“Biochemistry is the study of carbon compounds that crawl.” “We think we have found the basic mechanism by which life comes from life.” —Francis H. C. Crick “The biochemistry and biophysics are the notes required for life; they conspire, collectively, to generate the real unit of life, the organism.”

This high-yield material includes molecular biology, genetics, cell biology, and principles of metabolism (especially vitamins, cofactors, minerals, and single-enzyme-deficiency diseases). When studying metabolic pathways, emphasize important regulatory steps and enzyme deficiencies that result in disease, as well as reactions targeted by pharmacologic interventions. For example, understanding the defect in Lesch-Nyhan syndrome and its clinical consequences is higher yield than memorizing every intermediate in the purine salvage pathway.

Do not spend time learning details of organic chemistry, mechanisms, or physical chemistry. Detailed chemical structures are infrequently tested; however, many structures have been included here to help students learn reactions and the important enzymes involved. Familiarity with the biochemical techniques that have medical relevance—such as ELISA, immunoelectrophoresis, Southern blotting, and PCR—is useful. Review the related biochemistry when studying pharmacology or genetic diseases as a way to reinforce and integrate the material.

H1 histone (linker) Supercoiled structure Heterochromatin Euchromatin Metaphase chromosome Nucleosome (H2A, H2B, H3, H4) 2 DNA DNA double-helix

DNA exists in the condensed, chromatin form to fit into the nucleus. DNA loops twice around a histone octamer to form a nucleosome (“beads on a string”). H1 binds to the nucleosome and to “linker DNA,” thereby stabilizing the chromatin fiber.

Phosphate groups give DNA a ⊖ charge. Lysine and arginine give histones a ⊕ charge.

In mitosis, DNA condenses to form chromosomes. DNA and histone synthesis occurs during S phase.

Mitochondria have their own DNA, which is circular and does not utilize histones.

Heterochromatin Condensed, appears darker on EM (labeled H HeteroChromatin = Highly Condensed. in A ; Nu, nucleolus). Sterically inaccessible, Barr bodies (inactive X chromosomes) may be thus transcriptionally inactive. • methylation, visible on the periphery of nucleus.

• acetylation.

Histone methylation Usually causes reversible transcriptional Histone Methylation Mostly Makes DNA Mute. suppression, but can also cause activation depending on location of methyl groups.

Histone acetylation Removal of histone's ⊕ charge □ relaxed DNA Histone Acetylation makes DNA Active. coiling □• transcription.

Histone deacetylation Removal of acetyl groups □ tightened DNA coiling □• transcription.

Nucleotides NucleoSide = base + (deoxy)ribose (Sugar). NucleoTide = base + (deoxy)ribose + phosphaTe; linked by 3′-5′ phosphodiester bond.

PURines (A,G)—2 rings. PYrimidines (C,U,T)—1 ring.

Deamination reactions: Cytosine □ uracil Adenine □ hypoxanthine Guanine □ xanthine 5-methylcytosine □ thymine

Uracil found in RNA; thymine in DNA. Methylation of uracil makes thymine.

Purine (A, G) Pyrimidine (C, U, T) 5′ end of incoming nucleotide bears the triphosphate (energy source for the bond). Triphosphate bond is target of 3′ hydroxyl attack.

PURe As Gold. CUT the PY (pie). Thymine has a methyl. C-G bond (3 H bonds) stronger than A-T bond (2 H bonds). • C-G content □• melting temperature of DNA. "C-G bonds are like Crazy Glue." purr until they GAG): Glycine Aspartate Glutamine

De novo pyrimidine Various immunosuppressive, antineoplastic, and antibiotic drugs function by interfering with and purine synthesis nucleotide synthesis: (de novo requires aspartate, Glutamine + CO2 glycine, glutamine, and THF)

Lefunomide 6-MP,

Mycophenolate,(impaired in

Pyrimidine synthesis:

Leflunomide: inhibits dihydroorotate dehydrogenase 5-fluorouracil (5-FU) and its prodrug capecitabine: form 5-F-dUMP, which inhibits thymidylate synthase (• dTMP)

Purine synthesis: 6-mercaptopurine (6-MP) and its prodrug azathioprine: inhibit de novo purine synthesis

Mycophenolate and ribavirin: inhibit inosine monophosphate dehydrogenase

Purine and pyrimidine synthesis: • Hydroxyurea: inhibits ribonucleotide reductase

AMP GMP • Methotrexate (MTX), trimethoprim (TMP), and pyrimethamine: inhibit dihydrofolate reductase (• deoxythymidine monophosphate [dTMP]) in humans, bacteria, and protozoa, 5-FU,

MTX, TMP, pyrimethamine

ADA, adenosine deaminase; APRT, adenine phosphoribosyltransferase; HGPRT, hypoxanthine guanine phosphoribosyltransferase; XO, xanthine oxidase.

Defective purine salvage due to absent HGPRT, which converts hypoxanthine to IMP and guanine to GMP. Results in excess uric acid production and de novo purine synthesis. X-linked recessive.

Findings: intellectual disability, self-mutilation, aggression, hyperuricemia (orange "sand" [sodium urate crystals] in diaper), gout, dystonia, macrocytosis.

Treatment: allopurinol or febuxostat (2nd line).

HGPRT: Hyperuricemia Gout Pissed off (aggression, self-mutilation) Retardation (intellectual disability) DysTonia

Unambiguous Each codon specifies only 1 amino acid.

Commaless, Read from a fixed starting point as a continuous Exceptions: some viruses. nonoverlapping sequence of bases.

Universal Genetic code is conserved throughout Exception in humans: mitochondria. evolution.

DNA replication Eukaryotic DNA replication is more complex than in prokaryotes but uses many enzymes analogous to those listed below. In both prokaryotes and eukaryotes, DNA replication is semiconservative, involves continuous and discontinuous (Okazaki fragment) synthesis, and occurs in the 5′ □ 3′ direction.

B Y-shaped region along DNA template where leading and lagging strands are synthesized.

C Unwinds DNA template at replication fork. Helicase Halves DNA. Deficient in Bloom syndrome (BLM gene mutation).

Single-stranded Prevent strands from reannealing. binding proteins

F Makes an RNA primer on which DNA polymerase III can initiate replication.

H Prokaryotes only. Degrades RNA primer; Same functions as DNA polymerase III, also replaces it with DNA. excises RNA primer with 5′ □ 3′ exonuclease.

I Catalyzes the formation of a phosphodiester Joins Okazaki fragments. bond within a strand of double-stranded DNA. Ligase Links DNA.

Mutations in DNA Severity of damage: silent << missense < nonsense < frameshift. Types of single nucleotide (point) mutations: • Transition—purine to purine (eg, A to G) or pyrimidine to pyrimidine (eg, C to T).

ƒTransversion—purine to pyrimidine (eg, A to T) or pyrimidine to purine (eg, C to G). Single nucleotide substitutions

Silent mutation Nucleotide substitution codes for same (synonymous) amino acid; often base change in 3rd position of codon (tRNA wobble).

Missense mutation Nucleotide substitution results in changed amino acid (called conservative if new amino acid has similar chemical structure). Examples include sickle cell disease (substitution of glutamic acid with valine).

Nonsense mutation Nucleotide substitution results in early stop codon (UGA, UAA, UAG). Usually results in nonfunctional protein. Stop the nonsense! Other mutations

Frameshift mutation Deletion or insertion of a number of nucleotides not divisible by 3 • misreading of all nucleotides downstream. Protein may be shorter or longer, and its function may be disrupted or altered. Examples include Duchenne muscular dystrophy, Tay-Sachs disease.

Splice site mutation Retained intron in mRNA • protein with impaired or altered function. Examples include rare causes of cancers, dementia, epilepsy, some types of β-thalassemia, Gaucher disease, Marfan syndrome.

Lac operon Classic example of a genetic response to an environmental change. Glucose is the preferred metabolic substrate in E coli, but when glucose is absent and lactose is available, the lac operon is activated to switch to lactose metabolism. Mechanism of shift:

Low glucose □• adenylate cyclase activity □• generation of cAMP from ATP □ activation of catabolite activator protein (CAP) □• transcription.

High lactose □ unbinds repressor protein from repressor/operator site □• transcription.

Binds CAP site,

Lacl LacZ LacY LacACAP site Promoter Operator Repressor protein Lacoperon Bindsoperator, blockstranscription organization of a eukaryotic gene Exon Intron Exon Intron Exon

Regulation of gene expression

Silencer DNA locus where regulatory proteins (“repressors”) bind, decreasing expression of a gene on the same chromosome.

Initial transcript is called heterogeneous nuclear RNA (hnRNA). hnRNA is then modified and becomes mRNA.

The following processes occur in the nucleus:

Capping of 5′ end (addition of 7-methylguanosine cap)

Polyadenylation of 3′ end (≈ 200 As)

Splicing out of introns

Capped, tailed, and spliced transcript is called mRNA.

mRNA is transported out of nucleus to be translated in cytosol.

mRNA quality control occurs at cytoplasmic processing bodies (P-bodies), which contain exonucleases, decapping enzymes, and microRNAs; mRNAs may be degraded or stored in P-bodies for future translation.

Poly-A polymerase does not require a template. AAUAAA = polyadenylation signal.

Eukaryotes RNA polymerase I makes rRNA, the most common (rampant) type; present only in nucleolus. RNA polymerase II makes mRNA (massive), microRNA (miRNA), and small nuclear RNA (snRNA). RNA polymerase III makes 5S rRNA, tRNA (tiny). No proofreading function, but can initiate chains. RNA polymerase II opens DNA at promoter site.

I, II, and III are numbered in the same order that their products are used in protein synthesis: rRNA, mRNA, then tRNA.

α-amanitin, found in Amanita phalloides (death cap mushrooms), inhibits RNA polymerase II. Causes severe hepatotoxicity if ingested.

Actinomycin D, also called dactinomycin, inhibits RNA polymerase in both prokaryotes and eukaryotes.

Prokaryotes 1 RNA polymerase (multisubunit complex) Rifampin inhibits DNA-dependent RNA makes all 3 kinds of RNA. polymerase in prokaryotes.

Splicing of pre-mRNA Part of process by which precursor mRNA (pre-mRNA) is transformed into mature mRNA. Alterations in snRNP assembly can cause clinical disease; eg, in spinal muscular atrophy, snRNP assembly is affected due to • SMN protein congenital degeneration of anterior horns of spinal cord symmetric weakness (hypotonia, or "floppy baby syndrome").

Primary transcript combines with small nuclear ribonucleoproteins (snRNPs) and other proteins to form spliceosome.

RNA polymerases P P OOH 3˜OH 3˜Cleavage at 5˜splice site; lariat-shaped (loop) intermediate is generated. Cleavage at 3˜splice site; lariat is released to precisely remove intron and join 2 exons. Exon 1 Exon 2 Spliceosome+P UGAAG3˜Exon 1 Mature mRNA Exon 2 P UGAAG

Structure 75–90 nucleotides, 2° structure, cloverleaf form, anticodon end is opposite 3′ aminoacyl end. All tRNAs, both eukaryotic and prokaryotic, have CCA at 3′ end along with a high percentage of chemically modified bases. The amino acid is covalently bound to the 3′ end of the tRNA. CCA Can Carry Amino acids. T-arm: contains the TΨC (ribothymidine, pseudouridine, cytidine) sequence necessary for tRNAribosome binding. T-arm Tethers tRNA molecule to ribosome. D-arm: contains Dihydrouridine residues necessary for tRNA recognition by the correct aminoacyltRNA synthetase. D-arm allows Detection of the tRNA by aminoacyl-tRNA

synthetase. Attachment site: the 5′-CCA-3′ is the amino acid acceptor site.

Charging Aminoacyl-tRNA synthetase (uses ATP; 1 unique enzyme per respective amino acid) and binding of charged tRNA to the codon are responsible for the accuracy of amino acid selection. Aminoacyl-tRNA synthetase matches an amino acid to the tRNA by scrutinizing the amino acid before and after it binds to tRNA. If an incorrect amino acid is attached, the bond is hydrolyzed. A mischarged tRNA reads the usual codon but inserts the wrong amino acid.

3. eIFs released when the mRNA and the ribosomal 60S subunit assemble with the complex. Requires GTP.

Aminoacyl-tRNA binds to A site (except for initiator methionine, which binds the P site), requires an elongation factor and GTP. rRNA ("ribozyme") catalyzes peptide bond formation, transfers growing polypeptide to amino acid in A site.

Ribosome advances 3 nucleotides toward 3′ end of mRNA, moving peptidyl tRNA to P site (translocation).

ATP—tRNA Activation (charging).

GTP—tRNA Gripping and Going places (translocation).

Think of "going APE": A site = incoming Aminoacyl-tRNA. P site = accommodates growing Peptide. E site = holds Empty tRNA as it Exits.

Termination Eukaryotic release factors (eRFs) recognize the stop codon and halt translation • completed polypeptide is released from ribosome. Requires GTP.

Trimming Removal of Nor C-terminal propeptides from zymogen to generate mature protein (eg, trypsinogen to trypsin).

Covalent alterations Phosphorylation, glycosylation, hydroxylation, methylation, acetylation, and ubiquitination.

Chaperone protein Intracellular protein involved in facilitating and maintaining protein folding. In yeast, heat shock proteins (eg, HSP60) are expressed at high temperatures to prevent protein denaturing/misfolding.

Cell cycle phases Checkpoints control transitions between phases of cell cycle. This process is regulated by cyclins, cyclin-dependent kinases (CDKs), and tumor suppressors. M phase (shortest phase of cell cycle) includes mitosis (prophase, prometaphase, metaphase, anaphase, telophase) and cytokinesis (cytoplasm splits in two). G1 and G0 are of variable duration.

GO G1Growth DNASynthesis INTERPHASERb, p53 modulate Grestriction point G2 M CytokinesisS Mitosis

Site of synthesis of secretory (exported) proteins and of N-linked oligosaccharide addition to lysosomal and other proteins.

Nissl bodies (RER in neurons)—synthesize peptide neurotransmitters for secretion.

Free ribosomes—unattached to any membrane; site of synthesis of cytosolic, peroxisomal, and mitochondrial proteins.

Mucus-secreting goblet cells of the small intestine and antibody-secreting plasma cells are rich in RER.

Proteins within organelles (eg, ER, Golgi bodies, lysosomes) are formed in RER.

Cell trafficking Golgi is distribution center for proteins and lipids from ER to vesicles and plasma membrane. Posttranslational events in Golgi include modifying N-oligosaccharides on asparagine, adding O-oligosaccharides on serine and threonine, and adding mannose-6-phosphate to proteins for lysosomal trafficking. Endosomes are sorting centers for material from outside the cell or from the Golgi, sending it to lysosomes for destruction or back to the membrane/Golgi for further use.

I-cell disease (inclusion cell disease/mucolipidosis type II)—inherited lysosomal storage disorder (autosomal recessive); defect in N-acetylglucosaminyl-1-phosphotransferase failure of the Golgi to phosphorylate mannose residues (• mannose-6-phosphate) on glycoproteins proteins are secreted extracellularly rather than delivered to lysosomes. Results in coarse facial features, gingival hyperplasia, clouded corneas, restricted joint movements, claw hand deformities, kyphoscoliosis, and high plasma levels of lysosomal enzymes. Often fatal in childhood.

Key:

Abundant, cytosolic ribonucleoprotein that traffics polypeptide-ribosome complex from the cytosol to the RER. Absent or COPI dysfunctional SRP accumulation of protein in cytosol.

trans COPI: Golgi Golgi (retrograde); cis-Golgi

Anterograde • ER. COPII: ER • cis-Golgi (anterograde).

Golgi apparatus “Two (COPII) steps forward (anterograde); one (COPI) step back (retrograde).” Clathrin: trans-Golgi • lysosomes; plasma membrane • endosomes (receptormediated endocytosis [eg, LDL receptor Rough activity]). endoplasmic reticulum

Peroxisome Membrane-enclosed organelle involved in: β-oxidation of very-long-chain fatty acids (VLCFA) (strictly peroxisomal process) α-oxidation of branched-chain fatty acids (strictly peroxisomal process)

Catabolism of amino acids and ethanol

Synthesis of cholesterol, bile acids, and plasmalogens (important membrane phospholipid, especially in white matter of brain) Zellweger syndrome—autosomal recessive disorder of peroxisome biogenesis due to mutated PEX genes. Hypotonia, seizures, hepatomegaly, early death.

Refsum disease—autosomal recessive disorder of α-oxidation phytanic acid not metabolized to pristanic acid. Scaly skin, ataxia, cataracts/night blindness, shortening of 4th toe, epiphyseal dysplasia. Treatment: diet, plasmapheresis.

Adrenoleukodystrophy—X-linked recessive disorder of β-oxidation due to mutation in ABCD1 gene VLCFA buildup in adrenal glands, white (leuko) matter of brain, testes. Progressive disease that can lead to adrenal gland crisis, coma, and death.

Proteasome Barrel-shaped protein complex that degrades damaged or ubiquitin-tagged proteins. Defects in the ubiquitin-proteasome system have been implicated in some cases of Parkinson disease.

Cytoskeletal elements A network of protein fibers within the cytoplasm that supports cell structure, cell and organelle movement, and cell division.

Cylindrical outer structure composed of a helical array of polymerized heterodimers of αand β-tubulin. Each dimer has 2 GTP bound. Incorporated into flagella, cilia, mitotic spindles. Grows slowly, collapses quickly. Also involved in slow axoplasmic transport in neurons.

Molecular motor proteins—transport cellular cargo toward opposite ends of microtubule.

REtrograde to microtubule (+ -)—DYnein.

Anterograde to microtubule (- +)—Kinesin.

Clostridium tetani, herpes simplex virus, poliovirus, and rabies virus use dynein for retrograde transport to the neuronal cell body.

Drugs that act on microtubules (Microtubules Get Constructed Very Poorly):

Paclitaxel (anticancer) Negative end Near Nucleus. Positive end Points to Periphery.

REaDY? AttacK!

Cilia structure 9 doublet + 2 singlet arrangement of microtubules

A . Basal body (base of cilium below cell membrane) consists of 9 microtubule triplets

B with no central microtubules. Axonemal dynein—ATPase that links peripheral 9 doublets and causes bending of cilium by differential sliding of doublets. Gap junctions enable coordinated ciliary movement.

Kartagener syndrome (1° ciliary dyskinesia)— immotile cilia due to a dynein arm defect. Autosomal recessive. Results in • male and female fertility due to immotile sperm and dysfunctional fallopian tube cilia, respectively; of ectopic pregnancy. Can cause bronchiectasis, recurrent sinusitis, chronic ear infections, conductive hearing loss, and situs inversus (eg, dextrocardia on CXR C).

nasal nitric oxide (used as screening test). (Kartagener's restaurant: take-out only; there's no dynein "dine-in".)

Na+-K+ ATPase is located in the plasma membrane with ATP site on cytosolic side. For each ATP consumed, 3 Na+ leave the cell (pump phosphorylated) and 2 K+ enter the cell (pump dephosphorylated).

Plasma membrane is an asymmetric lipid bilayer containing cholesterol, phospholipids, sphingolipids, glycolipids, and proteins.

Pumpkin = pump K+ in.

Ouabain (a cardiac glycoside) inhibits by binding to K+ site.

Cardiac glycosides (digoxin and digitoxin) directly inhibit the Na+-K+ ATPase, which leads to indirect inhibition of Na+/Ca2+ exchange □• [Ca2+]i □• cardiac contractility.

Cleavage of procollagen Cand N-terminals

Formation of cross-links (stabilized by lysyl oxidase) Collagen fber

Synthesis—translation of collagen α chains (preprocollagen)—usually Gly-X-Y (X and Y are proline or lysine). Collagen is 1⁄3 glycine; glycine content of collagen is less variable than that of lysine and proline. Hydroxyproline is used for lab quantification of collagen. Hydroxylation—hydroxylation of specific proline and lysine residues. Requires vitamin C; deficiency • scurvy. Glycosylation—glycosylation of pro-α-chain hydroxylysine residues and formation of procollagen via hydrogen and disulfide bonds (triple helix of 3 collagen α chains). Problems forming triple helix • osteogenesis imperfecta. Exocytosis—exocytosis of procollagen into extracellular space. Proteolytic processing—cleavage of disulfide-rich terminal regions of procollagen insoluble tropocollagen. Cross-linking—reinforcement of many staggered tropocollagen molecules by covalent lysine-hydroxylysine cross-linkage (by copper-containing lysyl oxidase) to make collagen fibrils. Problems with cross-linking

Menkes disease.

Genetic bone disorder (brittle bone disease) caused by a variety of gene defects (most commonly COL1A1 and COL1A2).

Most common form is autosomal dominant with • production of otherwise normal type I collagen. Manifestations include:

Multiple fractures and bone deformities after minimal trauma (eg, during birth)

B due to the translucent connective tissue over choroidal veins

Some forms have tooth abnormalities, including opalescent teeth that wear easily due to lack of dentin (dentinogenesis imperfecta)

May be confused with child abuse. Treat with bisphosphonates to
• fracture risk. Patients can't BITE:

Faulty collagen synthesis causing hyperextensible skin A , hypermobile joints B , and tendency to bleed (easy bruising).

Multiple types. Inheritance and severity vary. Can be autosomal dominant or recessive. May be associated with joint dislocation, berry and aortic aneurysms, organ rupture.

Hypermobility type (joint instability): most common type.

Classical type (joint and skin symptoms): caused by a mutation in type V collagen (eg, COL5A1, COL5A2).

Vascular type (fragile tissues including vessels [eg, aorta], muscles, and organs that are prone to rupture [eg, gravid uterus]): mutations in type III procollagen (eg, COL3A1).

X-linked recessive connective tissue disease caused by impaired copper absorption and transport due to defective Menkes protein (ATP7A, vs ATP7B in Wilson disease). Low copper levels (vs high levels in Wilson disease). Leads to • activity of lysyl oxidase (copper is a necessary cofactor) • defective collagen. Results in brittle, "kinky" hair, growth retardation, hypotonia, • risk of cerebral aneurysms.

Elastin Stretchy protein within skin, lungs, large arteries, elastic ligaments, vocal cords, ligamenta flava (connect vertebrae relaxed and stretched conformations). Rich in nonhydroxylated proline, glycine, and lysine residues, vs the hydroxylated residues of collagen. Tropoelastin with fibrillin scaffolding. Cross-linking takes place extracellularly and gives elastin its elastic properties. Broken down by elastase, which is normally inhibited by α1-antitrypsin. α1-Antitrypsin deficiency results in unopposed elastase activity, which can cause COPD. Changes with aging: • dermal collagen and elastin, • synthesis of collagen fibrils; cross-linking remains normal. Marfan syndrome—autosomal dominant (with variable expression) connective tissue disorder affecting skeleton, heart, and eyes. FBN1 gene mutation on chromosome 15 (fifteen) results in defective fibrillin, a glycoprotein that forms a sheath around elastin. Findings: tall with long extremities; pectus carinatum (more specific) or pectus excavatum A ; hypermobile joints; long, tapering fingers and toes (arachnodactyly); cystic medial necrosis of aorta; aortic root aneurysm rupture or dissection (most common cause of death); mitral valve prolapse. Subluxation of lenses, typically upward and temporally (vs downward and medially in homocystinuria).

Polymerase chain Molecular biology lab procedure used to amplify a desired fragment of DNA. Useful as a diagnostic reaction tool (eg, neonatal HIV, herpes encephalitis).

Denaturation—DNA is heated to ~95°C to separate the strands. Annealing—Sample is cooled to ~55°C. DNA primers, a heat-stable DNA polymerase (Taq), and deoxynucleotide triphosphates (dNTPs) are added. DNA primers anneal to the specific sequence to be amplified on each strand. Elongation—Temperature is increased to ~72°C. DNA polymerase attaches dNTPs to the strand to replicate the sequence after each primer.

Heating and cooling cycles continue until the DNA sample size is sufficient.

CRISPR/Cas9 A genome editing tool derived from bacteria. Consists of a guide RNA (gRNA) , which is complementary to a target DNA sequence, and an endonuclease (Cas9), which makes a single-or double-strand break at the target site . Break imperfectly repaired by nonhomologous end joining (NHEJ) accidental frameshift mutations (“knock-out”) , or a donor DNA sequence can be added to fill in the gap using homology-directed repair (HDR) . Not used clinically. Potential applications include removing virulence factors from pathogens, replacing disease-causing alleles of genes with healthy variants, and specifically targeting tumor cells.

Southern blot 1. DNA sample is enzymatically cleaved into smaller pieces, which are separated on a gel by electrophoresis, and then transferred to a filter.

2. Filter is exposed to radiolabeled DNA probe that recognizes and anneals to its complementary strand.

3. Resulting double-stranded, labeled piece of

DNA is visualized when filter is exposed to film. Northern blot Similar to Southern blot, except that an RNA sample is electrophoresed. Useful for studying

DRoP: mRNA levels, which are reflective of gene

Southern = DNAexpression.

Northern = RNAWestern blot Sample protein is separated via gel electrophoresis Western = Protein and transferred to a membrane. Labeled antibody is used to bind to relevant protein.

Southwestern blot Identifies DNA-binding proteins (eg, c-Jun, c-Fos [leucine zipper motif]) using labeled double-stranded DNA probes.

Flow cytometry Laboratory technique to assess size, granularity, and protein expression (immunophenotype) of individual cells in a sample. Cells are tagged with antibodies specific to Commonly used in workup of hematologic abnormalities (eg, leukemia, paroxysmal nocturnal hemoglobinuria, fetal RBCs in mother’s blood) and immunodeficiencies (eg, CD4+ cell count in HIV). Fluorescent label Antibody Anti-CD3 Ab Laser

makes label fuoresce Laser Detector 104 103 Anti-CD8 Ab Fluorescence is detected; labeled cells are counted Cell surface or intracellular proteins. Antibodies are then tagged with a unique fluorescent dye. Sample is analyzed one cell at a time by focusing a laser on the cell and measuring light scatter and intensity of fluorescence.

Data are plotted either as histogram (one measure) or scatter plot (any two measures, as shown). In illustration:

Cells in left lower quadrant ⊖ for both CD8 and CD3.

CD8-expressing cells also express CD3.

Cells in left upper quadrant ⊕ for CD3 and 100 ⊖ for CD8. 100 101 102 103 104

CD8 CD8 and CD3.

and ⊖ for CD3. In this example, right lower quadrant is empty because all

Microarrays Thousands of nucleic acid sequences are arranged in grids on glass or silicon. DNA or RNA probes are hybridized to the chip, and a scanner detects the relative amounts of complementary binding. Used to profile gene expression levels of thousands of genes simultaneously to study certain diseases and treatments. Able to detect single nucleotide polymorphisms (SNPs) and copy number variations (CNVs) for a variety of applications including genotyping, clinical genetic testing, forensic analysis, cancer mutations, and genetic linkage analysis.

Karyotyping Colchicine is added to cultured cells to halt chromosomes in metaphase. Chromosomes are stained, ordered, and numbered according to morphology, size, arm-length ratio, and banding pattern (arrows in A point to extensive abnormalities in a cancer cell). Can be performed on a sample of blood, bone marrow, amniotic fluid, or placental tissue. Used to diagnose chromosomal imbalances (eg, autosomal trisomies, sex chromosome disorders).

Fluorescent DNA or RNA probe binds to specific gene site of interest on chromosomes (arrows in A point to abnormalities in a cancer cell, whose karyotype is seen above; each fluorescent color represents a chromosome-specific probe).

Used for specific localization of genes and direct visualization of chromosomal anomalies at the molecular level.

Microdeletion—no fluorescence on a chromosome compared to fluorescence at the same locus on the second copy of that chromosome.

Translocation—fluorescence signal that corresponds to one chromosome is found in a different chromosome (two white arrows in A show fragments of chromosome 17 that have translocated to chromosome 19).

Duplication—a second copy of a chromosome, resulting in a trisomy or tetrasomy (two blue arrows show duplicated chromosomes 8, resulting in a tetrasomy).

Molecular cloning Production of a recombinant DNA molecule in a bacterial host. Steps: 1.

Isolate eukaryotic mRNA (post-RNA processing) of interest.

2.

Add reverse transcriptase (an RNA-dependent DNA polymerase) to produce complementary DNA (cDNA, lacks introns).

3.

Insert cDNA fragments into bacterial plasmids containing antibiotic resistance genes.

4.

Transform (insert) recombinant plasmid into bacteria.

5.

Surviving bacteria on antibiotic medium produce cloned DNA (copies of cDNA).

Cre-lox system Can inducibly manipulate genes at specific developmental points (eg, to study a gene whose deletion causes embryonic death).

RNA interference Process whereby small non-coding RNA molecules target mRNAs to inhibit gene expression.

Codominance Both alleles contribute to the phenotype of the Blood groups A, B, AB; α1-antitrypsin heterozygote. deficiency; HLA groups.

Variable expressivity Patients with the same genotype have varying 2 patients with neurofibromatosis type 1 (NF1) phenotypes. may have varying disease severity.

Anticipation Increased severity or earlier onset of disease in Trinucleotide repeat diseases (eg, Huntington succeeding generations. disease).

Presence of genetically distinct cell lines in the same individual.

Somatic mosaicism—mutation arises from mitotic errors after fertilization and propagates through multiple tissues or organs.

Gonadal mosaicism—mutation only in egg or sperm cells. If parents and relatives do not have the disease, suspect gonadal (or germline) mosaicism.

McCune-Albright syndrome—due to Gs-protein activating mutation. Presents with unilateral café-au-lait spots

A with ragged edges, polyostotic fibrous dysplasia (bone is replaced by collagen and fibroblasts), and at least one endocrinopathy (eg, precocious puberty). Lethal if mutation occurs before fertilization (affecting all cells), but survivable in patients with mosaicism.

Locus heterogeneity Mutations at different loci can produce a similar Albinism. phenotype.

Allelic heterogeneity Different mutations in the same locus β-thalassemia. produce the same phenotype.

Heteroplasmy Presence of both normal and mutated mtDNA passed from mother to all children. mtDNA, resulting in variable expression in mitochondrially inherited disease.

Uniparental disomy Offspring receives 2 copies of a chromosome from 1 parent and no copies from the other parent. HeterodIsomy (heterozygous) indicates a meiosis I error. IsodIsomy (homozygous) indicates a meiosis II error or postzygotic chromosomal duplication of one of a pair of chromosomes, and loss of the other of the original pair.

Uniparental is euploid (correct number of chromosomes). Most occurrences of uniparental disomy (UPD) normal phenotype. Consider isodisomy in an individual manifesting a recessive disorder when only one parent is a carrier. Examples: Prader-Willi and Angelman syndromes.

If p and q represent the frequencies of alleles A and a, respectively, in a population, then p + q = 1: p2 = frequency of homozygosity for allele A q2 = frequency of homozygosity for allele a 2pq = frequency of heterozygosity (carrier frequency, if an autosomal recessive disease) Therefore, the sum of the frequencies of these genotypes is p2 + 2pq + q2 = 1.

The frequency of an X-linked recessive disease in males = q and in females = q2.

Hardy-Weinberg law assumptions include:

No mutation occurring at the locus

Natural selection is not occurring

If a population is in Hardy-Weinberg equilibrium, then the values of p and q remain constant from generation to generation.

Disorders of imprinting Imprinting—one gene copy is silenced by methylation, and only the other copy is expressed parent-of-origin effects.

Modes of inheritance

Autosomal dominant Often due to defects in structural genes. Many generations, both males and females are affected. AaaaAaAaaaaa

Often pleiotropic (multiple apparently unrelated effects) and variably expressive (different between individuals). Family history crucial to diagnosis. With one affected (heterozygous) parent, on average, 1/2 of children affected.

Autosomal recessive With 2 carrier (heterozygous) parents, on average: Often due to enzyme deficiencies. Usually seen ¼ of children will be affected (homozygous), in only 1 generation. Commonly more severe 1/2 of children will be carriers, and ¼ of than dominant disorders; patients often present children will be neither affected nor carriers. in childhood.

Aa • risk in consanguineous families. Unaffected individual with affected sibling has 2/3 probability of being a carrier.

X-linked recessive Sons of heterozygous mothers have a 50% Commonly more severe in males. Females chance of being affected. No male-to-male usually must be homozygous to be affected.

transmission. Skips generations.

transmit to all daughters but no sons. XXXXXXXYXYXYXXXXXXXYXYXY

X-linked dominant Transmitted through both parents. Mothers Examples: fragile X syndrome, Alport syndrome, transmit to 50% of daughters and sons; fathers hypophosphatemic rickets (also called X-linked hypophosphatemia)—phosphate wasting at proximal tubule • rickets-like presentation.

Mitochondrial Transmitted only through the mother. All inheritance offspring of affected females may show signs of disease. Variable expression in a population or even within a family due to heteroplasmy.

Mitochondrial myopathies—rare disorders; often present with myopathy, lactic acidosis, and CNS disease, eg, MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes). 2° to failure in oxidative phosphorylation. Muscle biopsy often shows “ragged red fibers” (due to accumulation of diseased mitochondria in the subsarcolemma of the muscle fiber).

Leber hereditary optic neuropathy—cell death in optic nerve neurons subacute bilateral vision loss in teens/young adults, 90% males. Usually permanent.

= a˜ected female.

Autosomal dominant Achondroplasia, autosomal dominant polycystic kidney disease, familial adenomatous polyposis, diseases familial hypercholesterolemia, hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome), hereditary spherocytosis, Huntington disease, Li-Fraumeni syndrome, Marfan syndrome, multiple endocrine neoplasias,

myotonic muscular dystrophy, neurofibromatosis type 1 (von Recklinghausen disease), neurofibromatosis type 2, tuberous sclerosis, von Hippel-Lindau disease.

Autosomal recessive Oculocutaneous albinism, autosomal recessive polycystic kidney disease (ARPKD), cystic diseases fibrosis, Friedreich ataxia, glycogen storage diseases, hemochromatosis, Kartagener syndrome, mucopolysaccharidoses (except Hunter syndrome), phenylketonuria, sickle cell anemia, sphingolipidoses (except Fabry disease), thalassemias, Wilson disease.

GENETICS Autosomal recessive; defect in CFTR gene on chromosome 7; commonly a deletion of Phe508. Most common lethal genetic disease in Caucasian population.

PATHOPHYSIOlOGY CFTR encodes an ATP-gated Cl− channel that secretes Cl− in lungs and GI tract, and reabsorbs Cl− in sweat glands. Most common mutation □ misfolded protein □ protein retained in RER and not transported to cell membrane, causing □ Cl− (and H2O) secretion; □ intracellular Cl− results in compensatory • Na+ reabsorption via epithelial Na+ channels (ENaC) □• H2O reabsorption □ abnormally thick mucus secreted into lungs and GI tract. • Na+ reabsorption also causes more negative transepithelial potential difference.

DIAGNOSIS □ Cl− concentration in pilocarpine-induced sweat test is diagnostic. Can present with contraction alkalosis and hypokalemia (ECF effects analogous to a patient taking a loop diuretic) because of ECF H2O/Na+ losses via sweating and concomitant renal K+/H+ wasting. • immunoreactive trypsinogen (newborn screening).

COMPlICATIONS Recurrent pulmonary infections (eg, S aureus [infancy and early childhood], P aeruginosa [adulthood], allergic bronchopulmonary aspergillosis [ABPA]), chronic bronchitis and bronchiectasis □ reticulonodular pattern on CXR, opacification of sinuses. Pancreatic insufficiency, malabsorption with steatorrhea, fat-soluble vitamin deficiencies (A, D, E, K), biliary cirrhosis, liver disease. Meconium ileus in newborns. Infertility in men (absence of vas deferens, spermatogenesis may be unaffected) and subfertility in women (amenorrhea, abnormally thick cervical mucus). Nasal polyps, clubbing of nails.

TREATMENT Multifactorial: chest physiotherapy, albuterol, aerosolized dornase alfa (DNase), and hypertonic saline facilitate mucus clearance. Azithromycin used as anti-inflammatory agent. Ibuprofen slows disease progression. Pancreatic enzyme replacement therapy for pancreatic insufficiency. In patients with Phe508 deletion: combination of lumacaftor (corrects misfolded proteins and improves their transport to cell surface) and ivacaftor (opens Cl− channels • improved chloride transport).

Ornithine transcarbamylase deficiency, Fabry disease, Wiskott-Aldrich syndrome, Ocular albinism, G6PD deficiency, Hunter syndrome, Bruton agammaglobulinemia, Hemophilia A and B, Lesch-Nyhan syndrome, Duchenne (and Becker) muscular dystrophy.

X-inactivation (lyonization)—one copy of female X chromosome forms a transcriptionally inactive Barr body. Female carriers variably affected depending on the pattern of inactivation of the X chromosome carrying the mutant vs normal gene.

X-linked disorder typically due to frameshift deletions or nonsense mutations truncated or absent dystrophin protein • progressive myofiber damage. Weakness begins in pelvic girdle muscles and progresses superiorly. Pseudohypertrophy of calf muscles due to fibrofatty replacement of muscle A . Waddling gait.

Onset before 5 years of age. Dilated cardiomyopathy is common cause of death.

Gowers sign—patient uses upper extremities to help stand up. Classically seen in Duchenne muscular dystrophy, but also seen in other muscular dystrophies and inflammatory myopathies (eg, polymyositis).

Females with Turner syndrome (45,XO) are more likely to have an X-linked recessive disorder.

Duchenne = deleted dystrophin.

Dystrophin gene (DMD) is the largest protein-coding human gene • chance of spontaneous mutation. Dystrophin helps anchor muscle fibers, primarily in skeletal and cardiac muscle. It connects the intracellular cytoskeleton (actin) to the transmembrane proteins αand β-dystroglycan, which are connected to the extracellular matrix (ECM). Loss of dystrophin • myonecrosis.

• CK and aldolase; genetic testing confirms diagnosis.

Rett syndrome Sporadic disorder seen almost exclusively in girls (affected males die in utero or shortly after birth). Most cases are caused by de novo mutation of MECP2 on X chromosome. Symptoms of Rett syndrome usually appear between ages 1–4 and are characterized by regression (Retturn) in motor, verbal, and cognitive abilities; ataxia; seizures; growth failure; and stereotyped hand-wringing.

Myotonic dystrophy (CTG)n AD Cataracts, Toupee (early balding in men), Gonadal atrophy in men, reduced fertility in women

Fragile X syndrome (CGG)n XD Chin (protruding), Giant Gonads

Findings: intellectual disability, flat facies, prominent epicanthal folds, single palmar crease, incurved 5th finger, gap between 1st 2 toes, duodenal atresia, Hirschsprung disease, congenital heart disease (eg, ASD), Brushfield spots. Associated with early-onset Alzheimer disease (chromosome 21 codes for amyloid precursor protein), • risk of AML/ALL.

95% of cases due to meiotic nondisjunction (• with advanced maternal age; from 1:1500 in women < 20 to 1:25 in women > 45 years old).

4% of cases due to unbalanced Robertsonian translocation, most typically between chromosomes 14 and 21. Only 1% of cases are due to postfertilization mitotic error.

Incidence 1:700.

Drinking age (21).

Most common viable chromosomal disorder and most common cause of genetic intellectual disability.

translucency and hypoplastic nasal bone. Markers for Down syndrome are HI up: hCG, • inhibin. The 5 A's of Down syndrome:

Findings: severe intellectual disability, rocker-bottom feet, microphthalmia, microcephaly, cleft liP/Palate, holoProsencephaly, Polydactyly, cutis aPlasia, congenital heart (Pump) disease, Polycystic kidney disease, omphalocele. Death usually occurs by age 1.

Incidence 1:15,000. Puberty (13). Defect in fusion of prechordal mesoderm midline defects.

Genetic disorders by chromosome 3 von Hippel-Lindau disease, renal cell carcinoma 4 ADPKD (PKD2), achondroplasia, Huntington disease 5 Cri-du-chat syndrome, familial adenomatous polyposis 7 Williams syndrome, cystic fibrosis 9 Friedreich ataxia, tuberous sclerosis (TSC1) 11 Wilms tumor, β-globin gene defects (eg, sickle cell disease, β-thalassemia), MEN1 13 Patau syndrome, Wilson disease, retinoblastoma (RB1), BRCA2 15 Prader-Willi syndrome, Angelman syndrome, Marfan syndrome 16 ADPKD (PKD1), α-globin gene defects (eg, α-thalassemia), tuberous sclerosis (TSC2) 17 Neurofibromatosis type 1, BRCA1, TP53 22 Neurofibromatosis type 2, DiGeorge syndrome (22q11)

X Fragile X syndrome, X-linked agammaglobulinemia, Klinefelter syndrome (XXY)

Chromosomal translocation that commonly involves chromosome pairs 21, 22, 13, 14, and 15. One of the most common types of translocation. Occurs when the long arms of 2 acrocentric chromosomes (chromosomes with centromeres near their ends) fuse at the centromere and the 2 short arms are lost.

Balanced translocations normally do not cause any abnormal phenotype. Unbalanced translocations can result in miscarriage, stillbirth, and chromosomal imbalance (eg, Down syndrome, Patau syndrome).

Cri-du-chat syndrome Cri du chat = cry of the cat. Congenital deletion on short arm of chromosome 5 (46,XX or XY, 5p−). Findings: microcephaly, moderate to severe intellectual disability, high-pitched crying/meowing, epicanthal folds, cardiac abnormalities (VSD).

Williams syndrome Congenital microdeletion of long arm of chromosome 7 (deleted region includes elastin gene). Findings: distinctive "elfin" facies A , intellectual disability, hypercalcemia, well-developed verbal

skills, extreme friendliness with strangers, cardiovascular problems (eg, supravalvular aortic stenosis, renal artery stenosis). Think Will Ferrell in Elf.

Vitamins: water soluble

B1 (thiamine: TPP) B2 (riboflavin: FAD, FMN) B3 (niacin: NAD+) B5 (pantothenic acid: CoA) B6 (pyridoxine: PLP) B7 (biotin) B9 (folate) B12 (cobalamin) C (ascorbic acid)

All wash out easily from body except B12 and B9 (folate). B12 stored in liver for ~ 3–4 years. B9 stored in liver for ~ 3–4 months.

B-complex deficiencies often result in dermatitis, glossitis, and diarrhea.

Can be coenzymes (eg, ascorbic acid) or precursors to coenzymes (eg, FAD, NAD+).

Vitamin A Includes retinal, retinol, retinoic acid.

DEFICIENCY Night blindness (nyctalopia); dry, scaly skin (xerosis cutis); corneal squamous metaplasia • Bitot spots (keratin debris; foamy appearance on conjunctiva

A); corneal degeneration (keratomalacia); immunosuppression.

EXCESS Acute toxicity—nausea, vomiting, vertigo, and Isotretinoin is teratogenic. blurred vision. Chronic toxicity—alopecia, dry skin (eg, scaliness), hepatic toxicity and enlargement, arthralgias, and idiopathic intracranial hypertension. Teratogenic (cleft palate, cardiac abnormalities), therefore a ⊖ pregnancy test and two forms of contraception are required before isotretinoin (vitamin A derivative) is prescribed.

Vitamin B1 Also called thiamine.

DEFICIENCY Impaired glucose breakdown ATP depletion worsened by glucose infusion; highly aerobic tissues (eg, brain, heart) are affected first. In alcoholic or malnourished patients, give thiamine before dextrose to • risk of precipitating Wernicke encephalopathy.

Diagnosis made by • in RBC transketolase activity following vitamin B1 administration.

chronic alcohol consumption; presents with confabulation, personality changes, memory loss (permanent).

Wernicke-Korsakoff syndrome—damage to medial dorsal nucleus of thalamus, mammillary bodies. Presentation is combination of Wernicke encephalopathy and Korsakoff syndrome.

Dry beriberi—polyneuropathy, symmetric muscle wasting. Wet beriberi—high-output cardiac failure (dilated cardiomyopathy), edema.

DEFICIENCY Cheilosis (inflammation of lips, scaling and The 2 C's of B2.
fissures at the corners of the mouth), Corneal vascularization.

Vitamin B3 Also called niacin, nicotinic acid.

FUNCTION Constituent of NAD+, NADP+ (used in redox NAD derived from
Niacin (B3 ≈ 3 ATP). reactions). Derived from tryptophan. Synthesis
requires vitamins B2 and B6. Used to treat dyslipidemia; lowers levels of
VLDL and raises levels of HDL.

DEFICIENCY Glossitis. Severe deficiency leads to pellagra, which can also
be caused by Hartnup disease, malignant carcinoid syndrome (• tryptophan
metabolism), and isoniazid (• vitamin B6). Symptoms of pellagra:
Diarrhea, Dementia (also hallucinations), Dermatitis (C3/C4 dermatome
circumferential "broad collar" rash [Casal necklace], hyperpigmentation
of sun-exposed limbs

A).

The 3 D's of B3.

Hartnup disease—autosomal recessive. Deficiency of neutral amino acid
(eg, tryptophan) transporters in proximal renal tubular cells and on
enterocytes • neutral aminoaciduria and • absorption from the gut
□• tryptophan for conversion to niacin □ pellagra-like symptoms. Treat
with high- protein diet and nicotinic acid. Deficiency of vitamin B3 •
pellagra.

EXCESS Facial flushing (induced by prostaglandin, not Excess of vitamin
B3 • podagra. histamine; can avoid by taking aspirin with niacin),
hyperglycemia, hyperuricemia.

Vitamin B5 Also called pantothenic acid.

FUNCTION Essential component of coenzyme A (CoA, B5 is "pento"thenic
acid. a cofactor for acyl transfers) and fatty acid synthase.

DEFICIENCY Dermatitis, enteritis, alopecia, adrenal insufficiency.

Vitamin B6 Also called pyridoxine.

FUNCTION Converted to pyridoxal phosphate (PLP), a cofactor used in
transamination (eg, ALT and AST), decarboxylation reactions, glycogen
phosphorylase. Synthesis of glutathione, cystathionine, heme, niacin,
histamine, and neurotransmitters including serotonin, epinephrine,
norepinephrine (NE), dopamine, and GABA.

DEFICIENCY Convulsions, hyperirritability, peripheral neuropathy
(deficiency inducible by isoniazid and oral contraceptives),
sideroblastic anemia (due to impaired hemoglobin synthesis and iron
excess).

Vitamin B7 Also called biotin.

a 1-carbon group):

Pyruvate carboxylase: pyruvate (3C) • oxaloacetate (4C)

Acetyl-CoA carboxylase: acetyl-CoA (2C) • malonyl-CoA (3C)

Propionyl-CoA carboxylase: propionyl-CoA (3C) methylmalonyl-CoA (4C)

DEFICIENCY Relatively rare. Dermatitis, enteritis, alopecia. “Avidin in egg whites avidly binds biotin.” Caused by long-term antibiotic use or excessive ingestion of raw egg whites.

DEFICIENCY Macrocytic, megaloblastic anemia; hypersegmented PMNs; paresthesias and subacute combined degeneration (degeneration of dorsal columns, lateral corticospinal tracts, and spinocerebellar tracts) due to abnormal myelin. Associated with • serum homocysteine and methylmalonic acid levels, along with 2° folate deficiency. Prolonged deficiency irreversible nerve damage.

Vitamin C Also called ascorbic acid.

(eg, sprue, enteritis, Diphyllobothrium latum, achlorhydria, bacterial overgrowth, alcohol excess), lack of intrinsic factor (eg, pernicious anemia, gastric bypass surgery), absence of terminal ileum (surgical resection, eg, for Crohn disease), certain drugs (eg, metformin), or insufficient intake (eg, veganism).

Anti-intrinsic factor antibodies diagnostic for pernicious anemia.

Folate supplementation can mask the hematologic symptoms of B12 deficiency, but not the neurologic symptoms.

Fatty acids with odd number of carbons, branched-chain amino acids

CH3 to anabolic pathways Methylmalonyl-CoA

EXCESS Nausea, vomiting, diarrhea, fatigue, calcium oxalate nephrolithiasis. Can • iron toxicity in predisposed individuals by increasing dietary iron absorption (ie, can worsen hereditary hemochromatosis or transfusion-related iron overload).

REGUlATION • PTH, • Ca2+, • PO43− • 1,25-(OH)2D3 production. 1,25-(OH)2D3 feedback inhibits its own production.

• PTH • Ca2+ reabsorption and PO43− reabsorption in the kidney.

DEFICIENCY Rickets in children (deformity, such as genu varum “bowlegs” A), osteomalacia in adults (bone pain and muscle weakness), hypocalcemic tetany.

Caused by malabsorption, • sun exposure, poor diet, chronic kidney disease (CKD), advanced liver disease.

Give oral vitamin D to breastfed infants.

Deficiency is exacerbated by pigmented skin, premature birth.

EXCESS Hypercalcemia, hypercalciuria, loss of appetite, stupor. Seen in granulomatous diseases (• activation of vitamin D by epithelioid macrophages).

Vitamin E Includes tocopherol, tocotrienol.

FUNCTION Antioxidant (protects RBCs and membranes from free radical damage).

EXCESS Risk of enterocolitis in infants. High-dose supplementation may alter metabolism of vitamin K enhanced anticoagulant effects of warfarin.

Vitamin K Includes phytomenadione, phylloquinone, phytonadione, menaquinone.

FUNCTION Mineral essential for the activity of 100+ enzymes. Important in the formation of zinc fingers (transcription factor motif).

DEFICIENCY Delayed wound healing, suppressed immunity, male hypogonadism, • adult hair (axillary, facial, pubic), dysgeusia, anosmia. Associated with acrodermatitis enteropathica (A , defect in intestinal zinc absorption). May predispose to alcoholic cirrhosis.

Kwashiorkor Protein malnutrition resulting in skin lesions, edema due to • plasma oncotic pressure, liver malfunction (fatty change due to • apolipoprotein synthesis). Clinical picture is small child with swollen abdomen

A . Kwashiorkor results from protein- deficient MEALS: Malnutrition Edema Anemia Liver (fatty) Skin lesions (eg, hyperkeratosis,

Marasmus Malnutrition not causing edema. Diet is deficient in calories but no nutrients are entirely absent. Marasmus results in Muscle wasting

B .

Fomepizole—blocks alcohol DH; antidote For Overdoses of Methanol or Ethylene glycol.

• discouraging drinking. NAD+ is the limiting reagent. Alcohol dehydrogenase operates via zero-order kinetics.

Ethanol metabolism • NADH/ NAD+ ratio in liver, causing: Lactic acidosis— • pyruvate conversion to lactate Fasting hypoglycemia— gluconeogenesis due to of OAA to malate

Ketoacidosis—diversion of acetyl-CoA into ketogenesis rather than TCA cycle

Hepatosteatosis— • conversion of DHAP to glycerol-3-P 4B , which combines with glycerol-3-P to synthesize triglycerides • NADH/NAD+ ratio inhibits TCA cycle □• acetyl-CoA used in ketogenesis (• ketoacidosis), lipogenesis (• hepatosteatosis).

Mitochondria Fatty acid oxidation (β-oxidation), acetyl-CoA production, TCA cycle, oxidative phosphorylation, ketogenesis.

