharide of the biofilm. The *ica* operon has been shown to control the production of "slime". The *ica* genes can be tested for as a virulence marker. Many reports show that some strains of *Staphylococcus aureus* also contain the *ica* and are capable of producing exoslime.

Sources

Arciola CR, Baldassarri L, Montanaro L. Presence of *icaA* and *icaD* Genes and Slime Production in a Collection of Staphylococcal Strains from Catheter-Associated Infections. *J of Clin Micro*. 2001, 39(6):2151-2156.

ANATOMY OF SPIGELIAN HERNIA

Spigelian hernias are unusual abdominal wall defects with fewer than 400 cases reported in the world literature. The hernia occurs through the linea semilunaris (which runs lateral to the rectus abdominis muscle) and between the muscular fibers of the internal oblique muscle and the line of insertion of the external oblique aponeurosis into the anterior rectus sheath. Most commonly, it occurs at the junction of the semilunar line and the semicircular line.

Most spigelian hernias are small (1-2 cm in diameter) and develop in fourth to seventh decades of life. Incarceration is common with this form of hernia because the fascial ring is small and inelastic. Spigelian hernias should be repaired because of the risks associated with incarceration.

List the biologic effects of tamoxifen

- Antiestrogen compound
- Binds directly to the estrogen receptor and functions as a weak agonist/antagonist
- Long plasma half life
- Requires four weeks or longer to achieve steady state levels
- Side effects: hot flashes, amenorrhea, occas n/v, changes in serum lipid profile, thromboembolic events, cancer risk
- Employed as an adjuvant in postmenopausal women, as palliative in pre- and post- menopausal women for met disease

Describe the molecules suppressing malignancy

The three general causes for cells to become malignant are overactivation of a gene that promotes cell division, loss of function of a gene that normally restrains growth, and finally defects on DNA repair genes.

1) Genes that promote normal cell growth are referred to as *proto-oncogenes*, and activation of such genes by mutation, amplification, or dysregulation converts them to *oncogenes*. MEN IIA and MEN IIB are examples of oncogenes.

2) Genes that normally restrain growth are called *tumor suppressor genes*, and unregulated cell growth occurs if their function is lost. Given the diploid nature of mammalian cells, loss of one allele is unlikely to have significant consequences in most instances. This correctly predicts that the inheritance pattern of cancer in a family with a tumor suppressor gene is **autosomal dominant**, although the cellular mechanism is recessive.

3) The third category of genes contributing to malignancy consists of DNA repair genes. DNA polymerase has a finite error rate, and many environmental influences can damage DNA. Therefore, repair systems are essential to protect the integrity of the genome. When the repair system is faulty, the rate of accumulation of mutations is exponential as cell divisions occur. The likelihood of developing malignancy increases as these mutations begin to involve oncogenes and tumor suppressor genes.

Most inherited cancer predisposition syndromes involve the inheritance of one mutated allele, and one wild type allele. The hallmarks of a tumor suppressor gene are as follows: (1) the germline mutation that affects one allele generally causes a loss of function, (2) tumors also show loss of the second normal allele as a result of a somatic mutation, and (3) often the normal function of the gene is to suppress unrestrained cellular growth or to promote differentiation.

p53, for example, is a tumor suppressor gene involved in halting the cell cycle to allow for DNA repair; it also promotes apoptosis. Altered p53 function leads to unchecked cellular growth and inhibition of programmed cell death.

Selected list of Tumor Suppressor Genes Responsible for Familial Cancer Syndromes (Table 84-1)

<i>SYNDROME</i>	<i>GENE</i>	<i>TUMORS</i>
Familial Breast/Ovarian Cancer	BRCA1	Breast, ovarian, colon, prostate Cancer
Familial Breast Cancer	BRCA2	Male/Female breast cancer
Familial polyposis coli	APC	Intestinal polyposis, colorectal cancer
Familial Retinoblastoma	RB	Retinoblastoma, osteosarcoma
Li-Fraumeni	p53	Sarcomas, breast cancer
Familial Melanoma	p16	Melanoma, pancreatic cancer
Neurofibromatosis type 1	NF1	Neurofibroma, neuro-fibrosarcoma, and brain tumor
Tuberous sclerosis	TSC2	Angiofibroma, renal angiomyolipoma
Von Hippel-Lindau	VHL	Renal cell cancer, pheochromocytoma, retinal angioma, hemangioblastoma

Reference: *Harrison's Principles of Internal Medicine*. Collins, Trent, 14th edition; Chapter 84
Schwartz, 7th Edition

Fluoroquinolone antibiotics

Fluoroquinolones are bactericidal antibiotic which acts intracellularly by inhibiting topoisomerase II (DNA gyrase) and/or topoisomerase IV. Topoisomerases are essential bacterial enzymes that are critical catalysts in the duplication, transcription and repair of bacterial DNA. Fluoroquinolones are effective against most strains of G+/G- bacteria.

Fluoroquinolones get distributed to most body fluids and tissues. High concentrations are attained in kidney, gallbladder, liver, lungs, gynecologic tissue, prostatic tissue, phagocytic cells, urine, sputum and bile. It is also distributed in skin, fat, muscle, bone and cartilage. Indications and usage of fluoroquinolones include treatment of UTI, lower respiratory tract infection, skin, bone and joint infection.

Pharmacokinetics are linear with peak serum levels reached within 1 hour, elimination of majority of drugs at 12 hours, with half life of 6 hours. 50-70% of this drug is excreted in urine as unchanged molecule. Patients with renal insufficiency will have slightly prolonged half life while there is no significant change in pharmacokinetics in patients with chronic liver disease.

Use of fluoroquinolones are not recommended in pediatric population with exception of use of Ciprofloxacin when patients have been exposed to inhalation anthrax. Animal studies have shown permanent cartilage lesions in immature dogs with use of fluoroquinolones. This drug is also not recommended for use in pregnant women or breastfeeding mothers as it has shown to cause arthropathy in immature animals.

Other contraindication to the use of this medication include previous allergic reaction, hypersensitivity to quinolone derivatives or fluoroquinolones, photosensitivity, history of QT interval prolongation and history of tendonitis or tendon rupture.

Adverse effects include seizure (especially in patients with previous history of seizure, alcoholics or patients of theophylline), prolongation of QT interval, phototoxic reaction (especially with sparfloxacin) and Achilles tendonitis and tendon rupture.

References:

1. Drug Information for Health Care Professionals – 24th edition (2004)
2. Physician's Desk Reference, 1997