Cytoplasm Glycolysis, HMP shunt, and synthesis of cholesterol (SER), proteins (ribosomes, RER), fatty acids, and nucleotides.

Both Heme synthesis, Urea cycle, Gluconeogenesis. HUGs take two (both).

Enzyme terminology An enzyme's name often describes its function. For example, glucokinase is an enzyme that catalyzes the phosphorylation of glucose using a molecule of ATP. The following are commonly used enzyme descriptors.

Kinase Catalyzes transfer of a phosphate group from a high-energy molecule (usually ATP) to a substrate (eg, phosphofructokinase).

Phosphorylase Adds inorganic phosphate onto substrate without using ATP (eg, glycogen phosphorylase).

Phosphatase Removes phosphate group from substrate (eg, fructose-1,6-bisphosphatase).

Dehydrogenase Catalyzes oxidation-reduction reactions (eg, pyruvate dehydrogenase).

Hydroxylase Adds hydroxyl group (–OH) onto substrate (eg, tyrosine hydroxylase).

Carboxylase Transfers CO2 groups with the help of biotin (eg, pyruvate carboxylase).

Mutase Relocates a functional group within a molecule (eg, vitamin B12–dependent methylmalonyl-CoA mutase).

Synthase/synthetase Joins two molecules together using a source of energy (eg, ATP, acetyl-CoA, nucleotide sugar).

Rate-determining enzymes of metabolic processes

Summary of pathways

T B T T B B Glycogen UDP-glucose Glucose-1-phosphate Glucose Glucose-6-phosphate 6-phosphogluconolactone Fructose-6-phosphate Fructose-1,6-bisphosphate Glyceraldehyde-3-P DHAP 1,3-bisphosphoglycerate 3-phosphoglycerate 2-phosphoglycerate Phosphoenolpyruvate (PEP) Pyruvate Alanine Acetyl-CoA Glyceraldehyde Ribulose-5-phosphate Fructose-1-phosphate Fructose NH3 + CO2 Carbamoyl phosphate Citrulline Aspartate Argininosuccinate Urea cycle Ornithine Urea H2O Arginine Fumarate Oxaloacetate Malate TCA cycle Succinate Citrate Isocitrate ˜-

ketoglutarate Succinyl-CoA Methylmalonyl-CoA Propionyl-CoA Odd-chain fatty acids, isoleucine, valine, methionine, threonine Acetoacetate ˜-hydroxybutyrate Mevalonate Galactose Galactose-1-phosphate HMP shunt Fructose metabolism Lipid metabolism Galactose metabolism Gluconeogenesis Ketogenesis Glycolysis Protein metabolism Glycogenesis / glycogenolysis Lactate Acetoacetyl-CoA HMG-CoA Malonyl-CoA Triglycerides Glycerol Cholesterol B12 Irreversible, important point of regulation Requires thiamine cofactor (TPP)Requires biotin cofactor B T Fatty acids #Hexokinase/glucokinase Glucose-6-phosphatase (von Gierke disease) Glucose-6-phosphate dehydrogenase Transketolase Pyruvate kinase Pyruvate dehydrogenase HMG-CoA reductase Pyruvate carboxylase PEP carboxykinase Citrate synthase Triose phosphate isomerase Phosphofructokinase-1 Fructose-1,6-bisphosphatase Fructokinase (essential fructosuria) Aldolase B (fructose intolerance) Aldolase B (liver), A (muscle) Isocitrate dehydrogenase ˜-ketoglutarate dehydrogenase Ornithine transcarbamylase Propionyl-CoA carboxylase Carbamoyl phosphate synthetase I Galactokinase (mild galactosemia) Galactose-1-phosphate uridyltransferase (severe galactosemia)

NADH, NADPH, FADH2 Electrons

CoA, lipoamide Acyl groups

Phosphorylation of glucose to yield glucose-6-phosphate is catalyzed by glucokinase in the liver and hexokinase in other tissues. Hexokinase sequesters glucose in tissues, where it is used even when glucose concentrations are low. At high glucose concentrations, glucokinase helps to store glucose in liver.

Glucose-6-P Glucose-6-P ⊖ hexokinase.

Fructose-6-P ⊖ glucokinase. Fructose-6-P

Fructose-1,6-BP AMP ⊕, fructose-2,6-bisphosphate ⊕.

ATP ⊖, citrate ⊖.

Regulation by fructose-2,6bisphosphate

Fructose bisphosphatase-2 (FBPase-2) and phosphofructokinase-2 (PFK-2) are the same bifunctional enzyme whose function is reversed by phosphorylation by protein kinase A.

Fructose-1,6-BP

Fructose-2,6-BP

Fasting state: • glucagon □• cAMP □• protein FaBian the Peasant (FBP) has to work hard kinase A □• FBPase-2, • PFK-2, less when starving. glycolysis, more gluconeogenesis.

Fed state: • insulin □• cAMP □• protein Prince FredericK (PFK) works only when fed. kinase A □• FBPase-2, • PFK-2, more glycolysis, less gluconeogenesis.

Mitochondrial enzyme complex linking glycolysis and TCA cycle. Differentially regulated in fed (active)/fasting (inactive) states.

Reaction: pyruvate + NAD+ + CoA acetyl-CoA + CO2 + NADH.

Contains 3 enzymes requiring 5 cofactors: 1.

2.

3.

CoA (B5, pantothenic acid) 4.

FAD (B2, riboflavin) 5.

NAD+ (B3, niacin)

Activated by: • NAD+/NADH ratio, • ADP • Ca2+

The complex is similar to the α-ketoglutarate dehydrogenase complex (same cofactors, similar substrate and action), which converts α-ketoglutarate succinyl-CoA (TCA cycle).

The Lovely Coenzymes For Nerds.

Arsenic inhibits lipoic acid. Arsenic poisoning clinical findings: imagine a vampire (pigmentary skin changes, skin cancer), vomiting and having diarrhea, running away from a cutie (QT prolongation) with garlic breath.

FINDINGS Neurologic defects, lactic acidosis, • serum alanine starting in infancy.

TREATMENT • intake of ketogenic nutrients (eg, high fat content or • lysine and leucine).

Functions of different pyruvate metabolic pathways (and their associated cofactors): Alanine aminotransferase (B6): alanine carries amino groups to the liver from muscle Pyruvate carboxylase (biotin): oxaloacetate can replenish TCA cycle or be used in gluconeogenesis Pyruvate dehydrogenase (B1, B2, B3, B5, lipoic acid): transition from glycolysis to the TCA cycle Lactic acid dehydrogenase (B3): end of anaerobic glycolysis (major pathway in RBCs, WBCs, kidney medulla, lens, testes, and cornea)

Also called Krebs cycle. Pyruvate acetyl-CoA produces 1 NADH, 1 CO2.

The TCA cycle produces 3 NADH, 1 FADH2, 2 CO2, 1 GTP per acetyl-CoA = 10 ATP/ acetyl-CoA (2× everything per glucose). TCA cycle reactions occur in the mitochondria.

α-ketoglutarate dehydrogenase complex requires the same cofactors as the pyruvate dehydrogenase complex (vitamins B1, B2, B3, B5, lipoic acid).

Citrate Is Krebs' Starting Substrate For Making Oxaloacetate.

Electron transport NADH electrons from glycolysis enter mitochondria via the malate-aspartate or glycerol-3chain and oxidative phosphate shuttle. FADH2 electrons are transferred to complex II (at a lower energy level than phosphorylation NADH). The passage of electrons results in the formation of a proton gradient that, coupled to oxidative phosphorylation, drives the production of ATP.

Complex I Complex II Complex III Complex IV Complex V Rotenone Antimycin A Azide, Oligomycin (succinate dehydrogenase) Cyanide, CO2 NADH NAD+ FADH2 FAD 1/2O2 + 2H+ H2O H+H+ H+ H+ CoQ Cyto-chrome c space2,4-Dinitrophenol Aspirin overdose 1 NADH □ 2.5 ATP; 1 FADH2 □ 1.5 ATP.

Gluconeogenesis, irreversible enzymes Pathway Produces Fresh Glucose.

Pyruvate carboxylase In mitochondria. Pyruvate □ oxaloacetate. Requires biotin, ATP. Activated by acetyl-CoA.

Phosphoenolpyruvate In cytosol. Oxaloacetate Requires GTP. carboxykinase • phosphoenolpyruvate.

Fructose-1,6-In cytosol. Fructose-1,6-bisphosphate Citrate ⊕, AMP ⊖, fructose 2,6-bisphosphate ⊖. bisphosphatase □ fructose-6-phosphate.

Glucose-6-In ER. Glucose-6-phosphate □ glucose. phosphatase

Occurs primarily in liver; serves to maintain euglycemia during fasting. Enzymes also found in kidney, intestinal epithelium. Deficiency of the key gluconeogenic enzymes causes hypoglycemia. (Muscle cannot participate in gluconeogenesis because it lacks glucose-6-phosphatase).

Odd-chain fatty acids yield 1 propionyl-CoA during metabolism, which can enter the TCA cycle (as succinyl-CoA), undergo gluconeogenesis, and serve as a glucose source. Even-chain fatty acids cannot produce new glucose, since they yield only acetyl-CoA equivalents.

Also called HMP shunt. Provides a source of NADPH from abundantly available glucose-6-P (NADPH is required for reductive reactions, eg, glutathione reduction inside RBCs, fatty acid and cholesterol biosynthesis). Additionally, this pathway yields ribose for nucleotide synthesis. Two distinct phases (oxidative and nonoxidative), both of which occur in the cytoplasm. No ATP is used or produced.

Sites: lactating mammary glands, liver, adrenal cortex (sites of fatty acid or steroid synthesis), RBCs.

Transketolase, B˜

Fructose Nucleotide 1,6-bisphosphate synthesis

NADPH is necessary to keep glutathione reduced, which in turn detoxifies free radicals and peroxides. • NADPH in RBCs leads to hemolytic anemia due to poor RBC defense against oxidizing agents (eg, fava beans,

sulfonamides, nitrofurantoin, primaquine/ chloroquine, antituberculosis drugs). Infection (most common cause) can also precipitate hemolysis; inflammatory response produces free radicals that diffuse into RBCs, causing oxidative damage.

X-linked recessive disorder; most common human enzyme deficiency; more prevalent among African Americans. • malarial resistance.

Heinz bodies—denatured globin chains precipitate within RBCs due to oxidative stress.

Bite cells—result from the phagocytic removal of Heinz bodies by splenic macrophages. Think, "Bite into some Heinz ketchup."

Disorders of fructose metabolism

Essential fructosuria Involves a defect in fructokinase. Autosomal recessive. A benign, asymptomatic condition (fructokinase deficiency is kinder), since fructose is not trapped in cells. Hexokinase becomes 1° pathway for converting fructose to fructose-6-phosphate. Symptoms: fructose appears in blood and urine. Disorders of fructose metabolism cause milder symptoms than analogous disorders of galactose metabolism.

Hereditary deficiency of aldolase B. Autosomal recessive. Fructose-1-phosphate accumulates, causing a • in available phosphate, which results in inhibition of glycogenolysis and gluconeogenesis. Symptoms present following consumption of fruit, juice, or honey. Urine dipstick will be ⊖ (tests for glucose only); reducing sugar can be detected in the urine (nonspecific test for inborn errors of carbohydrate metabolism).

Symptoms: hypoglycemia, jaundice, cirrhosis, vomiting.

Treatment: • intake of fructose, sucrose (glucose + fructose), and sorbitol (metabolized to fructose).

Disorders of galactose metabolism

Hereditary deficiency of galactokinase. Galactitol accumulates if galactose is present in diet.

Fructose is to Aldolase B as Galactose is to

UridylTransferase (FAB GUT).

The more serious defects lead to PO_4^{3-} depletion.

Sorbitol An alternative method of trapping glucose in the cell is to convert it to its alcohol counterpart, sorbitol, via aldose reductase. Some tissues then convert sorbitol to fructose using sorbitol dehydrogenase; tissues with an insufficient amount/activity of this enzyme are at risk of intracellular sorbitol accumulation, causing osmotic damage (eg, cataracts, retinopathy, and peripheral neuropathy seen with chronic hyperglycemia in diabetes). High blood levels of galactose also result in conversion to the osmotically active galactitol

via aldose reductase. Liver, Ovaries, and Seminal vesicles have both enzymes (they LOSe sorbitol).

Lens has primarily aldose reductase. Retina, Kidneys, and Schwann cells have only aldose reductase (LuRKS).

Lactase deficiency Insufficient lactase enzyme dietary lactose intolerance. Lactase functions on the intestinal brush border to digest lactose (in milk and milk products) into glucose and galactose. Primary: age-dependent decline after childhood (absence of lactase-persistent allele), common in people of Asian, African, or Native American descent. Secondary: loss of intestinal brush border due to gastroenteritis (eg, rotavirus), autoimmune disease. Congenital lactase deficiency: rare, due to defective gene. Stool demonstrates • pH and breath shows • hydrogen content with lactose hydrogen breath test.

Intestinal biopsy reveals normal mucosa in patients with hereditary lactose intolerance.

FINDINGS Bloating, cramps, flatulence, osmotic diarrhea.

TREATMENT Avoid dairy products or add lactase pills to diet; lactose-free milk.

Amino acids Only l-amino acids are found in proteins.

Essential PVT TIM HaLL: Phenylalanine, Valine, Tryptophan, Threonine, Isoleucine, Methionine,

Histidine, Leucine, Lysine. Glucogenic: Methionine, histidine, valine. We met his valentine, she is so sweet (glucogenic). Glucogenic/ketogenic: Isoleucine, phenylalanine, threonine, tryptophan. Ketogenic: Leucine, Lysine. The onLy pureLy ketogenic amino acids.

Acidic Aspartic acid, glutamic acid. Negatively charged at body pH.

Basic Arginine, histidine, lysine. Arginine is most basic. Histidine has no charge at body pH. Arginine and histidine are required during periods of growth. Arginine and lysine are • in histones which bind negatively charged DNA. His lys (lies) are basic.

Transport of ammonia by alanine

Hyperammonemia Can be acquired (eg, liver disease) or hereditary Treatment: limit protein in diet. (eg, urea cycle enzyme deficiencies). May be given to • ammonia levels:

Presents with flapping tremor (eg, asterixis), • Lactulose to acidify GI tract and trap NH_4^+ slurring of speech, somnolence, vomiting, for excretion. cerebral edema, blurring of vision. • Antibiotics (eg, rifaximin, neomycin) to NH_3 changes relative amounts of • ammoniagenic bacteria.

α-ketoglutarate, glutamate, GABA, and • Benzoate, phenylacetate, or phenylbutyrate glutamine to favor • glutamine. CNS toxicity react with glycine or glutamine, forming may involve GABA, • α-ketoglutarate, TCA products that are excreted renally. cycle inhibition, and cerebral edema due to glutamine-induced osmotic shifts. NH NH

Most common urea cycle disorder. X-linked recessive (vs other urea cycle enzyme deficiencies, which are autosomal recessive). Interferes with the body's ability to eliminate ammonia. Often evident in the first few days of life, but may present later. Excess carbamoyl phosphate is converted to orotic acid (part of the pyrimidine synthesis pathway).

Findings: • orotic acid in blood and urine, • BUN, symptoms of hyperammonemia. No megaloblastic anemia (vs orotic aciduria).

, B6 Tryptophan

BH4, B6 Serotonin

Due to • phenylalanine hydroxylase or tetrahydrobiopterin (BH4) cofactor (malignant PKU). Tyrosine becomes essential.

phenylalanine • phenyl ketones in urine.

Findings: intellectual disability, growth retardation, seizures, fair complexion, eczema, musty body odor.

Treatment: • phenylalanine and • tyrosine in diet, tetrahydrobiopterin supplementation.

Maternal PKU—lack of proper dietary therapy during pregnancy. Findings in infant: microcephaly, intellectual disability, growth retardation, congenital heart defects.

Autosomal recessive. Incidence ≈ 1:10,000.

Screening occurs 2–3 days after birth (normal at birth because of maternal enzyme during fetal life).

Phenyl ketones—phenylacetate, phenyllactate, and phenylpyruvate.

Disorder of aromatic amino acid metabolism musty body odor.

PKU patients must avoid the artificial sweetener aspartame, which contains phenylalanine.

Autosomal recessive.

Presentation: vomiting, poor feeding, urine smells like maple syrup/burnt sugar. Causes severe CNS defects, intellectual disability, death.

I Love Vermont maple syrup from maple trees (with B1ranches).

Blocked degradation of branched amino acids (Isoleucine, Leucine, Valine) due to • branched-chain α-ketoacid dehydrogenase (B1). Causes • α-ketoacids in the blood, especially those of leucine.

Treatment: restriction of isoleucine, leucine, valine in diet, and thiamine supplementation.

Congenital deficiency of homogentisate oxidase in the degradative pathway of tyrosine to fumarate • pigment-forming homogentisic acid builds up in tissue A . Autosomal recessive. Usually benign.

Findings: bluish-black connective tissue, ear cartilage, and sclerae (ochronosis); urine turns black on prolonged exposure to air. May have debilitating arthralgias (homogentisic acid toxic to cartilage).

Causes (all autosomal recessive): • Cystathionine synthase deficiency (treatment: • methionine, • cysteine, • B6, B12, and folate in diet) • • affinity of cystathionine synthase for pyridoxal phosphate (treatment: •• B6 and

Methionine synthase (homocysteine methyltransferase) deficiency (treatment:

Methylenetetrahydrofolate reductase (MTHFR) deficiency (treatment: • folate in diet)

All forms result in excess homocysteine.

HOMOCYstinuria: □• Homocysteine in urine, Osteoporosis, Marfanoid habitus, Ocular changes (downward and inward lens subluxation), Cardiovascular effects (thrombosis and atherosclerosis • stroke and MI), kYphosis, intellectual disability, fair complexion. In homocystinuria, lens subluxes “down and in” (vs Marfan, “up and fans out”).

Hereditary defect of renal PCT and intestinal amino acid transporter that prevents reabsorption of Cystine, Ornithine, Lysine, and Arginine (COLA).

Excess cystine in the urine can lead to recurrent precipitation of hexagonal cystine stones A .

Treatment: urinary alkalinization (eg, potassium citrate, acetazolamide) and chelating agents (eg, penicillamine) • solubility of cystine stones; good hydration.

Autosomal recessive. Common (1:7000). Urinary cyanide-nitroprusside test is diagnostic.

Cystine is made of 2 cysteines connected by a disulfide bond.

Organic acidemias Most commonly present in infancy with poor feeding, vomiting, hypotonia, high anion gap metabolic acidosis, hepatomegaly, seizures. Organic acid accumulation:

Inhibits gluconeogenesis □• fasting blood glucose levels, • ketoacidosis □ high anion gap metabolic acidosis

Glycogen Branches have α-(1,6) bonds; linkages have α-(1,4) bonds.

Skeletal muscle Glycogen undergoes glycogenolysis □ glucose-1-phosphate □ glucose-6-phosphate, which is rapidly metabolized during exercise.

Hepatocytes Glycogen is stored and undergoes glycogenolysis to maintain blood sugar at appropriate levels. Glycogen phosphorylase liberates glucose-1-phosphate residues off branched glycogen until 4 glucose units remain on a branch. Then 4-α-d-glucanotransferase (debranching enzyme) moves 3 of the 4 glucose units from the branch to the linkage. Then α-1,6-glucosidase (debranching enzyme) cleaves off the last residue, liberating glucose. "Limit dextrin" refers to the two to four residues remaining on a branch after glycogen phosphorylase (˜-1,6-glucosidase) ˜-1,4-glucosidase

Note: A small amount of glycogen is degraded in lysosomes by α-1,4-glucosidase (acid maltase).

has already shortened it.

Gaucher disease Most common.

Hepatosplenomegaly, pancytopenia, osteoporosis, avascular necrosis of femur, bone crises, Gaucher cells C (lipid-laden macrophages resembling crumpled tissue paper). (β-glucosidase); treat with recombinant glucocerebrosidase C hepatosplenomegaly, foam cells (lipid-laden macrophages) D , Niemann-Pick disease Progressive neurodegeneration, "cherry-red" spot on macula A . Sphingomyelinase Sphingomyelin AR D Mucopolysaccharidoses Hurler syndrome Developmental delay, gargoylism, α-l-iduronidase Heparan sulfate, AR airway obstruction, corneal clouding, dermatan sulfate hepatosplenomegaly.

Hunter syndrome Mild Hurler + aggressive behavior, no Iduronate-2-sulfatase Heparan sulfate, XR corneal clouding. dermatan sulfate

No man picks (Niemann-Pick) his nose with his sphinger (sphingomyelinase).

aggressively aim for the X (X-linked recessive).

• incidence of Tay-Sachs, Niemann-Pick, some forms of Gaucher disease in Ashkenazi Jews.

Sphingolipidoses Tay-Sachs disease A Progressive neurodegeneration, developmental delay, hyperreflexia, hyperacusis, "cherry-red" spot on macula A , lysosomes with onion skin, no hepatosplenomegaly (vs Niemann-Pick). HeXosaminidase A ("TAy-SaX") GM2 ganglioside AR Fabry disease B Early: triad of episodic peripheral neuropathy, angiokeratomas B , hypohidrosis. Late: progressive renal failure, cardiovascular disease. α-galactosidase A Ceramide trihexoside (globotriaosylce-ramide) XR Metachromatic leukodystrophy Central and peripheral demyelination with

ataxia, dementia. Arylsulfatase A Cerebroside sulfate AR (palmitate, a 16C FA)

Fatty acid synthesis requires transport of citrate from mitochondria to cytosol. Predominantly occurs in liver, lactating mammary glands, and adipose tissue.

Long-chain fatty acid (LCFA) degradation requires carnitine-dependent transport into the mitochondrial matrix.

“SYtrate” = SYnthesis. CARnitine = CARnage of fatty acids.

Systemic 1° carnitine deficiency—no cellular uptake of carnitine no transport of LCFAs into mitochondria toxic accumulation of LCFAs in the cytosol. Causes weakness, hypotonia, hypoketotic hypoglycemia, dilated cardiomyopathy.

Medium-chain acyl-CoA dehydrogenase deficiency—• ability to break down fatty acids into acetyl-CoA • accumulation of fatty acyl carnitines in the blood with hypoketotic hypoglycemia. Causes vomiting, lethargy, seizures, coma, liver dysfunction, hyperammonemia. Can lead to sudden death in infants or children. Treat by avoiding fasting.

Ketone bodies In the liver, fatty acids and amino acids are metabolized to acetoacetate and β-hydroxybutyrate (to be used in muscle and brain). In prolonged starvation and diabetic ketoacidosis, oxaloacetate is depleted for gluconeogenesis. In alcoholism, excess NADH shunts oxaloacetate to malate. All of these processes lead to a buildup of acetyl-CoA, which is shunted into ketone body synthesis.

Ketone bodies: acetone, acetoacetate, β-hydroxybutyrate. Breath smells like acetone (fruity odor). Urine test for ketones can detect acetoacetate, but not β-hydroxybutyrate. RBCs cannot utilize ketones; they strictly use glucose. HMG-CoA lyase for ketone production. HMG-CoA reductase for cholesterol synthesis.

(liver) Fatty acids, amino acids Acetoacetate AcetoacetateAcetoneATP˜-hydroxybutyrate Expired by lungs TCA cycle (eg, skeletal muscle) ˜-hydroxybutyrate Acetoacetyl-CoA Acetoacetate ˜-hydroxybutyrateAcetyl-CoA HMG-CoA 2 Acetyl-CoA

Duration of exercise

Fasting and starvation Priorities are to supply sufficient glucose to the brain and RBCs and to preserve protein.

Fed state (after a Glycolysis and aerobic respiration. meal) Fasting (between Hepatic glycogenolysis (major); hepatic meals) gluconeogenesis, adipose release of FFA (minor). Starvation days 1–3 Blood glucose levels maintained by:

Adipose release of FFA

Muscle and liver, which shift fuel use from glucose to FFA

Insulin stimulates storage of lipids, proteins, and glycogen. Glucagon and epinephrine stimulate use of fuel reserves. Glycogen reserves depleted after day 1. RBCs lack mitochondria and therefore cannot use ketones. Weeks of starvation Carbohydrate Protein Fat 1 2 3 4 5 6 7 80 2 10 12 0 Starvation after day 3 Adipose stores (ketone bodies become the main source of energy for the brain). After these are depleted, vital protein degradation accelerates, leading to organ failure and death. Amount of excess stores determines survival time.

tissue lactate and alanine, and from

CoA (from odd-chain FFA—the only to the liver via Apo E 7 Endocytosis of LDL

PCSK9 Degrades LDL receptor □• serum LDL. Inhibition □• LDL receptor recycling □□ serum LDL.

Transfer of cholesteryl CETP esters to VLDL, IDL, LDL

HDL Mediates reverse cholesterol transport from peripheral tissues to liver. Acts as a repository for apolipoproteins C and E (which are needed for chylomicron and VLDL metabolism). Secreted from both liver and intestine. Alcohol • synthesis. HDL is Healthy.

Abetalipoproteinemia Autosomal recessive. Mutation in gene that encodes microsomal transfer protein (MTP). Chylomicrons, VLDL, LDL absent. Deficiency in ApoB-48, ApoB-100. Affected infants present with severe fat malabsorption, steatorrhea, failure to thrive. Later manifestations include retinitis pigmentosa, spinocerebellar degeneration due to vitamin E deficiency, progressive ataxia, acanthocytosis. Intestinal biopsy shows lipid-laden enterocytes. Treatment: restriction of long-chain fatty acids, large doses of oral vitamin E.

“I hate to disappoint you, but my rubber lips are immune to your charms.” —Batman & Robin “The fully engaged heart is the antibody for the infection of violence.”

Learning the components of the immune system and their roles in host defense at the cellular level is essential for both the understanding of disease pathophysiology and clinical practice. Know the immune mechanisms of responses to vaccines. Both congenital and acquired immunodeficiencies are very testable. Cell surface markers are high yield for understanding immune cell interactions and for laboratory diagnosis. Know the roles and functions of major cytokines and chemokines.

Lymph node A 2° lymphoid organ that has many afferents, 1 or more efferents. Encapsulated, with trabeculae

B . Functions are nonspecific filtration by macrophages, circulation of B and T cells, and immune response activation.

Lymph node cluster Cervical, supraclavicular Head and neck Upper respiratory tract infection Infectious mononucleosis Kawasaki disease

Mediastinal Trachea and esophagus Pulmonary TB Sarcoidosis (bilateral) 1° lung cancer Granulomatous disease Axillary Upper limb, breast, skin above umbilicus Mastitis Metastasis (especially breast cancer) Hilar Lungs Celiac Liver, stomach, spleen, pancreas, upper duodenum Superior mesenteric Lower duodenum, jejunum, ileum, colon to splenic fexure Inferior mesenteric Colon from splenic fexure to upper rectum Para-aortic Testes, ovaries, kidneys, uterus Metastasis Internal iliac External iliac Cervix, superior bladder, and body of uterus Lower rectum to anal canal (above pectinate line), bladder, vagina (middle third), cervix, prostate Superfcial inguinal Palpable lymph node Non-palpable lymph node Popliteal Right lymphatic duct drains right side of body above diaphragm into junction of the right Dorsolateral foot, posterior calf Lateral foot/leg cellulitis Anal canal (below pectinate line), skin below umbilicus (except popliteal area), scrotum, vulva Sexually transmitted infections Medial foot/leg cellulitis (superfcial inguinal) Mesenteric lymphadenitis Typhoid fever Ulcerative colitis Celiac disease Area of body drained Associated pathology

Thoracic duct drains below the diaphragm and left thorax and upper limb into junction of left subclavian and internal jugular veins (rupture of thoracic duct can cause chylothorax)

Spleen Located in LUQ of abdomen, anterolateral to left kidney, protected by 9th-11th ribs.

Sinusoids are long, vascular channels in red pulp (red arrows in A) with fenestrated “barrel hoop” basement membrane.

T cells are found in the periarteriolar lymphatic sheath (PALS) within the white pulp (white arrows in

A).

B cells are found in follicles within the white pulp.

The marginal zone, in between the red pulp and white pulp, contains macrophages and specialized B cells, and is where antigen-presenting cells (APCs) capture blood-borne antigens for recognition by lymphocytes.

Splenic macrophages remove encapsulated bacteria.

Splenic dysfunction (eg, postsplenectomy state, sickle cell disease autosplenectomy): • IgM □• complement activation □• C3b opsonization □• susceptibility to encapsulated organisms.

Postsplenectomy blood findings:

Thrombocytosis (loss of sequestration and removal)

Lymphocytosis (loss of sequestration)

Vaccinate patients undergoing splenectomy or with splenic dysfunction against encapsulated organisms (pneumococci, Hib, meningococci).

Located in the anterosuperior mediastinum. Site of T-cell differentiation and maturation. Encapsulated. Thymus epithelium is derived from Third pharyngeal pouch (endoderm), whereas thymic lymphocytes are of mesodermal origin. Cortex is dense with immature T cells; Medulla is pale with Mature T cells and Hassall corpuscles A containing epithelial reticular cells.

B , involutes by age 3 years.

seen in some immunodeficiencies (eg, SCID, DiGeorge syndrome).

Thymoma—neoplasm of thymus. Associated with myasthenia gravis, superior vena cava syndrome, pure red cell aplasia, Good syndrome.

Innate vs adaptive immunity HLA subtypes associated with diseases

Functions of natural Lymphocyte member of innate immune system.

killer cells Use perforin and granzymes to induce apoptosis of virally infected cells and tumor cells. Activity enhanced by IL-2, IL-12, IFN-α, and IFN-β. Induced to kill when exposed to a nonspecific activation signal on target cell and/or to an absence of MHC I on target cell surface. Also kills via antibody-dependent cell-mediated cytotoxicity (CD16 binds Fc region of bound IgG, activating the NK cell).

Major functions of B and T cells

B cells Humoral immunity. Recognize and present antigen—undergo somatic hypermutation to optimize antigen specificity. Produce antibody—differentiate into plasma cells to secrete specific immunoglobulins. Maintain immunologic memory—memory B cells persist and accelerate future response to antigen.

T cells Cell-mediated immunity. CD4+ T cells help B cells make antibodies and produce cytokines to recruit phagocytes and activate other leukocytes. CD8+ T cells directly kill virus-infected and tumor cells via perforin and granzymes (similar to NK cells). Delayed cell-mediated hypersensitivity (type IV). Acute and chronic cellular organ rejection. Rule of 8: MHC II × CD4 = 8; MHC I × CD8 = 8.

Differentiation of T cells

Cytotoxic T cell Helper T cell IL-6 TGF-˜, IL-1, IL-6 IFN-° IFN-°, IL-4 TGF-˜, IL-2 IFN-°, IL-12 IL-4, IL-10 IL-2, IL-4

IFN-°, IL-2 Activate macrophages and cytotoxic T cells

IL-4, IL-5, IL-6 Activate eosinophils, IL-10, IL-13 ˙ IgE

IL-17, IL-21, IL-22 Induce neutrophilic infammation

TGF-˜, IL-10, IL-35 Prevent autoimmunity (maintain tolerance) CD4

Tand B-cell activation APCs: B cells, dendritic cells, Langerhans cells, macrophages. Two signals are required for T-cell activation, B-cell activation, and class switching.

Th-cell activation as above. R B-cell receptor–mediated endocytosis. Exogenous antigen is presented on MHC II and recognized by TCR on Th cell. CD40 receptor on B cell binds CD40 ligand (CD40L) on Th cell. Th cells secrete cytokines that determine Ig class switching of B cells. B cells are activated, undergo class switching and affinity maturation, and begin producing antibodies.

Antibody structure and function Fab (containing the variable/hypervariable regions) consisting of light (L) and heavy (H) chains recognizes antigens. Fc region of IgM and IgG fixes complement. Heavy chain contributes to Fc and Fab regions. Light chain contributes only to Fab region. VHJHJLDVLHinge Complement binding Macrophage binding Fc region C = Constant V = Variable SS = Disulfde bond Fab regionHypervariable regionsCLCLCH1CH1CH2CH3CH2CH3SS SS SS SS Light chain Heavy chain Epitope Fab: ƒFragment, antigen binding ƒComplement binding • Determines idiotype: unique antigen-binding pocket; only 1 antigenic specificity expressed per B cell Fc (5C’s): • Confers (determines) isotype (IgM, IgD, etc)

Generation of antibody diversity (antigen independent) 1.

Random recombination of VJ (light-chain) or V(D)J (heavy-chain) genes 2.

Random addition of nucleotides to DNA during recombination by terminal deoxynucleotidyl transferase (TdT) 3.

Random combination of heavy chains with light chains

Generation of antibody specificity (antigen dependent) 4.

5.

ComplementactivationMembrane attack complex (MAC) Antibody activates complement, enhancing opsonization and lysis C3b OpsonizationNeutralizationAntibody prevents bacterial adherence Antibody promotes phagocytosis

IgG Main antibody in 2° response to an antigen. Most abundant isotype in serum. Fixes complement, opsonizes bacteria, neutralizes bacterial toxins and viruses. Only isotype that crosses the placenta (provides infants with passive immunity that starts to wane after birth). “IgGGreets the Growing fetus.”

Prevents attachment of bacteria and viruses to mucous membranes; does not fix complement. Monomer (in circulation) or dimer (with J chain when secreted). Crosses epithelial cells by transcytosis. Produced in GI tract (eg, by Peyer patches) and protects against gut infections (eg, Giardia). Most produced antibody overall, but has lower serum concentrations. Released into secretions (tears, saliva, mucus) and breast milk. Picks up

secretory component from epithelial cells, which protects the Fc portion from luminal proteases.

IgM Produced in the 1° (immediate) response to an antigen. Fixes complement. Antigen receptor on the surface of B cells. Monomer on B cell, pentamer with J chain when secreted. Pentamer enables avid binding to antigen while humoral response evolves.

IgD Unclear function. Found on surface of many B cells and in serum.

IgE Binds mast cells and basophils; cross-links when exposed to allergen, mediating immediate (type I) hypersensitivity through release of inflammatory mediators such as histamine. Contributes to immunity to parasites by activating eosinophils.

Opsonins—C3b and IgG are the two 1° Opsonin (Greek) = to prepare for eating. opsonins in bacterial defense; enhance phagocytosis. C3b also helps clear immune complexes.

Inhibitors—decay-accelerating factor (DAF, aka CD55) and C1 esterase inhibitor help prevent complement activation on self cells (eg, RBCs).

Spontaneous and microbial surfaces Amplifes generation of C3b called C2a but is now referred to as C2b.

C3 C3b B D Bb C3 C3aC3aC3bBb (C3 convertase) C3C2b C4b C2 C1 C4 C4a(C3 convertase) C1 C5 C5aC5b C6-C9 C3bBb3b (C5 convertase) C4b2b3b (C5 convertase) C4b2b C3bcomplex C1-like * * *Historically, the larger fragment of C2 was

Lysis, (C5b-9) (eg, mannose)

C1 esterase inhibitor Causes hereditary angioedema due to unregulated activation of kallikrein □• bradykinin. deficiency Characterized by • C4 levels. ACE inhibitors are contraindicated (also • bradykinin).

Paroxysmal nocturnal A defect in the PIGA gene preventing the formation of glycosylphosphatidylinositol (GPI) anchors for hemoglobinuria complement inhibitors, such as decay-accelerating factor (DAF/CD55) and membrane inhibitor of reactive lysis (MIRL/CD59). Causes complement-mediated intravascular hemolysis □• haptoglobin, dark urine

A .

Important cytokines Acute (IL-1, IL-6, TNF-α), then recruit (IL-8, IL-12).

Respiratory burst Also called oxidative burst. Involves the activation of the phagocyte NADPH oxidase complex (eg, in neutrophils, monocytes), which utilizes O2 as a substrate. Plays an important role in the immune response □ rapid release of reactive oxygen species (ROS). NADPH plays a role in both the creation and neutralization of ROS. Myeloperoxidase contains a blue-green, heme-containing pigment that gives sputum its color.

Phagocytes of patients with CGD can utilize H_2O_2 generated by invading organisms and convert it to ROS. Patients are at • risk for infection by catalase ⊕ species (eg, S aureus, Aspergillus) capable of neutralizing their own H_2O_2, leaving phagocytes without ROS for fighting infections.

Pyocyanin of P aeruginosa generates ROS to kill competing pathogens. Oxidative burst also leads to K^+ influx, which releases lysosomal enzymes. Lactoferrin is a protein found in secretory fluids and neutrophils that inhibits microbial growth via iron chelation.

Interferons IFN-α, IFN-β, IFN-γ mechanISm A part of innate host defense, interferons interfere with both RNA and DNA viruses. Cells infected with a virus synthesize these glycoproteins, which act on local cells, priming them for viral defense by downregulating protein synthesis to resist potential viral replication and by upregulating MHC expression to facilitate recognition of infected cells. Also play a major role in activating antitumor immunity.

clInIcal uSe Chronic HBV, Kaposi sarcoma, hairy cell leukemia, condyloma acuminatum, renal cell carcinoma, malignant melanoma, multiple sclerosis, chronic granulomatous disease.

adVerSe eFFectS Flu-like symptoms, depression, neutropenia, myopathy, interferon-induced autoimmunity.

T cells TCR (binds antigen-MHC complex) CD3 (associated with TCR for signal transduction) CD28 (binds B7 on APC)

Helper T cells CD4, CD40L, CXCR4/CCR5 (co-receptors for HIV)

Anergy State during which a cell cannot become activated by exposure to its antigen. T and B cells become anergic when exposed to their antigen without costimulatory signal (signal 2). Another mechanism of self-tolerance.

Vaccination Induces an active immune response (humoral and/or cellular) to specific pathogens.

Hypersensitivity types Four types (ABCD): Anaphylactic and Atopic (type I), AntiBody-mediated (type II), Immune Complex (type III), Delayed (cell-mediated, type IV). Types I, II, and III are all antibody-mediated.

Antibodies bind to cell-surface antigens □ cellular destruction, inflammation, and cellular dysfunction.

Cellular destruction—cell is opsonized (coated) by antibodies, leading to either:

Phagocytosis and/or activation of complement system.

NK cell killing (antibody-dependent cellular cytotoxicity).

Inflammation—binding of antibodies to cell surfaces activation of complement system and Fc receptor-mediated inflammation.

Cellular dysfunction—antibodies bind to cell surface receptors abnormal blockade or activation of downstream process.

Direct Coombs test—detects antibodies attached directly to the RBC surface. Indirect Coombs test—detects presence of unbound antibodies in the serum

Examples:

Hemolytic disease of the newborn

Examples:

Hyperacute transplant rejection Examples:

Immune complex—antigen-antibody (mostly IgG) complexes activate complement, which attracts neutrophils; neutrophils release lysosomal enzymes.

Can be associated with vasculitis and systemic manifestations.

Serum sickness—the prototypic immune complex disease. Antibodies to foreign proteins are produced and 1–2 weeks later, antibody-antigen complexes form and deposit in tissues complement activation • inflammation and tissue damage.

Arthus reaction—a local subacute immune complex-mediated hypersensitivity reaction. Intradermal injection of antigen into a presensitized (has circulating IgG) individual leads to immune complex formation in the skin (eg, enhanced local reaction to a booster vaccination). Characterized by edema, necrosis, and activation of complement.

In type III reaction, imagine an immune complex as 3 things stuck together: antigenantibody-complement.

Examples:

Poststreptococcal glomerulonephritis Fever, urticaria, arthralgia, proteinuria, lymphadenopathy occur 1–2 weeks after antigen exposure. Serum sickness-like reactions are associated with some drugs (may act as haptens, eg, penicillin) and infections (eg, hepatitis B).

Two mechanisms, each involving T cells: 1.

Direct cell cytotoxicity: CD8+ cytotoxic T cells kill targeted cells.

2.

Inflammatory reaction: effector CD4+ T cells recognize antigen and release inflammation-inducing cytokines (shown in illustration).

Response does not involve antibodies (vs types I, II, and III). Examples: contact dermatitis (eg, poison ivy, nickel allergy) and graft-versus-host disease.

Tests: PPD for TB infection; patch test for contact dermatitis; Candida skin test for T cell immune function.

4T's: T cells, Transplant rejections, TB skin tests, Touching (contact dermatitis).

Fourth (type) and last (delayed).

Allergic/ Type I hypersensitivity Within minutes Allergies: urticaria, anaphylactic reaction against plasma to 2-3 hr (due to pruritus reaction proteins in transfused release of preformed Anaphylaxis: blood inflammatory wheezing, IgA-deficient individuals mediators in hypotension, should receive blood degranulating mast respiratory arrest,

Donor plasma proteins, Host mast cell

Acute Type II hypersensitivity During transfusion Fever, hypotension, hemolytic reaction or within 24 hr tachypnea, transfusion Typically causes (due to preformed tachycardia, reaction intravascular hemolysis antibodies) flank pain,

Donor RBC with A and/ Host anti-A, anti-B IgG, incompatibility) (intravascular), jaundice (extravascular)

Febrile Cytokines created by Within 1-6 hr (due Fever, headaches, nonhemolytic donor WBCs accumulate to preformed chills, flushing transfusion during storage of blood cytokines) More common in reaction products children Donor WBC releases

Reactions prevented by leukoreduction of blood products

Respiratory distress, noncardiogenic pulmonary edema

Generally self limited and clinically silent Mild fever, hyperbilirubinemia Donor RBC with Host IgG foreign antigens

Antinuclear (ANA) Nonspecific screening antibody, often associated with SLE

Anticardiolipin, lupus anticoagulant SLE, antiphospholipid syndrome

Anti-dsDNA, anti-Smith SLE

Antisynthetase (eg, anti-Jo-1), anti-SRP, anti-Polymyositis, dermatomyositis helicase (anti-Mi-2)

IgA anti-endomysial, IgA anti-tissue Celiac disease transglutaminase, IgA and IgG deamidated gliadin peptide

Anti-glutamic acid decarboxylase, islet cell Type 1 diabetes mellitus cytoplasmic antibodies

Antiparietal cell, anti-intrinsic factor Pernicious anemia

Ataxia-telangiectasia A Defects in ATM gene failure to detect DNA damage failure to halt progression of cell cycle mutations accumulate; autosomal recessive Triad: cerebellar defects (Ataxia), spider Angiomas (telangiectasia A), IgA deficiency •• sensitivity to radiation (limit x-ray exposure) •AFP • IgA, IgG, and IgE Lymphopenia, cerebellar atrophy • risk of lymphoma and leukemia Hyper-IgM syndrome Most commonly due to defective CD40L on Th cells class switching defect; X-linked recessive Severe pyogenic infections early in life; opportunistic infection with Pneumocystis, Cryptosporidium, CMV Normal or • IgM •• IgG, IgA, IgE Failure to make germinal centers

Defect in lysosomal trafficking PLAIN: Progressive Giant granules (

B , arrows) in regulator gene (LYST) neurodegeneration, granulocytes and platelets.

Microtubule dysfunction in Lymphohistiocytosis, Pancytopenia phagosome-lysosome fusion; Albinism (partial), recurrent Mild coagulation defects autosomal recessive pyogenic Infections,

Bacteria Sepsis Encapsulated (Please SHINE my SKiS): Pseudomonas aeruginosa, Streptococcus pneumoniae, Haemophilus Influenzae type b, Neisseria meningitidis, Escherichia coli, Salmonella, Klebsiella pneumoniae, Group B Streptococcus

Some Bacteria Encapsulated Produce No species with early Serious granules: complement Staphylococcus, deficiencies Burkholderia cepacia, Neisseria with late Pseudomonas complement (C5- aeruginosa, Nocardia, C9) deficiencies Serratia

Viruses CMV, EBV, JC Enteroviral N/A N/A virus, VZV, chronic encephalitis, infection with poliovirus respiratory/GI viruses (live vaccine

Fungi/parasites Candida (local), PCP, GI giardiasis (no IgA) Candida (systemic), N/A Cryptococcus Aspergillus, Mucor

Note: B-cell deficiencies tend to produce recurrent bacterial infections, whereas T-cell deficiencies produce more fungal and viral infections.

Hyperacute A Within minutes Pre-existing recipient antibodies react to donor antigen (type II hypersensitivity reaction), activate complement Widespread thrombosis of graft vessels (arrows within glomerulus A) ischemia/necrosis Graft must be removed Acute B Weeks to months Cellular: CD8+ T cells and/ or CD4+ T cells activated against donor MHCs (type IV hypersensitivity reaction) Humoral: similar to hyperacute, except antibodies develop after transplant Vasculitis of graft vessels with dense interstitial lymphocytic infiltrate B Prevent/reverse with immunosuppressants Chronic C Months to years CD4+ T cells respond to

recipient APCs presenting donor peptides, including allogeneic MHC Both cellular and humoral components (type II and IV hypersensitivity reactions) Recipient T cells react and secrete cytokines proliferation of vascular smooth muscle, parenchymal atrophy, interstitial fibrosis Dominated by arteriosclerosis C Organ-specific examples: ƒChronic allograft nephropathy ƒBronchiolitis obliterans ƒAccelerated atherosclerosis (heart) ƒVanishing bile duct syndrome Graft-versus-host disease Varies Grafted immunocompetent T cells proliferate in the Maculopapular rash, jaundice, diarrhea, hepatosplenomegaly reject host cells with "foreign"

For immunocompromised patients, irradiate blood products prior to transfusion to prevent GVHD

Immunosuppressants Agents that block lymphocyte activation and proliferation. Reduce acute transplant rejection by suppressing cellular immunity (used as prophylaxis). Frequently combined to achieve greater efficacy with • toxicity. Chronic suppression • risk of infection and malignancy.

Cyclosporine Calcineurin inhibitor; Psoriasis, rheumatoid Nephrotoxicity, binds cyclophilin arthritis hypertension,

Blocks T-cell activation hyperlipidemia, by preventing IL-2 neurotoxicity, gingival transcription hyperplasia, hirsutism

Tacrolimus (FK506) Calcineurin inhibitor; Similar to cyclosporine, binds FK506 binding • risk of diabetes protein (FKBP) and neurotoxicity; Blocks T-cell activation no gingival by preventing IL-2 hyperplasia or transcription hirsutism

Both calcineurin inhibitors are highly nephrotoxic, especially in higher doses or in patients with decreased renal function

Sirolimus (Rapamycin) mTOR inhibitor; binds "PanSirtopenia" Kidney "sir-vives." FKBP (pancytopenia), Synergistic with

Blocks T-cell insulin resistance, cyclosporine

Basiliximab Monoclonal antibody; Edema, hypertension, blocks IL-2R tremor

Azathioprine Antimetabolite Rheumatoid arthritis, Pancytopenia 6-MP degraded by precursor of Crohn disease, xanthine oxidase; 6-mercaptopurine glomerulonephritis, toxicity • by

Mycophenolate Reversibly inhibits Lupus nephritis GI upset, Associated with

Mofetil IMP dehydrogenase, pancytopenia, invasive CMV preventing purine hypertension, infection synthesis of B and T hyperglycemia cells Less nephrotoxic and • transcription of

Many autoimmune and inflammatory disorders, adrenal insufficiency, asthma, CLL, non-Hodgkin lymphoma Cushing syndrome, osteoporosis,

hyperglycemia, diabetes, amenorrhea, adrenocortical atrophy, peptic ulcers, psychosis, cataracts, avascular necrosis (femoral head) Demargination of WBCs causes artificial leukocytosis

Adrenal insufficiency may develop if drug is stopped abruptly after chronic use "Support bacteria. They're the only culture some people have." "What lies behind us and what lies ahead of us are tiny matters compared to what lies within us." —Henry S. Haskins "Infectious disease is merely a disagreeable instance of a widely prevalent tendency of all living creatures to save themselves the bother of building, by their own efforts, the things they require."

Microbiology questions on the Step 1 exam often require two (or more) steps: Given a certain clinical presentation, you will first need to identify the most likely causative organism, and you will then need to provide an answer regarding some features of that organism or relevant antimicrobial agents. For example, a description of a child with fever and a petechial rash will be followed by a question that reads, "From what site does the responsible organism usually enter the blood?"

This section therefore presents organisms in two major ways: in individual microbial "profiles" and in the context of the systems they infect and the clinical presentations they produce. You should become familiar with both formats. When reviewing the systems approach, remind yourself of the features of each microbe by returning to the individual profiles. Also be sure to memorize the laboratory characteristics that allow you to identify microbes.

Flagellum Proteins Motility Pilus/fimbria Glycoprotein Mediate adherence of bacteria to cell surface; sex pilus forms during conjugation

Spore Keratin-like coat; dipicolinic acid; Gram ⊕ only peptidoglycan, DNA Survival: resist dehydration, heat, chemicals

Capsule Discrete layer usually made of polysaccharides Protects against phagocytosis (and rarely proteins) Slime (S) layer Loose network of polysaccharides Mediates adherence to surfaces, especially foreign surfaces (eg, indwelling catheters) Outer membrane Outer leaflet: contains endotoxin (LPS/LOS) Gram ⊖ only Embedded proteins: porins and other outer Endotoxin: lipid A induces TNF and IL-1; membrane proteins (OMPs) antigenic O polysaccharide component Inner leaflet: phospholipids Most OMPs are antigenic Porins: transport across outer membrane

Periplasm Space between cytoplasmic membrane Accumulates components exiting gram and outer membrane in gram ⊖ bacterial ⊖ cells, including hydrolytic enzymes (peptidoglycan in middle) (eg, β-lactamases)

Cell wall Peptidoglycan is a sugar backbone with peptide Net-like structure gives rigid support, protects side chains cross-linked by transpeptidase against osmotic pressure damage Cytoplasmic Phospholipid bilayer sac with embedded Site of oxidative and transport enzymes; PBPs membrane proteins (eg, penicillin-binding proteins involved in cell wall synthesis [PBPs]) and other enzymes Lipoteichoic acids induce TNF-α and

IL-1 Lipoteichoic acids (gram positive) only extend from membrane to exterior

Gram stain First-line lab test in bacterial identification. Bacteria with thick peptidoglycan layer retain crystal violet dye (gram ⊕); bacteria with thin peptidoglycan layer turn red or pink (gram ⊖) with counterstain. These bugs do not Gram stain well (These Little Microbes May Unfortunately Lack Real Color But Are Everywhere):

Treponema, Leptospira Too thin to be visualized

Mycoplasma, Ureaplasma No cell wall

India ink stain Cryptococcus neoformans D ; mucicarmine can also be used to stain thick polysaccharide capsule red

Silver stain Fungi (eg, Coccidioides

E , Pneumocystis jirovecii), Legionella, Helicobacter pylori

Properties of growth media The same type of media can possess both (or neither) of these properties.

Selective media Favors the growth of particular organism while preventing growth of other organisms. Example: Thayer-Martin agar contains antibiotics that allow the selective growth of Neisseria by inhibiting the growth of other sensitive organisms.

Aerobes Use an O2-dependent system to generate ATP. Examples include Nocardia, Pseudomonas aeruginosa, Mycobacterium tuberculosis, and Bordetella pertussis. Reactivation of M tuberculosis (eg, after immunocompromise or TNF-α inhibitor use) has a predilection for the apices of the lung.

Anaerobes Examples include Clostridium, Bacteroides, Fusobacterium, and Actinomyces israelii. They lack catalase and/or superoxide dismutase and are thus susceptible to oxidative damage. Generally foul smelling (short-chain fatty acids), are difficult to culture, and produce gas in tissue (CO2 and H2).

Anaerobes Can’t Breathe Fresh Air.

Anaerobes are normal flora in GI tract, typically pathogenic elsewhere. AminO2glycosides are ineffective against anaerobes because these antibiotics require O2 to enter into bacterial cell.

Examples are Pseudomonas aeruginosa, Streptococcus pneumoniae A , Haemophilus influenzae type b, Neisseria meningitidis, Escherichia coli, Salmonella, Klebsiella pneumoniae, and group B Strep. Their capsules serve as an antiphagocytic virulence factor.

Capsular polysaccharide + protein conjugate serves as an antigen in vaccines.

Please SHiNE my SKiS.

Are opsonized, and then cleared by spleen. Asplenics (No Spleen Here) have • opsonizing ability and thus • risk for severe infections; need vaccines to protect against:

Some vaccines containing polysaccharide capsule antigens are conjugated to a carrier protein, enhancing immunogenicity by promoting T-cell activation and subsequent class switching. A polysaccharide antigen alone cannot be presented to T cells.

Pneumococcal vaccines: PCV13 (pneumococcal conjugate vaccine), PPSV23 (pneumococcal polysaccharide vaccine with no conjugated protein).

H influenzae type b (conjugate vaccine).

Meningococcal vaccine (conjugate vaccine).

Catalase-positive Catalase degrades H2O2 into H2O and bubbles of O2 A before it can be converted to microbicidal organisms products by the enzyme myeloperoxidase. People with chronic granulomatous disease (NADPH oxidase deficiency) have recurrent infections with certain catalase ⊕ organisms.

Examples: Nocardia, Staphylococci, Serratia, Candida, Listeria, E coli, Burkholderia cepacia, Pseudomonas, Aspergillus, Helicobacter pylori, Bordetella pertussis.

Viridans streptococci (S mutans, S sanguinis) Dental plaques, infective endocarditis

P aeruginosa Respiratory tree colonization in patients with cystic fibrosis, ventilator-associated pneumonia Contact lens–associated keratitis

Some gram ⊕ bacteria can form spores A when nutrients are limited. Spores lack metabolic activity and are highly resistant to heat and chemicals. Core contains dipicolinic acid. Must autoclave to kill spores (as is done to surgical equipment) by steaming at 121°C for 15 minutes.

Examples: B anthracis (anthrax), B cereus (food poisoning), C botulinum (botulism), C difficile (pseudomembranous colitis), C perfringens (gas gangrene), C tetani (tetanus).

Bacterial virulence factors These promote evasion of host immune response.

pieces of environmental naked bacterial chromosomal DNA (from bacterial cell lysis). The transfer and expression of newly transferred genes is called transformation. A feature of many bacteria, especially S pneumoniae, Hinfluenzae type b, and Neisseria (SHiN).

Adding deoxyribonuclease degrades naked DNA, preventing transformation.

into bacterial DNA of part of the chromosome bacterial chromosomal DNA, termed high- frequency recombination (Hfr) cell. Transfer of leading part of plasmid and a few flanking F+ cell F– cell Hfr cellF– cell Hfr cell F– cell Hfr cell Recombinant chromosomal genes. High-frequency recombination may integrate some of those bacterial genes. Recipient cell remains F– but now may have new bacterial genes.

Generalized A packaging "error." Lytic phage infects Cleavage of Bacterial DNA packaged bacterium, leading to cleavage of bacterial phage DNA. Parts of bacterial chromosomal DNA may become packaged in phage capsid. Phage infects another bacterium, transferring these genes.

Release of new phage Infects other Genes transferred from lysed cell bacteria to new bacteria

Specialized An "excision" event. Lysogenic phage infects bacterium; viral DNA incorporates into bacterial chromosome. When phage DNA is excised, flanking bacterial genes may be excised with it. DNA is packaged into phage capsid and can infect another bacterium. Genes for the following 5 bacterial toxins are encoded in a lysogenic phage (ABCD'S): Group A strep erythrogenic toxin, Botulinum toxin, Cholera toxin, Diphtheria toxin, Shiga toxin.

Release of new phage Infects other Genes di˜erent from from lysed cell bacteria donor and recipient (specialized segment of DNA), which can copy and excise itself and then insert into the same DNA molecule or an unrelated DNA (eg,

Integration of genes Transposon plasmid or chromosome). Critical in creating plasmids with multiple drug resistance and DNA transfer across species lines (eg, Tn1546 with vanA from Enterococcus to S aureus).

Main features of exotoxins and endotoxins Bacteria with exotoxins

Downstream cellular reaction Exotoxin TNF, IL-1, IL-6 Host cell Endotoxin

Toxin prevents release of inhibitory (GABA and glycine) neurotransmitters from Renshaw cells in spinal cord spastic paralysis, risus sardonicus, trismus (lockjaw)

Toxin prevents release of stimulatory (ACh) signals at neuromuscular junction flaccid paralysis (floppy baby) aAn AB toxin (aka, two-component toxin [or three for anthrax]) with B enabling binding and triggering uptake (endocytosis) of the active A component. The A components are usually ADP ribosyltransferases; others have enzymatic activities as listed in chart.

Bacteria with exotoxins (continued)

Clostridium Alpha toxin Phospholipase (lecithinase) Degradation of phospholipids myonecrosis perfringens that degrades tissue and ("gas gangrene") and hemolysis ("double zone" cell membranes of hemolysis on blood agar)

Streptococcus Streptolysin O Protein that degrades cell Lyses RBCs; contributes to β-hemolysis; pyogenes membrane host antibodies against toxin (ASO) used to diagnose rheumatic fever (do not confuse with immune complexes of poststreptococcal glomerulonephritis)

Cross-links β region of TCR to MHC class II on APCs outside of the antigen binding site overwhelming release of IL-1, IL-2, IFN-γ, and TNF-α • shock Toxic shock syndrome: fever, rash, shock; other toxins cause scalded skin syndrome (exfoliative toxin) and food poisoning (heat-stable enterotoxin)

Toxic shock–like syndrome: fever, rash, shock; scarlet fever

Endotoxin LPS found in outer membrane of gram ⊖ bacteria (both cocci and rods). Composed of O antigen + core polysaccharide + lipid A (the toxic component). Released upon cell lysis or by living cells by blebs detaching from outer surface membrane (vs exotoxin, which is actively secreted). Three main effects: macrophage activation (TLR4/CD14), complement activation, and tissue factor activation.

ENDOTOXINS: Edema Nitric oxide DIC/Death Outer membrane TNF-α O-antigen + core polysaccharide + lipid A eXtremely heat stable IL-1 and IL-6 Neutrophil chemotaxis Shock

IL-1, IL-6 Fever Fever and hypotension HypotensionNitric oxide TNF-α hemolysis, hemolysis,

Important tests are in bold. Important pathogens are in bold italics. Note: Enterococcus is either ˜or °-hemolytic.

(No hemolysis, grows in bile) Novobiocin sensitivity

Growth in 6.5% NaCl and PYR Status -hemolytic bacteria Gram ⊕ cocci. Partial oxidation of hemoglobin causes greenish or brownish color without clearing around growth on blood agar A . Include the following organisms: -hemolytic bacteria Gram ⊕ cocci. Complete lysis of RBCs pale/clear area surrounding colony on blood agar A . Include the following organisms:

Gram ⊕, β-hemolytic, catalase ⊕, coagulase ⊕ cocci in clusters A . Protein A (virulence factor) binds Fc-IgG, inhibiting complement activation and phagocytosis. Commonly colonizes the nares, ears, axilla, and groin.

Causes:

Inflammatory disease—skin infections, organ abscesses, pneumonia (often after influenza virus infection), endocarditis, septic arthritis, and osteomyelitis.

Toxin-mediated disease—toxic shock syndrome (TSST-1), scalded skin syndrome (exfoliative toxin), rapid-onset food poisoning (enterotoxins).

MRSA (methicillin-resistant S aureus)— important cause of serious nosocomial and community-acquired infections; resistance due to altered penicillin-binding protein. mecA gene from staphylococcal chromosomal cassette involved in penicillin resistance.

TSST-1 is a superantigen that binds to MHC II and T-cell receptor, resulting in polyclonal T-cell activation and cytokine release.

Staphylococcal toxic shock syndrome (TSS)— fever, vomiting, rash, desquamation, shock, end-organ failure. TSS results in • AST, • ALT, • bilirubin. Associated with prolonged use of vaginal tampons or nasal packing.

Compare with Streptococcus pyogenes TSS (a toxic shock–like syndrome associated with painful skin infection).

S aureus food poisoning due to ingestion of preformed toxin short incubation period (2–6 hr) followed by nonbloody diarrhea and emesis. Enterotoxin is heat stable not destroyed by cooking.

S aureus makes coagulase and toxins. Forms fibrin clot around itself abscess.

Gram ⊕, catalase ⊕, coagulase ⊖, urease ⊕ cocci in clusters. Novobiocin sensitive. Does not ferment mannitol (vs S aureus).

Normal flora of skin; contaminates blood cultures.

Infects prosthetic devices (eg, hip implant, heart valve) and IV catheters by producing adherent biofilms.

Staphylococcus Gram ⊕, catalase ⊕, coagulase ⊖, urease ⊕ cocci in clusters. Novobiocin resistant. saprophyticus Normal flora of female genital tract and perineum.

Second most common cause of uncomplicated UTI in young women (most common is E coli).

Gram ⊕, α-hemolytic, lancet-shaped diplococci

A . Encapsulated. IgA protease. Optochin sensitive and bile soluble. Most commonly causes:

Pneumococcus is associated with “rusty” sputum, sepsis in patients with sickle cell disease, and asplenic patients.

No virulence without capsule.

Gram ⊕, α-hemolytic cocci. Optochin resistant and bile insoluble. Normal flora of the oropharynx.

Streptococcus mutans and S mitis cause dental caries.

S sanguinis makes dextrans that bind to fibrin-platelet aggregates on damaged heart valves, causing subacute bacterial endocarditis.

Viridans group strep live in the mouth, because they are not afraid of-the-chin (op-to-chin resistant).

Sanguinis = blood. Think, "there is lots of blood in the heart" (endocarditis).

Gram ⊕ cocci in chains A . Group A strep cause:

Pyogenic—pharyngitis, cellulitis, impetigo ("honey-crusted" lesions), erysipelas

Toxigenic—scarlet fever, toxic shock–like syndrome, necrotizing fasciitis

Immunologic—rheumatic fever, glomerulonephritis

Bacitracin sensitive, β-hemolytic, pyrrolidonyl arylamidase (PYR) ⊕. Hyaluronic acid capsule and M protein inhibit phagocytosis. Antibodies to M protein enhance host defenses against S pyogenes but can give rise to rheumatic fever.

ASO titer or anti-DNase B antibodies indicate recent S pyogenes infection.

"Ph"yogenes pharyngitis can result in rheumatic "phever" and glomerulonephritis.

Strains causing impetigo can induce glomerulonephritis.

Scarlet fever—blanching, sandpaper-like body rash, strawberry tongue, and circumoral pallor in the setting of group A streptococcal pharyngitis (erythrogenic toxin ⊕).

Bacillus anthracis Gram ⊕, spore-forming rod that produces anthrax toxin (an exotoxin consisting of protective antigen, lethal factor, and edema factor). Has a polypeptide capsule (poly d-glutamate). Colonies show a halo of projections, sometimes referred to as "medusa head" appearance.

Cutaneous anthrax Painless papule surrounded by vesicles □ ulcer with black eschar A (painless, necrotic) □ uncommonly progresses to bacteremia and death.

Pulmonary anthrax Inhalation of spores, most commonly from contaminated animals or animal products, although also a potential bioweapon □ flu-like symptoms that rapidly progress to fever, pulmonary hemorrhage, mediastinitis (CXR may show widened mediastinum), and shock. Also called woolsorter's disease.

Gram ⊕ cocci, bacitracin resistant, β-hemolytic, colonizes vagina; causes pneumonia, meningitis, and sepsis, mainly in babies.

Produces CAMP factor, which enlarges the area of hemolysis formed by S aureus. (Note: CAMP stands for the authors of the test, not cyclic AMP.) Hippurate test ⊕. PYR ⊖.

Screen pregnant women at 35–37 weeks of gestation with rectal and vaginal swabs. Patients with ⊕ culture receive intrapartum penicillin/ampicillin prophylaxis.

Bacillus cereus Gram ⊕ rod. Causes food poisoning. Spores survive cooking rice (reheated rice syndrome).

Keeping rice warm results in germination of spores and enterotoxin formation. Emetic type causes nausea and vomiting within 1–5 hours. Caused by cereulide, a preformed toxin. Diarrheal type causes watery, nonbloody diarrhea and GI pain within 8–18 hours. Management: supportive care (antibiotics are ineffective against toxins).

Clostridia Gram ⊕, spore-forming, obligate anaerobic rods. Tetanus toxin and botulinum toxin are proteases that cleave SNARE proteins involved in neurotransmission.

Clostridium tetani Produces tetanospasmin, an exotoxin causing Tetanus is tetanic paralysis. tetanus. Tetanospasmin blocks release of GABA and glycine from Renshaw cells in spinal cord. Causes spastic paralysis, trismus (lockjaw), risus sardonicus (raised eyebrows and open grin), opisthotonos (spasms of spinal extensors). Prevent with tetanus vaccine. Treat with antitoxin +/− vaccine booster, antibiotics, diazepam (for muscle spasms), and wound debridement.

Produces a heat-labile toxin that inhibits ACh release at the neuromuscular junction, causing botulism. In adults, disease is caused by ingestion of preformed toxin. In babies, ingestion of spores (eg, in honey) leads to disease (floppy baby syndrome). Treat with human botulinum immunoglobulin.

Symptoms of botulism (the 4 D’s): Diplopia, Dysarthria, Dysphagia, Dyspnea.

Botulinum is from bad bottles of food, juice, and honey (causes a descending flaccid paralysis).

Local botulinum toxin A (Botox) injections used to treat focal dystonia, hyperhidrosis, muscle spasms, and cosmetic reduction of facial wrinkles.

Produces α-toxin (lecithinase, a phospholipase) that can cause myonecrosis (gas gangrene A ; presents as soft tissue crepitus) and hemolysis.

If heavily spore-contaminated food is cooked but left standing too long at < 60°C, spores germinate • vegetative bacteria • heat-labile enterotoxin • food poisoning symptoms in 10-12 hours, resolution in 24 hours.

Perfringens perforates a gangrenous leg.

Produces toxins A and B, which damage enterocytes. Both toxins lead to watery diarrhea

B . Often 2° to antibiotic use, especially clindamycin or ampicillin; associated with PPIs.

Diagnosed by PCR or antigen detection of one or both toxins in stool. Complications: toxic megacolon.

Difficile causes diarrhea.

Treatment: oral vancomycin, metronidazole, or fidaxomicin. For recurrent cases, consider repeating prior regimen or fecal microbiota transplant.

Gram ⊕ rods occurring in angular arrangements; transmitted via respiratory droplets. Causes diphtheria via exotoxin encoded by β-prophage. Potent exotoxin inhibits protein synthesis via ADP-ribosylation of EF-2, leading to possible necrosis in pharynx, cardiac, and CNS tissue.

Symptoms include pseudomembranous pharyngitis (grayish-white membrane A) with lymphadenopathy. Toxin dissemination may cause myocarditis, arrhythmias, neuropathies.

Lab diagnosis based on gram ⊕ rods with metachromatic (blue and red) granules and ⊕ Elek test for toxin.

Toxoid vaccine prevents diphtheria.

on Löffler media). Black colonies on cystine-tellurite agar. ABCDEFG:

Elongation Factor 2 Granules Treatment: antibiotic therapy +/− diphtheria antitoxin.

Gram ⊕, facultative intracellular rod; acquired by ingestion of unpasteurized dairy products and cold deli meats, transplacental transmission, by vaginal transmission during birth. Grows well at refrigeration temperatures (“cold enrichment”).

Forms “rocket tails” (red in A) via actin polymerization that allow intracellular movement and cell-to-cell spread across cell membranes, thereby avoiding antibody. Characteristic tumbling motility in broth.

Can cause amnionitis, septicemia, and spontaneous abortion in pregnant women; granulomatosis infantiseptica; meningitis in immunocompromised patients, neonates, and older adults; mild, self-limited gastroenteritis in healthy individuals.

Treatment: ampicillin.

Nocardia vs Both are gram ⊕ and form long, branching filaments resembling fungi. Actinomyces

Found in soil Normal oral, reproductive, and GI flora

Causes pulmonary infections in Causes oral/facial abscesses that drain through immunocompromised (can mimic TB but sinus tracts; often associated with dental caries/ with ⊖ PPD); cutaneous infections after extraction and other maxillofacial trauma; trauma in immunocompetent; can spread to forms yellow "sulfur granules"; can also cause CNS PID with IUDs

Treat with sulfonamides (TMP-SMX) Treat with penicillin

Treatment is a SNAP: Sulfonamides—Nocardia; Actinomyces—Penicillin

Gram ⊕ acid fast rods (pink rods, arrows in A). Mycobacterium tuberculosis (TB, often resistant to multiple drugs).

M avium-intracellulare (causes disseminated, non-TB disease in AIDS; often resistant to multiple drugs). Prophylaxis with azithromycin when CD4+ count < 50 cells/ mm . M scrofulaceum (cervical lymphadenitis in children). M marinum (hand infection in aquarium handlers).

TB symptoms include fever, night sweats, weight loss, cough (nonproductive or productive), hemoptysis.

Cord factor creates a "serpentine cord" appearance in virulent M tuberculosis strains; activates macrophages (promoting granuloma formation) and induces release of TNF-α. Sulfatides (surface glycolipids) inhibit phagolysosomal fusion.

Healing by fbrosis Progressive primary tuberculosis Calcifcation (AIDS, malnutrition) (PPD false positives from BCG vaccination. PPD ⊕ if current infection or past exposure. PPD ⊖ if no infection and in sarcoidosis or

HIV infection (especially with low CD4+ cell count).

Caseating granulomas with central necrosis and Langhans giant cell (single example in A) are characteristic of 2° tuberculosis.

Leprosy Also called Hansen disease. Caused by Mycobacterium leprae, an acid-fast bacillus that likes cool temperatures (infects skin and superficial nerves—"glove and stocking" loss of sensation A) and cannot be grown in vitro. Diagnosed via skin biopsy or tissue PCR. Reservoir in United States: armadillos. Leprosy has 2 forms (many cases fall temporarily between two extremes):

Lepromatous—presents diffusely over the skin, with Leonine (Lion-like) facies B , and is communicable (high bacterial load); characterized by low cell-mediated immunity with a largely Th2 response. Lepromatous form can be Lethal.

Tuberculoid—limited to a few hypoesthetic, hairless skin plaques; characterized by high cell- mediated immunity with a largely Th1-type

response and low bacterial load. Treatment: dapsone and rifampin for tuberculoid form; clofazimine is added for lepromatous form.

Important tests are in bold. Important pathogens are in bold italics.
aPleomorphic rod/coccobacillus

Neisseria Gram ⊖ diplococci. Metabolize glucose Acid production: MeninGococci—Maltose and and produce IgA proteases. Contain Glucose; Gonococci—Glucose. lipooligosaccharides (LOS) with strong endotoxin activity. N gonorrhoeae is often intracellular (within neutrophils)

A .

No vaccine due to antigenic variation of pilus Vaccine (type B vaccine available for at-risk proteins individuals)

Causes gonorrhea, septic arthritis, neonatal Causes meningococcemia with petechial conjunctivitis (2–5 days after birth), pelvic hemorrhages and gangrene of toes

B , inflammatory disease (PID), and Fitz-Hugh– meningitis, Waterhouse-Friderichsen Curtis syndrome syndrome (adrenal insufficiency, fever, DIC,

Diagnosed with NAT Diagnosed via culture-based tests or PCR

Condoms • sexual transmission, erythromycin Rifampin, ciprofloxacin, or ceftriaxone eye ointment prevents neonatal blindness prophylaxis in close contacts

Treatment: ceftriaxone (+ azithromycin Treatment: ceftriaxone or penicillin G or doxycycline, for possible chlamydial coinfection)

Small gram ⊖ (coccobacillary) rod. Aerosol transmission. Nontypeable (unencapsulated) strains are the most common cause of mucosal infections (otitis media, conjunctivitis, bronchitis) as well as invasive infections since the vaccine for capsular type b was introduced. Produces IgA protease.

Culture on chocolate agar, which contains factors V (NAD+) and X (hematin) for growth; can also be grown with S aureus, which provides factor V via RBC hemolysis.

A , can be “cherry red” in children; “thumb sign” on lateral neck x-ray

B), Meningitis, Otitis media, and Pneumonia.

Vaccine contains type b capsular polysaccharide (polyribosylribitol phosphate) conjugated to diphtheria toxoid or other protein. Given between 2 and 18 months of age.

Does not cause the flu (influenza virus does).

Treatment: amoxicillin +/– clavulanate for mucosal infections; ceftriaxone for meningitis; rifampin prophylaxis for close contacts.

Acinetobacter Gram ⊖, strictly aerobic, oxidase ⊖ coccobacillus. Commensal opportunist but increasingly baumannii associated with resistant hospital-acquired infections, especially in ICU. Can cause ventilator-associated pneumonia and septicemia in immunocompromised patients.

Gram ⊖ rod. Gram stains poorly—use silver stain. Grow on charcoal yeast extract medium with iron and cysteine. Detected by presence of antigen in urine. Labs may show hyponatremia.

Aerosol transmission from environmental water source habitat (eg, air conditioning systems, hot water tanks). No person-to-person transmission.

Treatment: macrolide or quinolone.

Gram ⊖, aerobic coccobacillus. Virulence factors include pertussis toxin (disables Gi), adenylate cyclase toxin (• cAMP), and tracheal cytotoxin. Three clinical stages:

Catarrhal—low-grade fevers, Coryza.

Paroxysmal—paroxysms of intense cough followed by inspiratory "whooP" ("whooping cough"), posttussive vomiting.

Convalescent—gradual recovery of chronic cough. Prevented by Tdap, DTaP vaccines. May be mistaken as viral infection due to lymphocytic infiltrate resulting from immune response. Treatment: macrolides; if allergic use TMP-SMX.

Gram ⊖, aerobic coccobacillus. Transmitted via ingestion of contaminated animal products (eg, unpasteurized milk). Survives in macrophages in the reticuloendothelial system. Can form noncaseating granulomas. Typically presents with undulant fever, night sweats, and arthralgia.

Treatment: doxycycline + rifampin or streptomycin.

Think of a French legionnaire (soldier) with his silver helmet, sitting around a campfire (charcoal) with his iron dagger—he is no sissy (cysteine).

Legionnaires' disease—severe pneumonia (often unilateral and lobar A), fever, GI and CNS symptoms. Common in smokers and in chronic lung disease.

Pontiac fever—mild flu-like syndrome.

Aeruginosa—aerobic; motile, catalase ⊕, gram ⊖ rod. Non-lactose fermenting. Oxidase ⊕. Frequently found in water. Has a grape-like odor.

PSEUDOMONAS is associated with: Pneumonia, Sepsis, Ecthyma gangrenosum, UTIs, Diabetes, Osteomyelitis, Mucoid polysaccharide capsule, Otitis externa (swimmer's ear), Nosocomial infections (eg, catheters,

equipment), Addicts (drug abusers), Skin infections (eg, hot tub folliculitis, wound infection in burn victims).

Mucoid polysaccharide capsule may contribute to chronic pneumonia in cystic fibrosis patients due to biofilm formation.

Produces PEEP: Phospholipase C (degrades cell membranes); Endotoxin (fever, shock); Exotoxin A (inactivates EF-2); Pigments: pyoverdine and pyocyanin (blue-green pigment A ; also generates reactive oxygen species).

Corneal ulcers/keratitis in contact lens wearers/ minor eye trauma.

Ecthyma gangrenosum—rapidly progressive, necrotic cutaneous lesion

B caused by Pseudomonas bacteremia. Typically seen in immunocompromised patients.

Treatments include "CAMPFIRE" drugs:

Polymyxins (eg, polymyxin B, colistin)

Fluoroquinolones (eg, ciprofloxacin, levofloxacin)

ThIRdand fourth-generation cephalosporins (eg, ceftazidime, cefepime)

Extended-spectrum penicillins (eg, piperacillin, ticarcillin)

Yersinia enterocolitica Gram ⊖ pleomorphic rod/coccobacillus. Usually transmitted from pet feces (eg, puppies), contaminated milk, or pork. Can cause acute bloody diarrhea, pseudoappendicitis (right lower abdominal pain due to mesenteric adenitis and/or terminal ileitis), reactive arthritis in adults.

Gram ⊖ rod; intestinal flora that causes lobar pneumonia in alcoholics and diabetics when aspirated. Very mucoid colonies A caused by abundant polysaccharide capsules. Dark red "currant jelly" sputum (blood/mucus).

Also cause of nosocomial UTIs. Associated with evolution of multidrug resistance (MDR).

ABCDE's of Klebsiella: Aspiration pneumonia aBscess in lungs and liver "Currant jelly" sputum Diabetes EtOH abuse

Campylobacter jejuni Gram ⊖, comma or S shaped (with polar flagella) A , oxidase ⊕, grows at 42°C ("Campylobacter likes the hot campfire").

Major cause of bloody diarrhea, especially in children. Fecal-oral transmission through person-to-person contact or via ingestion of undercooked contaminated poultry or meat, unpasteurized milk. Contact with infected animals (dogs, cats, pigs) is also a risk factor.

Common antecedent to Guillain-Barré syndrome and reactive arthritis.

Vibrio cholerae Gram ⊖, flagellated, comma shaped A , oxidase ⊕, grows in alkaline media. Endemic to developing countries. Produces profuse rice-water diarrhea via enterotoxin that permanently activates Gs, • cAMP. Sensitive to stomach acid (acid labile); requires large inoculum (high ID50) unless host has • gastric acidity. Transmitted via ingestion of contaminated water or uncooked food (eg, raw shellfish). Treat promptly with oral rehydration solution.

Curved, flagellated (motile), gram ⊖ rod A that is triple ⊕: catalase ⊕, oxidase ⊕, and urease ⊕ (can use urea breath test or fecal antigen test for diagnosis). Urease produces ammonia, creating an alkaline environment, which helps H pylori survive in acidic mucosa. Colonizes mainly antrum of stomach; causes gastritis and peptic ulcers (especially duodenal). Risk factor for peptic ulcer disease, gastric adenocarcinoma, and MALT lymphoma.

Most common initial treatment is triple therapy: Amoxicillin (metronidazole if penicillin allergy) + Clarithromycin + Proton pump inhibitor; Antibiotics Cure Pylori. Bismuth-based quadruple therapy if concerned about macrolide resistance.

Jarisch-Herxheimer Flu-like syndrome (fever, chills, headache, myalgia) after antibiotics are started; due to killed reaction bacteria (usually spirochetes) releasing toxins.

Chlamydiae cannot make their own ATP. They are obligate intracellular organisms that cause mucosal infections. 2 forms:

Elementary body (small, dense) is “Enfectious” and Enters cell via Endocytosis; transforms into reticulate body.

Reticulate body Replicates in cell by fission; Reorganizes into elementary bodies.

A , nongonococcal urethritis, PID, and reactive arthritis.

Chlamydophila pneumoniae and Chlamydophila psittaci cause atypical pneumonia; transmitted by aerosol.

Chlamydial cell wall lacks classic peptidoglycan (due to reduced muramic acid), rendering β-lactam antibiotics ineffective.

Chlamys = cloak (intracellular).

C psittaci—has an avian reservoir (parrots), causes atypical pneumonia.

Lab diagnosis: PCR, nucleic acid amplification test. Cytoplasmic inclusions (reticulate bodies) seen on Giemsa or fluorescent antibody-stained smear.

Treatment: azithromycin (favored because one-time treatment) or doxycycline. Add ceftriaxone for possible concomitant gonorrhea.

Rickettsial diseases and vector-borne illnesses Treatment: doxycycline.

Rickettsia rickettsii, vector is tick. Despite its name, disease occurs primarily in the South Atlantic states, especially North Carolina. Rash typically starts at wrists A and ankles and then spreads to trunk, palms, and soles.

Classic triad—headache, fever, rash (vasculitis).

Palms and soles rash is seen in Coxsackievirus A infection (hand, foot, and mouth disease), Rocky Mountain spotted fever, and 2° Syphilis (you drive CARS using your palms and soles).

Q fever is caused by a Quite Complicated Bug because it has no rash or vector and its causative organism can survive outside in its endospore form. Not in the Rickettsia genus, but closely related.

Classic cause of atypical "walking pneumonia" (insidious onset, headache, nonproductive cough, patchy or diffuse interstitial infiltrate).

Occurs frequently in those <30 years old; outbreaks in military recruits, prisons, colleges.

X-ray looks worse than patient. High titer of cold agglutinins (IgM), which can agglutinate RBCs.

Treatment: macrolides, doxycycline, or fluoroquinolone (penicillin ineffective since Mycoplasma has no cell wall).

Not seen on Gram stain. Pleomorphic

A . Bacterial membrane contains sterols for stability. Grown on Eaton agar.

Mycoplasma gets cold without a coat (no cell wall).

Can cause atypical variant of Stevens-Johnson syndrome, typically in children and adolescents.

Mississippi and Ohio Macrophage filled River Valleys with Histoplasma (smaller than RBC)

Eastern and Central Broad-based budding US, Great Lakes of Blastomyces (same size as RBC)

Southwestern US, Spherule (much larger California than RBC) filled with endospores of Coccidioides

Latin America Budding yeast of Paracoccidioides with "captain's wheel" formation (much larger than RBC)

Palatal/tongue ulcers, splenomegaly, pancytopenia

Disseminates to bone/ skin (may mimic SCC)

Disseminates to skin/ bone

Similar to blastomycosis, males > females Histo hides (within macrophages)

Associated with bird or bat droppings (eg, spelunking)

Associated with dust exposure in endemic areas (eg, archeological excavations, earthquakes)

Paracoccidio parasails with the captain's wheel all the way to Latin America alba = white. Dimorphic; forms pseudohyphae and budding yeasts at 20°C A , germ tubes at 37°C B .

Systemic or superficial fungal infection. Causes oral C and esophageal thrush in immunocompromised (neonates, steroids, diabetes, AIDS), vulvovaginitis (diabetes, use of antibiotics), diaper rash, endocarditis (IV drug users), disseminated candidiasis (especially in neutropenic patients), chronic mucocutaneous candidiasis.

Treatment: oral fluconazole/topical azoles for vaginal; nystatin, azoles, or, rarely, echinocandins for oral; fluconazole, echinocandins, or amphotericin B for esophageal or systemic disease.

E .

5–10 µm with narrow budding. Heavily encapsulated yeast. Not dimorphic.

Found in soil, pigeon droppings. Acquired through inhalation with hematogenous dissemination to meninges. Highlighted with India ink (clear halo G) and mucicarmine (red inner capsule H). Latex agglutination test detects polysaccharide capsular antigen and is more sensitive and specific.

Causes cryptococcosis, cryptococcal meningitis, cryptococcal encephalitis ("soap bubble" lesions in brain), primarily in immunocompromised.

Treatment: amphotericin B + flucytosine followed by fluconazole for cryptococcal meningitis.

Irregular, broad, nonseptate hyphae branching at wide angles I .

Causes mucormycosis, mostly in ketoacidotic diabetic and/or neutropenic patients (eg, leukemia). Inhalation of spores fungi proliferate in blood vessel walls, penetrate cribriform plate, and enter brain. Rhinocerebral, frontal lobe abscess; cavernous sinus thrombosis. Headache, facial pain, black necrotic eschar on face J ; may have cranial nerve involvement.

Treatment: surgical debridement, amphotericin B or isavuconazole.

Pneumocystis jirovecii Causes Pneumocystis pneumonia (PCP), a diffuse interstitial pneumonia A . Yeast-like fungus (originally classified as protozoan). Most infections are asymptomatic. Immunosuppression (eg,

AIDS) predisposes to disease. Diffuse, bilateral ground-glass opacities on chest imaging, with pneumatoceles B . Diagnosed by bronchoalveolar lavage or lung biopsy. Disc-shaped yeast seen on methenamine silver stain of lung tissue C or with fluorescent antibody. Treatment/prophylaxis: TMP-SMX, pentamidine, dapsone (prophylaxis as single agent, or treatment in combination with TMP), atovaquone. Start prophylaxis when CD4+ count drops to < 200 cells/mm3 in HIV patients.

Causes sporotrichosis. Dimorphic fungus. Exists as a cigar-shaped yeast at 37 °C in the human body and as hyphae with spores in soil (conidia). Lives on vegetation. When spores are traumatically introduced into the skin, typically by a thorn ("rose gardener's disease"), causes local pustule or ulcer with nodules along draining lymphatics (ascending lymphangitis A). Disseminated disease possible in immunocompromised host.

Treatment: itraconazole or potassium iodide (only for cutaneous/lymphocutaneous).

Think of a rose gardener who smokes a cigar and pot.

Toxoplasma Immunocompetent: gondii mononucleosis-like symptoms, ⊖ heterophile antibody test Reactivation in AIDS □ brain abscesses usually seen as multiple ring-enhancing lesions on MRI

A Congenital toxoplasmosis: classic triad of chorioretinitis, hydrocephalus, and intracranial calcifications

Cysts in meat (most Serology, biopsy Sulfadiazine + common); oocysts (tachyzoite)

Plasmodium P vivax/ovale P falciparum P malariae A B Malaria—fever, headache, anemia, splenomegaly P vivax/ovale—48-hr cycle (tertian; includes fever on first day and third day, thus fevers are actually 48 hr apart); dormant form (hypnozoite) in liver P falciparum—severe; irregular fever patterns; parasitized RBCs occlude capillaries in brain (cerebral malaria), kidneys, lungs P malariae—72-hr cycle (quartan) Anopheles mosquito Blood smear: trophozoite ring form within RBC A , schizont containing merozoites; red granules (Schüffner stippling) B throughout RBC cytoplasm seen with P vivax/ovale Chloroquine (for sensitive species); if resistant, use mefloquine or atovaquone/ proguanil If life-threatening, use intravenous quinidine or artesunate (test for G6PD deficiency) For P vivax/ovale, add primaquine for hypnozoite (test for G6PD deficiency) Babesia C Babesiosis—fever and hemolytic anemia; predominantly in northeastern United States; asplenia • risk of severe disease Ixodes tick (also vector for Borrelia burgdorferi and Anaplasma spp) Blood smear: ring form C1 , "Maltese cross" C2 ; PCR Atovaquone + azithromycin

Intestinal tapeworm Ingestion of larvae encysted in Praziquantel undercooked pork

Cysticercosis, Ingestion of eggs in food Praziquantel; albendazole for neurocysticercosis (cystic contaminated with human neurocysticercosis CNS lesions, seizures)

D (“eggshell Ingestion of eggs in food Albendazole calcification”) in liver E ; cyst contaminated with dog feces rupture can cause anaphylaxis Sheep are an intermediate host

Liver and spleen enlargement (S mansoni, egg with lateral spine

A), fibrosis, inflammation, portal hypertension

Chronic infection with S haematobium (egg with terminal spine

B) can lead to squamous cell carcinoma of the bladder (painless hematuria) and pulmonary hypertension Snails are intermediate host; Praziquantel cercariae penetrate skin of humans in contact with contaminated fresh water (eg, swimming or bathing)

Associated with cholangiocarcinoma

Sarcoptes scabiei Mites burrow into stratum corneum and Common in children, crowded populations cause scabies—pruritus (worse at night) and (jails, nursing homes); transmission through serpiginous burrows (lines) often between skin-to-skin contact (most common) or via fingers and toes

A . fomites. Treatment: permethrin cream, washing/drying all clothing/bedding, treat close contacts.

Pediculus humanus/ Blood-sucking lice that cause intense pruritus Phthirus pubis with associated excoriations, commonly on scalp and neck (head lice), waistband and axilla (body lice), or pubic and perianal regions (pubic lice).

Body lice can transmit Rickettsia prowazekii (epidemic typhus), Borrelia recurrentis (relapsing fever), Bartonella quintana (trench fever).

Treatment: pyrethroids, malathion, or ivermectin lotion, and nit B combing. Children with head lice can be treated at home without interrupting school attendance.

Biliary tract disease, cholangiocarcinoma Clonorchis sinensis

Brain cysts, seizures Taenia solium (neurocysticercosis)

Naked virus Enveloped virus Enveloped virus Bacteriophage with icosahedral capsid with icosahedral capsid with helical capsid

Generally, enveloped viruses acquire their envelopes from plasma membrane when they exit from cell. Exceptions include herpesviruses, which acquire envelopes from nuclear membrane.

Naked (nonenveloped) viruses include Papillomavirus, Adenovirus, Parvovirus, Polyomavirus, Calicivirus, Picornavirus, Reovirus, and Hepevirus.

Purified nucleic acids of most dsDNA viruses (except poxviruses and HBV) and ⊕ strand ssRNA (≈ mRNA) viruses are infectious. Naked nucleic acids of ⊖ strand ssRNA and dsRNA viruses are not infectious. They require polymerases contained in the complete virion.

DNA = PAPP; RNA = CPR and hepevirus.

Give PAPP smears and CPR to a naked hippie (hepevirus).

Enveloped DNA viruses Have Helpful Protection (Herpesvirus, Hepadnavirus, Poxvirus).

Some general rules—all DNA viruses: DNA viruses All replicate in the nucleus (except poxvirus). "Pox is out of the box (nucleus)."

Papillomavirus No DS and circular HPV–warts (serotypes 1, 2, 6, 11), CIN, cervical cancer (most commonly 16, 18) (PML) in HIV BK virus—transplant patients, commonly targets kidney JC: Junky Cerebrum; BK: Bad Kidney

Parvovirus No SS and linear B19 virus—aplastic crises in sickle cell disease, (smallest DNA virus) "slapped cheek" rash in children (erythema infectiosum, or fifth disease); infects RBC precursors and endothelial cells RBC destruction • hydrops fetalis and death in fetus, pure RBC aplasia and rheumatoid arthritis–like symptoms in adults

Herpesviruses Enveloped, DS, and linear viruses

Herpes Respiratory Gingivostomatitis, keratoconjunctivitis A , Most commonly latent in trigeminal simplex secretions, saliva herpes labialis (cold sores)

B , herpetic ganglia virus-1 whitlow on finger, temporal lobe encephalitis, Most common cause of sporadic esophagitis, erythema multiforme encephalitis, can present as altered mental status, seizures, and/or aphasia

Herpes Sexual contact, Herpes genitalis

C , neonatal herpes Most commonly latent in sacral simplex perinatal ganglia virus-2 Viral meningitis more common with HSV-2 than with HSV-1

Varicella-Respiratory Varicella-zoster (chickenpox D , shingles E), Latent in dorsal root or trigeminal Zoster virus secretions, encephalitis, pneumonia ganglia; CN V1 branch (HHV-3) contact with fluid Most common complication of shingles is post-involvement can cause herpes

Epstein-Barr Respiratory virus (HHV-4) secretions, saliva; aka "kissing disease," (common in teens, young adults)

Mononucleosis—fever, hepatosplenomegaly F , pharyngitis, and lymphadenopathy (especially posterior cervical nodes); avoid contact sports until resolution due to risk of splenic rupture

Associated with lymphomas (eg, endemic Burkitt lymphoma), nasopharyngeal carcinoma (especially Asian adults), lymphoproliferative disease in transplant patients Infects B cells through CD21, "Must be 21 to drink Beer in a Barr" ⊕ Monospot test—heterophile antibodies detected by agglutination of sheep or horse RBCs

Use of amoxicillin in mononucleosis can cause characteristic maculopapular rash HSV identification Viral culture for skin/genitalia.

CSF PCR for herpes encephalitis.

Tzanck test—a smear of an opened skin vesicle to detect multinucleated giant cells A commonly seen in HSV-1, HSV-2, and VZV infection. PCR of skin lesions is test of choice.

Tzanck heavens I do not have herpes.

Intranuclear eosinophilic Cowdry A inclusions also seen with HSV-1, HSV-2, VZV.

HIV CD4, CXCR4, CCR5

Rhinovirus ICAM-1 (I came to see the rhino) RNA viruses All replicate in the cytoplasm (except retrovirus and influenza virus). "Retro flu is outta cyt (sight)."

SS, single-stranded; DS, double-stranded; ⊕, positive sense; ⊖, negative sense; a= arbovirus, arthropod borne (mosquitoes, ticks).

Influenza viruses Orthomyxoviruses. Enveloped, ⊖ ssRNA viruses with 8-segment genome. Contain hemagglutinin (binds sialic acid and promotes viral entry) and neuraminidase (promotes progeny virion release) antigens. Patients at risk for fatal bacterial superinfection, most commonly S aureus, S pneumoniae, and H influenzae.

Reformulated vaccine ("the flu shot") contains viral strains most likely to appear during the flu season, due to the virus' rapid genetic change.

Killed viral vaccine is most frequently used.

Live attenuated vaccine contains temperature-sensitive mutant that replicates in the nose but not in the lung; administered intranasally.

Treatment: supportive +/- neuraminidase inhibitor (eg, oseltamivir, zanamivir).

Rubella virus A togavirus. Causes rubella, once known as German (3-day) measles. Fever, postauricular and other lymphadenopathy, arthralgias, and fine, maculopapular rash that starts on face and spreads centrifugally to involve trunk and extremities A . Causes mild disease in children but

serious congenital disease (a TORCH infection). Congenital rubella findings include “blueberry muffin” appearance due to dermal extramedullary hematopoiesis.

Paramyxoviruses Paramyxoviruses cause disease in children. They include those that cause parainfluenza (croup), mumps, measles, RSV, and human metapneumovirus, which causes respiratory tract infection (bronchiolitis, pneumonia) in infants. All contain surface F (fusion) protein, which causes respiratory epithelial cells to fuse and form multinucleated cells. Palivizumab (monoclonal antibody against F protein) prevents pneumonia caused by RSV infection in premature infants. Palivizumab for Paramyxovirus (RSV) Prophylaxis in Preemies.

Acute Also called croup. Caused by parainfluenza viruses. Virus membrane contains hemagglutinin laryngotracheobronchitis (binds sialic acid and promotes viral entry) and neuraminidase (promotes progeny virion release) antigens. Results in a “seal-like” barking cough and inspiratory stridor. Narrowing of upper trachea and subglottis leads to characteristic steeple sign on x-ray A . Severe croup can result in pulsus paradoxus 2° to upper airway obstruction.

Mumps virus Uncommon due to effectiveness of MMR Mumps makes your parotid glands and testes as vaccine. big as POM-Poms.

Symptoms: Parotitis A , Orchitis (inflammation of testes), aseptic Meningitis, and Pancreatitis. Can cause sterility (especially after puberty).

A . Negri bodies (cytoplasmic inclusions B) commonly found in Purkinje cells of cerebellum and in hippocampal neurons. Rabies has long incubation period (weeks to months) before symptom onset. Postexposure prophylaxis is wound cleaning plus immunization with killed vaccine and rabies immunoglobulin. Example of passive-active immunity.

Travels to the CNS by migrating in a retrograde fashion (via dynein motors) up nerve axons after binding to ACh receptors.

Progression of disease: fever, malaise • agitation, photophobia, hydrophobia, hypersalivation • paralysis, coma • death.

Infection more commonly from bat, raccoon, and skunk bites than from dog bites in the United States; aerosol transmission (eg, bat caves) also possible.

A filovirus A that targets endothelial cells, phagocytes, hepatocytes. Following an incubation period of up to 21 days, presents with abrupt onset of flu-like symptoms, diarrhea/vomiting, high fever, myalgia. Can progress to DIC, diffuse hemorrhage, shock.

Diagnosed with RT-PCR within 48 hr of symptom onset. High mortality rate.

Transmission requires direct contact with bodily fluids, fomites (including dead bodies), infected bats or primates (apes/monkeys); high incidence of nosocomial infection.

Supportive care, no definitive treatment. Strict isolation of infected individuals and barrier practices for health care workers are key to preventing transmission.

Extrahepatic manifestations of hepatitis B and C

Anti-HBe Antibody to HBeAg; indicates low transmissibility.

Relative concentration of reactants

Level of detection

Incubation Prodrome, period acute disease gp120: gp41:

Diploid genome (2 molecules of RNA). The 3 structural genes (protein coded for): p17: Matrix protein • env (gp120 and gp41): • Formed from cleavage of gp160 to form Lipid envelope envelope glycoproteins.

• gp120—attachment to host CD4+ T cell. p24: • gp41—fusion and entry.

RNA proteins, respectively.

• pol—Reverse transcriptase, Integrase, Protease; RIP "Pol" (Paul)

Reverse transcriptase synthesizes dsDNA from genomic RNA; dsDNA integrates into host genome.

Virus binds CD4 as well as a coreceptor, either CCR5 on macrophages (early infection) or CXCR4 on T cells (late infection).

Homozygous CCR5 mutation = immunity. Heterozygous CCR5 mutation = slower course.

Presumptive diagnosis made with HIV-1/2 Ag/ Western blot tests are no longer recommended Ab immunoassays. These immunoassays by the CDC for confirmatory testing. detect viral p24 Ag capsid protein and IgG Abs HIV-1/2 Ag/Ab testing is not recommended in to HIV-1/2. Very high sensitivity/specificity. babies with suspected HIV due to maternally

Viral load tests determine the amount of viral transferred antibody. Use HIV viral load RNA in the plasma. High viral load associated instead. with poor prognosis. Also use viral load to monitor effect of drug therapy. Use HIV genotyping to determine appropriate therapy.

AIDS diagnosis: ≤ 200 CD4+ cells/mm3 (normal: 500–1500 cells/mm3) or HIV ⊕ with AIDS-defining condition (eg, Pneumocystis pneumonia).

HIV-1 NAT HIV-1 NAT NAT: nucleic acid test

Time course of untreated HIV infection +/- Acute HIV infection Skin and mucous Systemic immuno-Viral dissemination membrane defciency/AIDS-Seeding of lymphoid organs Clinical latency infections defning illnesses

Dashed lines on CD4+ count axis indicate moderate immunocompromise Four stages of untreated infection: (< 400 CD4+ cells/mm3) and when AIDS-defining illnesses emerge (< 200 1. Flu-like (acute) CD4+ cells/mm3). 2. Feeling fine (latent)

Most patients who do not receive treatment eventually die of complications of 3. Falling count HIV infection. 4. Final crisis During clinical latency phase, virus replicates in lymph nodes

Common diseases of • CD4+ cell count reactivation of past infections (eg, TB, HSV, shingles), dissemination of HIV-positive adults bacterial infections and fungal infections (eg, coccidioidomycosis), and non-Hodgkin lymphomas.

Prions Prion diseases are caused by the conversion of a normal (predominantly α-helical) protein termed prion protein (PrPc) to a β-pleated form (PrPsc), which is transmissible via CNS-related tissue (iatrogenic CJD) or food contaminated by BSE-infected animal products (variant CJD). PrPsc resists protease degradation and facilitates the conversion of still more PrPc to PrPsc. Resistant to standard sterilizing procedures, including standard autoclaving. Accumulation of PrPsc results in spongiform encephalopathy and dementia, ataxia, and death.

Creutzfeldt-Jakob disease—rapidly progressive dementia, typically sporadic (some familial forms).

Bovine spongiform encephalopathy—also called “mad cow disease.”

Kuru—acquired prion disease noted in tribal populations practicing human cannibalism.

Normal flora: Neonates delivered by C-section have no flora but are rapidly colonized after birth. dominant

B cereus Reheated rice. “Food poisoning from reheated rice? Be serious!” (B cereus)

C botulinum Improperly canned foods (toxins), raw honey (spores)

Salmonella Poultry, meat, and eggs

S aureus Meats, mayonnaise, custard; preformed toxin a V vulnificus can also cause wound infections from contact with contaminated water or shellfish.

Common causes of pneumonia

Common causes of meningitis

Give ceftriaxone and vancomycin empirically (add ampicillin if Listeria is suspected).

Viral causes of meningitis: enteroviruses (especially coxsackievirus), HSV-2 (HSV-1 = encephalitis), HIV, West Nile virus (also causes encephalitis), VZV.

In HIV: Cryptococcus spp.

Note: Incidence of Group B streptococcal meningitis in neonates has • greatly due to screening and antibiotic prophylaxis in pregnancy. Incidence of H influenzae meningitis has • greatly due to conjugate H influenzae vaccinations. Today, cases are usually seen in unimmunized children.

Assume if no other information is available S aureus (most common overall)

Vertebral involvement S aureus, M tuberculosis (Pott disease)

IV drug abuse S aureus; also Pseudomonas, Candida

Elevated ESR and CRP sensitive but not specific.

Radiographs are insensitive early but can be useful in chronic osteomyelitis (A , left). MRI is best for detecting acute infection and detailing anatomic involvement (A , right).

sigNs aND symPtoms No inflammation Thin, white discharge

A with fishy odor lab FiNDiNgs Clue cells pH > 4.5 ⊕ KOH whiff test

Inflammation (“strawberry Inflammation cervix”) Thick, white, “cottage cheese” Frothy, yellow-green, foul-discharge

B pH normal (4.0–4.5) pH > 4.5 Metronidazole Azoles Treat sexual partner(s)

TORCH infections Microbes that may pass from mother to fetus. Transmission is transplacental in most cases, or via delivery (especially HSV-2). Nonspecific signs common to many ToRCHHeS infections include hepatosplenomegaly, jaundice, thrombocytopenia, and growth retardation. Other important infectious agents include Streptococcus agalactiae (group B streptococci), E coli, and Listeria monocytogenes—all causes of meningitis in neonates. Parvovirus B19 causes hydrops fetalis.

Red rashes of childhood Sexually transmitted infections

Top bugs—Chlamydia trachomatis (subacute, often undiagnosed), Neisseria gonorrhoeae (acute).

C trachomatis—most common bacterial STI in the United States.

Signs include cervical motion tenderness, adnexal tenderness, purulent cervical discharge

A .

PID may include salpingitis, endometritis, hydrosalpinx, and tubo-ovarian abscess.

Salpingitis is a risk factor for ectopic pregnancy, infertility, chronic pelvic pain, and adhesions.

Can lead to perihepatitis (Fitz-Hugh–Curtis syndrome)—infection and inflammation of liver capsule and "violin string" adhesions of peritoneum to liver

B .

Nosocomial infections E coli (UTI) and S aureus (wound infection) are the two most common causes.

Rash Beginning at head and moving down with Rubella virus postauricular lymphadenopathy

Beginning at head and moving down; preceded by Measles virus cough, coryza, conjunctivitis, and Koplik spots

Can also lead to myalgia and paralysis Poliovirus

Tetanus Muscle spasms and spastic paralysis (eg, lockjaw, Clostridium tetani

Branching rods in oral infection, sulfur granules Actinomyces israelii

Chronic granulomatous disease Catalase ⊕ microbes, especially S aureus

Human bite Human oral flora (eg, Eikenella, Fusobacterium)

Neutropenic patients Candida albicans (systemic), Aspergillus

Pneumonia in cystic fibrosis, burn infection Pseudomonas aeruginosa

Puncture wound, lockjaw Clostridium tetani

Pus, empyema, abscess S aureus

Fluoroquinolones Ciprofoxacin Levofoxacin, etc Quinolone Nalidixic acid Chloramphenicol Clindamycin Linezolid Macrolides Azithromycin Clarithromycin Erythromycin Streptogramins Quinupristin Dalfopristin Rifampin Aminoglycosides Gentamicin Glycylcycline Tigecycline Neomycin Amikacin Tobramycin Streptomycin Tetracyclines Tetracycline Doxycycline Minocycline PROTEIN SYNTHESIS Penicillinase-sensitive penicillins Penicillin G, V Ampicillin Amoxicillin Penicillinase-resistant penicillins Oxacillin Nafcillin Dicloxacillin Antipseudomonal Ticarcillin Piperacillin Cephalosporins (I-V) 1st—Cefazolin, etc 2nd—Cefoxitin, etc 3rd—Ceftriaxone, etc 4th—Cefepime 5th—Ceftaroline PEPTIDOGLYCAN SYNTHESIS CELL WALL SYNTHESIS MEMBRANE INTEGRITY GYRASEDNA INTEGRITY (via free radicals) mRNA SYNTHESIS (RNA polymerase) Carbapenems Imipenem Meropenem Ertapenem Doripenem Monobactams Aztreonam PEPTIDOGLYCAN CROSS-LINKING

Glycopeptides Vancomycin Bacitracin 30S SUBUNIT 50S SUBUNIT 50S 30S30S 50S 30S 50S Sulfonamides Sulfamethoxazole Sulfsoxazole Sulfadiazine FOLIC ACID SYNTHESIS AND REDUCTION (DNA methylation) PABA DHF THF Trimethoprim Cellmembrane Cellwall BACTERIAL CELL DNA mRNA DNA gyrase Ribosomes RNA polymerase – – – – – – – – – Metronidazole – Daptomycin (gram ˜) Polymyxins (gram °)

Penicillin G, V Penicillin G (IV and IM form), penicillin V (oral). Prototype β-lactam antibiotics.

mecHaNism D-Ala-D-Ala structural analog. Bind penicillin-binding proteins (transpeptidases). Block transpeptidase cross-linking of peptidoglycan in cell wall. Activate autolytic enzymes.

cliNical Use Mostly used for gram ⊕ organisms (S pneumoniae, S pyogenes, Actinomyces). Also used for gram ⊖ cocci (mainly N meningitidis) and spirochetes (mainly T pallidum). Bactericidal for gram ⊕ cocci, gram ⊕ rods, gram ⊖ cocci, and spirochetes. β-lactamase sensitive.

aDVerse eFFects Hypersensitivity reactions, direct Coombs ⊕ hemolytic anemia, drug-induced interstitial nephritis.

resistaNce β-lactamase cleaves the β-lactam ring. Mutations in PBPs.

aDVerse eFFects Hypersensitivity reactions, rash, pseudomembranous colitis.

mecHaNism oF resistaNce Penicillinase (a type of β-lactamase) cleaves β-lactam ring.

Penicillinase-resistant penicillins Dicloxacillin, nafcillin, oxacillin.

mecHaNism Same as penicillin. Narrow spectrum; penicillinase resistant because bulky R group blocks access of β-lactamase to β-lactam ring.

cliNical Use S aureus (except MRSA). “Use naf (nafcillin) for staph.”
aDVerse eFFects Hypersensitivity reactions, interstitial nephritis.

mecHaNism oF resistaNce MRSA has altered penicillin-binding protein target site.

Antipseudomonal penicillins Piperacillin, ticarcillin.

mecHaNism Same as penicillin. Extended spectrum. Penicillinase sensitive; use with β-lactamase inhibitors.

cliNical Use Pseudomonas spp. and gram ⊖ rods.

aDVerse eFFects Hypersensitivity reactions.

4th generation (cefepime)—gram ⊖ organisms, with • activity against Pseudomonas and gram ⊕ organisms.

5th generation (ceftaroline)—broad gram ⊕ and gram ⊖ organism coverage; unlike 1st–4th generation cephalosporins, ceftaroline covers MRSA, and Enterococcus faecalis—does not cover Pseudomonas.

aDVerse eFFects Hypersensitivity reactions, autoimmune hemolytic anemia, disulfiram-like reaction, vitamin K deficiency. Low rate of cross-reactivity even in penicillin-allergic patients.

• nephrotoxicity of aminoglycosides.

mecHaNism oF resistaNce Inactivated by cephalosporinases (a type of β-lactamase). Structural change in penicillin-binding proteins (transpeptidases).

cliNical Use Gram ⊕ cocci, gram ⊖ rods, and anaerobes. Wide spectrum and significant side effects limit use to life-threatening infections or after other drugs have failed. Meropenem has a • risk of seizures and is stable to dehydropeptidase I.

aDVerse eFFects GI distress, rash, and CNS toxicity (seizures) at high plasma levels.

mecHaNism oF resistaNce Inactivated by carbapenemases produced by, eg, K pneumoniae, E coli, E aerogenes.

mecHaNism Less susceptible to β-lactamases. Prevents peptidoglycan cross-linking by binding to penicillin-binding protein 3. Synergistic with aminoglycosides. No cross-allergenicity with penicillins.

cliNical Use Gram ⊖ rods only—no activity against gram ⊕ rods or anaerobes. For penicillin-allergic patients and those with renal insufficiency who cannot tolerate aminoglycosides.

aDVerse eFFects Usually nontoxic; occasional GI upset.

mecHaNism Inhibits cell wall peptidoglycan formation by binding D-Ala-D-Ala portion of cell wall precursors. Bactericidal against most bacteria (bacteriostatic against C difficile). Not susceptible to β-lactamases.

cliNical Use Gram ⊕ bugs only—for serious, multidrug-resistant organisms, including MRSA, S epidermidis, sensitive Enterococcus species, and Clostridium difficile (oral dose for pseudomembranous colitis).

aDVerse eFFects Well tolerated in general but NOT trouble Free. Nephrotoxicity, Ototoxicity, Thrombophlebitis, diffuse Flushing (red man syndrome A idiopathic reaction largely preventable by pretreatment with antihistamines), DRESS syndrome.

mecHaNism oF resistaNce Occurs in bacteria (eg, Enterococcus) via amino acid modification of D-Ala-D-Ala to D-Ala-D-Lac. “If you Lack a D-Ala (dollar), you can’t ride the van (vancomycin).”

Specifically target smaller bacterial ribosome (70S, made of 30S and 50S subunits), leaving human ribosome (80S) unaffected.

All are bacteriostatic, except aminoglycosides (bactericidal) and linezolid (variable).

Chloramphenicol, Clindamycin Erythromycin (macrolides) Linezolid "Buy AT 30, CCEL (sell) at 50." cliNical Use Severe gram ⊖ rod infections. Synergistic with β-lactam antibiotics. Neomycin for bowel surgery.

aDVerse eFFects Nephrotoxicity, Neuromuscular blockade (absolute contraindication with myasthenia gravis), Ototoxicity (especially with loop diuretics), Teratogenicity.

mecHaNism oF resistaNce Bacterial transferase enzymes inactivate the drug by acetylation, phosphorylation, or adenylation.

Tetracyclines Tetracycline, doxycycline, minocycline.

mecHaNism Bacteriostatic; bind to 30S and prevent attachment of aminoacyl-tRNA. Limited CNS penetration. Doxycycline is fecally eliminated and can be used in patients with renal failure. Do not take tetracyclines with milk (Ca^{2+}), antacids (eg, Ca^{2+} or Mg^{2+}), or iron-containing preparations because divalent cations inhibit drugs' absorption in the gut.

cliNical Use Borrelia burgdorferi, M pneumoniae. Drugs' ability to accumulate intracellularly makes them very effective against Rickettsia and Chlamydia. Also used to treat acne. Doxycycline effective against community-acquired MRSA.

aDVerse eFFects GI distress, discoloration of teeth and inhibition of bone growth in children, photosensitivity. Contraindicated in pregnancy.

mecHaNism oF resistaNce • uptake or • efflux out of bacterial cells by plasmid-encoded transport pumps.

mecHaNism Tetracycline derivative. Binds to 30S, inhibiting protein synthesis. Generally bacteriostatic.

cliNical Use Broad-spectrum anaerobic, gram ⊖, and gram ⊕ coverage. Multidrug-resistant organisms (MRSA, VRE) or infections requiring deep tissue penetration.

aDVerse eFFects GI symptoms: nausea, vomiting.

mecHaNism Blocks peptidyltransferase at 50S ribosomal subunit. Bacteriostatic.

cliNical Use Meningitis (Haemophilus influenzae, Neisseria meningitidis, Streptococcus pneumoniae) and rickettsial diseases (eg, Rocky Mountain spotted fever [Rickettsia rickettsii]). Limited use due to toxicity but often still used in developing countries because of low cost.

aDVerse eFFects Anemia (dose dependent), aplastic anemia (dose independent), gray baby syndrome (in premature infants because they lack liver UDP-glucuronosyltransferase).

mecHaNism oF resistaNce Plasmid-encoded acetyltransferase inactivates the drug.

mecHaNism Blocks peptide transfer (translocation) at 50S ribosomal subunit. Bacteriostatic.

aDVerse eFFects Pseudomembranous colitis (C difficile overgrowth), fever, diarrhea.

mecHaNism Inhibits protein synthesis by binding to 50S subunit and preventing formation of the initiation complex.

cliNical Use Gram ⊕ species including MRSA and VRE.

Macrolides Azithromycin, clarithromycin, erythromycin.

mecHaNism Inhibit protein synthesis by blocking translocation ("macroslides"); bind to the 23S rRNA of the 50S ribosomal subunit. Bacteriostatic.

cliNical Use Atypical pneumonias (Mycoplasma, Chlamydia, Legionella), STIs (Chlamydia), gram ⊕ cocci (streptococcal infections in patients allergic to penicillin), and B pertussis.

aDVerse eFFects MACRO: Gastrointestinal Motility issues, Arrhythmia caused by prolonged QT interval, acute Cholestatic hepatitis, Rash, eOsinophilia. Increases serum concentration of theophylline, oral anticoagulants. Clarithromycin and erythromycin inhibit cytochrome P-450.

mecHaNism oF resistaNce Methylation of 23S rRNA-binding site prevents binding of drug.

Polymyxins Colistin (polymyxin E), polymyxin B.

mecHaNism Cation polypeptides that bind to phospholipids on cell membrane of gram ⊖ bacteria. Disrupt cell membrane integrity □ leakage of cellular components □ cell death.

cliNical Use Salvage therapy for multidrug-resistant gram ⊖ bacteria (eg, P aeruginosa, E coli, K pneumoniae). Polymyxin B is a component of a triple antibiotic ointment used for superficial skin infections.

aDVerse eFFects Nephrotoxicity, neurotoxicity (eg, slurred speech, weakness, paresthesias), respiratory failure.

Sulfonamides Sulfamethoxazole (SMX), sulfisoxazole, sulfadiazine.

mecHaNism Inhibit dihydropteroate synthase, thus inhibiting folate synthesis. Bacteriostatic (bactericidal when combined with trimethoprim).

Sulfonamides, dapsonecliNical Use Gram ⊕, gram ⊖, Nocardia. TMP-SMX for synthase simple UTI.

aDVerse eFFects Hypersensitivity reactions, hemolysis if G6PD deficient, nephrotoxicity (tubulointerstitial nephritis), photosensitivity, Stevens-Johnson syndrome, kernicterus in infants, displace other drugs from albumin (eg, warfarin).

mecHaNism oF resistaNce Altered enzyme (bacterial dihydropteroate synthase), • uptake, or • PABA synthesis.

Trimethoprim, mecHaNism Similar to sulfonamides, but structurally distinct Purines Thymidine Methionine agent.

cliNical Use Leprosy (lepromatous and tuberculoid), DNA, RNA DNA Protein Pneumocystis jirovecii prophylaxis, or treatment when used in combination with TMP.

aDVerse eFFects Hemolysis if G6PD deficient, methemoglobinemia, agranulocytosis.

mecHaNism Inhibits bacterial dihydrofolate reductase. Bacteriostatic.

cliNical Use Used in combination with sulfonamides (trimethoprim-sulfamethoxazole [TMPSMX]), causing sequential block of folate synthesis. Combination used for UTIs, Shigella, Salmonella, Pneumocystis jirovecii pneumonia treatment and prophylaxis, toxoplasmosis prophylaxis.

aDVerse eFFects Hyperkalemia (high doses), megaloblastic anemia, leukopenia, granulocytopenia, which may be avoided with coadministration of leucovorin (folinic acid). TMP Treats Marrow Poorly.

cliNical Use Gram ⊖ rods of urinary and GI tracts (including Pseudomonas), some gram ⊕ organisms, otitis externa.

mecHaNism oF resistaNce Chromosome-encoded mutation in DNA gyrase, plasmid-mediated resistance, efflux pumps.

mecHaNism Lipopeptide that disrupts cell membranes of gram ⊕ cocci by creating transmembrane channels.

aDVerse eFFects Myopathy, rhabdomyolysis.

mecHaNism Forms toxic free radical metabolites in the bacterial cell that damage DNA. Bactericidal, antiprotozoal.

aDVerse eFFects Disulfiram-like reaction (severe flushing, tachycardia, hypotension) with alcohol; headache, metallic taste.

Plasma Cell wall membrane Interior of cell

Rifamycins Rifampin, rifabutin.

mecHaNism Inhibit DNA-dependent RNA polymerase. Rifampin's 4R's: cliNical Use Mycobacterium tuberculosis; delay resistance to dapsone when used for leprosy. Used for meningococcal prophylaxis and chemoprophylaxis in contacts of children with H influenzae type b.

aDVerse eFFects Minor hepatotoxicity and drug interactions (• cytochrome P-450); orange body fluids (nonhazardous side effect). Rifabutin favored over rifampin in patients with HIV infection due to less cytochrome P-450 stimulation.

Rifampin ramps up cytochrome P-450, but rifabutin does not.

mecHaNism oF resistaNce Mutations reduce drug binding to RNA polymerase. Monotherapy rapidly leads to resistance.

mecHaNism • synthesis of mycolic acids. Bacterial catalaseperoxidase (encoded by KatG) needed to convert INH to active metabolite.

mecHaNism oF resistaNce Mutations leading to underexpression of KatG.

mecHaNism Mechanism uncertain. Pyrazinamide is a prodrug that is converted to the active compound pyrazinoic acid. Works best at acidic pH (eg, in host phagolysosomes).

cliNical Use Mycobacterium tuberculosis.

aDVerse eFFects Hyperuricemia, hepatotoxicity.

mecHaNism • carbohydrate polymerization of mycobacterium cell wall by blocking arabinosyltransferase.

cliNical Use Mycobacterium tuberculosis.

aDVerse eFFects Optic neuropathy (red-green color blindness, usually reversible). Pronounce "eyethambutol." mecHaNism Interferes with 30S component of ribosome.

cliNical Use Mycobacterium tuberculosis (2nd line).

aDVerse eFFects Tinnitus, vertigo, ataxia, nephrotoxicity.

Antimicrobial cliNicalsceNario meDicatioN prophylaxis Exposure to meningococcal infection Ceftriaxone, ciprofloxacin, or rifampin

History of recurrent UTIs TMP-SMX

Malaria prophylaxis for travelers Atovaquone-proguanil, mefloquine, doxycycline, primaquine, or chloroquine (for areas with sensitive species)

Prevention of gonococcal conjunctivitis in newborn Erythromycin ointment on eyes

Prevention of postsurgical infection due to Cefazolin

Prophylaxis of strep pharyngitis in child with Benzathine penicillin G or oral penicillin V prior rheumatic fever

Treatment of highly MRSA: vancomycin, daptomycin, linezolid, tigecycline, ceftaroline, doxycycline. resistant bacteria VRE: linezolid, tigecycline, and streptogramins (quinupristin, dalfopristin). Multidrug-resistantP aeruginosa, multidrug-resistantAcinetobacter baumannii: polymyxins B and E (colistin).

aDVerse eFFects Fever/chills ("shake and bake"), hypotension, nephrotoxicity, arrhythmias, anemia, IV phlebitis ("amphoterrible"). Hydration • nephrotoxicity.

toxicity.

mecHaNism Same as amphotericin B. Topical use only as too toxic for systemic use.

cliNical Use "Swish and swallow" for oral candidiasis (thrush); topical for diaper rash or vaginal candidiasis.

mecHaNism Inhibits DNA and RNA biosynthesis by conversion to 5-fluorouracil by cytosine deaminase.

cliNical Use Systemic fungal infections (especially meningitis caused by Cryptococcus) in combination with amphotericin B.

aDVerse eFFects Bone marrow suppression.

Azoles Clotrimazole, fluconazole, isavuconazole, itraconazole, ketoconazole, miconazole, voriconazole.

mecHaNism Inhibit fungal sterol (ergosterol) synthesis by inhibiting the cytochrome P-450 enzyme that converts lanosterol to ergosterol.

cliNical Use Local and less serious systemic mycoses. Fluconazole for chronic suppression of cryptococcal meningitis in AIDS patients and candidal infections of all types. Itraconazole may be used for Blastomyces, Coccidioides, Histoplasma, Sporothrix schenckii. Clotrimazole and miconazole for topical fungal infections. Voriconazole for Aspergillus and some Candida. Isavuconazole for serious Aspergillus and Mucor infections.

aDVerse eFFects Testosterone synthesis inhibition (gynecomastia, especially with ketoconazole), liver dysfunction (inhibits cytochrome P-450).

mecHaNism Inhibits the fungal enzyme squalene epoxidase.

cliNical Use Dermatophytoses (especially onychomycosis—fungal infection of finger or toe nails).

aDVerse eFFects GI upset, headaches, hepatotoxicity, taste disturbance.
Echinocandins Anidulafungin, caspofungin, micafungin.

mecHaNism Inhibit cell wall synthesis by inhibiting synthesis of β-glucan.

cliNical Use Invasive aspergillosis, Candida.

aDVerse eFFects GI upset, flushing (by histamine release).

mecHaNism Interferes with microtubule function; disrupts mitosis. Deposits in keratin-containing tissues (eg, nails).

cliNical Use Oral treatment of superficial infections; inhibits growth of dermatophytes (tinea, ringworm).

aDVerse eFFects Teratogenic, carcinogenic, confusion, headaches, disulfiram-like reaction, • cytochrome P-450 and warfarin metabolism.

mecHaNism Blocks detoxification of heme into hemozoin. Heme accumulates and is toxic to plasmodia.

cliNical Use Treatment of plasmodial species other than P falciparum (frequency of resistance in P falciparum is too high). Resistance due to membrane pump that • intracellular concentration of drug. Treat P falciparum with artemether/lumefantrine or atovaquone/proguanil. For life-threatening malaria, use quinidine in US (quinine elsewhere) or artesunate.

aDVerse eFFects Retinopathy; pruritus (especially in dark-skinned individuals).

Antihelminthic Pyrantel pamoate, Ivermectin, Mebendazole (microtubule inhibitor), Praziquantel (• Ca2+ therapy permeability, • vacuolization), Diethylcarbamazine. Helminths get PIMP'D.

Zidovudine (ZDV,

Acyclovir, etc (HSV, VZV)

Oseltamivir, zanamivir mecHaNism Inhibit influenza neuraminidase □• release of progeny virus.

Infuenza A, B cliNical Use Treatment and prevention of influenza A and B. Beginning therapy within 48 hours of symptom onset may shorten duration of illness.

Acyclovir, famciclovir, valacyclovir Ganciclovir mecHaNism 5'-monophosphate formed by a CMV viral kinase. Guanosine analog. Triphosphate formed by cellular kinases. Preferentially inhibits viral DNA polymerase.

cliNical Use CMV, especially in immunocompromised patients. Valganciclovir, a prodrug of ganciclovir, has better oral bioavailability.

mecHaNism Viral DNA/RNA polymerase inhibitor and Foscarnet = pyrofosphate analog. HIV reverse transcriptase inhibitor. Binds to pyrophosphate-binding site of enzyme. Does not require any kinase activation.

cliNical Use CMV retinitis in immunocompromised patients when ganciclovir fails; acyclovir-resistant HSV.

aDVerse eFFects Nephrotoxicity, electrolyte abnormalities (hypoor hypercalcemia, hypoor hyperphosphatemia, hypokalemia, hypomagnesemia) can lead to seizures.

mecHaNism oF resistaNce Mutated DNA polymerase.

mecHaNism Preferentially inhibits viral DNA polymerase. Does not require phosphorylation by viral kinase.

cliNical Use CMV retinitis in immunocompromised patients; acyclovir-resistant HSV. Long half-life.

aDVerse eFFects Nephrotoxicity (coadminister with probenecid and IV saline to • toxicity).

HIV therapy Antiretroviral therapy (ART): often initiated at the time of HIV diagnosis. Strongest indication for use with patients presenting with AIDS-defining illness, low CD4+ cell counts (< 500 cells/mm3), or high viral load. Regimen consists of 3 drugs to prevent resistance: 2 NRTIs and preferably an integrase inhibitor. All ARTs are active against HIV-1 and HIV-2 with the exception of NNRTIs and enfuvirtide.

Abacavir (ABC) Didanosine (ddI) Emtricitabine (FTC) Lamivudine (3TC) Stavudine (d4T) Tenofovir (TDF) Zidovudine (ZDV,

Competitively inhibit nucleotide binding to reverse transcriptase and terminate the DNA chain (lack a 3′ OH group). Tenofovir is a nucleoTide; the others are nucleosides. All need to be phosphorylated to be active.

ZDV can be used for general prophylaxis and during pregnancy to • risk of fetal transmission.

Have you dined (vudine) with my nuclear (nucleosides) family?

Bone marrow suppression (can be reversed with granulocyte colony-stimulating factor [G-CSF] and erythropoietin), peripheral neuropathy, lactic acidosis (nucleosides), anemia (ZDV), pancreatitis (didanosine).

Abacavir contraindicated if patient has HLA-B*5701 mutation due to • risk of hypersensitivity.

Hepatitis C therapy Chronic HCV infection treated with multidrug therapy that targets specific steps within HCV replication cycle (HCV-encoded proteins). Examples of drugs are provided.

Grazoprevir Inhibits NS3/4A, a viral protease, preventing Grazoprevir: headache, fatigue Simeprevir viral replication Simeprevir: photosensitivity reactions, rash

Ribavirin Inhibits synthesis of guanine nucleotides by Hemolytic anemia, severe teratogen competitively inhibiting IMP dehydrogenase Used as adjunct in cases refractory to newer medications

Disinfection and Goals include the reduction of pathogenic organism counts to safe levels (disinfection) and the sterilization inactivation of all microbes including spores (sterilization).

Autoclave Pressurized steam at > 120°C. Sporicidal. May not reliably inactivate prions.

Alcohols Denature proteins and disrupt cell membranes. Not sporicidal.

Chlorhexidine Denatures proteins and disrupts cell membranes. Not sporicidal.

Chlorine Oxidizes and denatures proteins. Sporicidal.

SAFe Children Take Really Good Care.

“Digressions, objections, delight in mockery, carefree mistrust are signs of health; everything unconditional belongs in pathology.” “You cannot separate passion from pathology any more than you can separate a person’s spirit from his body.”

The fundamental principles of pathology are key to understanding diseases in all organ systems. Major topics such as inflammation and neoplasia appear frequently in questions across different organ systems, and such topics are definitely high yield. For example, the concepts of cell injury and inflammation are key to understanding the inflammatory response that follows myocardial infarction, a very common subject of board questions. Similarly, a familiarity with the early cellular changes that culminate in the development of neoplasias—for example, esophageal or colon cancer—is critical. Finally, make sure you recognize the major tumor-associated genes and are comfortable with key cancer concepts such as tumor staging and metastasis.

Apoptosis ATP-dependent programmed cell death. Intrinsic and extrinsic pathways; both pathways activate caspases (cytosolic proteases)
 cellular breakdown including cell shrinkage, chromatin condensation, membrane blebbing, and formation of apoptotic bodies, which are then phagocytosed. Characterized by deeply eosinophilic cytoplasm and basophilic nucleus, pyknosis, and karyorrhexis. Cell membrane typically remains intact without significant inflammation (unlike necrosis). DNA laddering (fragments in multiples of 180 bp) is a sensitive indicator of apoptosis.

Executioner caspases Cytoplasmic bleb Apoptotic body Ligands for macrophage cell receptors Macrophage Cytotoxic T cell Perforin Granzyme B FasL TNF-αTNFRFas Misfolded proteins Hypoxia p53 activation BAX/BAK Cytochrome C Bcl-2 Initiator caspases Initiator caspases Nuclear fragmentation (mitochondrial) pathway (death receptor) pathway DNA damage Radiation, ROS, toxins Cytoskeletal dispersion

Necrosis Exogenous injury plasma membrane damage cell undergoes enzymatic degradation and protein denaturation, intracellular components leak local inflammatory reaction (unlike apoptosis).

Ischemia Inadequate blood supply to meet demand. Mechanisms include • arterial perfusion (eg, atherosclerosis), • venous drainage (eg, testicular torsion, Budd-Chiari syndrome), shock. Regions most vulnerable to hypoxia/ischemia and subsequent infarction:

Brain ACA/MCA/PCA boundary areasa,b

Colon Splenic flexure (Griffith point),a rectosigmoid junction (Sudeck point)a aWatershed areas (border zones) receive blood supply from most distal branches of 2 arteries with limited collateral vascularity. These areas are susceptible to ischemia from hypoperfusion. bNeurons most vulnerable to hypoxic-ischemic insults include Purkinje cells of the cerebellum and pyramidal cells of the hippocampus and neocortex (zones 3, 5, 6).

Types of infarcts

Red infarct Occurs in venous occlusion and tissues with multiple blood supplies (eg, liver, lung A , intestine, testes), and with reperfusion (eg, after angioplasty). Reperfusion injury is due to damage by free radicals.

Pale infarct Occurs in solid organs with a single (endarterial) blood supply (eg, heart, kidney B).

Free radical injury Free radicals damage cells via membrane lipid peroxidation, protein modification, DNA breakage. Initiated via radiation exposure (eg, cancer therapy), metabolism of drugs (phase I), redox reactions, nitric oxide (eg, inflammation), transition metals, WBC (eg, neutrophils, macrophages) oxidative burst. Free radicals can be eliminated by scavenging enzymes (eg, catalase, superoxide dismutase, glutathione peroxidase), spontaneous decay, antioxidants (eg, vitamins A, C, E), and certain metal carrier proteins (eg, transferrin, ceruloplasmin). Examples:

Oxygen toxicity: retinopathy of prematurity (abnormal vascularization), bronchopulmonary dysplasia, reperfusion injury after thrombolytic therapy

Drug/chemical toxicity: acetaminophen overdose (hepatotoxicity), carbon tetrachloride (converted by cytochrome P-450 into CCl3 free radical fatty liver [cell injury • apolipoprotein synthesis fatty change], centrilobular necrosis)

Metal storage diseases: hemochromatosis (iron) and Wilson disease (copper)

Types of calcification Calcium deposits appear deeply basophilic (arrow in A) on H&E stain.

Lipofuscin A yellow-brown “wear and tear” pigment A associated with normal aging. Composed of polymers of lipids and phospholipids complexed with protein. May be derived through lipid peroxidation of polyunsaturated lipids of subcellular membranes. Autopsy of elderly person will reveal deposits in heart, colon, liver, kidney, eye, and other organs.

Primary amyloidosis AL (from Ig Light chains) Seen in Plasma cell disorders Manifestations include: (eg, multiple myeloma) • Cardiac (eg, restrictive

GI (eg, macroglossia, hepatomegaly)

Renal (eg, nephrotic syndrome)

Hematologic (eg, easy bruising, splenomegaly)

Neurologic (eg, neuropathy)

Musculoskeletal (eg, carpal tunnel syndrome)

Inflammation Response to eliminate initial cause of cell injury, to remove necrotic cells resulting from the original insult, and to initiate tissue repair. Divided into acute and chronic. The inflammatory response itself can be harmful to the host if the reaction is excessive (eg, septic shock), prolonged (eg, persistent infections such as TB), or inappropriate (eg, autoimmune diseases such as SLE).

Fever Pyrogens (eg, LPS) induce macrophages to release IL-1 and TNF □• COX activity in perivascular cells of hypothalamus □• PGE2 □• temperature set point Acute inflammation Transient and early response to injury or infection. Characterized by neutrophils in tissue A , often with associated edema. Rapid onset (seconds to minutes) and short duration (minutes to days). Represents a reaction of the innate immune system (ie, less specific response than chronic inflammation).

STIMuLI Infections, trauma, necrosis, foreign bodies.

Leukocyte Extravasation predominantly occurs at postcapillary venules. extravasation

GlyCAM-1, CD34

L-selectin CD11/18 integrins (LFA-1, Mac-1) VLA-4 integrin

Chronic inflammation Prolonged inflammation characterized by mononuclear infiltration (macrophages, lymphocytes, plasma cells), which leads to

simultaneous tissue destruction and repair (including angiogenesis and fibrosis). May be preceded by acute inflammation.

STIMuLI Persistent infections (eg, TB, T pallidum, certain fungi and viruses) type IV hypersensitivity, autoimmune diseases, prolonged exposure to toxic agents (eg, silica) and foreign material.

MeDIATOrS Macrophages are the dominant cells. Interaction of macrophages and T lymphocytes chronic inflammation.

OuTCOMeS Scarring, amyloidosis, and neoplastic transformation (eg, chronic HCV infection chronic inflammation hepatocellular carcinoma; Helicobacter pylori infection chronic gastritis • gastric adenocarcinoma).

FGF Stimulates angiogenesis TGF-β Angiogenesis, fibrosis

EGF Stimulates cell growth via tyrosine kinases (eg, EGFR/ErbB1)

HISTOLOGY Focus of epithelioid cells (activated macrophages with abundant pink cytoplasm) surrounded by lymphocytes and multinucleated giant cells (formed by fusion of several activated macrophages). Two types: Caseating: associated with Central necrosis. Seen with infectious etiologies (eg, TB, fungal). Noncaseating A : no central necrosis. Seen with autoimmune diseases (eg, sarcoidosis, Crohn disease).

APCs present antigens to CD4+ Th cells and secrete IL-12 • CD4+ Th cells differentiate into Th1 cells Th1 secretes IFN-γ • macrophage activation

Macrophages • cytokine secretion (eg, TNF) formation of epithelioid macrophages and giant cells. Anti-TNF therapy can cause sequestering granulomas to break down • disseminated disease. Always test for latent TB before starting anti-TNF therapy.

Associated with hypercalcemia due to • 1α-hydroxylase activity in activated macrophages, resulting in • vitamin D activity.

Bacterial: Mycobacteria (tuberculosis, leprosy), Bartonella henselae (cat scratch disease; stellate necrotizing granulomas), Listeria monocytogenes (granulomatosis infantiseptica), Treponema pallidum (3° syphilis)

Fungal: endemic mycoses (eg, histoplasmosis)

Parasitic: schistosomiasis Immune-mediated: sarcoidosis, Crohn disease, 1° biliary cholangitis, subacute (de Quervain/ granulomatous) thyroiditis

Vasculitis: granulomatosis with polyangiitis (Wegener), eosinophilic granulomatosis with polyangiitis (Churg-Strauss), giant cell (temporal) arteritis, Takayasu arteritis

Foreign bodies: berylliosis, talcosis, hypersensitivity pneumonitis

Scar formation Occurs when repair cannot be accomplished by cell regeneration alone. Nonregenerated cells (2° to severe acute or chronic

injury) are replaced by connective tissue. 70–80% of tensile strength regained at 3 months; little tensile strength regained thereafter. Associated with excess TGF-β.

Normal cells Normal cells with basal apical polarity. See cervical example A , which shows normal cells and spectrum of dysplasia, as discussed below.

Loss of uniformity in cell size and shape (pleomorphism); loss of tissue orientation; nuclear changes (eg, • nuclear:cytoplasmic ratio) A .

Carcinoma in situ/ Irreversible severe dysplasia that involves the entire thickness of epithelium but does not preinvasive penetrate the intact basement membrane A .

Cells have invaded basement membrane using collagenases and hydrolases (metalloproteinases). Cell-cell contacts lost by inactivation of E-cadherin.

Metastasis Spread to distant organ(s) via lymphatics or blood.

Tumor nomenclature Carcinoma implies epithelial origin, whereas sarcoma denotes mesenchymal origin. Both terms generally imply malignancy. Benign tumors are usually well-differentiated and well-demarcated, with low mitotic activity, no metastases, and no necrosis. Malignant tumors (cancers) may show poor differentiation, erratic growth, local invasion, metastasis, and • apoptosis.

Terms for non-neoplastic malformations include hamartoma (disorganized overgrowth of tissues in their native location, eg, Peutz-Jeghers polyps) and choristoma (normal tissue in a foreign location, eg, gastric tissue located in distal ileum in Meckel diverticulum).

Epithelium Adenoma, papilloma Adenocarcinoma, papillary carcinoma

Blood cells Leukemia, lymphoma

Tumor grade vs stage Differentiation—degree to which a tumor resembles its tissue of origin. Well-differentiated tumors (often less aggressive) closely resemble their tissue of origin, whereas poorly differentiated tumors (often more aggressive) do not.

Anaplasia—complete lack of differentiation of cells in a malignant neoplasm.

Grade Degree of cellular differentiation and mitotic activity on histology. Ranges from low grade (well-differentiated) to high grade (poorly differentiated, undifferentiated, or anaplastic). Low grade High grade

Stage Degree of localization/spread based on site and size of 1° lesion, spread to regional lymph nodes, presence of metastases. Based on clinical (c) or pathologic (p) findings. Stage T generally has more prognostic value than

Lymphgrade (eg, a high-stage yet low-grade tumor is node N tumor). Stage determines Survival. Blood or lymphatic vessel

TNM staging system (Stage = Spread):

Spread to otherT = Tumor size/invasiveness, N = Node organs and tissues involvement, M = Metastases, eg, cT3N1M0. Each TNM factor has independent prognostic value; N and M are often most important.

Cancer epidemiology Skin cancer (basal > squamous >> melanoma) is the most common cancer (not included below).

Common metastases Most sarcomas spread hematogenously; most carcinomas spread via lymphatics. However, Four Carcinomas Route Hematogenously: Follicular thyroid carcinoma, Choriocarcinoma, Renal cell carcinoma, and Hepatocellular carcinoma.

Brain Lung > breast > melanoma, colon, kidney 50% of brain tumors are from metastases A Commonly seen as multiple well-circumscribed tumors at gray/white matter junction

CD and lung are the most common sites Sometimes Penetrates liver) of metastasis after the regional lymph nodes

Bone Prostate, Breast > Kidney, Thyroid, Lung (Painful Bones Kill The Lungs)

Bone metastasis E F >> 1° bone tumors (eg,

G Bone metastasis can be:

Lytic (eg, thyroid, kidney, non-small cell lung cancer)

Blastic (eg, prostate, small cell lung cancer)

Mixed (eg, breast cancer)

Tumor suppressor Loss of function □• cancer risk; both (two) alleles of a tumor suppressor gene must be lost for genes expression of disease.

EBV Burkitt lymphoma, Hodgkin lymphoma, nasopharyngeal carcinoma, 1° CNS lymphoma (in immunocompromised patients)

HBV, HCV Hepatocellular carcinoma

Serum tumor markers Tumor markers should not be used as the 1° tool for cancer diagnosis or screening. They may be used to monitor tumor recurrence and response to therapy, but definitive diagnosis is made via biopsy. Some can be associated with non-neoplastic conditions.

P-glycoprotein Also known as multidrug resistance protein 1 (MDR1). Classically seen in adrenocortical carcinoma but also expressed by other cancer cells (eg, colon, liver). Used to pump out toxins, including

chemotherapeutic agents (one mechanism of • responsiveness or resistance to chemotherapy over time).

Psammoma bodies Laminated, concentric spherules with dystrophic calcification A , PSaMMOMa bodies are seen in:

Papillary carcinoma of thyroid

Cachexia Weight loss, muscle atrophy, and fatigue that occur in chronic disease (eg, cancer, AIDS, heart failure, COPD). Mediated by TNF-α, IFN-γ, IL-1, and IL-6.

effusions, periostosis of tubular bones Endocrine “One pill makes you larger, and one pill makes you small.” “I was under medication when I made the decision not to burn the tapes.” “I wondher why ye can always read a doctor’s bill an’ ye niver can read his purscription.” “One of the first duties of the physician is to educate the masses not to take medicine.”

Preparation for pharmacology questions is straightforward. Know all the mechanisms, clinical use, and important adverse effects of key drugs and their major variants. Obscure derivatives are low-yield. Learn their classic and distinguishing toxicities as well as major drug-drug interactions. Reviewing associated biochemistry, physiology, and microbiology concepts can be useful while studying pharmacology. The exam has a strong emphasis on ANS, CNS, antimicrobial, and cardiovascular agents as well as on NSAIDs, which are covered throughout the text. Specific drug dosages or trade names are generally not testable. The exam may use graphs to test various pharmacology content, so make sure you are comfortable interpreting them.

Michaelis-Menten Km is inversely related to the affinity of the [S] = concentration of substrate; V = velocity. kinetics enzyme for its substrate.

Vmax is directly proportional to the enzyme concentration.

curve (ie, Michaelis-Menten kinetics); however, enzymatic reactions that exhibit a

Effects of enzyme inhibition kinetics (eg, hemoglobin).

Lineweaver-Burk plot The closer to 0 on the Y-axis, the higher the 1

Vmax. V

The closer to 0 on the X-axis, the higher the Km. −K

The higher the Km, the lower the affinity.

1 Competitive inhibitors cross each other, [S] whereas noncompetitive inhibitors do not. Effects of enzyme inhibition

Kompetitive inhibitors increase Km.

Bioavailability (F) Fraction of administered drug reaching systemic circulation unchanged. For an IV dose, F = 100%. Orally: F typically < 100% due to incomplete absorption and first-pass metabolism. Can be calculated from the area under the curve in a plot of plasma concentration over time.

Volume of distribution Theoretical volume occupied by the total amount of drug in the body relative to its plasma (Vd) concentration. Apparent Vd of plasma protein–bound drugs can be altered by liver and kidney disease (• protein binding, • Vd). Drugs may distribute in more than one compartment. amount of drug in the body

Low Intravascular Large/charged molecules; plasma protein bound Medium ECF Small hydrophilic molecules High All tissues including Small lipophilic molecules, especially if bound fat to tissue protein

Clearance (CL) The volume of plasma cleared of drug per unit time. Clearance may be impaired with defects in cardiac, hepatic, or renal function. rate of elimination of drug

Half-life (t1/2) The time required to change the amount of drug in the body by 1⁄2 during elimination. In first-order kinetics, a drug infused at a constant rate takes 4–5 half-lives to reach steady state. It takes 3.3 half-lives to reach 90% of the steady-state level.

t1/2 = 0.7 × Vd in first-order elimination CL

Drug metabolism Geriatric patients lose phase I first. Patients who are slow acetylators have • side effects from certain drugs because of • rate of metabolism (eg, isoniazid).

Elimination of drugs

Weak bases Examples: TCAs, amphetamines. Trapped in acidic environments. Treat overdose with ammonium chloride to acidify urine.

TCA toxicity is generally treated with sodium bicarbonate to overcome the sodium channel-blocking activity of TCAs, but not for accelerating drug elimination.

pKa pH at which drugs (weak acid or base) are 50% ionized and 50% nonionized. The pKa represents the strength of the weak acid or base.

Efficacy Maximal effect a drug can produce. Represented by the y-value (Vmax). • y-value = • Vmax = • efficacy. Unrelated to potency (ie, efficacious drugs can have high or low potency). Partial agonists have less efficacy than full agonists.

Potency Amount of drug needed for a given effect. Represented by the x-value (EC50). Left shifting = • EC50 = • potency = • drug needed. Unrelated to efficacy (ie, potent drugs can have high or low efficacy).

0.1 1.0 10 100 1000 0.1 1.0 10 100 1000 0.1 1.0 10 100 1000 Agonist dose Agonist dose Agonist dose

Therapeutic index Measurement of drug safety. TD50 median toxic dose

Therapeutic window—dosage range that can safely and effectively treat disease.

% of patients responding

TITE: Therapeutic Index = TD50 / ED50.

Safer drugs have higher TI values. Drugs with lower TI values frequently require monitoring (eg, Warfarin, Theophylline, Digoxin, Antiepileptic drugs, Lithium; Warning! These Drugs Are Lethal!).

LD50 (lethal median dose) often replaces TD50 in animal studies.

Types of drug interactions Autonomic receptors

SOMATICSmooth muscle, gland cells, nerve terminals, cardiac muscle Sweat glands Smooth muscle, gland cells, nerve terminals, cardiac muscle Renal vasculature smooth muscle Cardiac muscle, vessels Skeletal muscle ParasympatheticBrainstem Spinal cord Post (long) SympatheticPost (short) ACh NN Pre (long) ACh NN AChM ACh D NE M D1 ACh NM ACh NN ACh NN ACh NN Adrenal medulla Voluntary motor nerve Neuromuscular junction Catecholamine transmission Blood ˜1˜2°1 Epi ˜1˜2°1°2 NE ˜1˜2°1 Pre (short) Pelvic splanchnic nerves and CNs III, VII, IX and X are part of the parasympathetic nervous system. Adrenal medulla is directly innervated by preganglionic sympathetic fibers. Sweat glands are part of the sympathetic pathway but are innervated by cholinergic fibers (sympathetic nervous system results in a “chold” sweat).

M˜-receptor bladder function via coordination of sympathetic and parasympathetic nervous Pelvic nerve β˜-receptor (parasympatheticsystems.

• ⊕ parasympathetic □• urine voiding. Some (sympathetic input) sphincter autonomic drugs act on smooth muscle External urethral receptors to treat bladder dysfunction.

q • vascular smooth muscle contraction, • pupillary dilator muscle contraction (mydriasis), • intestinal and bladder sphincter muscle contraction i • sympathetic (adrenergic) outflow, • insulin release, • lipolysis, • platelet aggregation, • aqueous humor production s • heart rate, • contractility (one heart), • renin release, • lipolysis s Vasodilation, bronchodilation (two lungs), • lipolysis, • insulin release, glycogenolysis, • uterine tone (tocolysis), • aqueous humor production, β3 s •lipolysis, • thermogenesis in skeletal muscle, • bladder relaxation Cholinergic (accommodation), • insulin release, endothelium-mediated vasodilation Dopamine

D1 s Relaxes renal vascular smooth muscle, activates direct pathway of striatum D2 i Modulates transmitter release, especially in brain,

inhibits indirect “After qisses (kisses), you get a qiq (kick) out of siq (sick) sqs (super qinky sex).”

H1, ˜1, V1,

Protein HAVe 1M&M.

M1, M3 kinase C Lipids ° 1, ° 2, ° 3, D1, Receptor

Gs ATP H2, V2

M2, ˜2, D2 inhibit themselves.

Autonomic drugs Release of norepinephrine from a sympathetic nerve ending is modulated by NE itself, acting on presynaptic α2-autoreceptors • negative feedback. Amphetamines use the NE transporter (NET) to enter the presynaptic terminal, where they utilize the vesicular monoamine transporter (VMAT) to enter neurosecretory vesicles. This displaces NE from the vesicles. Once NE reaches a concentration threshold within the presynaptic terminal, the action of NET is reversed, and NE is expelled into the synaptic cleft, contributing to the characteristics and effects of • NE observed in patients taking amphetamines.

ACh NE Choline Choline+ Acetyl-CoA Ca2+ Choline + acetate AChE ACh receptor DOPA Dopamine Reuptake Di˜usion, metabolism NET VMAT Adrenoreceptors ˜ or °Cocaine, TCAs, amphetamine Botulinum toxin -Ca2+ NE + --AChE inhibitors AXON Tyrosine ACh Tyrosine ˜2 AT II Reserpine - Release-modulating receptors Negativefeedback AXON ChAT -+ Amphetamine, ephedrine + + represents transporters.

Atropine Muscarinic antagonist. Used to treat bradycardia and for ophthalmic applications.

Eye • pupil dilation, cycloplegia Blocks muscarinic effects (DUMBBELSS) of anticholinesterases, but not the nicotinic

Airway Bronchodilation, • secretions effects.

AdVERSE EFFECTS body temperature (due to sweating); • HR; dry mouth; dry, flushed skin; cycloplegia; constipation; disorientation Can cause acute angle-closure glaucoma in elderly (due to mydriasis), urinary retention in men with prostatic hyperplasia, and hyperthermia in infants.

Side effects: Hot as a hare Fast as a fiddle Dry as a bone Red as a beet Blind as a bat Mad as a hatter Full as a flask

Jimson weed (Datura) gardener’s pupil (mydriasis due to plant alkaloids) priapism. Indirect sympathomimetics

Ephedrine Indirect general agonist, releases stored catecholamines Narcolepsy, obesity, ADHD.

Causes vasoconstriction and local anesthesia.

Caution when giving β-blockers if cocaine intoxication is suspected (can lead to unopposed α1 activation • extreme hypertension, coronary vasospasm).

Nasal decongestion (pseudoephedrine), urinary incontinence, hypotension.

β1, refex tachycardia

Epinephrine response exhibits reversal of mean arterial Phenylephrine response is suppressed but not reversed pressure from a net increase (the α response) to a net because it is a "pure" α-agonist (lacks β-agonist decrease (the β2 response). properties).

In platelets: • cAMP □ inhibition of platelet aggregation

Cardiac stress testing (dipyridamole only, due to coronary vasodilation)

Prevention of coronary stent restenosis Nausea, headache, facial flushing, hypotension, abdominal pain aCilostazol is a PDE-3 inhibitor, but due to its indications is categorized as a platelet inhibitor together with dipyridamole. bDipyridamole is a nonspecific PDE inhibitor, leading to inhibition of platelet aggregation. It also prevents adenosine reuptake by platelets □• extracellular adenosine □• vasodilation.

Beers criteria Widely used criteria developed to reduce potentially inappropriate prescribing and harmful polypharmacy in the geriatric population. Includes > 50 medications that should be avoided in elderly patients due to • efficacy and/or • risk of adverse events. Examples: α-blockers (• risk of hypotension)

Anticholinergics, antidepressants, antihistamines, opioids (• risk of delirium, sedation, falls, constipation, urinary retention)

Benzodiazepines (• risk of delirium, sedation, falls)

NSAIDs (• risk of GI bleeding, especially with concomitant anticoagulation)

PPIs (• risk of C difficile infection)

AChE inhibitors, organophosphates Atropine > pralidoxime

Antimuscarinic, anticholinergic agents Physostigmine (crosses BBB), control hyperthermia

Arsenic Dimercaprol, succimer β-blockers Atropine, glucagon, saline

Iron (Fe) Deferoxamine, deferasirox, deferiprone

Salicylates $NaHCO_3$ (alkalinize urine), dialysis

Warfarin Vitamin K (delayed effect), PCC (prothrombin complex concentrate)/FFP (immediate effect)

Anticholinergics (eg, atropine, TCAs, Sympatholytics (eg, α2-agonists) tropicamide, scopolamine, antihistamines)

Drugs of abuse (eg, amphetamines, cocaine, Drugs of abuse (eg, heroin/opioids) LSD), meperidine

Sympathomimetics Parasympathomimetics (eg, pilocarpine), organophosphates

Sulfa drugs Sulfonamide antibiotics, Sulfasalazine, Scary Sulfa Pharm FACTS Probenecid, Furosemide, Acetazolamide, Celecoxib, Thiazides, Sulfonylureas. Patients with sulfa allergies may develop fever, urinary tract infection, Stevens-Johnson syndrome, hemolytic anemia, thrombocytopenia, agranulocytosis, acute interstitial nephritis, and urticaria (hives).

"Medicine is a science of uncertainty and an art of probability." "There are two kinds of statistics: the kind you look up and the kind you make up." "On a long enough timeline, the survival rate for everyone drops to zero." "There are three kinds of lies: lies, damned lies, and statistics."

A heterogenous mix of epidemiology, biostatistics, ethics, law, healthcare delivery, patient safety, quality improvement, and more falls under the heading of public health sciences. Biostatistics and epidemiology are the foundations of evidence-based medicine and are very high yield. Make sure you can quickly apply biostatistical equations such as sensitivity, specificity, and predictive values in a problem-solving format. Also, know how to set up your own 2 × 2 tables. Quality improvement and patient safety topics were introduced a few years ago on the exam and represent trends in health system science. Medical ethics questions often require application of principles. Typically, you are presented with a patient scenario and then asked how you would respond.

Clinical trial Experimental study involving humans. Compares therapeutic benefits of ≥2 treatments, or of treatment and placebo. Study quality improves when study is randomized, controlled, and double-blinded (ie, neither patient nor doctor knows whether the patient is in the treatment or control group). Triple-blind refers to the additional blinding of the researchers analyzing the data. Four phases ("Does the drug SWIM?").

Evaluation of Sensitivity and specificity are fixed properties Disease diagnostic tests of a test. PPV and NPV vary depending on disease prevalence in population being tested.

SN-N-OUT = highly SeNsitive test, when Negative, rules OUT disease

SP-P-IN = highly SPecific test, when Positive, rules IN disease

PPV varies directly with pretest probability (baseline risk, such as prevalence of disease):

NPV varies inversely with prevalence or pretest

Quantifying risk Definitions and formulas are based on the classic 2 × 2 or contingency table.

Odds ratio Typically used in case-control If in a case-control study, 20/30 lung a/c ad studies. Represents the odds of cancer patients and 5/25 healthy b/d bc exposure among cases (a/c) vs individuals report smoking, the OR odds of exposure among controls is 8; so the lung cancer patients are 8 (b/d). times more likely to have a history of smoking.

Relative risk Typically used in cohort studies. Risk of developing disease in the exposed group divided by risk in the unexposed group. RR = 1 □ no association between exposure and disease. RR > 1 □ exposure associated with occurrence. RR < 1 □ exposure associated with disease occurrence.

If 5/10 people exposed to radiation are a/(a + b) diagnosed with cancer, and 1/10 people c/(c + d) not exposed to radiation are diagnosed with cancer, the RR is 5; so people exposed to radiation have a 5 times greater risk of developing cancer.

For rare diseases (low prevalence), OR approximates RR.

Relative risk The proportion of risk reduction If 2% of patients who receive a flu RRR = 1 − RR reduction attributable to the intervention as shot develop the flu, while 8% of compared to a control. unvaccinated patients develop the flu, then RR = 2/8 = 0.25, and RRR = 0.75.

Attributable The difference in risk between If risk of lung cancer in smokers is 21% a c risk exposed and unexposed groups. and risk in nonsmokers is 1%, then the a + b c + d attributable risk is 20%. RR − 1

Absolute The difference in risk (not the If 8% of people who receive a placebo c a risk proportion) attributable to the vaccine develop the flu vs 2% of people c + d a + b reduction intervention as compared to a who receive a flu vaccine, then ARR = control. 8%–2% = 6% = 0.06.

Number Number of patients who need to NNT = 1/ARR needed to be treated for 1 patient to benefit. treat Lower number = better treatment.

Number Number of patients who need to NNH = 1/AR needed to be exposed to a risk factor for 1 harm patient to be harmed. Higher number = safer exposure.

Case fatality Percentage of deaths occurring If 4 patients die among 10 cases of deaths rate among those with disease. meningitis, case fatality rate is 40%. cases

Incidence vs # of new cases Incidence looks at new cases(incidents).

Incidence = (per unit of time) prevalence # of people at risk Prevalence =# of existing cases (at a point in Prevalence looks at all current cases.

Total # of people time) 1 − prevalence of disease

Prevalence ≈ incidence for short duration disease Prevalence ~ pretest probability.

(eg, common cold). • prevalence □• PPV and • NPV.

Prevalence > incidence for chronic diseases, due to large # of existing cases (eg, diabetes).

Precision (reliability) The consistency and reproducibility of a test. Random error • precision in a test. The absence of random variation in a test. • precision □• standard deviation.

• precision □□ statistical power (1 −β).

Accuracy (validity) The closeness of test results to the true values. Systematic error • accuracy in a test. The absence of systematic error or bias in a test.

ROC curve demonstrates how well a diagnostic 1 test can distinguish between 2 groups (eg, disease vs healthy). Plots the true-positive rate (sensitivity) against the false-positive rate (1 − specificity).

The better performing test will have a higher area under the curve (AUC), with the curve closer to the upper left corner.

No predictive value (AUC = 0.5)TP rate (sensitivity) FP rate (1 − specifcity) 1 A ctual test (0.5 < AU C < 1)

Selection bias Nonrandom sampling or treatment allocation of subjects such that study population is not representative of target population. Most commonly a sampling bias.

Berkson bias—cases and/ or controls selected from hospitals are less healthy and have different exposures than general population

Attrition bias—participants lost to follow up have a different prognosis than those who complete the study Randomization

Ensure the choice of the right comparison/reference group

Recall bias Awareness of disorder alters Patients with disease recall Decrease time from exposure recall by subjects; common in exposure after learning of to follow-up retrospective studies similar cases

Measurement bias Information is gathered in a Using a faulty automatic Use objective, standardized, systemically distorted manner sphygmomanometer to and previously tested methods measure BP of data collection that are Hawthorne effect—participants planned ahead of time change behavior upon Use placebo group awareness of being observed

Procedure bias Subjects in different groups are Patients in treatment group not treated the same spend more time in highly specialized hospital units

Blinding (masking) and use of placebo reduce influence of participants and researchers on procedures and interpretation of outcomes as neither are aware of group assignments

Confounding bias Factor related to both exposure and outcome (but not on causal path) distorts effect of exposure on outcome (vs effect modification, in which the exposure leads to different outcomes in subgroups stratified by the factor)

An uncontrolled study shows an association between drinking coffee and lung cancer. However, coffee drinkers also smoke more, which can account for the association Multiple/repeated studies

Crossover studies (subjects act as their own controls)

Matching (patients with similar characteristics in both treatment and control groups)

Lead-time bias Early detection is confused Early detection makes it seem Measure "back-end" survival with • survival like survival has increased, (adjust survival according to but the disease's natural the severity of disease at the history has not changed time of diagnosis)

Length-time bias Screening test detects diseases A slowly progressive cancer A randomized controlled trial with long latency period, is more likely detected by a assigning subjects to the while those with shorter screening test than a rapidly screening program or to no latency period become progressive cancer screening symptomatic earlier

Mode = most common value. Least affected by outliers.

Measures of Standard deviation = how much variability σ = SD; n = sample size. dispersion exists in a set of values, around the mean of Variance = $(SD)2$. these values. SE = $\sigma/\sqrt{n}$.

Standard error = an estimate of how much SE • as n •. variability exists in a (theoretical) set of sample means around the true population mean.

Normal distribution Gaussian, also called bell-shaped. Mean = median = mode.

68% 95% 99.7%

Bimodal Suggests two different populations (eg, metabolic polymorphism such as fast vs slow acetylators; age at onset of Hodgkin lymphoma; suicide rate by age).

Positive skew Typically, mean > median > mode.

Asymmetry with longer tail on right.

Negative skew Typically, mean < median < mode. Mode Asymmetry with longer tail on left.

Statistical hypotheses Outcomes of statistical hypothesis testing

Correct result Stating that there is an effect or difference when Reality one exists (null hypothesis rejected in favor of HH alternative hypothesis). Stating that there is no effect or difference when none exists (null hypothesis not rejected).

Blue shading = correct result.

Confidence interval Range of values within which the true mean of the population is expected to fall, with a specified probability.

CI for sample mean = $\bar{x}$ ± Z(SE) The 95% CI (corresponding to α = .05) is often used. As sample size increases, CI narrows. For the 95% CI, Z = 1.96. For the 99% CI, Z = 2.58.

If the 95% CI for a mean difference between 2 variables includes 0, then there is no significant difference and H0 is not rejected.

If the 95% CI for odds ratio or relative risk includes 1, H0 is not rejected.

If the CIs between 2 groups do not overlap statistically significant difference exists.

If the CIs between 2 groups overlap usually no significant difference exists.

Meta-analysis A method of statistical analysis that pools summary data (eg, means, RRs) from multiple studies for a more precise estimate of the size of an effect. Also estimates heterogeneity of effect sizes between studies. Improves power, strength of evidence, and generalizability of study findings. Limited by quality of individual studies and bias in study selection.

Autonomy Obligation to respect patients as individuals (truth-telling, confidentiality), to create conditions necessary for autonomous choice (informed consent), and to honor their preference in accepting or not accepting medical care.

Beneficence Physicians have a special ethical (fiduciary) duty to act in the patient's best interest. May conflict with autonomy (an informed patient has the right to decide) or what is best for society (eg, mandatory TB treatment). Traditionally, patient interest supersedes.

Nonmaleficence "Do no harm." Must be balanced against beneficence; if the benefits outweigh the risks, a patient may make an informed decision to proceed (most surgeries and medications fall into this category).

Justice To treat persons fairly and equitably. This does not always imply equally (eg, triage).

Informed consent A process (not just a document/signature) that requires:

Disclosure: discussion of pertinent information (using medical interpreter, if needed)

Understanding: ability to comprehend

Capacity: ability to reason and make one's own decisions (distinct from competence, a legal determination)

Voluntariness: freedom from coercion and manipulation

Patients must have an intelligent understanding of their diagnosis and the risks/benefits of proposed treatment and alternative options, including no treatment.

Patient must be informed that he or she can revoke written consent at any time, even orally.

Exceptions to informed consent (WIPE it away):

Waiver—patient explicitly waives the right of informed consent

Therapeutic Privilege—withholding information when disclosure would severely harm the patient or undermine informed decision-making capacity

Consent for minors A minor is generally any person < 18 years old. Parental consent laws in relation to healthcare vary by state. In general, parental consent should be obtained, but exceptions exist for emergency treatment (eg, blood transfusions) or if minor is legally emancipated (eg, married, self-supporting, or in the military).

Situations in which parental consent is usually not required:

Sex (contraception, STIs, pregnancy)

Rock and roll (emergency/trauma) Physicians should always encourage healthy minor-guardian communication.

Physician should seek a minor's assent even if their consent is not required.

Physician must determine whether the patient is psychologically and legally capable of making a particular healthcare decision. Note that decisions made with capacity cannot be revoked simply if the patient later loses capacity. Intellectual disability alone (eg, Down syndrome, autism) is not an exclusion criterion for informed decision-making.

Capacity is determined by a physician for a specific healthcare-related decision (eg, to refuse medical care). Competency is determined by a

judge and usually refers to more global categories of decision making (eg, legally unable to make any healthcare-related decision).

Components (think GIEMSA):

Decision is consistent with patient's values and Goals

Patient is Informed (knows and understands)

Decision is not a result of altered Mental status (eg, delirium, psychosis, intoxication), Mood disorder

Patient is ≥ 18 years of Age or otherwise legally emancipated

Advance directives Instructions given by a patient in anticipation of the need for a medical decision. Details vary per state law.

Oral advance directive Incapacitated patient's prior oral statements commonly used as guide. Problems arise from variance in interpretation. If patient was informed, directive was specific, patient made a choice, and decision was repeated over time to multiple people, then the oral directive is more valid.

Do not resuscitate DNR order prohibits cardiopulmonary resuscitation (CPR). Other resuscitative measures that may order follow (eg, feeding tube) are also typically avoided.

Confidentiality Confidentiality respects patient privacy and autonomy. If the patient is incapacitated or the situation is emergent, disclosing information to family and friends should be guided by professional judgment of patient's best interest. The patient may voluntarily waive the right to confidentiality (eg, insurance company request). General principles for exceptions to confidentiality:

Potential physical harm to others is serious and imminent

Alternative means to warn or protect those at risk is not possible

Self-harm is likely

Steps can be taken to prevent harm

Examples of exceptions to patient confidentiality (many are state specific) include the following ("The physician's good judgment SAVED the day"):

Suicidal/homicidal patients.

Abuse (children, elderly, and/or prisoners).

Duty to protect—state-specific laws that sometimes allow physician to inform or somehow protect potential Victim from harm.

Epileptic patients and other impaired automobile drivers.

Reportable Diseases (eg, STIs, hepatitis, food poisoning); physicians may have a duty to warn public officials, who will then notify people at risk. Dangerous communicable diseases, such as TB or Ebola, may require involuntary treatment.

Patient is not adherent. Attempt to identify the reason for nonadherence and determine his/her willingness to change; do not coerce the patient into adhering and do not refer him/her to another physician.

A patient's family member asks you not to disclose the results of a test if the prognosis is poor because the patient will be "unable to handle it."

Attempt to identify why the family member believes such information would be detrimental to the patient's condition. Explain that as long as the patient has decision-making capacity and does not indicate otherwise, communication of information concerning his/her care will not be withheld. However, if you believe the patient might seriously harm himself/herself or others if informed, then you may invoke therapeutic privilege and withhold the information.

Patient is suicidal. Assess the seriousness of the threat. If it is serious, suggest that the patient remain in the hospital voluntarily; patient can be hospitalized involuntarily if he/she refuses.

Discounted fee-for-Patient pays for each individual service at a discounted rate predetermined by providers and payers service (eg, PPOs).

Medicare and Medicaid—federal social healthcare programs that originated from amendments to the Social Security Act.

Medicare is available to patients ≥ 65 years old, < 65 with certain disabilities, and those with end-stage renal disease.

Medicaid is joint federal and state health assistance for people with limited income and/ or resources.

MedicarE is for Elderly. MedicaiD is for Destitute.

The 4 parts of Medicare:

Part A: HospitAl insurance, home hospice care

Part B: Basic medical bills (eg, doctor's fees, diagnostic testing)

Part C: (parts A + B = Combo) delivered by approved private companies

Part D: Prescription Drugs

Hospice care Medical care focused on providing comfort and palliation instead of definitive cure. Available to patients on Medicare or Medicaid and in most private insurance plans whose life expectancy is < 6 months. During end-of-life care, priority is given to improving the patient's

comfort and relieving pain (often includes opioid, sedative, or anxiolytic medications). Facilitating comfort is prioritized over potential side effects (eg, respiratory depression). This prioritization of positive effects over negative effects is called the principle of double effect.

Common causes of death (US) by age

Safety culture Organizational environment in which everyone Event reporting systems collect data on errors for can freely bring up safety concerns without internal and external monitoring. fear of censure. Facilitates error identification.

Human factors design Forcing functions (those that prevent undesirable actions [eg, connecting feeding syringe to IV tubing]) are the most effective. Standardization improves process reliability (eg, clinical pathways, guidelines, checklists). Simplification reduces wasteful activities (eg, consolidating electronic medical records).

Deficient designs hinder workflow and lead to staff workarounds that bypass safety features (eg, patient ID barcodes affixed to computers due to unreadable wristbands).

PDSA cycle Process improvement model to test changes in real clinical setting. Impact on patients:

Swiss cheese model Focuses on systems and conditions rather than an individual's error. The risk of a threat becoming a reality is mitigated by differing layers and types of defenses. Patient harm can occur despite multiple safeguards when "the holes in the cheese line up."

Types of medical May involve patient identification, diagnosis, monitoring, nosocomial infection, medications, errors procedures, devices, documentation, handoffs. Medical errors should be disclosed to patients, independent of immediate outcome (harmful or not).

"Symptoms, then, are in reality nothing but the cry from suffering organs." "Man is an intelligence in servitude to his organs." "When every part of the machine is correctly adjusted and in perfect harmony, health will hold dominion over the human organism by laws as natural and immutable as the laws of gravity." —Andrew T. Still

Skin, and Connective Tissue 445

In this section, we have divided the High-Yield Facts into the major Organ Systems. Within each Organ System are several subsections, including Embryology, Anatomy, Physiology, Pathology, and Pharmacology. As you progress through each Organ System, refer back to information in the previous subsections to organize these basic science subsections into a "vertically integrated" framework for learning. Below is some general advice for studying the organ systems by these subsections.

Relevant embryology is included in each organ system subsection. Embryology tends to correspond well with the relevant anatomy, especially with regard to congenital malformations.

Several topics fall under this heading, including gross anatomy, histology, and neuroanatomy. Do not memorize all the small details; however, do not ignore anatomy altogether. Review what you have already learned and what you wish you had learned. Many questions require two or more steps. The first step is to identify a structure on anatomic cross section, electron micrograph, or photomicrograph. The second step may require an understanding of the clinical significance of the structure.

When studying, stress clinically important material. For example, be familiar with gross anatomy and radiologic anatomy related to specific diseases (eg, Pancoast tumor, Horner syndrome), traumatic injuries (eg, fractures, sensory and motor nerve deficits), procedures (eg, lumbar puncture), and common surgeries (eg, cholecystectomy). There are also many questions on the exam involving x-rays, CT scans, and neuro MRI scans. Many students suggest browsing through a general radiology atlas, pathology atlas, and histology atlas. Focus on learning basic anatomy at key levels in the body (eg, sagittal brain MRI; axial CT of the midthorax, abdomen, and pelvis). Basic neuroanatomy (especially pathways, blood supply, and functional anatomy), associated neuropathology, and neurophysiology have good yield. Please note that many of the photographic images in this book are for illustrative purposes and are not necessarily reflective of Step 1 emphasis.

The portion of the examination dealing with physiology is broad and concept oriented and thus does not lend itself as well to fact-based review. Diagrams are often the best study aids, especially given the increasing number of questions requiring the interpretation of diagrams. Learn to apply basic physiologic relationships in a variety of ways (eg, the Fick equation, clearance equations). You are seldom asked to perform complex calculations. Hormones are the focus of many questions, so learn their sites of production and action as well as their regulatory mechanisms.

A large portion of the physiology tested on the USMLE Step 1 is clinically relevant and involves understanding physiologic changes associated with pathologic processes (eg, changes in pulmonary function with COPD). Thus, it is worthwhile to review the physiologic changes that are found with common pathologies of the major organ systems (eg, heart, lungs, kidneys, GI tract) and endocrine glands.

Questions dealing with this discipline are difficult to prepare for because of the sheer volume of material involved. Review the basic principles and hallmark characteristics of the key diseases. Given the clinical orientation of Step 1, it is no longer sufficient to know only the “buzzword” associations of certain diseases (eg, café-au-lait macules and neurofibromatosis); you must also know the clinical descriptions of these findings.

Given the clinical slant of the USMLE Step 1, it is also important to review the classic presenting signs and symptoms of diseases as well as

their associated laboratory findings. Delve into the signs, symptoms, and pathophysiology of major diseases that have a high prevalence in the United States (eg, alcoholism, diabetes, hypertension, heart failure, ischemic heart disease, infectious disease). Be prepared to think one step beyond the simple diagnosis to treatment or complications.

The examination includes a number of color photomicrographs and photographs of gross specimens that are presented in the setting of a brief clinical history. However, read the question and the choices carefully before looking at the illustration, because the history will help you identify the pathologic process. Flip through an illustrated pathology textbook, color atlases, and appropriate Web sites in order to look at the pictures in the days before the exam. Pay attention to potential clues such as age, sex, ethnicity, occupation, recent activities and exposures, and specialized lab tests.

Preparation for questions on pharmacology is straightforward. Learning all the key drugs and their characteristics (eg, mechanisms, clinical use, and important side effects) is high yield. Focus on understanding the prototype drugs in each class. Avoid memorizing obscure derivatives. Learn the "classic" and distinguishing toxicities of the major drugs. Do not bother with drug dosages or trade names. Reviewing associated biochemistry, physiology, and microbiology can be useful while studying pharmacology. There is a strong emphasis on ANS, CNS, antimicrobial, and cardiovascular agents as well as NSAIDs. Much of the material is clinically relevant. Newer drugs on the market are also fair game.

"As for me, except for an occasional heart attack, I feel as young as I ever did." "Hearts will never be practical until they are made unbreakable." —The Wizard of Oz "As the arteries grow hard, the heart grows soft." —H. L. Mencken "Nobody has ever measured, not even poets, how much the heart can hold." "Only from the heart can you touch the sky." "It is not the size of the man but the size of his heart that matters."

The cardiovascular system is one of the highest yield areas for the boards and, for some students, may be the most challenging. Focusing on understanding the mechanisms instead of memorizing the details can make a big difference, especially for this topic. Pathophysiology of atherosclerosis and heart failure, MOA of drugs (particular physiology interactions) and their adverse effects, ECGs of heart blocks, the cardiac cycle, and the Starling curve are some of the more high-yield topics. Differentiating between systolic and diastolic dysfunction is also very important. Heart murmurs and maneuvers that affect these murmurs have also been high yield and may be asked in a multimedia format.

Septation of the chambers

Septum primum grows toward endocardial cushions, narrowing foramen primum. Foramen secundum forms in septum primum (foramen primum regresses). Septum secundum develops on the right side of septum primum, as foramen secundum maintains right-to-left shunt. Septum secundum expands and covers most of foramen secundum. The residual foramen is the

foramen ovale. Remaining portion of septum primum forms the one-way valve of the foramen ovale.

6.

Septum primum closes against septum secundum, sealing the foramen ovale soon after birth because of • LA pressure and • RA pressure.

7.

Septum secundum and septum primum fuse during infancy/early childhood, forming the atrial septum.

Patent foramen ovale—caused by failure of septum primum and septum secundum to fuse after birth; most are left untreated. Can lead to paradoxical emboli (venous thromboemboli entering the systemic arterial circulation) as can occur in ASD.

Muscular interventricular septum forms. Opening is called interventricular foramen. Aorticopulmonary septum rotates and fuses with muscular ventricular septum to form membranous interventricular septum, closing interventricular foramen.

Growth of endocardial cushions separates atria from ventricles and contributes to both atrial septation and membranous portion of the interventricular septum.

Ventricular septal defect—most common congenital cardiac anomaly, usually occurs in membranous septum.

Primitive ventricle Trabeculated part of left and right ventricles

Primitive atrium Trabeculated part of left and right atria

Left horn of sinus venosus Coronary sinus

Right horn of sinus venosus Smooth part of right atrium (sinus venarum)

Endocardial cushion Atrial septum, membranous interventricular septum; AV and semilunar valves

Posterior, subcardinal, and supracardinal veins Inferior vena cava (IVC)

Primitive pulmonary vein Smooth part of left atrium

Prostaglandins E1 and E2 kEEp PDA open.

Ductus arteriosus Ligamentum arteriosum Near the left recurrent laryngeal nerve

Allantois urachus Median umbilical ligament Urachus is part of allantoic duct between bladder and umbilicus

Blood in umbilical vein has a Po2 of ≈ 30 mm Hg and is ≈ 80% saturated with O2. Umbilical arteries have low O2 saturation. 3 important shunts:

Blood entering fetus through the umbilical vein is conducted via the ductus venosus into the IVC, bypassing hepatic circulation.

of the highly Oxygenated blood reaching the heart via the IVC is directed through the foramen Ovale into the left atrium.

blood from the SVC passes through the RA RV main pulmonary artery • Ductus arteriosus • Descending aorta; shunt is due to high fetal pulmonary artery resistance (due partly to low O2 tension).

At birth, infant takes a breath • resistance in pulmonary vasculature left atrial pressure vs right atrial pressure foramen ovale closes (now called fossa ovalis); • in O2 (from respiration) and • in prostaglandins (from placental separation) closure of ductus arteriosus.

Indomethacin helps close the patent Ductus arteriosus ligamentum arteriosum (remnant of ductus arteriosus). Come In and close the Door.

Anatomy of the heart

LA is the most posterior part of the heart A ; enlargement of the LA (eg, in mitral stenosis) can lead to compression of the esophagus (dysphagia) and/or the left recurrent laryngeal nerve, a branch of the vagus nerve, causing hoarseness (Ortner syndrome).

RV is the most anterior part of the heart and most commonly injured in trauma.

Key:

LAD and its branches supply anterior 2/3 of interventricular septum, anterolateral papillary muscle, and anterior surface of LV. Most commonly occluded.

PDA supplies AV node (dependent on dominance), posterior 1/3 of interventricular septum, posterior 2/3 walls of ventricles, and posteromedial papillary muscle.

RCA supplies SA node (blood supply independent of dominance). Infarct may cause nodal dysfunction (bradycardia or heart block). Right (acute) marginal artery supplies RV.

Dominance:

Right-dominant circulation (85%) = PDA arises from RCA.

Left-dominant circulation (8%) = PDA arises from LCX.

from both LCX and RCA. Coronary blood flow peaks in early diastole.

Force of contraction is proportional to end-diastolic length of cardiac muscle fiber (preload).

contractility with catecholamines, positive inotropes (eg, digoxin).

contractility with loss of functional myocardium (eg, MI), β-blockers (acutely), non-dihydropyridine Ca2+ channel blockers, dilated cardiomyopathy.

Resistance, pressure, flow

ΔP = Q × R Similar to Ohm's law: ΔV = I × R Volumetric flow rate (Q) = flow velocity (v) ×

Q πr4 Total resistance of vessels in series: RT = R1 + R2 + R3 . . . Total resistance of vessels in parallel: 1 111

Capillaries have highest total cross-sectional area and lowest flow velocity. Pressure gradient drives flow from high pressure to low pressure. Arterioles account for most of TPR. Veins provide most of blood storage capacity. Viscosity depends mostly on hematocrit. Viscosity • in hyperproteinemic states (eg, multiple myeloma), polycythemia. Viscosity • in anemia.

volume, venous tone TPR TPRCardiac output/venous return Cardiac output/venous return Vascularfunction curve Cardiac function curve ↓↓↓↓↓↓volume, venous tone inotropy inotropy Mean systemic pressure Normal

Intersection of curves = operating point of heart (ie, venous return and CO are equal, as circulatory system is a closed system).

Changes often occur in tandem, and may be reinforcing (eg, exercise • inotropy and • TPR to maximize CO) or compensatory (eg, HF • inotropy fluid retention to • preload to maintain CO).

Pressure-volume loops and cardiac cycle The black loop represents normal cardiac physiology.

Phases—left ventricle: valve opening; period of highest O2 consumption

Heart sounds:

S1—mitral and tricuspid valve closure. Loudest at mitral area.

S2—aortic and pulmonary valve closure. Loudest at left upper sternal border.

Considered abnormal if palpable.

Jugular venous pulse (JVP): a wave—atrial contraction. Absent in atrial fibrillation (AF).

filling phase. Best heard at apex with patient in left lateral decubitus position. Associated with • filling pressures (eg, MR, AR, HF, ventricles (but can be normal in children, young adults, athletes, and pregnancy).

S4—in late diastole ("atrial kick"). Best heard at apex with patient in left lateral decubitus position. High atrial pressure. Associated with ventricular noncompliance (eg, hypertrophy).

Left atrium must push against stiff LV wall.

bulging into atrium).

x descent—downward displacement of closed (aka J.V.P) ejection phase. Reduced or absent in tricuspid regurgitation and right HF because pressure gradients are reduced. v wave—• right atrial pressure due to filling 0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 ("villing") against closed tricuspid valve.

Time (sec) y descent—RA emptying into RV. Prominent in constrictive pericarditis, absent in cardiac tamponade.

120 • ESV due to • resistance and due to • LA volume/pressure from because of impaired ventricular filling

Splitting of S2

Wide splitting Seen in conditions that delay RV emptying (eg, E pulmonic stenosis, right bundle branch block). S1 A2P2 Causes delayed pulmonic sound (especially on inspiration). An exaggeration of normal Abnormal delay splitting.

Fixed splitting Heard in ASD. ASD left-to-right shunt • RA and RV volumes • flow through pulmonic valve delayed pulmonic valve S1 A2P2 closure (independent of respiration). I closure (eg, aortic stenosis, left bundle branch S1 P2A2 block). Normal order of semilunar valve closure is reversed so that P2 sound occurs before delayed A2 sound. On inspiration, P2 closes later and moves closer to A2, "paradoxically" eliminating the split. On expiration, the split can be heard (opposite to physiologic splitting).

Auscultation of the heart (eg, physiologic murmur) Aortic valve sclerosis Where to listen: APT M 111234567777777 Left sternal border: Aortic regurgitation Pulmonic regurgitation cardiomyopathy PA M T

Aortic area: Systolic murmur

Pulmonic area:

Tricuspid area:

Mitral area (apex):

Crescendo-decrescendo systolic ejection murmur and soft S2 (ejection click may be present). LV >> aortic pressure during systole. Loudest at

heart base; radiates to carotids. “Pulsus parvus et tardus”—pulses are weak with a delayed peak. Can lead to Syncope, Angina, and Dyspnea on exertion (SAD). Most commonly due to age-related calcification in older patients (> 60 years old) or in younger patients with early-onset calcification of bicuspid aortic valve.

Holosystolic, high-pitched “blowing murmur.” Mitral—loudest at apex and radiates toward axilla. MR is often due to ischemic heart disease (post-MI), MVP, LV dilatation. Tricuspid—loudest at tricuspid area. TR commonly caused by RV dilatation. Rheumatic fever and infective endocarditis can cause either MR or TR.

Late systolic crescendo murmur with midsystolic click (MC) due to sudden tensing of chordae tendineae as mitral leaflets prolapse into the LA (Chordae cause Crescendo with Click). Most frequent valvular lesion. Best heard over apex. Loudest just before S2. Usually benign. Can predispose to infective endocarditis. Can be caused by myxomatous degeneration (1° or 2° to connective tissue disease such as Marfan or Ehlers-Danlos syndrome), rheumatic fever (particularly in developing countries), chordae rupture.

High-pitched “blowing” early diastolic decrescendo murmur. Best heard at base (aortic root dilation) or left sternal border (valvular disease). Long diastolic murmur, hyperdynamic pulse, and head bobbing when severe and chronic. Wide pulse pressure. Causes include Bicuspid aortic valve, Endocarditis, Aortic root dilation, Rheumatic fever (BEAR). Progresses to left HF.

Follows opening snap (OS; due to abrupt halt in leaflet motion in diastole, after rapid opening due to fusion at leaflet tips). Delayed rumbling mid-to-late diastolic murmur (• interval between S2 and OS correlates with • severity). LA >> LV pressure during diastole.

Often a late (and highly specific) sequela of rheumatic fever. Chronic MS can result in pulmonary congestion/hypertension and LA dilation atrial fibrillation and Ortner syndrome.

Patent ductus arteriosus Continuous machine-like murmur. Best heard at left infraclavicular area. Loudest at S2. Often due to congenital rubella or prematurity.

“PDAs (Public Displays of Affection) are continuously annoying.”

Phase 0 = rapid upstroke and depolarization— voltage-gated Na+ channels open.

Phase 1 = initial repolarization—inactivation of voltage-gated Na+ channels. Voltage-gated K+ channels begin to open.

Phase 2 = plateau—Ca2+ influx through voltage-gated Ca2+ channels balances K+ efflux. Ca2+ influx triggers Ca2+ release from sarcoplasmic reticulum and myocyte contraction.

Phase 3 = rapid repolarization—massive K+ efflux due to opening of voltage-gated slow delayed-rectifier K+ channels and closure of voltage-gated Ca2+ channels.

Phase 4 = resting potential—high K+ permeability through K+ channels.

In contrast to skeletal muscle:

Cardiac muscle action potential has a plateau due to Ca2+ influx and K+ efflux.

Cardiac muscle contraction requires Ca2+ influx from ECF to induce Ca2+ release from sarcoplasmic reticulum (Ca2+-induced Ca2+ release).

Cardiac myocytes are electrically coupled to each other by gap junctions.

Occurs in all cardiac myocytes except for those in the SA and AV nodes.

Occurs in the SA and AV nodes. Key differences from the ventricular action potential include:

Phase 0 = upstroke—opening of voltage-gated Ca2+ channels. Fast voltage-gated Na+ channels are permanently inactivated because of the less negative resting potential of these cells. Results in a slow conduction velocity that is used by the AV node to prolong transmission from the atria to ventricles.

Phases 1 and 2 are absent.

Phase 3 = repolarization—inactivation of the Ca2+ channels and • activation of K+ channels □• K+ efflux.

Phase 4 = slow spontaneous diastolic depolarization due to If ("funny current"). If channels responsible for a slow, mixed Na+/K+ inward current; different from INa in phase 0 of ventricular action potential. Accounts for automaticity of SA and AV nodes. The slope of phase 4 in the SA node determines HR. ACh/adenosine • the rate of diastolic depolarization and □ HR, while catecholamines • depolarization and □ HR. Sympathetic stimulation • the chance that If channels are open and thus • HR.

Electrocardiogram Conduction pathway: SA node □ atria □ bundle of His □ right and left bundle branches □ Purkinje fibers left bundle branch divides into left anterior and posterior fascicles.

SA node—located at junction of RA and SVC; "pacemaker" inherent dominance with slow phase of upstroke.

AV node—located in posteroinferior part of interatrial septum. Blood supply usually from RCA. 100-msec delay allows time for ventricular filling.

Pacemaker rates: SA > AV > bundle of His/ Purkinje/ventricles.

Speed of conduction: His-Purkinje > Atria > Ventricles > AV node. He Parks At Ventura Avenue.

P wave—atrial depolarization.

PR interval—time from start of atrial depolarization to start of ventricular depolarization (normally 120-200 msec).

QRS complex—ventricular depolarization (normally < 100 msec).

QT interval—ventricular depolarization, mechanical contraction of the ventricles, ventricular repolarization.

T wave—ventricular repolarization. T-wave inversion may indicate ischemia or recent MI. J point—junction between end of QRS complex and start of ST segment. ST segment—isoelectric, ventricles depolarized. U wave—prominent in hypokalemia (think hyp“U”kalemia), bradycardia.

SA node AV node Bundle of His

Torsades de pointes Polymorphic ventricular tachycardia, characterized by shifting sinusoidal waveforms on ECG; can progress to ventricular fibrillation (VF). Long QT interval predisposes to torsades de pointes. Caused by drugs, • K+, • Mg2+, • Ca2+, congenital abnormalities. Treatment includes magnesium sulfate.

Drug-induced long QT (ABCDE): AntiArrhythmics (class IA, III) AntiBiotics (eg, macrolides) Anti“C”ychotics (eg, haloperidol) AntiDepressants (eg, TCAs) AntiEmetics (eg, ondansetron)

Torsades de pointes = twisting of the points

Brugada syndrome Autosomal dominant disorder most common in Asian males. ECG pattern of pseudo-right bundle branch block and ST elevations in V1-V3. • risk of ventricular tachyarrhythmias and SCD. Prevent SCD with implantable cardioverter-defibrillator (ICD).

Atrial fibrillation Chaotic and erratic baseline with no discrete P waves in between RR˜ RR ˜RR˜RR irregularly spaced QRS complexes. Irregularly irregular heartbeat. Most common risk factors include hypertension and coronary artery disease (CAD). Occasionally seen after binge drinking (“holiday heart syndrome”). Can lead to thromboembolic events, particularly stroke.

Treatment: anticoagulation, rate and rhythm control and/or cardioversion.

First-degree The PR interval is prolonged (> 200 msec). Benign and
AV block asymptomatic. No treatment required.

<<PR1PR2PR3P wave, absent QRS =PR1PR2P wave, absent QRS

Baroreceptors and chemoreceptors Receptors: • Aortic arch transmits via vagus nerve to solitary nucleus of medulla (responds to changes in BP).

• Carotid sinus (dilated region at carotid bifurcation) transmits via glossopharyngeal nerve to solitary nucleus of medulla (responds to changes in BP).

Baroreceptors: parasympathetic stimulation □ vasoconstriction, • HR, • contractility, • BP. Important in the response to severe hemorrhage.

Carotid massage—• pressure on carotid sinus □• stretch □• afferent baroreceptor firing □• AV node refractory period □• HR.

Component of Cushing reflex (triad of hypertension, bradycardia, and respiratory depression)—• intracranial pressure constricts arterioles □ cerebral ischemia □• pCO2 and □ pH □ central reflex sympathetic • in perfusion pressure (hypertension) □• stretch □ peripheral reflex baroreceptor– induced bradycardia.

Chemoreceptors:

Peripheral—carotid and aortic bodies are stimulated by • Pco2, • pH of blood, and • Po2 (< 60 mm Hg).

Central—are stimulated by changes in pH and Pco2 of brain interstitial fluid, which in turn are influenced by arterial CO2 as H+ cannot cross the blood-brain barrier. Do not directly respond to Po2. Central chemoreceptors become less responsive with chronically • Pco2 (eg, COPD) □• dependence on peripheral chemoreceptors to detect • O2 to drive respiration.

pressures in mm Hg) is a good approximation of left atrial pressure. In mitral stenosis, PCWP > LV end diastolic pressure. PCWP is measured with pulmonary artery catheter (Swan-Ganz catheter).

Autoregulation How blood flow to an organ remains constant over a wide range of perfusion pressures.

Capillary fluid Starling forces determine fluid movement through capillary membranes: exchange • Pc = capillary hydrostatic pressure—pushes fluid out of capillary πi = interstitial fluid colloid osmotic pressure—pulls fluid out of capillary Jv = net fluid flow = Kf [(Pc – Pi) –σ(πc –πi)] Kf = capillary permeability to fluid σ= reflection coefficient (measure of capillary permeability to protein) Edema—excess fluid outflow into interstitium commonly caused by: • • capillary pressure (□ Pc; eg, HF) • □ capillary permeability (□ Kf; eg, toxins, infections, burns) • □ interstitial fluid colloid osmotic pressure (• πi; eg, lymphatic blockage) • □ plasma proteins (• πc; eg, nephrotic syndrome, liver failure, protein malnutrition)

D-transposition of great vessels leaves LV (posterior) □ separation of systemic

Pulmonary and pulmonary circulations. Not compatible artery with life unless a shunt is present to allow mixing of blood (eg, VSD, PDA, or patent foramen ovale).

Left Due to failure of the aorticopulmonary septum to ventricle spiral ("egg on a string" appearance on CXR).

Without surgical intervention, most infants die Right ventricle within the first few months of life.

Tricuspid atresia Absence of tricuspid valve and hypoplastic RV; requires both ASD and VSD for viability.

Tetralogy of Fallot

Caused by anterosuperior displacement of the infundibular septum. Most common cause of early childhood cyanosis. Pulmonary infundibular stenosis (most important determinant for prognosis) Right ventricular hypertrophy (RVH)— boot-shaped heart on CXR

Pulmonary stenosis forces right-to-left flow across VSD RVH, "tet spells" (often caused by crying, fever, and exercise due to exacerbation of RV outflow obstruction).

PROVe.

Squatting: • SVR, • right-to-left shunt, improves cyanosis.

Associated with 22q11 syndromes.

lEFT-TO-RIGHT SHuNTS Acyanotic at presentation; cyanosis may occur Right-to-Left shunts: eaRLy cyanosis. years later. Frequency: VSD > ASD > PDA. Left-to-Right shunts: "LateR" cyanosis.

Ventricular septal Asymptomatic at birth, may manifest weeks O2 saturation • in RV and pulmonary artery. defect later or remain asymptomatic throughout life. Most self resolve; larger lesions B may lead to LV overload and HF.

Defect in interatrial septum C ; wide, fixed split S2. Ostium secundum defects most common and usually an isolated finding; ostium primum defects rarer and usually occur with other cardiac anomalies. Symptoms range from none to HF. Distinct from patent foramen ovale in that septa are missing tissue rather than unfused.

O2 saturation • in RA, RV, and pulmonary artery. May lead to paradoxical emboli (systemic venous emboli use ASD to bypass lungs and become systemic arterial emboli).

Associated with Down syndrome.

In fetal period, shunt is right to left (normal). In neonatal period, • pulmonary vascular resistance shunt becomes left to right progressive RVH and/or LVH and HF.

Associated with a continuous, "machine-like" murmur. Patency is maintained by PGE synthesis and low O2 tension. Uncorrected PDA D can

eventually result in late cyanosis in the lower extremities (differential cyanosis).

PDA is normal in utero and normally closes only after birth.

Uncorrected left-to-right shunt (VSD, ASD, PDA) □□ pulmonary blood flow • pathologic remodeling of vasculature □ pulmonary arterial hypertension. RVH occurs to compensate □ shunt becomes right to left. Causes late cyanosis, clubbing E , and polycythemia. Age of onset varies.

Coarctation of the aorta

Aortic narrowing F near insertion of ductus arteriosus ("juxtaductal"). Associated with bicuspid aortic valve, other heart defects, and Turner syndrome. Hypertension in upper extremities and weak, delayed pulse in lower extremities (brachial-femoral delay). With age, intercostal arteries enlarge due to collateral circulation; arteries erode ribs □ notched appearance on CXR.

Complications include HF, • risk of cerebral hemorrhage (berry aneurysms), aortic rupture, and possible endocarditis.

defect associations Alcohol exposure in utero (fetal alcohol VSD, PDA, ASD, tetralogy of Fallot syndrome)

Infant of diabetic mother Transposition of great vessels, VSD

Marfan syndrome MVP, thoracic aortic aneurysm and dissection, aortic regurgitation

Turner syndrome Bicuspid aortic valve, coarctation of aorta 22q11 syndromes Truncus arteriosus, tetralogy of Fallot

Hypertension Persistent systolic BP ≥ 130 mm Hg and/or diastolic BP ≥ 80 mm Hg.

RISK FACTORS • age, obesity, diabetes, physical inactivity, excess salt intake, excess alcohol intake, cigarette smoking, family history; African American > Caucasian > Asian.

FEATuRES 90% of hypertension is 1° (essential) and related to • CO or • TPR. Remaining 10% mostly 2° to renal/renovascular diseases such as fibromuscular dysplasia (characteristic "string of beads" appearance of renal artery A , usually seen in women of child-bearing age) and atherosclerotic renal artery stenosis or to 1° hyperaldosteronism. Hypertensive urgency—severe (≥ 180/≥ 120 mm Hg) hypertension without acute end-organ damage. Hypertensive emergency—severe hypertension with evidence of acute end-organ damage (eg, encephalopathy, stroke, retinal hemorrhages and exudates, papilledema, MI, HF, aortic dissection, kidney injury, microangiopathic hemolytic anemia, eclampsia).

PREdISPOSES TO CAD, LVH, HF, atrial fibrillation; aortic dissection, aortic aneurysm; stroke; CKD (hypertensive nephropathy); retinopathy.

Xanthomas Plaques or nodules composed of lipid-laden histiocytes in skin A , especially the eyelids (xanthelasma

B).

Tendinous xanthoma Lipid deposit in tendon C , especially Achilles.

Corneal arcus Lipid deposit in cornea. Common in elderly (arcus senilis D), but appears earlier in life with hypercholesterolemia.

Arteriosclerosis Hardening of arteries, with arterial wall thickening and loss of elasticity.

Arteriolosclerosis Common. Affects small arteries and arterioles. Two types: hyaline (thickening of vessel walls 2° to plasma protein leak into endothelium in essential hypertension or diabetes mellitus A) and hyperplastic ("onion skinning" in severe hypertension B with proliferation of smooth muscle cells).

Atherosclerosis Very common. Disease of elastic arteries and largeand medium-sized muscular arteries; a form of arteriosclerosis caused by buildup of cholesterol plaques in intima.

lOCATION Abdominal aorta > Coronary artery > Popliteal artery > Carotid artery > circle of Willis. A CoPy Cat named Willis.

RISK FACTORS Modifiable: smoking, hypertension, dyslipidemia (• LDL, • HDL), diabetes. Non-modifiable: age, sex (• in men and postmenopausal women), family history.

SYMPTOMS Angina, claudication, but can be asymptomatic.

PROGRESSION Inflammation important in pathogenesis: endothelial cell dysfunction □ macrophage and LDL accumulation □ foam cell formation □ fatty streaks □ smooth muscle cell migration (involves PDGF and FGF), proliferation, and extracellular matrix deposition □ fibrous plaque □ complex atheromas A □ calcification (calcium content correlates with risk of complications).

COMPlICATIONS Aneurysms, ischemia, infarcts, peripheral vascular disease, thrombus, emboli.

Aortic aneurysm Localized pathologic dilation of the aorta. May cause abdominal and/or back pain, which is a sign of leaking, dissection, or imminent rupture.

Abdominal aortic Usually associated with atherosclerosis. Risk factors include history of tobacco use, • age, male aneurysm sex, family history. May present as palpable pulsatile abdominal mass (arrows in A point to outer dilated calcified aortic wall, with partial crescent-shaped non-opacification of aorta due to flap/ clot). Most often infrarenal (distal to origin of renal arteries).

Traumatic aortic Due to trauma and/or deceleration injury, most commonly at aortic isthmus (proximal descending rupture aorta just distal to origin of left subclavian artery). X-ray may reveal widened mediastinum.

Longitudinal intimal tear forming a false lumen. Associated with hypertension, bicuspid aortic valve, inherited connective tissue disorders (eg, Marfan syndrome). Can present with tearing, sudden-onset chest pain radiating to the back +/− markedly unequal BP in arms. CXR can show mediastinal widening. Can result in organ ischemia, aortic rupture, death. Two types:

Stanford type A (proximal): involves Ascending aorta (red arrow in

A). May extend to aortic arch or descending aorta (blue arrow in

A). May result in acute aortic regurgitation or cardiac tamponade. Treatment: surgery.

Stanford type B (distal): involves only descending aorta (Below left subclavian artery). Treatment: β-blockers, then vasodilators.

Angina Chest pain due to ischemic myocardium 2° to coronary artery narrowing or spasm; no myocyte necrosis.

Stable—usually 2° to atherosclerosis (≥ 70% occlusion); exertional chest pain in classic distribution (usually with ST depression on ECG), resolving with rest or nitroglycerin.

Vasospastic (also called Prinzmetal or Variant)—occurs at rest 2° to coronary artery spasm; transient ST elevation on ECG. Smoking is a risk factor; hypertension and hypercholesterolemia are not. Triggers include cocaine, alcohol, and triptans. Treat with Ca2+ channel blockers, nitrates, and smoking cessation (if applicable).

Unstable—thrombosis with incomplete coronary artery occlusion; +/− ST depression and/or T-wave inversion on ECG but no cardiac biomarker elevation (unlike NSTEMI); • in frequency or intensity of chest pain or any chest pain at rest.

Sudden cardiac death Death from cardiac causes within 1 hour of onset of symptoms, most commonly due to a lethal arrhythmia (eg, VF). Associated with CAD (up to 70% of cases), cardiomyopathy (hypertrophic, dilated), and hereditary ion channelopathies (eg, long QT syndrome, Brugada syndrome). Prevent with ICD.

Evolution of Commonly occluded coronary arteries: LAD > RCA > circumflex. myocardial infarction Symptoms: diaphoresis, nausea, vomiting, severe retrosternal pain, pain in left arm and/or jaw, shortness of breath, fatigue.

0–24 hr Dark mottling Early coagulative necrosis Ventricular arrhythmia, HF, □ cell content released into cardiogenic shock blood; edema, hemorrhage, wavy fibers □ hypercontraction of

Dark mottling; stripes) pale with tetrazolium stain

Tissue surrounding infarct pericarditis shows acute inflammation with neutrophils 3–14 days Macrophages, then granulation Free wall rupture tamponade; tissue at margins papillary muscle rupture due to macrophage-mediated

LV pseudoaneurysm (risk of rupture) 2 weeks to several Contracted scar complete Dressler syndrome, HF, months arrhythmias, true ventricular aneurysm (risk of mural thrombus)

Multiples of upper limit of normal return to normal after 48 hours.

Large MIs lead to greater elevations in troponin I and CK-MB. Exact curves vary with testing procedure.

ECG changes can include ST elevation (STEMI, transmural infarct), ST depression (NSTEMI, subendocardial infarct), hyperacute (peaked) T waves, T-wave inversion, new left bundle branch block, and pathologic Q waves or poor R wave progression (evolving or old transmural infarct).

Ventricular 3–14 days: free wall rupture contained by adherent pericardium or scar tissue B ; • CO, risk of pseudoaneurysm arrhythmia, embolus from mural thrombus. formation

Ventricular free wall 5–14 days: free wall rupture C cardiac tamponade. LV hypertrophy and previous MI protect rupture against free wall rupture. Acute form usually leads to sudden death.

60–70% of cases are familial, autosomal dominant (most commonly due to mutations in genes encoding sarcomeric proteins, such as myosin binding protein C and β-myosin heavy chain). Causes syncope during exercise and may lead to sudden death (eg, in young athletes) due to ventricular arrhythmia.

Findings: S4, systolic murmur. May see mitral regurgitation due to impaired mitral valve closure.

Treatment: cessation of high-intensity athletics, use of β-blocker or non-dihydropyridine Ca2+ channel blockers (eg, verapamil). ICD if syncope occurs.

Diastolic dysfunction ensues.

Marked ventricular concentric hypertrophy (sarcomeres added in parallel) B , often septal predominance. Myofibrillar disarray and fibrosis.

Physiology of HOCM—asymmetric septal hypertrophy and systolic anterior motion of mitral valve outflow obstruction dyspnea, possible syncope.

Other causes of concentric LV hypertrophy: chronic HTN, Friedreich ataxia.

Postradiation fibrosis, Löffler endocarditis, Endocardial fibroelastosis (thick fibroelastic tissue in endocardium of young children), Amyloidosis, Sarcoidosis, Hemochromatosis (although dilated cardiomyopathy is more common) (Puppy LEASH).

Diastolic dysfunction ensues. Can have low-voltage ECG despite thick myocardium (especially in amyloidosis).

Löffler endocarditis—associated with hypereosinophilic syndrome; histology shows eosinophilic infiltrates in myocardium.

Heart failure Clinical syndrome of cardiac pump dysfunction congestion and low perfusion. Symptoms include dyspnea, orthopnea, fatigue; signs include S3 heart sound, rales, jugular venous distention (JVD), pitting edema

A .

Systolic dysfunction—reduced EF, • EDV; • contractility often 2° to ischemia/MI or dilated cardiomyopathy.

Diastolic dysfunction—preserved EF, normal EDV; • compliance (• EDP) often 2° to myocardial hypertrophy.

Right HF most often results from left HF. Cor pulmonale refers to isolated right HF due to pulmonary cause.

ACE inhibitors or angiotensin II receptor blockers, β-blockers (except in acute decompensated HF), and spironolactone • mortality. Loop and thiazide diuretics are used mainly for symptomatic relief. Hydralazine with nitrate therapy improves both symptoms and mortality in select patients.

of hemosiderin-laden macrophages (“HF” cells) in lungs. Right heart failure

Shock Inadequate organ perfusion and delivery of nutrients necessary for normal tissue and cellular function. Initially may be reversible but life threatening if not treated promptly.

Compression of the heart by fluid (eg, blood, effusions [arrows in A] in pericardial space) • CO. Equilibration of diastolic pressures in all 4 chambers. Findings: Beck triad (hypotension, distended neck veins, distant heart sounds), • HR, pulsus paradoxus. ECG shows low-voltage QRS and electrical alternans B (due to “swinging” movement of heart in large effusion).

Pulsus paradoxus—• in amplitude of systolic BP by > 10 mm Hg during inspiration. Seen in constrictive Pericarditis, obstructive pulmonary disease (eg, Croup, OSA, Asthma, COPD), cardiac Tamponade (Pea COAT).

Bacterial endocarditis Acute—S aureus (high virulence). Large vegetations on previously normal valves A . Rapid onset. Subacute—viridans streptococci (low virulence). Smaller vegetations on congenitally

abnormal or diseased valves. Sequela of dental procedures. Gradual onset. Symptoms: fever (most common), new murmur, Roth spots (round white spots on retina surrounded by hemorrhage B), Osler nodes (Ouchy raised lesions on finger or toe pads C due to immune complex deposition), Janeway lesions (small, painless, erythematous lesions on palm or sole) D , splinter hemorrhages E on nail bed. Associated with glomerulonephritis, septic arterial or pulmonary emboli. May be nonbacterial (marantic/thrombotic) 2° to malignancy, hypercoagulable state, or lupus.

FROM JANE with ♥: Fever Roth spots Osler nodes Murmur Janeway lesions Anemia Nail-bed hemorrhage Emboli

Requires multiple blood cultures for diagnosis. If culture ⊖, most likely Coxiella burnetii,

Bartonella spp. Mitral valve is most frequently involved. Tricuspid valve endocarditis is associated with

IV drug abuse (don't "tri" drugs). Associated with S aureus, Pseudomonas, and Candida. S bovis (gallolyticus) is present in colon cancer, S epidermidis on prosthetic valves.

Native valve endocarditis may be due to HACEK organisms (Haemophilus, Aggregatibacter [formerly Actinobacillus], Cardiobacterium, Eikenella, Kingella).

Inflammation of the pericardium [A , red arrows]. Commonly presents with sharp pain, aggravated by inspiration, and relieved by sitting up and leaning forward. Often complicated by pericardial effusion [between yellow arrows in A]. Presents with friction rub. ECG changes include widespread ST-segment elevation and/or PR depression.

Causes include idiopathic (most common; presumed viral), confirmed infection (eg, coxsackievirus B), neoplasia, autoimmune (eg, SLE, rheumatoid arthritis), uremia, cardiovascular (acute STEMI or Dressler syndrome), radiation therapy.

Treatment: NSAIDs, colchicine, glucocorticoids, dialysis (uremia).

Myocarditis Inflammation of myocardium global enlargement of heart and dilation of all chambers. Major cause of SCD in adults < 40 years old. Presentation highly variable, can include dyspnea, chest pain, fever, arrhythmias (persistent tachycardia out of proportion to fever is characteristic). Multiple causes:

Viral (eg, adenovirus, coxsackie B, parvovirus B19, HIV, HHV-6); lymphocytic infiltrate with focal necrosis highly indicative of viral myocarditis.

Parasitic (eg, Trypanosoma cruzi, Toxoplasma gondii)

Bacterial (eg, Borrelia burgdorferi, Mycoplasma pneumoniae, Corynebacterium diphtheriae)

Toxins (eg, carbon monoxide, black widow venom)

Drugs (eg, doxorubicin, cocaine)

Autoimmune (eg, Kawasaki disease, sarcoidosis, SLE, polymyositis/dermatomyositis)

Complications include sudden death, arrhythmias, heart block, dilated cardiomyopathy, HF, mural thrombus with systemic emboli.

Buerger disease Heavy smokers, males < 40 years old. Segmental thrombosing vasculitis with vein and (thromboangiitis Intermittent claudication. May lead to nerve involvement. obliterans) gangrene

C , autoamputation of digits, Treatment: smoking cessation.

superficial nodular phlebitis. Raynaud phenomenon is often present.

Kawasaki disease Asian children < 4 years old. CRASH and burn on a Kawasaki. (mucocutaneous Conjunctival injection, Rash (polymorphous May develop coronary artery aneurysms E ; lymph node □ desquamating), Adenopathy (cervical), thrombosis or rupture can cause death. syndrome) Strawberry tongue (oral mucositis) D , Hand-Treatment: IV immunoglobulin and aspirin. foot changes (edema, erythema), fever.

Polyarteritis nodosa Usually middle-aged men. Hepatitis B seropositivity in 30% of patients. Fever, weight loss, malaise, headache. GI: abdominal pain, melena. Hypertension, neurologic dysfunction, cutaneous eruptions, renal damage.

Typically involves renal and visceral vessels, not pulmonary arteries.

Different stages of transmural inflammation with fibrinoid necrosis.

Innumerable renal microaneurysms F and spasms on arteriogram (string of pearls appearance).

Treatment: corticosteroids, cyclophosphamide.

Granulomatosis with polyangiitis (Wegener)

Upper respiratory tract: perforation of nasal septum, chronic sinusitis, otitis media, mastoiditis.

Lower respiratory tract: hemoptysis, cough, dyspnea.

Renal: hematuria, red cell casts.

Triad:

Necrotizing glomerulonephritis PR3-ANCA/c-ANCA H (anti-proteinase 3). CXR: large nodular densities. Treatment: cyclophosphamide, corticosteroids.

Cardiac tumors Most common heart tumor is a metastasis (eg, melanoma).

Myxomas Most common 1° cardiac tumor in adults (arrows in A). 90% occur in the atria (mostly left atrium). Myxomas are usually described as a "ball valve" obstruction in the left atrium (associated with multiple syncopal episodes). IL-6 production by tumor constitutional symptoms (eg, fever, weight loss). May auscultate early diastolic "tumor plop" sound. Histology: gelatinous material, myxoma cells immersed in glycosaminoglycans. Adults make myxed drinks.

Calcium channel Amlodipine, clevidipine, nicardipine, nifedipine, nimodipine (dihydropyridines, act on vascular blockers smooth muscle); diltiazem, verapamil (non-dihydropyridines, act on heart).

MECHANISM Block voltage-dependent L-type calcium channels of cardiac and smooth muscle • muscle contractility. Vascular smooth muscle—amlodipine = nifedipine > diltiazem > verapamil. Heart—verapamil > diltiazem > amlodipine = nifedipine (verapamil = ventricle).

ClINICAl uSE Dihydropyridines (except nimodipine): hypertension, angina (including vasospastic type), Raynaud phenomenon. Nimodipine: subarachnoid hemorrhage (prevents cerebral vasospasm). Nicardipine, clevidipine: hypertensive urgency or emergency. Non-dihydropyridines: hypertension, angina, atrial fibrillation/flutter.

AdvERSE EFFECTS Gingival hyperplasia.

Dihydropyridine: peripheral edema, flushing, dizziness.

Non-dihydropyridine: cardiac depression, AV block, hyperprolactinemia (verapamil), constipation.

MECHANISM • cGMP smooth muscle relaxation. Vasodilates arterioles > veins; afterload reduction.

ClINICAl uSE Severe hypertension (particularly acute), HF (with organic nitrate). Safe to use during pregnancy. Frequently coadministered with a β-blocker to prevent reflex tachycardia.

AdvERSE EFFECTS Compensatory tachycardia (contraindicated in angina/CAD), fluid retention, headache, angina, drug-induced lupus.

Nitrates Nitroglycerin, isosorbide dinitrate, isosorbide mononitrate.

MECHANISM Vasodilate by • NO in vascular smooth muscle • in cGMP and smooth muscle relaxation. Dilate veins >> arteries. • preload.

ClINICAl uSE Angina, acute coronary syndrome, pulmonary edema.

AdvERSE EFFECTS Reflex tachycardia (treat with β-blockers), hypotension, flushing, headache, "Monday disease" in industrial exposure: development of tolerance for the vasodilating action during the work week and loss of tolerance over the weekend • tachycardia, dizziness, headache upon

reexposure. Contraindicated in right ventricular infarction, hypertrophic cardiomyopathy, and with concurrent PDE-5 inhibitor use.

Verapamil is similar to β-blockers in effect. Pindolol and acebutolol are partial β-agonists that should be used with caution in angina.

MECHANISM Inhibits the late phase of inward sodium current thereby reducing diastolic wall tension and oxygen consumption. Does not affect heart rate or blood pressure.

ClINICAl uSE Angina refractory to other medical therapies.

AdvERSE EFFECTS Constipation, dizziness, headache, nausea.

MECHANISM A neprilysin inhibitor; prevents degradation of natriuretic peptides, angiotensin II, and substance P □• vasodilation, • ECF volume.

ClINICAl uSE Used in combination with valsartan (an ARB) to treat HFrEF.

AdvERSE EFFECTS Hypotension, hyperkalemia, cough, dizziness; contraindicated with ACE inhibitors due to angioedema.

Cardiac glycosides Digoxin.

MECHANISM Direct inhibition of Na+/K+ ATPase inhibition of Na+/Ca2+ exchanger.

[Ca2+]i • positive inotropy. Stimulates vagus nerve □• HR.

ClINICAl uSE HF (• contractility); atrial fibrillation (• conduction at AV node and depression of SA node).

AdvERSE EFFECTS Cholinergic effects (nausea, vomiting, diarrhea), blurry yellow vision (think van Glow), arrhythmias, AV block. Can lead to hyperkalemia, which indicates poor prognosis. Factors predisposing to toxicity: renal failure (• excretion), hypokalemia (permissive for digoxin binding at K+-binding site on Na+/K+ ATPase), drugs that displace digoxin from tissue-binding sites, and • clearance (eg, verapamil, amiodarone, quinidine).

ANTIdOTE Slowly normalize K+, cardiac pacer, anti-digoxin Fab fragments, Mg2+.

Antiarrhythmics— Slow or block (•) conduction (especially in depolarized cells). • slope of phase 0 depolarization. Are sodium channel state dependent (selectively depress tissue that is frequently depolarized [eg, tachycardia]). blockers (class I)

Class IA Quinidine, Procainamide, Disopyramide.

“The Queen Proclaims Diso’s pyramid.”

MECHANISM Moderate Na+ channel blockade.

• AP duration, • effective refractory period (ERP) in ventricular action potential, • QT interval, some potassium channel blocking effects.

ClINICAl uSE Both atrial and ventricular arrhythmias, especially re-entrant and ectopic SVT and VT.

AdvERSE EFFECTS Cinchonism (headache, tinnitus with quinidine), reversible SLE-like syndrome (procainamide), HF (disopyramide), thrombocytopenia, torsades de pointes due to • QT interval.

Class IB Lidocaine, MexileTine. "I'd Buy Liddy's Mexican Tacos." 0 mV

MECHANISM Weak Na+ channel blockade.

• AP duration. Preferentially affect ischemic or depolarized Purkinje and ventricular tissue. Phenytoin can also fall into the IB category.

ClINICAl uSE Acute ventricular arrhythmias (especially post-MI), digitalis-induced arrhythmias. IB is Best post-MI.

AdvERSE EFFECTS CNS stimulation/depression, cardiovascular depression.

Class IC Flecainide, Propafenone. "Can I have Fries, Please." 0 mV

MECHANISM Strong Na+ channel blockade. Significantly prolongs ERP in AV node and accessory bypass tracts. No effect on ERP in Purkinje and ventricular tissue. Minimal effect on AP duration.

ClINICAl uSE SVTs, including atrial fibrillation. Only as a last resort in refractory VT.

AdvERSE EFFECTS Proarrhythmic, especially post-MI (contraindicated). IC is Contraindicated in structural and ischemic heart disease.

Antiarrhythmics— Metoprolol, propranolol, esmolol, atenolol, timolol, carvedilol.

MECHANISM Decrease SA and AV nodal activity by • cAMP, • Ca2+ currents. Suppress abnormal pacemakers by • slope of phase 4. AV node particularly sensitive—• PR interval. Esmolol very short acting.

ClINICAl uSE SVT, ventricular rate control for atrial fibrillation and atrial flutter.

AdvERSE EFFECTS Impotence, exacerbation of COPD and asthma, cardiovascular effects (bradycardia, AV block, HF), CNS effects (sedation, sleep alterations). May mask the signs of hypoglycemia. Metoprolol can cause dyslipidemia. Propranolol can exacerbate vasospasm in vasospastic angina. β-blockers (except the nonselective αand β-antagonists carvedilol and labetalol) cause unopposed α1-agonism if given alone for pheochromocytoma or for cocaine toxicity (unsubstantiated). Treat β-blocker overdose with saline, atropine, glucagon.

Antiarrhythmics— Amiodarone, Ibutilide, Dofetilide, Sotalol. AIDS. potassium channel blockers (class III)

MECHANISM • AP duration, • ERP, • QT interval.

ClINICAl uSE Atrial fibrillation, atrial flutter; ventricular tachycardia (amiodarone, sotalol).

Antiarrhythmics— Diltiazem, Verapamil calcium channel blockers (class IV)

MECHANISM Decrease conduction Velocity, ERP, • PR interval.

ClINICAl uSE Prevention of nodal arrhythmias (eg, SVT), rate control in atrial fibrillation.

AdvERSE EFFECTS Constipation, flushing, edema, cardiovascular effects (HF, AV block, sinus node depression).

Adenosine • K+ out of cells hyperpolarizing the cell and • ICa, decreasing AV node conduction. Drug of choice in diagnosing/terminating certain forms of SVT. Very short acting (~ 15 sec). Effects blunted by theophylline and caffeine (both are adenosine receptor antagonists). Adverse effects include flushing, hypotension, chest pain, sense of impending doom, bronchospasm.

Magnesium Effective in torsades de pointes and digoxin toxicity.

MECHANISM IVabradine prolongs slow depolarization (phase "IV") by selectively inhibiting "funny" sodium channels (If).

ClINICAl uSE Chronic stable angina in patients who cannot take β-blockers. Chronic HFrEF.

AdvERSE EFFECTS Luminous phenomena/visual brightness, hypertension, bradycardia.

"If you skew the endocrine system, you lose the pathways to self." "We have learned that there is an endocrinology of elation and despair, a chemistry of mystical insight, and, in relation to the autonomic nervous system, a meteorology and even . . . an astro-physics of changing moods." "Chocolate causes certain endocrine glands to secrete hormones that affect your feelings and behavior by making you happy." —Elaine Sherman, Book of Divine Indulgences

The endocrine system comprises widely distributed organs that work in a highly integrated manner to orchestrate a state of hormonal equilibrium within the body. Generally speaking, endocrine diseases can be classified either as diseases of underproduction or overproduction, or as conditions involving the development of mass lesions—which themselves may be associated with underproduction or overproduction of hormones. Therefore, study the endocrine system first by learning the glands, their hormones, and their regulation, and then by integrating disease manifestations with diagnosis and management. Take time to learn the multisystem connections.

Thyroid diverticulum arises from floor of primitive pharynx and descends into neck. Connected to tongue by thyroglossal duct, which normally disappears but may persist as cysts or the pyramidal lobe of thyroid. Foramen cecum is normal remnant of thyroglossal duct.

Most common ectopic thyroid tissue site is the tongue (lingual thyroid). Removal may result in hypothyroidism if it is the only thyroid tissue present.

Thyroglossal duct cyst A presents as an anterior midline neck mass that moves with swallowing or protrusion of the tongue (vs persistent cervical sinus leading to pharyngeal cleft cyst in lateral neck).

Thyroid follicular cells derived from endoderm.

Superior surface of kidney

Secretes FSH, LH, ACTH, TSH, prolactin, Proopiomelanocortin derivatives—β-endorphin, GH, and β-endorphin. Melanotropin (MSH) ACTH, and MSH. Go pro with a BAM! secreted from intermediate lobe of pituitary. FLAT PiG: FSH, LH, ACTH, TSH, PRL, GH. Derived from oral ectoderm (Rathke pouch). B-FLAT: Basophils—FSH, LH, ACTH, TSH.

α subunit—hormone subunit common to Acid PiG: Acidophils — PRL, GH. TSH, LH, FSH, and hCG.

β subunit—determines hormone specificity. Stores and releases vasopressin (antidiuretic hormone, or ADH) and oxytocin, both made in the hypothalamus (supraoptic and paraventricular nuclei) and transported to posterior pituitary via neurophysins (carrier proteins). Derived from neuroectoderm.

Adrenal cortex (derived from mesoderm) and medulla (derived from neural crest).

CORTEX Zona Fasciculata ACTH, CRH Glucocorticoids Cortisol

Capsule ACTH, CRHDHEA

Zona Reticularis Preganglionic Catecholamines Epi, NEChroma˜n cells sympathetic fbers MEDULLA

GFR corresponds with Salt (mineralocorticoids), Sugar (glucocorticoids), and Sex (androgens). “The deeper you go, the sweeter it gets.”

Sleep, hypoglycemia, stress Growth hormone IGF-1 Anterior pituitary Posterior pituitary Somatostatin Amino acid uptake Protein synthesis Amino acid uptake Protein synthesis Glucose uptake Lipolysis DNA and RNA synthesis Chondroitin sulfate Collagen Cell size and number Aging, obesity, glucose GHRH

Antidiuretic hormone Also called vasopressin.

soUrce Synthesized in hypothalamus (supraoptic and paraventricular nuclei), stored and secreted by posterior pituitary.

FUnction Regulates b1ood pressure (V1-receptors) and serum osmolality (V2-receptors). Primary function is serum osmolality regulation (ADH • serum osmolality, • urine osmolality) via regulation of aquaporin channel insertion in principal cells of renal collecting duct.

regUlAtion Plasma osmolality (1°); hypovolemia.

Also called somatotropin. Secreted by anterior pituitary.

Stimulates linear growth and muscle mass through IGF-1 (somatomedin C) secretion by liver. • insulin resistance (diabetogenic).

Released in pulses in response to growth hormone–releasing hormone (GHRH).

Secretion • during exercise, deep sleep, puberty, hypoglycemia, CKD.

Secretion • by glucose, somatostatin, somatomedin (regulatory molecule secreted by liver in response to GH acting on target tissues).

Excess secretion of GH (eg, pituitary adenoma) may cause acromegaly (adults) or gigantism (children). Treatment: somatostatin analogs (eg, octreotide) or surgery.

ADH level is • in central diabetes insipidus (DI), normal or • in nephrogenic DI.

Nephrogenic DI can be caused by mutation in V2-receptor.

Desmopressin (ADH analog) is a treatment for central DI and nocturnal enuresis.

Thyroid hormones Thyroid produces triiodothyronine (T3) and thyroxine (T4), iodine-containing hormones that control the body’s metabolic rate.

soUrce Follicles of thyroid. 5’-deiodinase converts T4 (the major thyroid product) to T3 in peripheral tissue (5, 4, 3). Peripheral conversion is inhibited by glucocorticoids, β-blockers, and propylthiouracil (PTU). Reverse T3 (rT3) is a metabolically inactive byproduct of the peripheral conversion of T4 and its production is increased by growth hormone and glucocorticoids. Functions of thyroid peroxidase include oxidation, organification of iodine, and coupling of monoiodotyrosine (MIT) and diiodotyrosine (DIT). Inhibited by PTU and methimazole. DIT + DIT = T4. DIT + MIT = T3. Wolff-Chaikoff effect—excess iodine temporarily turns off thyroid peroxidase □• T3/T4 production (protective autoregulatory effect).

FUnction Only free hormone is active. T3 binds nuclear receptor with greater affinity than T4. T3 functions —7B’s:

Bone growth (synergism with GH) β-adrenergic effects. • β1 receptors in heart □• CO, HR, SV, contractility; β-blockers alleviate adrenergic symptoms in thyrotoxicosis

Basal metabolic rate • (via Na+/K+-ATPase activity □• O2 consumption, RR, body temperature)

Blood sugar (• glycogenolysis, gluconeogenesis) regUlAtion TRH ⊕ TSH release • ⊕ follicular cells. Thyroid-stimulating immunoglobulin (TSI) may ⊕ follicular cells in Graves disease. Negative feedback primarily by free T3/T4:

Anterior pituitary □• sensitivity to TRH

Thyroxine-binding globulin (TBG) binds most T3/T4 in blood. Bound T3/T4 = inactive. • • TBG in pregnancy, OCP use (estrogen □• TBG) □• total T3/T4 • • TBG in steroid use, nephrotic syndrome

TSI T3, T4

Downstream thyroid function T3 T4 T4 > T3 (to circulation) I− I− I2 Na+ MIT, DIT Thyroglobulin Oxidation + Proteases5'-deiodinase Tyrosine DITMIT DITDIT Thyroid peroxidase Thyroid peroxidase TG TG TG TG TG Endocytosis Organifcation Coupling reaction Deiodinase PTU MIT MIT DIT DIT T3 T3 T4 T3 T4 MIT PTU, methimazole soUrce Chief cells of parathyroid

FUnction • free Ca2+ in the blood (1° function) 1,25-(OH)2D3 (calcitriol) production by activating 1α-hydroxylase in PCT Tri to make D3 in the PCT

PTH • serum Ca2+, • serum PO43−, • urine PO43− , • urine cAMP

RANK-L (receptor activator of NF-κB ligand) secreted by osteoblasts and osteocytes; binds RANK (receptor) on osteoclasts and their precursors to stimulate osteoclasts and • Ca2+ like PTH and is commonly increased in malignancies (eg, squamous cell carcinoma of the lung, renal cell carcinoma) serum Mg2+ □• PTH secretion •• serum Mg2+ □• PTH secretion Common causes of • Mg2+ include diarrhea, aminoglycosides, diuretics, alcohol abuse ¸ ionized Ca2+, ˜ PO 3− , or 1,25-(OH)2 D 1,25-(OH)2 D3 Four para-thyroid glandsFeedback inhibition of PTH synthesis Vitamin D activity ˜ Ca2+ and PO4 3−˜ PTH released into circulation 25-OH D3 Bone Intestines 1,25-(OH)2 D3 1˜-hydroxylase ˜ Ca2+ and ˜ PO4 3− ˜ Ca2+ and ˜ PO4 3− released from bone ˜ absorption of Ca2+ and PO4 3− Renal tubular cells ˜ 1,25-(OH)2 D synthesis3 Urine Ca2+ , ˜ PO4 3− Reabsorption: ˜ Ca2+ , PO4 3−˜ ˜ ˜

Calcium homeostasis Plasma Ca2+ exists in three forms:

Ionized/free (~ 45%, active form)

Bound to albumin (~ 40%)

Bound to anions (~ 15%) pH (less H+) □ albumin binds more Ca2+ □• ionized Ca2+ (eg, cramps, pain, paresthesias, carpopedal spasm) □• PTH

Ionized/free Ca2+ is 1° regulator of PTH; changes in pH alter PTH secretion, whereas changes in albumin concentration do not soUrce Parafollicular cells (C cells) of thyroid. Calcitonin opposes actions of PTH. Not important in normal Ca2+ homeostasis

FUnction • bone resorption of Ca2+.

Calcitonin tones down serum Ca2+ levels and regUlAtion serum Ca2+ •
calcitonin secretion.

soUrce Made by α cells of pancreas.

FUnction Promotes glycogenolysis, gluconeogenesis, lipolysis, ketogenesis. Elevates blood sugar levels to maintain homeostasis when bloodstream glucose levels fall too low (ie, fasting state).

regUlAtion Secreted in response to hypoglycemia. Inhibited by insulin, hyperglycemia, somatostatin.

synthesis Preproinsulin (synthesized in RER of pancreatic β cells)
 cleavage of "presignal" • proinsulin (stored in secretory granules)
 cleavage of proinsulin exocytosis of insulin and C-peptide equally. Insulin and C-peptide are • in insulinoma and sulfonylurea use, whereas exogenous insulin lacks C-peptide.

regUlAtion Glucose is the major regulator of insulin release. • insulin response with oral vs IV glucose due to incretins (eg, glucagon-like peptide 1 [GLP-1], glucose-dependent insulinotropic polypeptide [GIP]), which are released after meals and • β cell sensitivity to glucose. Release by α2, by β2 stimulation (2 = regulates insulin) closes K+ channels (target of sulfonylureas) . Voltage-gated Ca2+ channels open and stimulation of insulin exocytosis

Tyrosine phosphorylationPhosphoinositide-3 kinase pathway RAS/MAPkinasepathwayVesicles Cell growth, containing GLUT4 DNAGlycogen, lipid, protein synthesis synthesis), inducing glucose uptake (carriermediated transport) into insulin-dependent tissue and gene transcription.

Anabolic effects of insulin: • • glucose transport in skeletal muscle and adipose tissue • glycogen synthesis and storage • triglyceride synthesis • • Na+ retention (kidneys) • protein synthesis (muscles) • cellular uptake of K+ and amino acids • glucagon release • lipolysis in adipose tissue

Unlike glucose, insulin does not cross placenta.

Insulin-dependent glucose transporters: • GLUT4: adipose tissue, striated muscle (exercise can also • GLUT4 expression) Insulin-independent transporters:

GLUT1: RBCs, brain, cornea, placenta

GLUT2 (bidirectional): β islet cells, liver, kidney, GI tract (think 2-way street)

GLUT3: brain, placenta

GLUT5 (Fructose): spermatocytes, GI tract

SGLT1/SGLT2 (Na+-glucose cotransporters): kidney, small intestine

Brain prefers glucose, but may use ketone bodies during starvation. RBCs utilize glucose, as they lack mitochondria for aerobic metabolism.

BRICK LIPS (insulin-independent glucose uptake): Brain, RBCs, Intestine, Cornea, Kidney, Liver, Islet (β) cells, Placenta, Spermatocytes.

Cholesterol desmolase Aldosterone synthase 21-hydroxylation 11˜-hydroxylation ZONA GLOMERULOSA Mineralocorticoids ZONA FASCICULATA Glucocorticoids Adrenal cortex Peripheral tissue ZONA RETICULARIS Androgens Estrogens, DHT Cholesterol (via StARa) Pregnenolone Progesterone 11-deoxycorticosterone Corticosterone Aldosterone 17-hydroxyprogesterone 17-hydroxypregnenolone 11-deoxycortisol Cortisone Glycyrrhetinic acid Cortisol Dehydroepiandrosterone (DHEA) Anastrozole, letrozole, exemestane Finasteride Androstenedione Testosterone Dihydrotestosterone (DHT) Angiotensin II 3˜-hydroxysteroid dehydrogenase Estrone Estradiol Aromatase Aromatase 17°-hydroxylase 17,20-lyase 17,20-lyase17°-hydroxylase 5°-reductase AMetyrapone aRate-limiting step.

17α-hydroxylasea •••••• androstenedione XY: ambiguous genitalia, undescended testes XX: lacks 2° sexual development 21-hydroxylasea •••••• renin activity • 17-hydroxy-progesterone Most common Presents in infancy (salt wasting) or childhood (precocious puberty) XX: virilization 11β-hydroxylasea • aldosterone • 11-deoxycorti-costerone (results in •BP) ••••• renin activity Presents in infancy (severe hypertension) or childhood (precocious puberty) XX: virilization aAll congenital adrenal enzyme deficiencies are autosomal recessive disorders and most are characterized by skin hyperpigmentation (due to • MSH production, which is coproduced and secreted with ACTH) and bilateral adrenal gland enlargement (due to • ACTH stimulation).

If deficient enzyme starts with 1, it causes hypertension; if deficient enzyme ends with 1, it causes virilization in females.

Ghrelin Stimulates hunger (orexigenic effect) and GH release (via GH secretagog receptor). Produced by stomach. Sleep deprivation, fasting, or Prader-Willi syndrome □• ghrelin production. Ghrelin makes you hunghre and ghrow. Acts on lateral area of hypothalamus (hunger center) to • appetite.

Leptin Satiety hormone. Produced by adipose tissue. Mutation of leptin gene □ central obesity. (Obese people have • leptin due to • adipose tissue but also appear resistant to leptin's anorexigenic effect.) Sleep deprivation or starvation □• leptin production. Leptin keeps you thin. Acts on ventromedial area of hypothalamus (satiety center) to • appetite.

Endocannabinoids Act at cannabinoid receptors in hypothalamus and nucleus accumbens, two key brain areas for the homeostatic and hedonic control of food intake □• appetite. Exogenous cannabinoids cause “the munchies.”

Signaling pathways of endocrine hormones

Signaling pathways of steroid hormones

Binding to receptor

Steroid hormones are lipophilic and therefore must circulate bound to specific binding globulins, which • their solubility.

In men, • sex hormone–binding globulin (SHBG) lowers free testosterone gynecomastia. In women, • SHBG raises free testosterone hirsutism.

estrogen (eg, OCPs, pregnancy) □• SHBG.

Syndrome of inappropriate antidiuretic hormone secretion

Characterized by:

Euvolemic hyponatremia with continued urinary Na+ excretion

Urine osmolality > serum osmolality Body responds to water retention with aldosterone and • ANP and BNP □• urinary Na+ secretion • normalization of extracellular fluid volume □ euvolemic hyponatremia. Very low serum Na+ levels can lead to cerebral edema, seizures. Correct slowly to prevent osmotic demyelination syndrome (formerly called central pontine myelinolysis).

SIADH causes include:

Ectopic ADH (eg, small cell lung cancer)

Drugs (eg, SSRIs, carbamazepine, cyclophosphamide)

Treatment: fluid restriction (first line), salt tablets, IV hypertonic saline, diuretics, ADH antagonists (eg, conivaptan, tolvaptan, demeclocycline).

aNo water intake for 2–3 hr followed by hourly measurements of urine volume and osmolality as well as plasma Na+ concentration and osmolality. ADH analog (desmopressin) is administered if serum osmolality > 295–300 mOsm/kg, plasma Na+ ≥ 145 mEq/L, or urine osmolality does not rise despite a rising plasma osmolality.

Hypopituitarism Undersecretion of pituitary hormones due to:

Nonsecreting pituitary adenoma, craniopharyngioma

Sheehan syndrome—ischemic infarct of pituitary following postpartum bleeding; pregnancy-induced pituitary growth □• susceptibility to

hypoperfusion. Usually presents with failure to lactate, absent menstruation, cold intolerance

Empty sella syndrome—atrophy or compression of pituitary (which lies in the sella turcica), often idiopathic, common in obese women; associated with idiopathic intracranial hypertension

Pituitary apoplexy—sudden hemorrhage of pituitary gland, often in the presence of an existing pituitary adenoma. Usually presents with sudden onset severe headache, visual impairment (eg, bitemporal hemianopia, diplopia due to CN III palsy), and features of hypopituitarism

Treatment: hormone replacement therapy (corticosteroids, thyroxine, sex steroids, human growth hormone)

Acromegaly Excess GH in adults. Typically caused by pituitary adenoma.

Findings Large tongue with deep furrows, deep voice, • GH in children □ gigantism (• linear bone large hands and feet, coarsening of facial growth). HF most common cause of death. features with aging

A , frontal bossing, diaphoresis (excessive sweating), impaired glucose tolerance (insulin resistance), hypertension. • risk of colorectal polyps and cancer.

diAgnosis • serum IGF-1; failure to suppress serum GH following oral glucose tolerance test; pituitary mass seen on brain MRI.

treAtment Pituitary adenoma resection. If not cured, treat with octreotide (somatostatin analog), pegvisomant (GH receptor antagonist), or dopamine agonists (eg, cabergoline).

metAbolic Cold intolerance, • sweating, weight gain Heat intolerance, • sweating, weight loss (• basal metabolic rate □• calorigenesis), (• synthesis of Na+-K+ ATPase □• basal hyponatremia (• free water clearance) metabolic rate □• calorigenesis) sKin/hAir Dry, cool skin (due to • blood flow); coarse, Warm, moist skin (due to vasodilation); fine hair; brittle hair; diffuse alopecia; brittle nails; onycholysis (A); pretibial myxedema in Graves puffy facies and generalized nonpitting edema disease (myxedema) due to • GAGs in interstitial spaces □• osmotic pressure • water retention

Other causes Iodine deficiency (with goiter E), goitrogens (eg, amiodarone, lithium), Wolff-Chaikoff effect (thyroid gland downregulation in response to • iodide).

Graves disease Most common cause of hyperthyroidism. Thyroid-stimulating immunoglobulin (IgG, can cause transient neonatal hyperthyroidism; type II hypersensitivity) stimulates TSH receptors on thyroid (hyperthyroidism, diffuse goiter), dermal fibroblasts (pretibial myxedema), and orbital fibroblasts (Graves orbitopathy). Activation of T-cells □ lymphocytic infiltration of retroorbital space □• cytokines (eg, TNF-α, IFN-γ) □• fibroblast secretion of hydrophilic GAGs □• osmotic muscle swelling, muscle inflammation, and adipocyte count □ exophthalmos

A . Often presents during stress (eg, pregnancy). Associated with HLA-DR3 and HLA-B8.

Histology: tall, crowded follicular epithelial cells; scalloped colloid.

Toxic multinodular Focal patches of hyperfunctioning follicular cells distended with colloid working independently goiter of TSH (due to TSH receptor mutations in 60% of cases). • release of T3 and T4. Hot nodules are rarely malignant.

Thyroid storm Uncommon but serious complication that occurs when hyperthyroidism is incompletely treated/ untreated and then significantly worsens in the setting of acute stress such as infection, trauma, surgery. Presents with agitation, delirium, fever, diarrhea, coma, and tachyarrhythmia (cause of death). May see LFTs. Treat with the 4 P's: β-blockers (eg, Propranolol), Propylthiouracil, corticosteroids (eg, Prednisolone), Potassium iodide (Lugol iodine). Iodide load • T4 synthesis Wolff-Chaikoff effect.

Jod-Basedow Iodine-induced hyperthyroidism. Occurs when a patient with iodine deficiency and partially phenomenon autonomous thyroid tissue (eg, autonomous nodule) is made iodine replete. Can happen after iodine IV contrast or amiodarone use. Opposite to Wolff-Chaikoff effect.

Causes of goiter Smooth/diffuse: Graves disease, Hashimoto thyroiditis, iodine deficiency, TSH-secreting pituitary adenoma. Nodular: toxic multinodular goiter, thyroid adenoma, thyroid cancer, thyroid cyst.

Thyroid adenoma Benign solitary growth of the thyroid. Most are nonfunctional ("cold"), can rarely cause hyperthyroidism via autonomous thyroid hormone production ("hot" or "toxic"). Most common histology is follicular (arrows in A); absence of capsular or vascular invasion (unlike follicular carcinoma).

Thyroid cancer Typically diagnosed with fine needle aspiration; treated with thyroidectomy. Complications of surgery include hypocalcemia (due to removal of parathyroid glands), transection of recurrent laryngeal nerve during ligation of inferior thyroid artery (leads to dysphagia and dysphonia [hoarseness]), and injury to the external branch of the superior laryngeal nerve during ligation of superior thyroid vascular pedicle (may lead to loss of tenor usually noticeable in professional voice users).

Papillary carcinoma Most common, excellent prognosis. Empty-appearing nuclei with central clearing ("Orphan Annie" eyes) A , psamMoma bodies, nuclear grooves (Papi and Moma adopted OrphanAnnie).

• risk with RET/PTC rearrangements and BRAF mutations, childhood irradiation. Papillary carcinoma: most Prevalent, Palpable lymph nodes. Good prognosis.

Follicular carcinoma Good prognosis. Invades thyroid capsule and vasculature (unlike follicular adenoma), uniform follicles; hematogenous

spread is common. Associated with RAS mutation and PAX8-PPAR-γ translocations.

Medullary carcinoma From parafollicular “C cells”; produces calcitonin, sheets of polygonal cells in an amyloid stroma B (stains with Congo red). Associated with MEN 2A and 2B (RET mutations).

Undifferentiated/ Older patients; presents with rapidly enlarging neck mass compressive symptoms (eg, dyspnea, anaplastic carcinoma dysphagia, hoarseness); very poor prognosis. Associated with TP53 mutation.

(vitamin D defciency, ˜ Ca2+ intake, (hyperplasia, adenoma, chronic kidney disease) carcinoma) 1° hypoparathyroidism PTH-independent (surgical resection, hypercalcemia autoimmune) (excess Ca2+ intake, cancer, ° vitamin D)

Due to injury to parathyroid glands or their blood supply (usually during surgery), autoimmune destruction, or DiGeorge syndrome. Findings: tetany, hypocalcemia, hyperphosphatemia. Chvostek sign—tapping of facial nerve (tap the Cheek) contraction of facial muscles. Trousseau sign—occlusion of brachial artery with BP cuff (cuff the Triceps) carpal spasm.

Pseudohypoparathyroidism type 1A—autosomal dominant, maternally transmitted mutations (imprinted GNAS gene). GNAS1-inactivating mutation (coupled to PTH receptor) that encodes the Gs protein α subunit inactivation of adenylate cyclase when PTH binds to its receptor end-organ resistance (kidney and bone) to PTH. Physical findings: Albright hereditary osteodystrophy (shortened 4th/5th digits A , short stature, round face, subcutaneous calcifications, developmental delay). Labs: • PTH, • Ca2+, • PO43−.

Pseudopseudohypoparathyroidism—autosomal dominant, paternally transmitted mutations (imprinted GNAS gene) but without end-organ resistance to PTH due to normal maternal allele maintaining renal responsiveness to PTH.

Physical findings: same as Albright hereditary osteodystrophy. Labs: normal PTH, Ca2+, PO43−.

Usually due to parathyroid adenoma or hyperplasia. Hypercalcemia, hypercalciuria (renal stones), polyuria (thrones), hypophosphatemia, • PTH, • ALP, • urinary cAMP. Most often asymptomatic. May present with bone pain, weakness, constipation (“groans”), abdominal/flank pain (kidney stones, acute pancreatitis), neuropsychiatric disturbances (“psychiatric overtones”).

Osteitis fibrosa cystica—cystic bone spaces filled with brown fibrous tissue A (“brown tumor” consisting of osteoclasts and deposited hemosiderin from hemorrhages; causes bone pain). Due to • PTH, classically associated with 1° (but also seen with 2°) hyperparathyroidism.

“Stones, thrones, bones, groans, and psychiatric overtones.”

AcUte mAniFestAtions Polydipsia, polyuria, polyphagia, weight loss, DKA (type 1), hyperosmolar hyperglycemic state (type 2). Rarely, can be caused by unopposed secretion of GH and epinephrine. Also seen in patients on glucocorticoid therapy (steroid diabetes).

chronic comPlicAtions Nonenzymatic glycation:

Small vessel disease (diffuse thickening of basement membrane) □ retinopathy (hemorrhage, exudates, microaneurysms, vessel proliferation), glaucoma, nephropathy. Nodular glomerulosclerosis • progressive proteinuria (initially microalbuminuria; ACE inhibitors and ARBs are renoprotective) and arteriolosclerosis (causing hypertension) □ chronic kidney disease.

Large vessel atherosclerosis, CAD, peripheral vascular occlusive disease, gangrene □ limb loss, cerebrovascular disease. MI most common cause of death.

Osmotic damage (sorbitol accumulation in organs with aldose reductase and • or absent sorbitol dehydrogenase):

Neuropathy (motor, sensory [glove and stocking distribution], and autonomic degeneration).

Cataracts.

˜ muscle mass, weight loss ¸ plasma osmolality Osmotic diuresis Loss of water, Na+, and K+¸ thirst Hypovolemia Circulation failure, ˜ tissue perfusion Coma/death tissue glucose uptake ¸¸ glycogenolysis ¸ gluconeogenesis ¸ proteolysis Hyperventilation, Kussmaul respiration ¸ serum lactate ¸ lipolysis Hyperglycemia, glycosuria ¸ plasma free fatty acids ¸ ketogenesis, ketonemia, ketonuria Anion gap metabolic acidosis Vomiting

Diabetic ketoacidosis Insulin absent, ketones present (• complications). Insulin noncompliance or • requirements from • stress (eg, infection) □ excess fat breakdown and • ketogenesis from • free fatty acids • ketone bodies (β-hydroxybutyrate > acetoacetate).

comPlicAtions Life-threatening mucormycosis, cerebral edema, cardiac arrhythmias, HF.

treAtment IV fluids, IV insulin, K+ (to replete intracellular stores) +/− glucose to prevent hypoglycemia.

comPlicAtions Can progress to coma and death if untreated.

treAtment IV fluids, IV insulin, and K+ (to replete intracellular stores).

etiology • cortisol due to a variety of causes:

Exogenous corticosteroids □• ACTH □ bilateral adrenal atrophy. Most common cause.

Primary adrenal adenoma, hyperplasia, or carcinoma □• ACTH □ atrophy of uninvolved adrenal gland.

ACTH-secreting pituitary adenoma (Cushing disease); paraneoplastic ACTH secretion (eg, small cell lung cancer, bronchial carcinoids)□ bilateral adrenal hyperplasia. Cushing disease is responsible for the majority of endogenous cases of Cushing syndrome.

Findings CUSHING Syndrome: • Cholesterol, • Urinary free cortisol, Skin changes (thinning, striae A), Hypertension, Immunosuppression, Neoplasm (a cause, not a finding), Growth retardation (in children), • Sugar (hyperglycemia, insulin resistance). Also, amenorrhea, moon facies B , buffalo hump, osteoporosis, • weight (truncal obesity), hirsutism.

diAgnosis Screening tests include: • free cortisol on 24-hr urinalysis, • late night salivary cortisol, and no suppression with overnight low-dose dexamethasone test.

˜ 24-hr urine free cortisol, ˜ late night salivary cortisol, and/or inadequate suppression on 1 mg overnight dexamethasone test (consider adrenal CT to confrm)

CT of the chest/abdomen/pelvis MRI of the pituitary CT of the chest/abdomen/pelvis

Nelson syndrome Enlargement of pre-existing ACTH–secreting pituitary adenoma after bilateral adrenalectomy for refractory Cushing disease □• ACTH (hyperpigmentation), mass effect (headaches, bitemporal hemianopia). Treatment: transsphenoidal resection, postoperative pituitary irradiation for residual tumor.

Adrenal insufficiency Inability of adrenal glands to generate enough glucocorticoids +/− mineralocorticoids for the body’s needs. Symptoms include weakness, fatigue, orthostatic hypotension, muscle aches, weight loss, GI disturbances, sugar and/or salt cravings. Treatment: glucocorticoid/mineralocorticoid replacement.

Metyrapone stimulation test (conversion of 11-deoxycortisol to cortisol) Indeterminate cortisol results ↓AM or random cortisol, or ACTH stimulation test with ↓ peak cortisol Measure random serum ACTH Check AM or random cortisol, or ACTH stimulation test ↓/−/↑ACTH ↓↓11-deoxycortisol ↑↑ACTH ↑↑11-deoxycortisol ↑↑ACTH ↓11-deoxycortisol ↓ ACTH ↑ ACTH 2°/3° adrenal Normal response 1° adrenal 2°/3° adrenal 1° adrenal insu˜ciency to ↓ cortisol insu˜ciency insu˜ciency insu˜ciency

Most common tumor of the adrenal medulla in children, usually < 4 years old. Originates from Neural crest cells. Occurs anywhere along the sympathetic chain.

Most common presentation is abdominal distension and a firm, irregular mass that can cross the midline (vs Wilms tumor, which is smooth and unilateral). Less likely to develop hypertension than with

pheochromocytoma (Neuroblastoma is Normotensive). Can also present with opsoclonus-myoclonus syndrome ("dancing eyes-dancing feet").

• HVA and VMA (catecholamine metabolites) in urine. Homer-Wright rosettes (neuroblasts surrounding a central lumen A) characteristic of neuroblastoma and medulloblastoma. Bombesin and NSE ⊕. Associated with amplification of N-myc oncogene.

MEN 1 Pituitary tumors (prolactin or GH) Pancreatic endocrine tumors—Zollinger-Ellison syndrome, insulinomas, VIPomas, glucagonomas (rare) Parathyroid adenomas Associated with mutation of MEN1 (menin, a tumor suppressor, chromosome 11), angiofibromas, collagenomas, meningiomas

MEN 2A Parathyroid hyperplasia Medullary thyroid carcinoma—neoplasm of parafollicular C cells; secretes calcitonin; prophylactic thyroidectomy required Pheochromocytoma (secretes catecholamines) Associated with mutation in RET (codes for receptor tyrosine kinase)

Associated with marfanoid habitus; mutation in RET gene

MEN 1 = 3 P's: Pituitary, Parathyroid, and Pancreas

MEN 2A = 2 P's: Parathyroid and Pheochromocytoma

MEN 2B = 1 P: Pheochromocytoma

Insulinoma Tumor of pancreatic β cells overproduction of insulin • hypoglycemia. May see Whipple triad: low blood glucose, symptoms of hypoglycemia (eg, lethargy, syncope, diplopia), and resolution of symptoms after normalization of plasma glucose levels. Symptomatic patients have • blood glucose and • C-peptide levels (vs exogenous insulin use). ~ 10% of cases associated with MEN 1 syndrome. Treatment: surgical resection.

Glucagonoma Tumor of pancreatic α cells overproduction of glucagon. Presents with 6 D's: Dermatitis (necrolytic migratory erythema), Diabetes (hyperglycemia), DVT, Declining weight, Depression, Diarrhea. Treatment: octreotide, surgical resection.

Somatostatinoma Tumor of pancreatic δ cells overproduction of somatostatin • secretion of secretin, cholecystokinin, glucagon, insulin, gastrin, gastric inhibitory peptide (GIP). May present with diabetes/glucose intolerance, steatorrhea, gallstones, achlorhydria. Treatment: surgical resection; somatostatin analogs (eg, octreotide) for symptom control.

Carcinoid tumors arise from neuroendocrine cells most commonly in the intestine or lung. Rare and does not occur if tumor is limited to the GI tract. Prominent rosettes (arrow in A), chromogranin A ⊕ and synaptophysin ⊕). Neuroendocrine cells secrete 5-HT → recurrent diarrhea, wheezing, right-sided valvular heart disease (eg, tricuspid regurgitation, pulmonic stenosis), niacin deficiency (pellagra). 5-HT undergoes hepatic first-pass metabolism and enzymatic breakdown by MAO in

the lung. Treatment: surgical resection, somatostatin analog (eg, octreotide, telotristat) for symptom control.

Rule of thirds: 1/3 metastasize 1/3 present with 2nd malignancy 1/3 are multiple

Rapid acting (1-hr Bind insulin receptor (tyrosine kinase activity) Hypoglycemia, lipodystrophy, hypersensitivity peak): Lispro, Aspart, Liver: • glucose storage as glycogen reactions (rare), weight gain Glulisine (no LAG) Muscle: • glycogen, protein synthesis

Short acting (2–3 hr Fat: • TG storage peak): regular Cell membrane: • K+ uptake Intermediate acting (4–10 hr peak): NPH

Long acting (no real peak): detemir, glargine

Lispro, aspart, glulisine Regular NPH Detemir Glargine

Chlorpropamide, tolbutamide

Glipizide, glyburide

Meglitinides "-gliNs" Nateglinide,

Close K+ channels in pancreatic B cell membrane □ cell depolarizes □ insulin release via • Ca2+ influx.

DisulFIRam-like reaction (FIRst-generation only).

Rarely used.

Hypoglycemia (• risk in renal insufficiency), weight gain.

Amylin analogs • glucagon release, • gastric emptying. Hypoglycemia, nausea. • satiety (often desired). Pramlintide

Thionamides Propylthiouracil, methimazole.

mechAnism Block thyroid peroxidase, inhibiting the oxidation of iodide as well as the organification and coupling of iodine □ inhibition of thyroid hormone synthesis. PTU also blocks 5′-deiodinase □• Peripheral conversion of T4 to T3.

clinicAl Use Hyperthyroidism. PTU used in first trimester of pregnancy (due to methimazole teratogenicity); methimazole used in second and third trimesters of pregnancy (due to risk of PTU-induced hepatotoxicity). Not used to treat Graves ophthalmopathy (treated with corticosteroids).

AdVerse eFFects Skin rash, agranulocytosis (rare), aplastic anemia, hepatotoxicity. Methimazole is a possible teratogen (can cause aplasia cutis).

Levothyroxine, liothyronine mechAnism Hormone replacement for T4 (levothyroxine) or T3 (liothyronine).

clinicAl Use Hypothyroidism, myxedema. May be abused for weight loss. Distinguish exogenous hyperthyroidism from endogenous hyperthyroidism by using a combination of TSH receptor antibodies, radioactive iodine uptake, and/or measurement of thyroid blood flow on ultrasound.

AdVerse eFFects Tachycardia, heat intolerance, tremors, arrhythmias.

mechAnism Synthetic analog of aldosterone with little glucocorticoid effects.

clinicAl Use Mineralocorticoid replacement in 1° adrenal insufficiency.

AdVerse eFFects Similar to glucocorticoids; also edema, exacerbation of heart failure, hyperpigmentation.

mechAnism Sensitizes Ca2+-sensing receptor (CaSR) in parathyroid gland to circulating Ca2+ □• PTH.

clinicAl Use 2° hyperparathyroidism in patients with CKD receiving hemodialysis, hypercalcemia in 1° hyperparathyroidism (if parathyroidectomy fails), or in parathyroid carcinoma.

AdVerse eFFects Hypocalcemia.

mechAnism Nonabsorbable phosphate binder that prevents phosphate absorption from the GI tract.

clinicAl Use Hyperphosphatemia in CKD.

AdVerse eFFects Hypophosphatemia, GI upset.

“A good set of bowels is worth more to a man than any quantity of brains.” “Man should strive to have his intestines relaxed all the days of his life.” “All right, let’s not panic. I’ll make the money by selling one of my livers. I can get by with one.”

When studying the gastrointestinal system, be sure to understand the normal embryology, anatomy, and physiology and how it is affected in the various pathologic diseases. Study not only what a disease entails, but also its specific findings, so that you can differentiate between two similar diseases. For example, what specifically makes ulcerative colitis different than Crohn disease? Also, it is important to understand bile metabolism and which lab values increase or decrease depending on the disease process. Be comfortable with basic interpretation of abdominal x-rays, CT scans, and endoscopic images.

Ventral wall defects Developmental defects due to failure of rostral fold closure (eg, sternal defects [ectopia cordis]), lateral fold closure (eg, omphalocele, gastroschisis), or caudal fold closure (eg, bladder exstrophy).

Congenital umbilical Failure of umbilical ring to close after physiologic herniation of the midgut. Small defects usually hernia close spontaneously.

Tracheoesophageal Esophageal atresia (EA) with distal tracheoesophageal fistula (TEF) is the most common (85%) anomalies and often presents as polyhydramnios in utero (due to inability of fetus to swallow amniotic fluid). Neonates drool, choke, and vomit with first feeding. TEFs allow air to enter stomach (visible on CXR). Cyanosis is 2° to laryngospasm (to avoid reflux-related aspiration). Clinical test: failure to pass nasogastric tube into stomach. In H-type, the fistula resembles the letter H. In pure EA, CXR shows gasless abdomen.

Intestinal atresia Presents with bilious vomiting and abdominal distension within first 1–2 days of life. Duodenal atresia—failure to recanalize. Abdominal x-ray A shows "double bubble" (dilated stomach, proximal duodenum). Associated with Down syndrome. Jejunal and ileal atresia—disruption of mesenteric vessels (typically SMA) ischemic necrosis of fetal intestine segmental resorption: bowel becomes discontinuous. X-ray shows dilated loops of small bowel with air-fluid levels.

Most common cause of gastric outlet obstruction in infants (1:600). Palpable olive-shaped mass in epigastric region, visible peristaltic waves, and nonbilious projectile vomiting at ~ 2–6 weeks old. More common in firstborn males; associated with exposure to macrolides.

Results in hypokalemic hypochloremic metabolic alkalosis (2° to vomiting of gastric acid and subsequent volume contraction).

Ultrasound shows thickened and lengthened pylorus A .

Treatment: surgical incision of pyloric muscles (pyloromyotomy).

Retroperitoneal Retroperitoneal structures A are posterior to structures (and outside of) the peritoneal cavity. Injuries to retroperitoneal structures can cause blood or gas accumulation in retroperitoneal space.

SAD PUCKER: Suprarenal (adrenal) glands [not shown] Aorta and IVC Duodenum (2nd through 4th parts) Pancreas (except tail) Ureters [not shown] Colon (descending and ascending) Kidneys Esophagus (thoracic portion) [not shown] Rectum (partially) [not shown]

Omental foramen (epiploic foramen of Winslow)

Falciform ligament Liver to anterior abdominal Ligamentum teres hepatis Derivative of ventral mesentery wall (derivative of fetal umbilical vein), patent paraumbilical veins

Hepatoduodenal Liver to duodenum Portal triad: proper hepatic ligament artery, portal vein, common bile duct

Derivative of ventral mesentery Pringle maneuver—ligament is compressed manually or with a vascular clamp in omental foramen to control bleeding from hepatic inflow source

Borders the omental foramen, which connects the greater and lesser sacs

Part of lesser omentum

Esophagus Nonkeratinized stratified squamous epithelium. Upper 1/3, striated muscle; middle and lower 2/3 smooth muscle, with some overlap at the transition.

Ileum Peyer patches (arrow in D ; lymphoid aggregates in lamina propria, submucosa), plicae circulares (proximal ileum), and crypts of Lieberkühn. Largest number of goblet cells in the small intestine.

Colon Crypts of Lieberkühn with abundant goblet cells, but no villi E .

Arteries supplying GI structures are single and branch anteriorly.

Arteries supplying non-GI structures are paired and branch laterally and posteriorly.

Two areas of the colon have dual blood supply from distal arterial branches (“watershed regions”) susceptible in colonic ischemia:

Rectosigmoid junction—the last sigmoid arterial branch from the IMA and superior rectal artery

Nutcracker syndrome—compression of left renal vein between superior mesenteric artery and aorta. Characterized by abdominal (flank) pain and gross hematuria (from rupture of thin-walled renal varicosities).

Superior mesenteric artery syndrome— characterized by intermittent intestinal obstruction symptoms (primarily postprandial pain) when SMA and aorta compress transverse (third) portion of duodenum. Typically occurs in conditions associated with diminished mesenteric fat (eg, low body weight/malnutrition).

Celiac trunk Branches of celiac trunk: common hepatic, splenic, and left gastric. These constitute the main blood supply of the foregut. Strong anastomoses exist between:

Pathologic blood in portal HTN Flow through TIPS, re-establishing normal fow direction

Varicesof gut, butt, and caput (medusae) are commonly seen with portal hypertension.

Treatment with a transjugular intrahepatic portosystemic shunt (TIPS) between the portal vein and hepatic vein relieves portal hypertension by shunting blood to the systemic circulation, bypassing the liver. TIPS can precipitate hepatic encephalopathy due to • clearance of ammonia from shunting.

Pectinate line Also called dentate line. Formed where endoderm (hindgut) meets ectoderm.

Above pectinate line: internal hemorrhoids, adenocarcinoma.

Internal hemorrhoids receive visceral innervation and are therefore not painful.

Below pectinate line: external hemorrhoids, anal fissures, squamous cell carcinoma.

External hemorrhoids receive somatic innervation (inferior rectal branch of pudendal nerve) and are therefore painful if thrombosed.

Anal fissure—tear in anal mucosa below Pectinate line. Pain while Pooping; blood on toilet Paper. Located Posteriorly because this area is Poorly Perfused. Innervated by Pudendal nerve. Associated with low-fiber diets and constipation.

The functional unit of the liver is made up of hexagonally arranged lobules surrounding the central vein with portal triads on the edges (consisting of a portal vein, hepatic artery, bile ducts, as well as lymphatics) A .

Apical surface of hepatocytes faces bile canaliculi. Basolateral surface faces sinusoids.

Kupffer cells (specialized macrophages) located in sinusoids (black arrows in B ; yellow arrows show hepatic venule) clear bacteria and damaged or senescent RBCs.

Hepatic stellate (Ito) cells in space of Disse store vitamin A (when quiescent) and produce extracellular matrix (when activated). Responsible for hepatic fibrosis.

Branch of hepatic artery

Branch of portal vein

Zone I—periportal zone:

Best oxygenated, most resistant to circulatory compromise

Ingested toxins (eg, cocaine) Zone II—intermediate zone:

Yellow fever Zone III—pericentral vein (centrilobular) zone:

High concentration of cytochrome P-450

Most sensitive to metabolic toxins (eg, ethanol, CCl4, halothane, rifampin, acetaminophen)

Site of alcoholic hepatitis

Stellate cell Space of Disse

Gallstones that reach the confluence of the common bile and pancreatic ducts at the ampulla of Vater can block both the common bile and pancreatic ducts (double duct sign), causing both cholangitis and pancreatitis, respectively.

Tumors that arise in head of pancreas (usually ductal adenocarcinoma) can cause obstruction of common bile duct enlarged gallbladder with painless jaundice (Courvoisier sign).

Cholangiography shows filling defects in gallbladder (blue arrow) and cystic duct (red arrow) A .

Femoral sheath Fascial tube 3–4 cm below inguinal ligament. Contains femoral vein, artery, and canal (deep inguinal lymph nodes) but not femoral nerve.

Aponeurosis of external oblique muscle

Evagination of transversalis fascia Internal (deep) inguinal ring Ductus (vas) deferens Genital branch of genitofemoral

Hernias Protrusion of peritoneum through an opening, usually at a site of weakness. Contents may be at risk for incarceration (not reducible back into abdomen/pelvis) and strangulation (ischemia and necrosis). Complicated hernias can present with tenderness, erythema, fever.

Direct inguinal hernia Protrudes through inguinal (Hesselbach) triangle. Bulges directly through parietal peritoneum medial to the inferior epigastric vessels but lateral to the rectus abdominis. Goes through external (superficial) inguinal ring only. Covered by external spermatic fascia. Usually occurs in older men due to acquired weakness of transversalis fascia. MDs don’t LIe: Medial to inferior epigastric vessels = Direct hernia. Lateral to inferior epigastric vessels = Indirect hernia.

Femoral hernia Protrudes below inguinal ligament through femoral canal below and lateral to pubic tubercle. More common in females, but overall inguinal hernias are the most common. More likely to present with incarceration or strangulation (vs inguinal hernia).

Abdominal structures enter the thorax A ; may occur due to congenital defect of pleuroperitoneal membrane or from trauma. Commonly occurs on left side due to relative protection of right hemidiaphragm by liver. Most commonly a hiatal hernia, in which stomach herniates upward through the esophageal hiatus of the diaphragm.

Sliding hiatal hernia—gastroesophageal junction is displaced upward as gastric cardia slides into hiatus; “hourglass stomach.” Most gastric fundus common type. Associated with GERD.

Paraesophageal hiatal hernia— gastroesophageal junction is usually normal but gastric fundus protrudes into the thorax.

Goes through the internal (deep) inguinal ring, external (superficial) inguinal ring, and into the groin. Enters internal inguinal ring lateral to inferior epigastric vessels. Caused by failure of processus vaginalis to close (can form hydrocele). May be noticed in infants or discovered in adulthood. Much more common in males

B .

Follows the pathway of testicular descent. Covered by all 3 layers of spermatic fascia.

Gastrin G cells (antrum of stomach, duodenum) in chronic atrophic gastritis (eg, H pylori)

Intrinsic factor Parietal cells Vitamin B12–binding Autoimmune destruction (stomach A) protein (required for B12 of parietal cells □ chronic uptake in terminal ileum) gastritis and pernicious anemia. Gastric acid Parietal cells • stomach pH • by histamine, (stomach) vagal stimulation (ACh), gastrin • by somatostatin, GIP, prostaglandin, secretin

Pepsin Chief cells Protein digestion • Pepsinogen (inactive) is (stomach) stimulation converted to pepsin (active) in (ACh), local the presence of H+. acid by pancreatic (stomach, and biliary the gastric epithelium. duodenum, secretion with salivary glands, secretin pancreas) and Brunner glands (duodenum)

Gastrin • acid secretion primarily through its effects on enterochromaffin-like (ECL) cells (leading to histamine release) rather than through its direct effect on parietal cells.

Pancreatic secretions Isotonic fluid; low flow □ high Cl−, high flow □ high HCO_3^- .

Only monosaccharides (glucose, galactose, fructose) are absorbed by enterocytes. Glucose and galactose are taken up by SGLT1 (Na^+ dependent). Fructose is taken up via Facilitated diffusion by GLUT5. All are transported to blood by GLUT2.

d-xylose absorption test: simple sugar that requires intact mucosa for absorption, but does not require digestive enzymes. Helps distinguish GI mucosal damage from other causes of malabsorption.

Iron Absorbed as Fe^{2+} in duodenum Iron Fist, Bro

Clinically relevant in patients with small bowel disease or after resection (eg, vitamin B12

Vitamin B Absorbed in terminal ileum along with bile salts, requires intrinsic factor

Think of IgA, the Intra-gut Antibody

Unencapsulated lymphoid tissue A found in lamina propria and submucosa of ileum. Contain specialized M cells that sample and present antigens to immune cells.

B cells stimulated in germinal centers of Peyer patches differentiate into IgA-secreting plasma cells, which ultimately reside in lamina propria. IgA receives protective secretory component and is then transported across the epithelium to the gut to deal with intraluminal antigen.

Bilirubin Heme is metabolized by heme oxygenase to biliverdin, which is subsequently reduced to bilirubin. Unconjugated bilirubin is removed from blood by liver, conjugated with glucuronate, and excreted in bile. Direct bilirubin: conjugated with glucuronic acid; water soluble (dissolves in water). Indirect bilirubin: unconjugated; water insoluble.

Excreted in urine as urobilin (˜ yellow color)

Excreted in feces as stercobilin (˜ brown color of stool)

Most are benign and commonly affect parotid gland (80-85%). Nearly half of all submandibular gland neoplasms and most sublingual and minor salivary gland tumors are malignant. Typically present as painless mass/swelling. Facial paralysis or pain suggests malignant involvement.

Pleomorphic adenoma (benign mixed tumor)—most common salivary gland tumor A . Composed of chondromyxoid stroma and epithelium and recurs if incompletely excised or ruptured intraoperatively. May undergo malignant transformation.

Mucoepidermoid carcinoma—most common malignant tumor, has mucinous and squamous components.

Warthin tumor (papillary cystadenoma lymphomatosum)—benign cystic tumor with germinal centers. Typically found in smokers. Bilateral in 10%; multifocal in 10%. “Warriors from Germany love smoking.”

Barrett esophagus Specialized intestinal metaplasia A —replacement of nonkeratinized stratified squamous epithelium with intestinal epithelium (nonciliated columnar with goblet cells [stained blue in B]) in distal esophagus. Due to chronic gastroesophageal reflux disease (GERD). Associated with • risk of esophageal adenocarcinoma.

Most commonly gastric adenocarcinoma; lymphoma, GI stromal tumor, carcinoid (rare). Early aggressive local spread with node/liver metastases. Often presents late, with weight loss, abdominal pain, early satiety, and in some cases acanthosis nigricans or Leser-Trélat sign. Associated with blood type A.

Intestinal—associated with H pylori, dietary nitrosamines (smoked foods), tobacco smoking, achlorhydria, chronic gastritis. Commonly on lesser curvature; looks like ulcer with raised margins.

Diffuse—not associated with H pylori; most cases due to E-cadherin mutation; signet ring cells (mucin-filled cells with peripheral nuclei) A ; stomach wall grossly thickened and leathery (linitis plastica).

Erosions can be caused by: Especially common among alcoholics and

NSAIDs—• PGE2 □• gastric mucosa patients taking daily NSAIDs (eg, patients with protection rheumatoid arthritis)

Burns (Curling ulcer)—hypovolemia Burned by the Curling iron

Brain injury (Cushing ulcer)—• vagal Always Cushion the brain stimulation □• ACh □• H+ production

Mucosal inflammation, often leading to atrophy (hypochlorhydria • hypergastrinemia) and intestinal metaplasia (• risk of gastric cancers)

Hyperplasia of gastric mucosa □ hypertrophied rugae (look like brain gyri A). Causes excess mucus production with resultant protein loss and parietal cell atrophy with • acid production. Precancerous. Presents with Weight loss, Anorexia, Vomiting, Epigastric pain, Edema (due to protein loss) (WAVEE).

Virchow node—involvement of left supraclavicular node by metastasis from stomach.

Krukenberg tumor—bilateral metastases to ovaries. Abundant mucin-secreting, signet ring cells.

Sister Mary Joseph nodule—subcutaneous periumbilical metastasis.

Blumer shelf—palpable mass on digital rectal exam suggesting metastasis to rectouterine pouch (pouch of Douglas).

Hemorrhage Gastric, duodenal (posterior > anterior). Most common complication. Ruptured gastric ulcer on the lesser curvature of stomach □ bleeding from left gastric artery. An ulcer on the posterior wall of duodenum • bleeding from gastroduodenal artery.

Obstruction Pyloric channel, duodenal.

Perforation Duodenal (anterior > posterior). Anterior duodenal ulcers can perforate into the anterior abdominal cavity, potentially leading to pneumoperitoneum. May see free air under diaphragm (pneumoperitoneum) A with referred pain to the shoulder via irritation of phrenic nerve.

ComPliCations Malabsorption/malnutrition, colorectal cancer (• risk with pancolitis).

Fistulas (eg, enterovesical fistulae, which can Fulminant colitis, toxic megacolon, perforation. cause recurrent UTI and pneumaturia), phlegmon/abscess, strictures (causing obstruction), perianal disease.

intestinal maniFestation Diarrhea that may or may not be bloody. Bloody diarrhea.

eXtraintestinal maniFestations Rash (pyoderma gangrenosum, erythema nodosum), eye inflammation (episcleritis, uveitis), oral ulcerations (aphthous stomatitis), arthritis (peripheral, spondylitis).

Appendicitis Acute inflammation of the appendix (yellow arrows in A), can be due to obstruction by fecalith (red arrow in A) (in adults) or lymphoid hyperplasia (in children). Proximal obstruction of appendiceal lumen produces closed-loop obstruction □• intraluminal pressure □ stimulation of visceral afferent nerve fibers at T8-T10 □ initial diffuse periumbilical pain □ inflammation extends to serosa and irritates parietal peritoneum. Pain localized to RLQ/ McBurney point (1/3 the distance from right anterior superior iliac spine to umbilicus). Nausea, fever; may perforate □ peritonitis; may elicit psoas, obturator, and Rovsing signs, guarding and rebound tenderness on exam. Differential: diverticulitis (elderly), ectopic pregnancy (use hCG to rule out), pseudoappendicitis. Treatment: appendectomy.

Diverticula of the GI tract Zenker diverticulum

Pharyngoesophageal false diverticulum A . Esophageal dysmotility causes herniation of mucosal tissue at Killian triangle between the thyropharyngeal and cricopharyngeal parts of the inferior pharyngeal constrictor. Presenting symptoms: dysphagia, obstruction, gurgling, aspiration, foul breath, neck mass. Most common in elderly males.

Elder MIKE has bad breath: Elderly Males Inferior pharyngeal constrictor Killian triangle Esophageal dysmotility Halitosis

Meckel diverticulum True diverticulum. Persistence of the vitelline (omphalomesenteric) duct. May contain ectopic acid-secreting gastric mucosa and/or pancreatic tissue. Most common congenital anomaly of GI tract. Can cause hematochezia/ melena (less common), RLQ pain, intussusception, volvulus, or obstruction near terminal ileum. Contrast with omphalomesenteric cyst = cystic dilation of vitelline duct. Diagnosis: 99mTc-pertechnetate scan (aka Meckel scan) for uptake by heterotopic gastric mucosa.

The rule of 2's: 2 times as likely in males. 2 inches long. 2 feet from the ileocecal valve. 2% of population. Commonly presents in first 2 years of life. May have 2 types of epithelia (gastric/ pancreatic).

Congenital megacolon characterized by lack of ganglion cells/enteric nervous plexuses (Auerbach and Meissner plexuses) in distal segment of colon. Due to failure of neural crest cell migration. Associated with loss of function mutations in RET.

Presents with bilious emesis, abdominal distention, and failure to pass meconium within 48 hours • chronic constipation. Normal portion of the colon proximal to the aganglionic segment is dilated, resulting in a "transition zone."

Risk • with Down syndrome. Explosive expulsion of feces (squirt sign) empty rectum on digital exam. Diagnosed by absence of ganglionic cells on rectal suction biopsy. Treatment: resection. RET mutation in the REcTum.

Malrotation Anomaly of midgut rotation during fetal development improper positioning of bowel (small bowel clumped on the right side) A , formation of fibrous bands (Ladd bands). Can lead to volvulus, duodenal obstruction.

Volvulus Twisting of portion of bowel around its mesentery; can lead to obstruction and infarction. Can occur throughout the GI tract.

Chronic mesenteric "Intestinal angina": atherosclerosis of celiac artery, SMA, or IMA intestinal hypoperfusion ischemia • postprandial epigastric pain food aversion and weight loss.

Colonic ischemia Reduction in intestinal blood flow causes ischemia. Crampy abdominal pain followed by hematochezia. Commonly occurs at watershed areas (splenic flexure, rectosigmoid junction). Typically affects elderly. Thumbprint sign on imaging due to mucosal edema/hemorrhage.

Ileus Intestinal hypomotility without obstruction constipation and • flatus; distended/tympanic abdomen with • bowel sounds. Associated with abdominal surgeries, opiates, hypokalemia, sepsis. Treatment: bowel rest, electrolyte correction, cholinergic drugs (stimulate intestinal motility).

Colonic polyps Growths of tissue within the colon A . Grossly characterized as flat, sessile, or pedunculated on the basis of protrusion into colonic lumen. Generally classified by histologic type.

Submucosal polyps May include lipomas, leiomyomas, fibromas, and other lesions. Malignant potential tooth" pattern of crypts on biopsy. Up to 20% of cases of sporadic CRC. A B C Polyp Polyp Cancer SessilePedunculated

Lynch syndrome Previously called hereditary nonpolyposis colorectal cancer (HNPCC). Autosomal dominant mutation of mismatch repair genes (eg, MLH1, MSH2) with subsequent microsatellite instability. ~ 80% progress to CRC. Proximal colon is always involved. Associated with endometrial, ovarian, and skin cancers.

Diagnosis Iron deficiency anemia in males (especially > 50 years old) and postmenopausal females raises suspicion. Screening:

Low risk: screen at age 50 with colonoscopy (polyp seen in A); alternatives include flexible sigmoidoscopy, fecal occult blood testing (FOBT), fecal immunochemical testing (FIT), FIT-fecal DNA, CT colonography

Patients with a first-degree relative who has colon cancer: screen at age 40 with colonoscopy, or 10 years prior to the relative's presentation

Patients with IBD: distinct screening protocol “Apple core” lesion seen on barium enema x-ray B . CEA tumor marker: good for monitoring recurrence, should not be used for screening.

ePiDemiology Most patients are > 50 years old. ~ 25% have a family history.

Presentation Rectosigmoid > ascending > descending.

Right side (cecal, ascending) associated with occult bleeding; left side (rectosigmoid) associated with hematochezia and obstruction (narrower lumen).

Ascending—exophytic mass, iron deficiency anemia, weight loss.

Descending—infiltrating mass, partial obstruction, colicky pain, hematochezia.

Can present with S bovis (gallolyticus) bacteremia/endocarditis or as an episode of diverticulitis.

risK FaCtors Adenomatous and serrated polyps, familial cancer syndromes, IBD, tobacco use, diet of processed meat with low fiber.

Molecular Chromosomal instability pathway: mutations in APC cause FAP and most sporadic cases of CRC pathogenesis of via adenoma-carcinoma sequence; (firing order of events is “AK-53”). colorectal cancer Microsatellite instability pathway: mutations or methylation of mismatch repair genes (eg, MLH1) cause Lynch syndrome and some sporadic CRC (via serrated polyp pathway). Overexpression of COX-2 has been linked to colorectal cancer, NSAIDs may be chemopreventive.

Loss of tumor suppressor Loss of APC gene KRAS mutation gene(s) (TP53, DCC)

Cirrhosis—diffuse bridging fibrosis (via stellate cells) and regenerative nodules (red arrows in A ; white arrows show splenomegaly) disrupt normal architecture of liver; • risk for hepatocellular carcinoma (white arrow in B). Etiologies include alcohol, nonalcoholic steatohepatitis, chronic viral hepatitis, autoimmune hepatitis, biliary disease, genetic/metabolic disorders.

Portal hypertension—• pressure in portal venous system. Etiologies include cirrhosis (most common cause in Western countries), vascular obstruction (eg, portal vein thrombosis, Budd-

Chiari syndrome), schistosomiasis.

Eects of portal hypertension *Due to estrogen

Anorexia Nausea, vomiting Dull abdominal pain

Serum markers of liver pathology

Reye syndrome Rare, often fatal childhood hepatic encephalopathy.

Associated with viral infection (especially VZV and influenza) that has been treated with aspirin. Aspirin metabolites • β-oxidation by reversible inhibition of mitochondrial enzymes.

Findings: mitochondrial abnormalities, fatty liver (microvesicular fatty changes), hypoglycemia, vomiting, hepatomegaly, coma.

Avoid aspirin in children, except in those with Kawasaki disease.

Salicylates aren't a ray (Reye) of sunSHINE for kids: Steatosis of liver/hepatocytes Hypoglycemia/Hepatomegaly Infection (VZV, influenza) Not awake (coma) Encephalopathy

Alcoholic cirrhosis Final and usually irreversible form. Sclerosis around central vein (arrows in C) may be seen in early disease. Regenerative nodules surrounded by fibrous bands in response to chronic liver injury portal hypertension and end-stage liver disease.

Nonalcoholic fatty Metabolic syndrome (insulin resistance); ALT > AST (Lipids) liver disease obesity • fatty infiltration of hepatocytes A cellular "ballooning" and eventual necrosis. May cause cirrhosis and HCC. Independent of alcohol use.

Most common 1° malignant tumor of liver in adults

A . Associated with HBV (+/− cirrhosis) and all other causes of cirrhosis (including HCV, alcoholic and nonalcoholic fatty liver disease, autoimmune disease, hemochromatosis, Wilson disease, α1-antitrypsin deficiency) and specific carcinogens (eg, aflatoxin from Aspergillus). May lead to Budd-Chiari syndrome.

Findings: jaundice, tender hepatomegaly, ascites, polycythemia, anorexia. Spreads hematogenously.

Diagnosis: • α-fetoprotein; ultrasound or contrast CT/MRI

B , biopsy.

Hepatic adenoma Rare, benign liver tumor, often related to oral contraceptive or anabolic steroid use; may regress spontaneously or rupture (abdominal pain and shock).

Metastases GI malignancies, breast and lung cancer. Most common overall; metastases are rarely solitary.

Budd-Chiari syndrome Thrombosis or compression of hepatic veins with centrilobular congestion and necrosis congestive liver disease (hepatomegaly, ascites, varices, abdominal pain, liver failure). Absence of JVD. Associated with hypercoagulable states, polycythemia vera, postpartum state, HCC. May cause nutmeg liver (mottled appearance).

1-antitrypsin Misfolded gene product protein aggregates in In lungs, • α1-antitrypsin □ uninhibited elastase deficiency hepatocellular ER □ cirrhosis with in alveoli □□ elastic tissue • panacinar PAS ⊕ globules A in liver. Codominant trait. emphysema.

Often presents in young patients with liver damage and dyspnea without a history of smoking.

Jaundice Abnormal yellowing of the skin HOT Liver—common causes of • bilirubin and/or sclera A due to bilirubin deposition. level:

Hyperbilirubinemia 2° to • production Hemolysis or • clearance (impaired hepatic uptake, Obstruction conjugation, excretion). Tumor

Hereditary All autosomal recessive. hyperbilirubinemias

Gilbert syndrome Mildly • UDP-glucuronosyltransferase conjugation and impaired bilirubin uptake. Asymptomatic or mild jaundice usually with stress, illness, or fasting. • unconjugated bilirubin without overt hemolysis. Relatively common, benign condition.

Dubin-Johnson Conjugated hyperbilirubinemia due to defective liver excretion. Grossly black (Dark) liver due to syndrome impaired excretion of epinephrine metabolites. Benign.

Similar to Dubin-Johnson syndrome, but milder in presentation without black (Regular) liver. Due to impaired hepatic uptake and excretion.

Endothelial cells Hemoglobin circulating bilirubin Kuper cell (macrophage) Obstructive jaundice (downstream) (albumin bound, unconjugated, water insoluble) Space of Disse HEPATIC SINUSOID RSTQQBILIRUBIN UPTAKE CONJUGATION INTRACELLULAR TRANSPORT UDP-glucuronosyl-transferase Unconjugated bilirubin Conjugated bilirubin (bilirubin diglucuronide, water soluble) Bile canalicular lumen Hepatocyte Bile fow

Unknown cause of concentric “onion skin” bile duct fibrosis □ alternating strictures and dilation with “beading” of intraand extrahepatic bile ducts on ERCP, magnetic resonance cholangiopancreatography (MRCP).

Also called hepatolenticular degeneration. Autosomal recessive mutations in hepatocyte copper-transporting ATPase (ATP7B gene; chromosome 13) □• copper incorporation into apoceruloplasmin and excretion into bile □• serum ceruloplasmin. Copper accumulates, especially in liver, brain, cornea, kidneys; • urine copper.

Presents before age 40 with liver disease (eg, hepatitis, acute liver failure, cirrhosis), neurologic disease (eg, dysarthria, dystonia, tremor, parkinsonism), psychiatric disease, Kayser-Fleischer rings (deposits in Descemet membrane of cornea) A , hemolytic anemia, renal disease (eg, Fanconi syndrome).

Treatment: chelation with penicillamine or trientine, oral zinc. Liver transplant in acute liver failure related to Wilson disease.

Autosomal recessive. On HFE gene, located on chromosome 6; associated with HLA-A3. Leads to abnormal iron sensing and • intestinal absorption (• ferritin, • iron, • TIBC □• transferrin saturation). Iron overload can also be 2° to chronic transfusion therapy (eg, β-thalassemia major). Iron accumulates, especially in liver, pancreas, skin, heart, pituitary, joints. Hemosiderin (iron) can be identified on liver MRI or biopsy with Prussian blue stain A .

Presents after age 40 when total body iron > 20 g; iron loss through menstruation slows progression in women. Classic triad of cirrhosis, diabetes mellitus, skin pigmentation ("bronze diabetes"). Also causes restrictive cardiomyopathy (classic) or dilated cardiomyopathy (reversible), hypogonadism, arthropathy (calcium pyrophosphate deposition; especially metacarpophalangeal joints). HCC is common cause of death.

Treatment: repeated phlebotomy, iron (Fe) chelation with deferasirox, deferoxamine, deferiprone.

May present with pruritus, jaundice, dark urine, light-colored stool, hepatosplenomegaly. Typically with cholestatic pattern of LFTs (• conjugated bilirubin, • cholesterol, • ALP, • GGT).

Classically in middle-aged men Associated with ulcerative with ulcerative colitis. colitis. p-ANCA ⊕. • IgM. Can lead to 2° biliary cholangitis. • risk of cholangiocarcinoma and gallbladder cancer.

Autoimmune reaction Classically in middle-aged Anti-mitochondrial antibody ⊕, infiltrate women. • IgM. Associated with other +/- granulomas autoimmune conditions of lobular bile (eg, Hashimoto thyroiditis, ducts. rheumatoid arthritis, celiac disease). Treatment: ursodiol.

Extrahepatic biliary obstruction Patients with known May be complicated by □• pressure in intrahepatic obstructive lesions (gallstones, ascending cholangitis. ducts □ injury/ fibrosis and biliary strictures, pancreatic bile stasis. carcinoma).

• cholesterol and/or bilirubin, • bile salts, and Gender (female), Chronic hemolysis, gallbladder stasis all cause stones. age, obesity, genetics, biliary tract infection 2 types of stones:

Cholesterol stones (radiolucent with 10–20% opaque due to calcifications)—80% of stones. Associated with obesity, Crohn disease, advanced age, estrogen therapy, multiparity, rapid weight loss, Native American origin.

Pigment stones A (black = radiopaque, Ca2+ bilirubinate, hemolysis; brown = radiolucent, infection). Associated with Crohn disease, chronic hemolysis, alcoholic cirrhosis, advanced age, biliary infections, total parenteral nutrition (TPN).

Risk factors (4 F's): 1.

2.

3.

4.

Most common complication is cholecystitis; can also cause acute pancreatitis, ascending cholangitis.

Diagnose with ultrasound. Treat with elective cholecystectomy if symptomatic.

↓cholesterol 7αhydroxylase ↑Cholesterol, ↓bile salts, gallbladder stasis ↑Unconjugated bilirubin, gallbladder stasis Supersaturation of bile with calcium bilirubinate Pigment stones Supersaturation of bile with cholesterol Cholesterol stones

Choledocholithiasis Presence of gallstone(s) in common bile duct, often leading to elevated ALP, GGT, direct bilirubin, and/or AST/ALT.

Cholecystitis Acute or chronic inflammation of gallbladder. Calculous cholecystitis—most common type; due to gallstone impaction in the cystic duct resulting in inflammation and gallbladder wall thickening (arrows in B); can produce 2° infection. Acalculous cholecystitis—due to gallbladder stasis, hypoperfusion, or infection (CMV); seen in critically ill patients. Murphy sign: inspiratory arrest on RUQ palpation due to pain. Pain may radiate to right shoulder (due to irritation of phrenic nerve). • ALP if bile duct becomes involved (eg, ascending cholangitis). Diagnose with ultrasound or cholescintigraphy (HIDA scan). Failure to visualize gallbladder on HIDA scan suggests obstruction. Gallstone ileus—fistula between gallbladder and GI tract stone enters GI lumen obstructs at ileocecal valve (narrowest point); can see air in biliary tree (pneumobilia). Rigler triad: radiographic findings of pneumobilia, small bowel obstruction, gallstone (usually in iliac fossa).

Porcelain gallbladder Calcified gallbladder due to chronic cholecystitis; usually found incidentally on imaging C . Treatment: prophylactic cholecystectomy generally recommended due to • risk of gallbladder cancer (mostly adenocarcinoma).

Ascending cholangitis Infection of biliary tree usually due to obstruction that leads to stasis/bacterial overgrowth. Charcot triad of cholangitis includes jaundice, fever, RUQ pain. Reynolds pentad is Charcot triad plus altered mental status and shock (hypotension).

Autodigestion of pancreas by pancreatic enzymes (A shows pancreas [yellow arrows] surrounded by edema [red arrows]).

Causes: Idiopathic, Gallstones, Ethanol, Trauma, Steroids, Mumps, Autoimmune disease, Scorpion sting, Hypercalcemia/Hypertriglyceridemia (> 1000 mg/dL), ERCP, Drugs (eg, sulfa drugs, NRTIs, protease inhibitors). I GET SMASHED.

Diagnosis by 2 of 3 criteria: acute epigastric pain often radiating to the back, • serum amylase or lipase (more specific) to 3× upper limit of normal, or characteristic imaging findings.

Complications: pseudocyst B (lined by granulation tissue, not epithelium), abscess, necrosis, hemorrhage, infection, organ failure (ALI/ARDS, shock, renal failure), hypocalcemia (precipitation of Ca2+ soaps).

Chronic pancreatitis Chronic inflammation, atrophy, calcification of the pancreas A . Major causes include alcohol abuse and genetic predisposition (ie, cystic fibrosis); can be idiopathic. Complications include pancreatic insufficiency and pseudocysts. Pancreatic insufficiency (typically when <10% pancreatic function) may manifest with steatorrhea, fat-soluble vitamin deficiency, diabetes mellitus. Amylase and lipase may or may not be elevated (almost always elevated in acute pancreatitis).

Very aggressive tumor arising from pancreatic ducts (disorganized glandular structure with cellular infiltration A); often metastatic at presentation, with average survival ~ 1 year after diagnosis. Tumors more common in pancreatic head B (lead to obstructive jaundice). Associated with CA 19-9 tumor marker (also CEA, less specific).

Risk factors:

Jewish and African-American males Often presents with:

Abdominal pain radiating to back

Weight loss (due to malabsorption and anorexia)

Migratory thrombophlebitis—redness and tenderness on palpation of extremities (Trousseau syndrome)

Obstructive jaundice with palpable, nontender gallbladder (Courvoisier sign) Treatment: Whipple procedure (pancreaticoduodenectomy), chemotherapy, radiation therapy.

HCO3 ”alkaline tide”— ˜ blood pH after gastric acid secretion (eg, after meals, vomiting)

Misoprostol H+ K+ Sucralfate, bismuth

Histamine-2 blockers Cimetidine, ranitidine, famotidine, nizatidine. Take H2 blockers before you dine. Think “table for 2” to remember H2.

meCHanism Reversible block of histamine H2-receptors □• H+ secretion by parietal cells.

CliniCal Use Peptic ulcer, gastritis, mild esophageal reflux.

aDVerse eFFeCts Cimetidine is a potent inhibitor of cytochrome P-450 (multiple drug interactions); it also has antiandrogenic effects

(prolactin release, gynecomastia, impotence, • libido in males); can cross blood-brain barrier (confusion, dizziness, headaches) and placenta. Both cimetidine and ranitidine • renal excretion of creatinine. Other H2 blockers are relatively free of these effects.

Proton pump inhibitors Omeprazole, lansoprazole, esomeprazole, pantoprazole, dexlansoprazole.

meCHanism Irreversibly inhibit H+/K+ ATPase in stomach parietal cells.

CliniCal Use Peptic ulcer, gastritis, esophageal reflux, Zollinger-Ellison syndrome, component of therapy for H pylori, stress ulcer prophylaxis.

aDVerse eFFeCts • risk of C difficile infection, pneumonia, acute interstitial nephritis. Vitamin B12 malabsorption; • serum Mg^{2+} and • Ca^{2+} absorption (potentially leading to increased fracture risk in elderly).

Antacids Can affect absorption, bioavailability, or urinary excretion of other drugs by altering gastric and urinary pH or by delaying gastric emptying. All can cause hypokalemia. Overuse can also cause the following problems:

Bismuth, sucralfate meCHanism Bind to ulcer base, providing physical protection and allowing HCO_3 secretion to reestablish pH gradient in the mucous layer. Sucralfate requires acidic environment, not given with PPIs/H2 blockers.

CliniCal Use • ulcer healing, travelers' diarrhea (bismuth). Bismuth also used in quadruple therapy for H pylori gastritis.

aDVerse eFFeCts Diarrhea. Contraindicated in women of childbearing potential (abortifacient).

meCHanism Long-acting somatostatin analog; inhibits secretion of various splanchnic vasodilatory hormones.

CliniCal Use Acute variceal bleeds, acromegaly, VIPoma, carcinoid tumors.

aDVerse eFFeCts Nausea, cramps, steatorrhea. • risk of cholelithiasis due to CCK inhibition.

meCHanism A combination of sulfapyridine (antibacterial) and 5-aminosalicylic acid (anti-inflammatory). Activated by colonic bacteria.

CliniCal Use Ulcerative colitis, Crohn disease (colitis component).

aDVerse eFFeCts Malaise, nausea, sulfonamide toxicity, reversible oligospermia.

meCHanism Agonist at μ-opioid receptors; slows gut motility. Poor CNS penetration (low addictive potential).

CliniCal Use Diarrhea.

aDVerse eFFeCts Constipation, nausea.

meCHanism 5-HT3 antagonist; • vagal stimulation. Powerful central-acting antiemetic.

CliniCal Use Control vomiting postoperatively and in patients undergoing cancer chemotherapy.

aDVerse eFFeCts Headache, constipation, QT interval prolongation, serotonin syndrome.

meCHanism D2 receptor antagonist. • resting tone, contractility, LES tone, motility, promotes gastric emptying. Does not influence colon transport time.

CliniCal Use Diabetic and postoperative gastroparesis, antiemetic, persistent GERD.

aDVerse eFFeCts • parkinsonian effects, tardive dyskinesia. Restlessness, drowsiness, fatigue, depression, diarrhea. Drug interaction with digoxin and diabetic agents. Contraindicated in patients with small bowel obstruction, Parkinson disease (due to D2-receptor blockade), • seizure threshold.

meCHanism Inhibits gastric and pancreatic lipase □• breakdown and absorption of dietary fats. Taken with fat-containing meals.

CliniCal Use Weight loss.

aDVerse eFFeCts Abdominal pain, flatulence, bowel urgency/frequent bowel movements, steatorrhea; • absorption of fat-soluble vitamins.

Laxatives Indicated for constipation or patients on opiates requiring a bowel regimen.

meCHanism Substance P antagonist. Blocks NK1 (neurokinin-1) receptors in brain.

CliniCal Use Antiemetic for chemotherapy-induced nausea and vomiting.

“You’re always somebody’s type! (blood type, that is)” “All the soarings of my mind begin in my blood.” “The best blood will at some time get into a fool or a mosquito.”

When studying hematology, pay close attention to the many cross connections to immunology. Make sure you master the different types of anemias. Be comfortable interpreting blood smears. When reviewing oncologic drugs, focus on mechanisms and adverse effects rather than details of clinical uses, which may be lower yield.

Please note that solid tumors are covered in their respective organ system chapters.

Fetal erythropoiesis Fetal erythropoiesis occurs in: Young Liver Synthesizes Blood.

Bone marrow (18 weeks to adult)

Embryonic globins: ζ and ε. Fetal hemoglobin (HbF) =αγ From fetal to adult hemoglobin: 2 2.

Adult hemoglobin (HbA) =αβ Alpha Always; Gamma Goes, Becomes Beta.

1 22.

HbF has higher affinity for O2 due to less avid binding of 2,3-BPG, allowing HbF to extract O2 from maternal hemoglobin (HbA1 and HbA2) across the placenta. HbA2 (α2δ2) is a form of adult hemoglobin present in small amounts.

Site of erythropoiesis 50 40 % of total 30 globin synthesis 20

Hemolytic disease of Also known as erythroblastosis fetalis. the newborn

Neutrophils Acute inflammatory response cells. Numbers Hypersegmented neutrophils (nucleus has 6+ • in bacterial infections. Phagocytic. lobes) are seen in vitamin B / folate deficiency.

A 12 Multilobed nucleus A . Specific granules A left shift with • band cells (immature contain leukocyte alkaline phosphatase neutrophils) reflects states of • myeloid (LAP), collagenase, lysozyme, and proliferation (eg, bacterial infections, CML). lactoferrin. Azurophilic granules (lysosomes) Important neutrophil chemotactic agents: C5a, contain proteinases, acid phosphatase, IL-8, LTB4, kallikrein, platelet-activating factor. myeloperoxidase, and β-glucuronidase.

Carry O2 to tissues and CO2 to lungs. Anucleate and lack organelles; biconcave A , with large surface area-to-volume ratio for rapid gas exchange. Life span of 120 days. Source of energy is glucose (90% used in glycolysis, 10% used in HMP shunt). Membranes contain Cl−/HCO3 − antiporter, which allow RBCs to export HCO3 − and transport CO2 from the periphery to the lungs for elimination.

Eryth = red; cyte = cell. Erythrocytosis = polycythemia = • Hct. Anisocytosis = varying sizes. Poikilocytosis = varying shapes.

Reticulocyte = immature RBC; reflects erythroid proliferation.

Bluish color (polychromasia) on Wright-Giemsa stain of reticulocytes represents residual ribosomal RNA.

Involved in 1° hemostasis. Small cytoplasmic fragments A derived from megakaryocytes. Life span of 8–10 days. When activated by endothelial injury, aggregate with other platelets and interact with fibrinogen to form platelet plug. Contain dense granules (Ca2+ , ADP, Serotonin,

Histamine; CASH) and α granules (vWF, fibrinogen, fibronectin, platelet factor 4). Approximately 1⁄3 of platelet pool is stored in the spleen.

in petechiae. vWF receptor: GpIb. Fibrinogen receptor: GpIIb/IIIa. Thrombopoietin stimulates megakaryocyte proliferation. Alfa granules contain vWF, fibrinogen, fibronectin, platelet factor four.

Monocytes Found in blood, differentiate into macrophages Mono = one (nucleus); cyte = cell. in tissues. Large, kidney-shaped nucleus A . Extensive “frosted glass” cytoplasm.

Phagocytose bacteria, cellular debris, and senescent RBCs. Long life in tissues. Differentiate from circulating blood monocytes

A . Activated by γ-interferon. Can function as antigen-presenting cell via MHC II. Important cellular component of granulomas (eg, TB, sarcoidosis).

Macro = large; phage = eater.

Macrophage naming varies by specific tissue type (eg, Kupffer cells in liver, histiocytes in connective tissue, Langerhans cells in skin, osteoclasts in bone, microglial cells in brain).

Lipid A from bacterial LPS binds CD14 on macrophages to initiate septic shock.

Basophils Mediate allergic reaction. Densely basophilic Basophilic—stains readily with basic stains. granules A contain heparin (anticoagulant) Basophilia is uncommon, but can be a sign of and histamine (vasodilator). Leukotrienes myeloproliferative disorders, particularly CML. synthesized and released on demand.

Dendritic cells Highly phagocytic antigen-presenting cells (APCs) A . Function as link between innate and adaptive immune systems. Express MHC class II and Fc receptors on surface.

Defend against helminthic infections (major basic protein). Bilobate nucleus. Packed with large eosinophilic granules of uniform size

A . Highly phagocytic for antigen-antibody complexes.

Produce histaminase, major basic protein (MBP, a helminthotoxin), eosinophil peroxidase, eosinophil cationic protein, and eosinophilderived neurotoxin.

Eosin = pink dye; philic = loving.

Causes of eosinophilia = PACCMAN: Parasites Asthma Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) Chronic adrenal insufficiency Myeloproliferative disorders Allergic processes Neoplasia (eg, Hodgkin lymphoma)

Lymphocytes Refer to B cells, T cells, and NK cells. B cells and T cells mediate adaptive immunity. NK cells are part of the innate immune response. Round, densely staining nucleus with small amount of pale cytoplasm

A .

Natural killer cells Important in innate immunity, especially against intracellular pathogens. Larger than B and T cells, with distinctive cytoplasmic lytic granules (containing perforin and granzymes) that, when released, act on target cells to induce apoptosis. Distinguish between healthy and infected cells by identifying cell surface proteins (induced by stress, malignant transformation, or microbial infections).

Mediate humoral immune response. Originate from stem cells in bone marrow and matures in marrow. Migrate to peripheral lymphoid tissue (follicles of lymph nodes, white pulp of spleen, unencapsulated lymphoid tissue). When antigen is encountered, B cells differentiate into plasma cells (which produce antibodies) and memory cells. Can function as an APC.

B = Bone marrow.

Mediate cellular immune response. Originate from stem cells in the bone marrow, but mature in the thymus. Differentiate into cytotoxic T cells (express CD8, recognize MHC I), helper T cells (express CD4, recognize MHC II), and regulatory T cells. CD28 (costimulatory signal) necessary for T-cell activation. Most circulating lymphocytes are T cells (80%).

T = Thymus.

CD4+ helper T cells are the primary target of HIV.

Rule of 8: MHC II × CD4 = 8; MHC I × CD8 = 8.

Plasma cells Produce large amounts of antibody specific to Multiple myeloma is a plasma cell dyscrasia.

a particular antigen. “Clock-face” chromatin distribution and eccentric nucleus, abundant

RER, and well-developed Golgi apparatus (arrows in A). Found in bone marrow and normally do not circulate in peripheral blood.

ACTIVATIONADP binding to P2Y12 receptor induces GpIIb/IIIa expression at platelet surface Platelets release ADP and Ca2+ (necessary for coagulation cascade), TXA2 ADHESIONPlatelets bind vWF via GpIb receptor at the site of injury only (specifc) ˜ platelets undergo conformational change EXPOSUREvWF binds to exposed collagen vWF is from Weibel-Palade bodies of endothelial cells and °-granules of platelets INJURYEndothelial damage ˜ transient vasoconstriction via neural stimulation refex and endothelin (released from damaged cell) 4A

Temporary plug stops bleeding; unstable, easily dislodged

Thrombogenesis Formation of insoluble fibrin mesh. Aspirin irreversibly inhibits cyclooxygenase, thereby inhibiting TXA2 synthesis. Clopidogrel, prasugrel, and ticlopidine inhibit ADP-induced expression of GpIIb/IIIa by irreversibly blocking P2Y12 receptor. Abciximab, eptifibatide, and tirofiban inhibit GpIIb/IIIa directly. Ristocetin activates vWF to bind GpIb. Failure of aggregation with ristocetin assay occurs in von Willebrand disease and Bernard-Soulier syndrome. vWF carries/protects factor VIII; volksWagen Factories make gr8 cars. Platelet ADP (P2Y12) receptor GpIIb/IIIa insertion Subendothelial collagen GpIb GpIIb/IIIa Fibrinogen vWF Thrombin-thrombomodulin complex Protein C Activated protein C Vascular endothelial cells Inside endothelial cells (vWF + factor VIII) Thromboplastin tPA, PGI2 Arachidonic acid Aspirin COX TXA2 vWF Fibrinogen Inside platelets Clopidogrel, prasugrel, ticlopidine Defciency: Bernard-Soulier syndrome Defciency: Glanzmann thrombasthenia Defciency: von Willebrand disease Abciximab, eptifbatide, tirofban 4B 4A

Hemophilia A: defciency of factor VIII (XR) Hemophilia B: defciency of factor IX (XR) Hemophilia C: defciency of factor XI (AR)

Note: Kallikrein activates bradykinin * = require Ca2+ , phospholipid; Fibrin degradation = inhibited by vitamin K antagonist warfarin products (eg, D-dimer)

Fibrin mesh stabilizes = activates but not part of coagulation cascade

Collagen, basement membrane, activated platelets Tissue factor (extrinsic) pathway Combined pathway Fibrinolytic system ANTICOAGULANTS: LMWH (eg, dalteparin, enoxaparin) heparin direct Xa inhibitors (eg, apixaban) fondaparinux ANTICOAGULANTS: -heparin -LMWH -direct thrombin inhibitors (eg, argatroban, bivalirudin, dabigatran) Tissue factor VII VIIa XII Prothrombin Kallikrein Bradykinin ˜vasodilation ˜ permeability ˜ painKinin cascade HMWK Thrombin Plasminogen Plasmin THROMBOLYTICS: alteplase, reteplase, streptokinase, tenecteplase ANTIFIBRINOLYTICS:aminocaproic acid, tranexamic acid tPA XI XIa IX X II IXa VIIIa VIII with vWF XIIa Xa Va* * IIa I Fibrinogen Aggregation Fibrin monomers Ia Ca2+ XIIIa XIII V Contact activation (intrinsic) pathway ---** * * * # # REGULATORY ANTICOAGULANT PROTEINS: -proteins C and S –C1-esterase inhibitor ---

Procoagulation Vitamin K deficiency: • synthesis of factors II, VII, IX, X, protein C, protein S.

Reduced vitamin K (active) Inactive II, VII, IX, X, C, S Clotting factors Anti-coagulants -glutamyl carboxylase (vitamin K-dependent) Epoxide reductase Mature, carboxylated II, VII, IX, X, C, S Fibrinogen Fibrin Liver Oxidized vitamin K (inactive)

Warfarin inhibits vitamin K epoxide reductase. Vitamin K administration can potentially reverse inhibitory effect of warfarin on clotting factor synthesis (delayed). FFP or PCC administration reverses action of warfarin immediately and can be given with vitamin K in cases of severe bleeding.

Neonates lack enteric bacteria, which produce vitamin K. Early administration of vitamin K overcomes neonatal deficiency/coagulopathy.

Factor VII (seven)—shortest half-life.

Warfarin,

Factor II (two)—longest (tallest) half-life.

factors VIIa, IXa, Xa, XIa, XIIa.

Heparin enhances the activity of antithrombin.

Principal targets of antithrombin: thrombin and factor Xa.

Antithrombin ProteinCpathway pathway Heparin-like molecule (enhances ATIII activity) Thrombin-thrombomodulin complex (endothelial cells) Antithrombin III Protein C Requires protein S Activated protein C Inhibits thrombin (and VIIa, IXa, Xa, XIa, XIIa) Cleaves and inactivates Va, VIIIa resistant to inhibition by activated protein C.

tPA is used clinically as a thrombolytic.

Liver disease, abetalipoproteinemia Projections of varying size at ("spur cells") irregular intervals.

Liver disease, ESRD, pyruvate Smaller and more uniform ("burr cells") kinase deficiency projections than acanthocytes

Bone marrow infiltration (eg, RBC "sheds a tear" because it's ("teardrop cells") myelofibrosis) mechanically squeezed out of its home in the bone marrow

MAHAs (eg, DIC, TTP/HUS, Fragmented RBCs (eg, "helmet" cells) HELLP syndrome), mechanical hemolysis (eg, heart valve prosthesis)

G6PD deficiency Due to removal of Heinz bodies by cells") splenic macrophages

Hereditary elliptocytosis Caused by mutation in genes encoding RBC membrane proteins (eg, spectrin)

Hereditary spherocytosis, Small, spherical cells without autoimmune hemolytic anemia central pallor

HbC disease, Asplenia, "HALT," said the hunter to his Liver disease, Thalassemia target

Sickle cell anemia Sickling occurs with low O2 conditions (eg, high altitude, acidosis)

Sideroblastic anemias (eg, lead Perinuclear mitochondria with (eg, in ringed poisoning, myelodysplastic excess iron (forming ring in

sideroblasts) syndromes, alcoholism) ringed sideroblasts) Require Prussian blue stain to be visualized

Functional hyposplenia (eg, sickle Basophilic nuclear remnants (do cell disease), asplenia not contain iron) Usually removed by splenic macrophages

Sideroblastic anemias, thalassemias Basophilic ribosomal precipitates (do not contain iron)

G6PD deficiency Denatured and precipitated hemoglobin (contain iron) Phagocytic removal of Heinz bodies bite cells Requires supravital stain (eg, crystal violet) to be visualized

Reticulocyte index Also called corrected reticulocyte count. Used to correct falsely elevated reticulocyte count in anemia. Measures appropriate bone marrow response to anemic conditions (effective erythropoiesis). High reticulocyte index (RI) indicates compensatory RBC production; low RI indicates inadequate response to correct anemia. Calculated as:

Microcytic, hypochromic anemias MCV < 80 fL.

Iron deficiency • iron due to chronic bleeding (eg, GI loss, menorrhagia), malnutrition, absorption disorders, GI surgery (eg, gastrectomy), or • demand (eg, pregnancy) • final step in heme synthesis. Labs: • iron, • TIBC, • ferritin, • free erythrocyte protoporphyrin, • RDW, • RI. Microcytosis and hypochromasia (• central pallor)

A . Symptoms: fatigue, conjunctival pallor B , pica (persistent craving and compulsive eating of nonfood substances), spoon nails (koilonychia). May manifest as glossitis, cheilosis, Plummer-Vinson syndrome (triad of iron deficiency anemia, esophageal webs, and dysphagia).

-thalassemia α-globin gene deletions on chromosome 16 • α-globin synthesis. cis deletion (deletions occur on same chromosome) prevalent in Asian populations; trans deletion (deletions occur on separate chromosomes) prevalent in African populations. Normal is αα/αα.

2 (α −/α −; trans) or α-thalassemia minor Mild microcytic, hypochromic (αα/− −; cis) anemia; cis deletion may worsen outcome for the carrier's offspring 3 (− −/− α) Hemoglobin H disease (HbH); Moderate to severe microcytic excess β-globin forms β4 hypochromic anemia 4 (− −/− −) Hemoglobin Barts disease; Hydrops fetalis; incompatible no α-globin, excess γ-globin with life forms γ4 -thalassemia Point mutations in splice sites and promoter sequences on chromosome 11 • β-globin synthesis. Prevalent in Mediterranean populations.

-thalassemia minor (heterozygote): β chain is underproduced. Usually asymptomatic. Diagnosis confirmed by • HbA2 (> 3.5%) on electrophoresis.

-thalassemia major (homozygote): β chain is absent severe microcytic, hypochromic anemia with target cells and increased anisopoikilocytosis C

requiring blood transfusion (2° hemochromatosis). Marrow expansion ("crew cut" on skull x-ray) skeletal deformities (eg, "chipmunk" facies). Extramedullary hematopoiesis hepatosplenomegaly. • risk of parvovirus B19–induced aplastic crisis. • HbF (αγ), HbA (αδ). HbF is protective in the infant and disease becomes symptomatic only after 6 months, when fetal hemoglobin declines. HbS/β -thalassemia heterozygote: mild to moderate sickle cell disease depending on amount of β-globin production.

Microcytic, hypochromic anemias (continued)

Lead poisoning Lead inhibits ferrochelatase and ALA dehydratase •• heme synthesis and • RBC protoporphyrin. Also inhibits rRNA degradation RBCs retain aggregates of rRNA (basophilic stippling). Symptoms of LEAD poisoning:

Lead Lines on gingivae (Burton lines) and on metaphyses of long bones D on x-ray.

Encephalopathy and Erythrocyte basophilic stippling.

Abdominal colic and sideroblastic Anemia.

Drops—wrist and foot drop. Dimercaprol and EDTA are 1st line of treatment. Succimer used for chelation for kids (It "sucks" to be a kid who eats lead). Exposure risk • in old houses with chipped paint.

Sideroblastic anemia Causes: genetic (eg, X-linked defect in ALA synthase gene), acquired (myelodysplastic syndromes), and reversible (alcohol is most common; also lead poisoning, vitamin B6 deficiency, copper deficiency, drugs [eg, isoniazid, linezolid]). Lab findings: • iron, normal/• TIBC, • ferritin. Ringed sideroblasts (with iron-laden, Prussian blue–stained mitochondria) seen in bone marrow E . Peripheral blood smear: basophilic stippling of RBCs. Some acquired variants may be normocytic or macrocytic.

Treatment: pyridoxine (B6, cofactor for ALA synthase).

Interpretation of iron studies •• = 1° disturbance.

Transferrin—transports iron in blood.

TIBC—indirectly measures transferrin.

Ferritin—1° iron storage protein of body.

aEvolutionary reasoning—pathogens use circulating iron to thrive. The body has adapted a system in which iron is stored within the cells of the body and prevents pathogens from acquiring circulating iron.

Macrocytic anemias MCV > 100 fL.

Megaloblastic anemia Impaired DNA synthesis maturation of RBC macrocytosis, hypersegmented neutrophils nucleus of precursor cells in bone marrow (arrow in

A), glossitis. delayed relative to maturation of cytoplasm. Causes: vitamin B12 deficiency, folate deficiency, medications (eg, hydroxyurea, phenytoin, methotrexate, sulfa drugs).

Vitamin B12 Causes: pernicious anemia, malabsorption (cobalamin) (eg, Crohn disease), pancreatic insufficiency, deficiency gastrectomy, insufficient intake (eg, veganism), Diphyllobothrium latum (fish tapeworm).

• homocysteine, • methylmalonic acid.

Neurologic symptoms: reversible dementia, subacute combined degeneration (due to involvement of B12 in fatty acid pathways and myelin synthesis): spinocerebellar tract, lateral corticospinal tract, dorsal column dysfunction. Folate supplementation in vitamin B12 deficiency can correct the anemia, but worsens neurologic symptoms.

Historically diagnosed with the Schilling test, a test that determines if the cause is dietary insufficiency vs malabsorption.

Anemia 2° to insufficient intake may take several years to develop due to liver's ability to store B12 (as opposed to folate deficiency).

Nonhemolytic, normocytic anemias

Anemia of chronic disease

Inflammation (eg, • IL-6) □• hepcidin (released by liver, binds ferroportin on intestinal mucosal cells and macrophages, thus inhibiting iron transport) □□ release of iron from macrophages and • iron absorption from gut. Associated with conditions such as chronic infections, neoplastic disorders, chronic kidney disease, and autoimmune diseases (eg, SLE, rheumatoid arthritis).

• iron, • TIBC, • ferritin. Normocytic, but can become microcytic. Treatment: address underlying cause of inflammation, judicious use of blood transfusion, consider erythropoiesisstimulating agents such as EPO (eg, in chronic kidney disease).

Aplastic anemia Caused by failure or destruction of hematopoietic stem cells due to: • Radiation and drugs (eg, benzene, chloramphenicol, alkylating agents, antimetabolites)

Viral agents (eg, EBV, HIV, hepatitis viruses)

Idiopathic (immune mediated, 1° stem cell defect); may follow acute hepatitis • reticulocyte count, • EPO.

Pancytopenia characterized by anemia, leukopenia, and thrombocytopenia (not to be confused with aplastic crisis, which causes anemia only). Normal cell morphology, but hypocellular bone marrow with fatty infiltration

A (dry bone marrow tap).

Symptoms: fatigue, malaise, pallor, purpura, mucosal bleeding, petechiae, infection.

Treatment: withdrawal of offending agent, immunosuppressive regimens (eg, antithymocyte globulin, cyclosporine), bone marrow allograft, RBC/platelet transfusion, bone marrow stimulation (eg, GM-CSF).

 valine). Mutant HbA is termed HbS. Causes extravascular and intravascular hemolysis.

Pathogenesis: low O2, high altitude, or acidosis precipitates sickling (deoxygenated HbS polymerizes) anemia, vaso-occlusive disease.

Newborns are initially asymptomatic because of • HbF and • HbS. Heterozygotes (sickle cell trait) have resistance to malaria. 8% of African Americans carry an HbS allele. Sickle cells are crescent-shaped RBCs A . "Crew cut" on skull x-ray due to marrow expansion from • erythropoiesis (also seen in thalassemias).

Complications in sickle cell disease:

Aplastic crisis (transient arrest of erythropoiesis due to parvovirus B19).

Autosplenectomy (Howell-Jolly bodies) • risk of infection by encapsulated organisms (eg, S pneumoniae).

Splenic infarct/sequestration crisis.

Salmonella osteomyelitis.

Painful vaso-occlusive crises: dactylitis (painful swelling of hands/feet), priapism, acute chest syndrome (respiratory distress, new pulmonary infiltrates on CXR, common cause of death), avascular necrosis, stroke.

papillary necrosis • hematuria. Hb electrophoresis: •• HbA, • HbF, • HbS. Treatment: hydroxyurea (• HbF), hydration.

A normocytic anemia that is usually idiopathic and Coombs ⊕. Two types:

Warm AIHA–chronic anemia in which IgG causes RBC agglutination. Seen in SLE and CLL and with certain drugs (eg, α-methyldopa). "Warm weather is Good." + complement causes RBC agglutination upon exposure to cold • painful, blue fingers and toes. Seen in CLL, Mycoplasma pneumoniae infections, infectious Mononucleosis.

Spherocytes and agglutinated RBCs A on peripheral blood smear.

Warm AIHA treatment: steroids, rituximab, splenectomy (if refractory).

Cold AIHA treatment: cold avoidance, rituximab.

Direct Coombs test—anti-Ig antibody (Coombs reagent) added to patient's RBCs. RBCs agglutinate if RBCs are coated with Ig.

For comparison, Indirect Coombs test—normal RBCs added to patient's serum. If serum has anti-RBC surface Ig, RBCs agglutinate when Coombs reagent added.

aCorticosteroids cause neutrophilia, despite causing eosinopenia and lymphopenia. Corticosteroids • activation of neutrophil adhesion molecules, impairing migration out of the vasculature to sites of inflammation. In contrast, corticosteroids sequester eosinophils in lymph nodes and cause apoptosis of lymphocytes.

Neutrophil left shift • neutrophil precursors, such as band cells A left shift is a shift to a more immature cell in and metamyelocytes, in peripheral blood. the maturation process.

Usually seen with neutrophilia in the acute response to infection or inflammation. Called leukoerythroblastic reaction when left shift is seen with immature RBCs. Occurs with severe response (eg, fibrosis, tumor taking up space in marrow).

Ferrochelatase and Protoporphyrin, ALA ALA dehydratase (blood)

Microcytic anemia (basophilic stippling in peripheral smear A , ringed sideroblasts in bone marrow), GI and kidney disease.

Children—exposure to lead paint mental deterioration.

Adults—environmental exposure (eg, batteries, ammunition) • headache, memory loss, demyelination (peripheral neuropathy).

B . Most common porphyria. Exacerbated with alcohol consumption. Causes: familial, hepatitis C. Treatment: phlebotomy, sun avoidance, antimalarials (eg, hydroxychloroquine).

Hemophilia A, B, or C A — • Intrinsic pathway coagulation defect (• PTT).

A: deficiency of factor VIII; X-linked recessive.

B: deficiency of factor IX; X-linked recessive.

C: deficiency of factor XI; autosomal recessive. Hemorrhage in hemophilia—hemarthroses (bleeding into joints, eg, knee A), easy bruising, bleeding after trauma or surgery (eg, dental procedures).

Treatment: desmopressin + factor VIII concentrate (A); factor IX concentrate (B); factor XI concentrate (C).

Vitamin K deficiency • General coagulation defect. Bleeding time normal.

• activity of factors II, VII, IX, X, protein C, protein S.

Hereditary thrombosis syndromes leading to hypercoagulability

Blood transfusion risks include infection transmission (low), transfusion reactions, iron overload (may lead to 2° hemochromatosis), hypocalcemia (citrate is a Ca2+ chelator), and hyperkalemia (RBCs may lyse in old blood units).

Leukemia Lymphoid or myeloid neoplasm with widespread involvement of bone marrow. Tumor cells are usually found in peripheral blood.

Lymphoma Discrete tumor mass arising from lymph nodes. Presentations often blur definitions.

Both may present with constitutional ("B") signs/symptoms: low-grade fever, night sweats, weight loss.

Localized, single group of nodes with Multiple lymph nodes involved; extranodal contiguous spread (stage is strongest predictor involvement common; noncontiguous spread. of prognosis). Better prognosis. Worse prognosis.

Characterized by Reed-Sternberg cells. Majority involve B cells; a few are of T-cell lineage.

Bimodal distribution: young adulthood and Can occur in children and adults. > 55 years; more common in men except for nodular sclerosing type.

Associated with EBV. May be associated with autoimmune diseases and viral infections (eg, HIV, EBV, HTLV).

Hodgkin lymphoma Contains Reed-Sternberg cells: distinctive tumor giant cells; binucleate or bilobed with the 2 halves as mirror images ("owl eyes" A). RS cells are CD15+ and CD30+ B-cell origin. 2 owl eyes × 15 = 30.

Plasma cell dyscrasias Characterized by monoclonal immunoglobulin (Ig) overproduction due to plasma cell disorder. Labs: serum protein electrophoresis (SPEP) or free light chain (FLC) assay for initial tests (M spike on SPEP represents overproduction of a monoclonal Ig fragment). For urinalysis, use 24-hr urine protein electrophoresis (UPEP) to detect light chain, as routine urine dipstick detects only albumin. Confirm with bone marrow biopsy.

Multiple myeloma Overproduction of IgG (55% of cases) > IgA. Clinical features: CRAB

Bone lytic lesions ("punched out" on X-ray A) • Back pain. Peripheral blood smear shows Rouleaux formation B (RBCs stacked like poker chips). Urinalysis shows Ig light chains (Bence Jones proteinuria) with ⊖ urine dipstick. Bone marrow analysis shows > 10% monoclonal plasma cells with clock-face chromatin C and intracytoplasmic inclusions containing IgG. Complications: • infection risk, 1° amyloidosis (AL).

Overproduction of IgM (macroglobulinemia because IgM is the largest Ig). Clinical features:

Hyperviscosity syndrome:

Retinal hemorrhages Bone marrow analysis shows >10% small lymphocytes with IgM-containing vacuoles (lymphoplasmacytic lymphoma). Complication: thrombosis.

syndromes hematopoiesis defects in cell maturation with bilobed ("duet") nuclei A . Typically seen of nonlymphoid lineages. Caused by de novo after chemotherapy. mutations or environmental exposure (eg, radiation, benzene, chemotherapy). Risk of transformation to AML.

Leukemias Unregulated growth and differentiation of WBCs in bone marrow marrow failure anemia (• RBCs), infections (• mature WBCs), and hemorrhage (• platelets). Usually presents with • circulating WBCs (malignant leukocytes in blood); rare cases present with normal/• WBCs. Leukemic cell infiltration of liver, spleen, lymph nodes, and skin (leukemia cutis) possible.

A B C D E Chronic myeloproliferative disorders Malignant hematopoietic neoplasms with varying impacts on WBCs and myeloid cell lines.

tumor cell lysis, most often in lymphomas/ leukemias. Release of K+ hyperkalemia,

Arrhythmias, release of PO 3− • hyperphosphatemia, hypocalcemia due to Ca2+ sequestration

Seizures, by PO43−. • nucleic acid breakdown tetany hyperuricemia acute kidney injury.

hydration, allopurinol, rasburicase. injury

Hemophagocytic Systemic overactivation of macrophages and cytotoxic T cells fever, pancytopenia, lymphohistiocytosis hepatosplenomegaly, ••• serum ferritin levels. Can be inherited or 2° to strong immunologic activation (eg, after EBV infection, malignancy). Bone marrow biopsy shows macrophages phagocytosing marrow elements

A .

Direct thrombin Bivalirudin, Argatroban, Dabigatran (only oral agent in class). inhibitors mechanISm Directly inhibits activity of free and clot-associated thrombin. clInIcal USe Venous thromboembolism, atrial fibrillation. Can be used in HIT, when heparin is BAD for the patient. Does not require lab monitoring. adVeRSe eFFectS Bleeding; can reverse dabigatran with idarucizumab. Consider PCC and/or antifibrinolytics (eg, tranexamic acid) if no reversal agent available.

mechanISm Activates antithrombin, which • action of IIa (thrombin) and factor Xa. Short half-life.

clInIcal USe Immediate anticoagulation for pulmonary embolism (PE), acute coronary syndrome, MI, deep venous thrombosis (DVT). Used during pregnancy (does not cross placenta). Follow PTT.

adVeRSe eFFectS Bleeding, thrombocytopenia (HIT), osteoporosis, drug-drug interactions. For rapid reversal (antidote), use protamine sulfate (positively charged molecule that binds negatively charged heparin).

noteS Low-molecular-weight heparins (eg, enoxaparin, dalteparin)—act predominantly on factor Xa. Fondaparinux acts only on factor Xa. Have better bioavailability and 2–4× longer half life than unfractionated heparin; can be administered subcutaneously and without laboratory monitoring. LMWHs undergo renal clearance (vs hepatic clearance of unfractionated heparin) and are contraindicated in renal insufficiency. Not easily reversible.

Heparin-induced thrombocytopenia (HIT) type 2—development of IgG antibodies against heparin-bound platelet factor 4 (PF4). Antibody-heparin-PF4 complex activates platelets • thrombosis and thrombocytopenia. Highest risk with unfractionated heparin. HIT type 1 characterized by nonimmunologic milder drop in platelet count, usually asymptomatic.

mechanISm Inhibits epoxide reductase, which interferes The EX-PresidenT went to war(farin). with γ-carboxylation of vitamin K–dependent clotting factors II, VII, IX, X, and proteins C,

S. Metabolism affected by polymorphisms in the gene for vitamin K epoxide reductase complex (VKORC1). In laboratory assay, has effect on EXtrinsic pathway and • PT. Long half-life.

clInIcal USe Chronic anticoagulation (eg, venous thromboembolism prophylaxis, and prevention of stroke in atrial fibrillation). Not used in pregnant women (because warfarin, unlike heparin, crosses placenta). Follow PT/INR.

Bleeding, teratogenic, skin/tissue necrosis A , drug-drug interactions.

Initial risk of hypercoagulation: protein C has a shorter half-life than factors II and X. Existing protein C depletes before existing factors II and X deplete, and before warfarin can reduce factors II and X production hypercoagulation. Skin/tissue necrosis within first few days of large doses believed to be due to small vessel microthrombosis.

For reversal of warfarin, give vitamin K.

For rapid reversal, give fresh frozen plasma (FFP) or PCC.

Heparin “bridging”: heparin frequently used when starting warfarin. Heparin’s activation of antithrombin enables anticoagulation during initial, transient hypercoagulable state caused by warfarin. Initial heparin therapy reduces risk of recurrent venous thromboembolism and skin/tissue necrosis.

Metabolized by cytochrome P-450.

Direct factor Xa inhibitors ApiXaban, rivaroXaban.

mechanISm Bind to and directly inhibit factor Xa.

clInIcal USe Treatment and prophylaxis for DVT and PE; stroke prophylaxis in patients with atrial fibrillation. Oral agents do not usually require coagulation monitoring.

adVeRSe eFFectS Bleeding. Reverse with andeXanet alfa.

Thrombolytics Alteplase (tPA), reteplase (rPA), streptokinase, tenecteplase (TNK-tPA).

mechanISm Directly or indirectly aid conversion of plasminogen to plasmin, which cleaves thrombin and fibrin clots. • PT, • PTT, no change in platelet count.

clInIcal USe Early MI, early ischemic stroke, direct thrombolysis of severe PE.

adVeRSe eFFectS Bleeding. Contraindicated in patients with active bleeding, history of intracranial bleeding, recent surgery, known bleeding diatheses, or severe hypertension. Nonspecific reversal with antifibrinolytics (eg, aminocaproic acid, tranexamic acid), platelet transfusions, and factor corrections (eg, cryoprecipitate, FFP, PCC).

ADP receptor inhibitors Clopidogrel, prasugrel, ticagrelor (reversible), ticlopidine.

mechanISm Irreversibly block ADP (P2Y12) receptor, which prevents subsequent platelet aggregation. Prevent expression of glycoproteins IIb/IIIa on platelet surface.

clInIcal USe Acute coronary syndrome; coronary stenting. • incidence or recurrence of thrombotic stroke.

adVeRSe eFFectS Neutropenia (ticlopidine). TTP may be seen.

Glycoprotein IIb/IIIa inhibitors Abciximab, eptifibatide, tirofiban.

mechanISm Bind to the glycoprotein receptor IIb/IIIa (fibrinogen receptor) on activated platelets, preventing aggregation. Abciximab is made from monoclonal antibody Fab fragments.

clInIcal USe Unstable angina, percutaneous coronary intervention.

adVeRSe eFFectS Bleeding, thrombocytopenia.

Platinum agents (eg, cisplatin)

Alkylating agents:Azathioprine

Ifosfamide 5-fuorouracil Rb, p53 modulate Nitrosoureas (eg, carmustine) Hydroxyurea G restriction point Methotrexate 1 6-mercaptopurine

Nucleotide synthesis DNA RNA Cellular division MTX, 5-FU: ˜thymidine synthesis 6-MP: ˜de novo purine synthesis Hydroxyurea: inhibits ribonucleotide reductase Alkylating agents, platinum agents: cross-link DNA Bleomycin: DNA strand breakage Dactinomycin, doxorubicin: DNA intercalators Etoposide/teniposide: inhibits topoisomerase II Irinotecan/topotecan: inhibits topoisomerase I Vinca alkaloids: inhibit microtubule formation Paclitaxel: inhibits microtubule disassembly Protein

Azathioprine, Purine (thiol) analogs Preventing organ rejection, Myelosuppression; GI, liver 6-mercaptopurine □• de novo purine synthesis. rheumatoid arthritis, IBD, toxicity. Activated by HGPRT. SLE; used to wean patients Azathioprine and 6-MP are Azathioprine is metabolized off steroids in chronic disease metabolized by xanthine into 6-MP. and to treat steroid-refractory oxidase; thus both have • risk chronic disease. of toxicity with allopurinol or febuxostat.

Cladribine Purine analog • multiple Hairy cell leukemia. Myelosuppression, mechanisms (eg, inhibition nephrotoxicity, and of DNA polymerase, DNA neurotoxicity. strand breaks).

Cytarabine Pyrimidine analog □ DNA Leukemias (AML), lymphomas. Myelosuppression with (arabinofuranosyl chain termination. At higher megaloblastic anemia. cytidine) concentrations, inhibits DNA CYTarabine causes polymerase. panCYTopenia.

5-fluorouracil Pyrimidine analog bioactivated to 5-FdUMP, which covalently complexes with thymidylate synthase and folic acid. Capecitabine is a prodrug. This complex inhibits thymidylate synthase □• dTMP □• DNA synthesis.

Colon cancer, pancreatic cancer, actinic keratosis, basal cell carcinoma (topical).

Effects enhanced with the addition of leucovorin.

Myelosuppression, palmarplantar erythrodysesthesia (hand-foot syndrome).

Methotrexate Folic acid analog that competitively inhibits dihydrofolate reductase □• dTMP □• DNA synthesis.

Cancers: leukemias (ALL), lymphomas, choriocarcinoma, sarcomas.

Non-neoplastic: ectopic pregnancy, medical abortion (with misoprostol), rheumatoid arthritis, psoriasis, IBD, vasculitis.

Myelosuppression, which is reversible with leucovorin (folinic acid) “rescue.”

Hepatotoxicity. Mucositis (eg, mouth ulcers). Pulmonary fibrosis. Folate deficiency, which may be teratogenic (neural tube defects) without supplementation.

Nephrotoxicity.

aAll are S-phase specific except cladribine, which is cell cycle nonspecific.

Cyclophosphamide, ifosfamide

Myelosuppression; SIADH; Fanconi syndrome (ifosfamide); hemorrhagic cystitis and bladder cancer, prevented with mesna (sulfhydryl group of mesna binds toxic metabolites) and adequate hydration.

Microtubule inhibitors Cisplatin, carboplatin, oxaliplatin mechanISm Cross-link DNA.

clInIcal USe Testicular, bladder, ovary, GI, and lung carcinomas.

adVeRSe eFFectS Nephrotoxicity (including Fanconi syndrome), peripheral neuropathy, ototoxicity. Prevent nephrotoxicity with amifostine (free radical scavenger) and chloride (saline) diuresis.

Etoposide, teniposide mechanISm Inhibit topoisomerase II □• DNA degradation (cell cycle arrest in G2 and S phases).

clInIcal USe Solid tumors (particularly testicular and small cell lung cancer), leukemias, lymphomas.

adVeRSe eFFectS Myelosuppression, alopecia.

Irinotecan, topotecan mechanISm Inhibit topoisomerase I and prevent DNA unwinding and replication.

clInIcal USe Colon cancer (irinotecan); ovarian and small cell lung cancers (topotecan).

adVeRSe eFFectS Severe myelosuppression, diarrhea.

mechanISm Inhibits ribonucleotide reductase □• DNA Synthesis (S-phase specific).

clInIcal USe Myeloproliferative disorders (eg, CML, polycythemia vera), sickle cell disease (• HbF).

adVeRSe eFFectS Severe myelosuppression, megaloblastic anemia.

mechanISm Monoclonal antibody against VEGF. Inhibits angiogenesis (BeVacizumab inhibits Blood Vessel formation).

clInIcal USe Solid tumors (eg, colorectal cancer, renal cell carcinoma), wet age-related macular degeneration.

adVeRSe eFFectS Hemorrhage, blood clots, and impaired wound healing.

mechanISm EGFR tyrosine kinase inhibitor.

clInIcal USe Non-small cell lung cancer.

adVeRSe eFFectS Rash, diarrhea.

Cetuximab, panitumumab mechanISm Monoclonal antibodies against EGFR.

clInIcal USe Stage IV colorectal cancer (wild-type KRAS), head and neck cancer.

adVeRSe eFFectS Rash, elevated LFTs, diarrhea.

Imatinib, dasatinib, nilotinib mechanISm Tyrosine kinase inhibitors of bcr-abl (encoded by Philadelphia chromosome fusion gene in CML) and c-kit (common in GI stromal tumors).

clInIcal USe CML, GI stromal tumors (GISTs).

adVeRSe eFFectS Fluid retention.

mechanISm Monoclonal antibody against CD20, which is found on most B-cell neoplasms.

clInIcal USe Non-Hodgkin lymphoma, CLL, ITP, rheumatoid arthritis, TTP, AIHA.

adVeRSe eFFectS • risk of progressive multifocal leukoencephalopathy.

Bortezomib, carfilzomib mechanISm Proteasome inhibitors, induce arrest at G2-M phase and apoptosis.

clInIcal USe Multiple myeloma, mantle cell lymphoma.

adVeRSe eFFectS Peripheral neuropathy, herpes zoster reactivation.

Tamoxifen, raloxifene mechanISm Selective estrogen receptor modulators (SERMs)—receptor antagonists in breast and agonists in bone. Block the binding of estrogen to ER ⊕ cells.

clInIcal USe Breast cancer treatment (tamoxifen only) and prevention. Raloxifene also useful to prevent osteoporosis.

adVeRSe eFFectS Tamoxifen—partial agonist in endometrium, which • the risk of endometrial cancer. Raloxifene—no • in endometrial carcinoma (so you can relax!), because it is an estrogen receptor antagonist in endometrial tissue. Both • risk of thromboembolic events (eg, DVT, PE) and “hot flashes.” mechanISm Monoclonal antibody against HER-2 (c-erbB2), a tyrosine kinase receptor. Helps kill cancer cells that overexpress HER-2 through inhibition of HER-2 initiated cellular signaling and antibody-dependent cytotoxicity.

clInIcal USe HER-2 ⊕ breast cancer and gastric cancer (tras2zumab).

adVeRSe eFFectS Dilated cardiomyopathy. “Heartceptin” damages the heart.

Dabrafenib, vemurafenib mechanISm Recombinant uricase that catalyzes metabolism of uric acid to allantoin.

clInIcal USe Prevention and treatment of tumor lysis syndrome.

Bleomycin, Busulfan

Nonspecific common toxicities of nearly all cytotoxic chemotherapies include myelosuppression (neutropenia, anemia, thrombocytopenia), GI toxicity (nausea, vomiting, mucositis), alopecia.

Musculoskeletal, Skin, and Connective Tissue “Rigid, the skeleton of habit alone upholds the human frame.” “Beauty may be skin deep, but ugly goes clear to the bone.” “The function of muscle is to pull and not to push, except in the case of the genitals and the tongue.” “To thrive in life you need three bones. A wishbone. A backbone. And a funny bone.”

This chapter provides information you will need to understand certain anatomical dysfunctions, rheumatic diseases, and dermatologic conditions. Be able to interpret 3D anatomy in the context of radiologic imaging. For the rheumatic diseases, create instructional cases or personas that include the most likely presentation and symptoms: risk factors, gender, important markers (eg, autoantibodies), and other epidemiologic factors. Doing so will allow you to answer the higher order questions that are likely to be asked on the exam.

`mUsCUlosKElEtal, sKin, and ConnECtiVE tissUE—anatomy and physiology

Rotator cuff muscles Shoulder muscles that form the rotator cuff: SItS (small t is for teres minor).

Supraspinatus (suprascapular nerve)— abducts arm initially (before the action of the deltoid); most common rotator cuff injury (trauma or degeneration and impingement • tendinopathy or tear [arrow in

A]), assessed by “empty/full can” test nerves)—internally rotates and adducts arm Innervated primarily by C5-C6.

Axillary (C5-C6) Fractured surgical neck of humerus Flattened deltoid Anterior dislocation of humerus Loss of arm abduction at shoulder (> 15°) Loss of sensation over deltoid and lateral arm

Musculocutaneous Upper trunk compression • biceps (C5-6) reflex (C5-C7) Weakness of forearm flexion and supination Loss of sensation over lateral forearm

Radial (C5-T1) Compression of axilla, eg, due to crutches or Wrist drop: loss of elbow, wrist, and finger sleeping with arm over chair (“Saturday night extension palsy”) • grip strength (wrist extension necessary for

Midshaft fracture of humerus maximal action of flexors) Repetitive pronation/supination of forearm, eg, Loss of sensation over posterior arm/forearm and due to screwdriver use (“finger drop”) dorsal hand

Median (C5-T1) Supracondylar fracture of humerus proximal “Ape hand” and “Pope’s blessing” lesion of the nerve Loss of wrist flexion, flexion of lateral fingers, Carpal tunnel syndrome and wrist laceration thumb opposition, lumbricals of index and distal lesion of the nerve middle fingers

Loss of sensation over thenar eminence and dorsal and palmar aspects of lateral 31⁄2 fingers with proximal lesion

Ulnar (C8-T1) Fracture of medial epicondyle of humerus “funny bone” (proximal lesion) Fractured hook of hamate (distal lesion) from fall on outstretched hand

Radial deviation of wrist upon flexion (proximal lesion)

Loss of wrist flexion, flexion of medial fingers, abduction and adduction of fingers (interossei), actions of medial 2 lumbrical muscles

Loss of sensation over medial 11/2 fingers including hypothenar eminence

Humerus fractures, proximally to distally, follow the ARM (Axillary • Radial • Median)

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Erb palsy (“waiter’s tip”) Klumpke palsy (claw hand) Wrist drop Winged scapula Deltoid paralysis “Saturday night palsy” (wrist drop) Di⁄culty fexing elbow, variable sensory loss Decreased thumb function, “Pope’s blessing”

Intrinsic muscles of hand, claw hand

Erb palsy (“waiter’s Traction or tear Infants—lateral Deltoid, Abduction (arm tip”) of upper trunk: traction on neck supraspinatus hangs by side) C5-C6 roots during delivery medially rotated) Biceps brachii Flexion, supination Herb gets DIBs (arm extended and on tips pronated)

Klumpke palsy Traction or tear Infants—upward Intrinsic hand Total claw hand: of lower trunk: force on arm muscles: lumbricals normally C8-T1 roots during delivery lumbricals, flex MCP joints and

Adults—trauma interossei, extend DIP and PIP (eg, grabbing a thenar, joints tree branch to hypothenar break a fall)

Thoracic outlet Compression Cervical rib Same as Klumpke Atrophy of intrinsic syndrome of lower trunk (arrows in

A , palsy hand muscles; and subclavian Pancoast tumor ischemia, pain, vessels, most and edema commonly due to vascular within the compression scalene triangle

Winged scapula Lesion of long Axillary node Serratus anterior Inability to anchor thoracic nerve, dissection after scapula to thoracic roots C5-C7 mastectomy, cage cannot ("wings of stab wounds abduct arm heaven") above horizontal position

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Wrist region Scaphoid, Lunate, Triquetrum, Pisiform, A Hamate, Capitate, Trapezoid, Trapezium A.

(So Long To Pinky, Here Comes The Thumb) 1st MC Hamate is the most commonly fractured carpal bone, Trapezium typically due to a fall on an outstretched hand.

Complications of proximal scaphoid fractures include avascular necrosis and nonunion due to retrograde blood supply from a branch of the radial artery. Fracture not always seen on initial x-ray.

Dislocation of lunate may cause acute carpal tunnel syndrome.

Plane of section

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Distortions of the hand At rest, a balance exists between the extrinsic flexors and extensors of the hand, as well as the intrinsic muscles of the hand—particularly the lumbrical muscles (flexion of MCP, extension of DIP and PIP joints). "Clawing"—seen best with distal lesions of median or ulnar nerves. Remaining extrinsic flexors of the digits exaggerate the loss of the lumbricals fingers extend at MCP, flex at DIP and PIP joints. Deficits less pronounced in proximal lesions; deficits present during voluntary flexion of the digits.

Note: Atrophy of the thenar eminence (unopposable thumb "ape hand") can be seen in median nerve lesions, while atrophy of the hypothenar eminence can be seen in ulnar nerve lesions.

Actions of hip muscles

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Obturator (L2-L4) Sensory—medial thigh Motor—obturator externus, adductor longus, adductor brevis, gracilis, pectineus, adductor magnus Pelvic surgery • thigh sensation (medial) and adduction Femoral (L2-L4) Sensory—anterior thigh, medial leg Motor—quadriceps, iliacus, pectineus, sartorius Pelvic fracture • leg extension (• patellar reflex)

Superficial peroneal nerve:

Sensory—dorsum of foot (except webspace between hallux and 2nd digit) and brevis Deep peroneal nerve:

Motor—tibialis anterior Sensory—sole of foot Motor—biceps femoris (long head), triceps surae, plantaris, popliteus, flexor muscles of foot

Motor—gluteus medius, gluteus minimus, tensor fascia latae Trauma or compression of lateral aspect of leg, fibular neck fracture

Knee trauma, Baker cyst (proximal lesion); tarsal tunnel syndrome (distal lesion)

Iatrogenic injury during intramuscular injection to superomedial gluteal region (prevent by choosing superolateral quadrant, preferably anterolateral region) PED = Peroneal Everts and Dorsiflexes; if injured, foot dropPED

Loss of sensation on dorsum of foot

Foot drop—inverted and plantarflexed at rest, loss of eversion and dorsiflexion; “steppage gait”

TIP = Tibial Inverts and Plantarflexes; if injured, can’t stand on TIPtoes

Inability to curl toes and loss of sensation on sole; in proximal lesions, foot everted at rest with loss of inversion and plantar flexion

Trendelenburg sign/gait— pelvis tilts because weight-bearing leg cannot maintain alignment of pelvis through hip abduction

Lesion is contralateral to the side of the hip that drops, ipsilateral to extremity on which the patient stands

Knee exam Lateral femoral condyle to anterior tibia: ACL. Medial femoral condyle to posterior tibia: PCL. LAMP.

Ankle sprains Anterior TaloFibular ligament—most common ankle sprain overall, classified as a low ankle sprain. Due to overinversion/supination of foot. Anterior inferior tibiofibular ligament—most common high ankle sprain. Always Tears First.

Neurovascular pairing Nerves and arteries are frequently named together by the bones/regions with which they are associated. The following are exceptions to this naming convention.

Surgical neck of humerus Axillary Posterior circumflex

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Motoneuron action T-tubules are extensions of plasma membrane in contact with the sarcoplasmic reticulum, allowing potential to muscle for coordinated contraction of striated muscles. contraction

Action potential opens presynaptic voltage-gated Ca2+ channels, inducing acetylcholine (ACh) release. Postsynaptic ACh binding leads to muscle cell depolarization at the motor end plate. Depolarization travels over the entire muscle cell and deep into the muscle via the T-tubules. Membrane depolarization induces conformational changes in the voltage-sensitive dihydropyridine receptor (DHPR) and its mechanically coupled ryanodine receptor (RR) • Ca2+ release from the sarcoplasmic reticulum into the cytoplasm. Tropomyosin is blocking myosin-binding sites on the actin filament. Released Ca2+ binds to troponin C (TnC), shifting tropomyosin to expose the myosin-binding sites. The myosin head binds strongly to actin, forming a crossbridge. Pi is then released, initiating the power stroke. During the power stroke, force is produced as myosin pulls on the thin filament

A . Muscle shortening occurs, with shortening of H and I bands and between Z lines (HIZ shrinkage). The A band remains the same length (A band is Always the same length). ADP is released at the end of the power stroke. Binding of new ATP molecule causes detachment of myosin head from actin filament. Ca2+ is resequestered. ATP hydrolysis into ADP and Pi results in myosin head returning to high-energy position (cocked). The myosin head can bind to a new site on actin to form a crossbridge if Ca2+ remains available.

Sarcomere (Z line to Z line)

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Types of muscle fibers

Acetylcholine, bradykinin, etc

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Muscle proprioceptors Specialized sensory receptors that relay information about muscle dynamics.

Membranous Bones of calvarium, facial bones, and clavicle. Woven bone formed directly without cartilage. Later ossification remodeled to lamellar bone.

MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE `pathology SECTION III 459

Cell biology of bone

Osteoblast Builds bone by secreting collagen and catalyzing mineralization in alkaline environment via ALP. Differentiates from mesenchymal stem cells in periosteum. Osteoblastic activity measured by bone ALP, osteocalcin, propeptides of type I procollagen.

Osteoclast Dissolves ("crushes") bone by secreting H+ and collagenases. Differentiates from a fusion of monocyte/macrophage lineage precursors. RANK receptors on osteoclasts are stimulated by RANKL (RANK ligand, expressed on osteoblasts). OPG (osteoprotegerin, a RANKL decoy receptor) binds RANKL to prevent RANK-RANKL interaction □• osteoclast activity.

`mUsCUlosKElEtal, sKin, and ConnECtiVE tissUE—pathology

Overuse injuries of the elbow

Metacarpal neck Also called boxer's fracture. Common fracture fracture caused by direct blow with a closed fist (eg, from punching a wall). Most commonly seen in 4th and 5th metacarpals

A .

Entrapment of median nerve in carpal tunnel (between transverse carpal ligament and carpal bones) □ nerve compression □ paresthesia, pain, and numbness in distribution of median nerve. Thenar eminence atrophies

B but sensation spared, because palmar cutaneous branch enters hand external to carpal tunnel.

Suggested by ⊕ Tinel sign (percussion of wrist causes tingling) and Phalen maneuver (90° flexion of wrist causes tingling).

Associated with pregnancy (due to edema), rheumatoid arthritis, hypothyroidism, diabetes, acromegaly, dialysis-related amyloidosis; may be associated with repetitive use.

MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE `pathology SECTION III 460

Clavicle fractures Common in children and as birth trauma. Usually caused by a fall on outstretched hand or by direct trauma to shoulder. Weakest point at the junction of middle and lateral thirds; fractures at the middle third segment are most common. Presents as shoulder drop, shortened clavicle (lateral fragment is depressed due to arm weight and medially rotated by arm adductors [eg, pectoralis major]).

“Unhappy triad” Common injury in contact sports due to lateral force applied to a planted foot. Consists of damage to the ACL A , MCL, and medial meniscus (attached to MCL). However, lateral meniscus involvement is more common than with ACL and MCL injury. Presents with acute pain and signs of joint instability.

MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE `pathology SECTION III 461

Plantar fasciitis Inflammation of plantar aponeurosis characterized by heel pain (worse with first steps in the morning or after period of inactivity) and tenderness.

Developmental Abnormal acetabulum development in newborns. Major risk factor includes breech presentation. dysplasia of the hip Results in hip instability/dislocation. Commonly tested with Ortolani and Barlow maneuvers (manipulation of newborn hip reveals a “clunk”). Confirmed via ultrasound (x-ray not used until ~4–6 months because cartilage is not ossified).

Legg-Calvé-Perthes Idiopathic avascular necrosis of femoral head. Commonly presents between 5–7 years with disease insidious onset of hip pain that may cause child to limp. More common in males (4:1 ratio). Initial x-ray often normal.

Osgood-Schlatter Also called traction apophysitis. Overuse injury caused by repetitive strain and chronic avulsion of disease the secondary ossification center of proximal tibial tubercle. Occurs in adolescents after growth spurt. Common in running and jumping athletes. Presents with progressive anterior knee pain.

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Achondroplasia Failure of longitudinal bone growth (endochondral ossification) short limbs. Membranous ossification is not affected large head relative to limbs. Constitutive activation of fibroblast growth factor receptor (FGFR3) actually inhibits chondrocyte proliferation. > 85% of mutations occur sporadically; autosomal dominant with full penetrance (homozygosity is lethal). Associated with • paternal age. Most common cause of short-limbed dwarfism.

Trabecular (spongy) and cortical bone lose mass despite normal bone mineralization and lab values (serum Ca^{2+} and PO_4^{3-}).

Most commonly due to • bone resorption related to • estrogen levels and old age. Can be 2° to drugs (eg, steroids, alcohol, anticonvulsants, anticoagulants, thyroid replacement therapy) or other conditions (eg, hyperparathyroidism, hyperthyroidism, multiple myeloma, malabsorption syndromes, anorexia).

Diagnosed by bone mineral density measurement by DEXA (dual-energy X-ray absorptiometry) at the lumbar spine, total hip, and femoral neck, with a T-score of ≤–2.5 or by a fragility fracture (eg, fall from standing

height, minimal trauma) at hip or vertebra. One time screening recommended in women ≥ 65 years old.

Prophylaxis: regular weight-bearing exercise and adequate Ca2+ and vitamin D intake throughout adulthood.

Treatment: bisphosphonates, teriparatide, SERMs, rarely calcitonin; denosumab (monoclonal antibody against RANKL).

Can lead to vertebral compression fractures A —acute back pain, loss of height, kyphosis. Also can present with fractures of femoral neck, distal radius (Colles fracture).

Central expansion Restricted of intervertebral intervertebral disc foramen

Osteopetrosis Failure of normal bone resorption due to defective osteoclasts thickened, dense bones that are prone to fracture. Mutations (eg, carbonic anhydrase II) impair ability of osteoclast to generate acidic environment necessary for bone resorption. Overgrowth of cortical bone fills marrow space pancytopenia, extramedullary hematopoiesis. Can result in cranial nerve impingement and palsies due to narrowed foramina.

X-rays show diffuse symmetric sclerosis (bone-in-bone, “stone bone” A). Bone marrow transplant is potentially curative as osteoclasts are derived from monocytes.

Defective mineralization of osteoid (osteomalacia) or cartilaginous growth plates (rickets, only in children). Most commonly due to vitamin D deficiency.

X-rays show osteopenia and “Looser zones” (pseudofractures) in osteomalacia, epiphyseal widening and metaphyseal cupping/fraying in rickets. Children with rickets have pathologic bow legs (genu varum

A), bead-like costochondral junctions (rachitic rosary B), craniotabes (soft skull).

• serum PO43− . Hyperactivity of osteoblasts • ALP.

Also called Paget disease of bone. Common, localized disorder of bone remodeling caused by • osteoclastic activity followed by • osteoblastic activity that forms poor-quality bone. Serum Ca2+ , phosphorus, and PTH levels are normal. • ALP. Mosaic pattern of woven and lamellar bone (osteocytes within lacunae in chaotic juxtapositions); long bone chalk-stick fractures. • blood flow from • arteriovenous shunts may cause high-output heart failure. • risk of osteosarcoma.

Hat size can be increased due to skull thickening A ; hearing loss is common due to auditory foramen narrowing.

Stages of Paget disease: activity Treatment: bisphosphonates.

Avascular necrosis of bone

Infarction of bone and marrow, usually very painful. Most common site is femoral head (watershed zone) A (due to insufficiency of medial circumflex femoral artery). Causes include Corticosteroids, Alcoholism, Sickle cell disease, Trauma, SLE, “the Bends” (caisson/decompression disease), LEgg-Calvé-Perthes disease (idiopathic), Gaucher disease, Slipped capital femoral epiphysis—CASTS Bend LEGS.

Branch of obturator artery

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MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE `pathology SECTION III 465

Anaplastic small blue cells of neuroectodermal origin (resemble lymphocytes)

F .

Differentiate from conditions with similar morphology (eg, lymphoma, chronic osteomyelitis) by testing for t(11;22) (fusion protein EWS-FLI1).

“Onion skin” periosteal reaction in bone.

Aggressive with early metastases, but responsive to chemotherapy.

11 + 22 = 33 (Patrick Ewing’s jersey number).

MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE `pathology SECTION III 466

Joint Findings Osteophytes (bone spurs), joint space narrowing, subchondral sclerosis and cysts. Synovial fluid noninflammatory (WBC < 2000/mm3). Development of Heberden nodes B (at DIP) and Bouchard nodes C (at PIP), and 1st CMC; not MCP.

Erosions, juxta-articular osteopenia, soft tissue swelling, subchondral cysts, joint space narrowing. Deformities: cervical subluxation, ulnar finger deviation, swan neck

D , boutonniere E . Involves MCP, PIP, wrist; not DIP or 1st CMC.

*Extraarticular manifestations include rheumatoid nodules (fibrinoid necrosis with palisading histiocytes) in subcutaneous tissue and lung (+ pneumoconiosis • Caplan syndrome), interstitial lung disease, pleuritis, pericarditis, anemia of chronic disease, neutropenia + splenomegaly (Felty syndrome), AA amyloidosis, Sjögren syndrome, scleritis, carpal tunnel syndrome.

MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE `pathology SECTION III 467

Findings Acute inflammatory monoarthritis caused by precipitation of monosodium urate crystals in joints A . Risk factors: male sex, hypertension, obesity, diabetes, dyslipidemia, alcohol use. Strongest risk factor is hyperuricemia, which can be caused by:

Underexcretion of uric acid (90% of patients)—largely idiopathic, potentiated by renal failure; can be exacerbated by certain medications (eg, thiazide diuretics).

Overproduction of uric acid (10% of patients)—Lesch-Nyhan syndrome, PRPP excess, • cell turnover (eg, tumor lysis syndrome), von Gierke disease.

Crystals are needle shaped and ⊖ birefringent under polarized light (yellow under parallel light, blue under perpendicular light B). Serum uric acid levels may be normal during an acute attack.

symptoms Asymmetric joint distribution. Joint is swollen, red, and painful. Classic manifestation is painful MTP joint of big toe (podagra). Tophus formation C (often on external ear, olecranon bursa, or Achilles tendon). Acute attack tends to occur after a large meal with foods rich in purines (eg, red meat, seafood), trauma, surgery, dehydration, diuresis, or alcohol consumption (alcohol metabolites compete for same excretion sites in kidney as uric acid □• uric acid secretion and subsequent buildup in blood).

tREatmEnt Acute: NSAIDs (eg, indomethacin), glucocorticoids, colchicine. Chronic (preventive): xanthine oxidase inhibitors (eg, allopurinol, febuxostat).

Previously called pseudogout. Deposition of The blue P’s—blue (when Parallel), Positive calcium pyrophosphate crystals within the birefringence, calcium Pyrophosphate, joint space. Occurs in patients > 50 years old; Pseudogout both sexes affected equally. Usually idiopathic, sometimes associated with hemochromatosis, hyperparathyroidism, joint trauma.

Pain and swelling with acute inflammation (pseudogout) and/or chronic degeneration (pseudo-osteoarthritis). Most commonly affected joint is the knee.

Chondrocalcinosis (cartilage calcification) on x-ray.

Crystals are rhomboid and weakly ⊕ birefringent under polarized light (blue when parallel to light)

A .

Acute treatment: NSAIDs, colchicine, glucocorticoids. Prophylaxis: colchicine.

Septic arthritis S aureus, Streptococcus, and Neisseria gonorrhoeae are common causes. Affected joint is swollen A , red, and painful. Synovial

fluid purulent (WBC > 50,000/mm3). Gonococcal arthritis—STI that presents as either purulent arthritis (eg, knee) or triad of polyarthralgia, tenosynovitis (eg, hand), dermatitis (eg, pustules).

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MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE `pathology SECTION III 470

Libman-Sacks Endocarditis—nonbacterial, verrucous thrombi usually on mitral or aortic valve and can be present on either surface of the valve (but usually on undersurface). LSE in SLE.

Lupus nephritis (glomerular deposition of DNA-anti-DNA immune complexes) can be nephritic or nephrotic (causing hematuria or proteinuria). Most common and severe type is diffuse proliferative.

Common causes of death in SLE: Renal disease (most common), Infections, Cardiovascular disease (accelerated CAD).

In an anti-SSA ⊕ pregnant woman, • risk of newborn developing neonatal lupus congenital heart block, periorbital/diffuse rash, transaminitis, and cytopenias at birth.

RASH OR PAIN: Rash (malar

A or discoid B) Arthritis (nonerosive) Serositis (eg, pleuritis, pericarditis) Hematologic disorders (eg, cytopenias) Oral/nasopharyngeal ulcers (usually painless) Renal disease Photosensitivity Antinuclear antibodies Immunologic disorder (anti-dsDNA, anti-Sm, antiphospholipid) Neurologic disorders (eg, seizures, psychosis)

Lupus patients die with Redness In their Cheeks.

Mixed connective Features of SLE, systemic sclerosis, and/or tissue disease polymyositis. Associated with anti-U1 RNP antibodies (speckled ANA).

1° or 2° autoimmune disorder (most commonly in SLE).

Diagnosed based on clinical criteria including history of thrombosis (arterial or venous) or spontaneous abortion along with laboratory findings of lupus anticoagulant, anticardiolipin, anti-β2 glycoprotein I antibodies.

Treatment: systemic anticoagulation.

Anticardiolipin antibodies can cause false-positive VDRL/RPR.

Lupus anticoagulant can cause prolonged PTT that is not corrected by the addition of normal platelet-free plasma.

symptoms Pain and stiffness in proximal muscles (eg, shoulders, hips), often with fever, malaise, weight loss. Does not cause muscular weakness.

More common in women > 50 years old; associated with giant cell (temporal) arteritis.

Findings • ESR, • CRP, normal CK.

tREatmEnt Rapid response to low-dose corticosteroids.

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MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE `pathology SECTION III 472

Raynaud phenomenon • blood flow to skin due to arteriolar (small vessel) vasospasm in response to cold or stress: color change from white (ischemia) to blue (hypoxia) to red (reperfusion). Most often in the fingers A and toes. Called Raynaud disease when 1° (idiopathic), Raynaud syndrome when 2° to a disease process such as mixed connective tissue disease, SLE, or CREST syndrome (limited form of systemic sclerosis). Digital ulceration (critical ischemia) seen in 2° Raynaud syndrome. Treat with calcium2+ channel blockers.

MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE `dERmatology SECTION III 473

Scleroderma Systemic sclerosis. Triad of autoimmunity, noninflammatory vasculopathy, and collagen deposition with fibrosis. Commonly sclerosis of skin, manifesting as puffy, taut skin A without wrinkles, fingertip pitting B . Can involve other systems, eg, renal (scleroderma renal crisis; treat with ACE inhibitors), pulmonary (interstitial fibrosis, pulmonary HTN), GI (esophageal dysmotility and reflux), cardiovascular. 75% female. 2 major types:

Diffuse scleroderma—widespread skin involvement, rapid progression, early visceral involvement. Associated with anti-Scl-70 antibody (anti-DNA topoisomerase-I antibody) and anti-RNA polymerase III.

Limited scleroderma—limited skin involvement confined to fingers and face. Also with CREST syndrome: Calcinosis cutis C , anti-Centromere antibody, Raynaud phenomenon, Esophageal dysmotility, Sclerodactyly, and Telangiectasia. More benign clinical course.

`mUsCUlosKElEtal, sKin,and ConnECtiVEtissUE—dERmatology

Skin layers Skin has 3 layers: epidermis, dermis, subcutaneous fat (hypodermis, subcutis). Epidermal layers: Come, Let’s Get Sun Burned.

MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE `dERmatology SECTION III 474

Tight junctions (zonula occludens) A –prevents paracellular movement of solutes; composed of claudins and occludins.

Adherens junction (belt desmosome, zonula adherens) B –forms “belt” connecting actin cytoskeletons of adjacent cells with CADherins (Ca2+-dependent adhesion proteins). Loss of E-cadherin promotes metastasis.

Desmosome (spot desmosome, macula adherens) C –structural support via intermediate filament interactions. Autoantibodies to desmoglein 1 and/or 3 • pemphigus vulgaris.

D –channel proteins called connexons permit electrical and chemical communication between cells.

E –connects keratin in basal cells to underlying basement membrane. Autoantibodies • bullous pemphigoid. (Hemidesmosomes are down "bullow.")

Integrins–membrane proteins that maintain integrity of basolateral membrane by binding to collagen, laminin, and fibronectin in basement membrane.

MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE `dERmatology SECTION III 475

MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE `dERmatology SECTION III 476

Seborrheic dermatitis Erythematous, well-demarcated plaques A with greasy yellow scales in areas rich in sebaceous glands, such as scalp, face, and periocular region. Common in both infants (cradle cap) and adults, associated with Parkinson disease. Sebaceous glands are not inflamed, but play a role in disease development. Possibly associated with Malassezia spp. Treatment: topical antifungals and corticosteroids.

MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE `dERmatology SECTION III 477

Acne Multifactorial etiology—• sebum/androgen production, abnormal keratinocyte desquamation, Cutibacterium acnes colonization of the pilosebaceous unit (comedones), and inflammation (papules/pustules A , nodules, cysts). Treatment: retinoids, benzoyl peroxide, and antibiotics.

Pseudofolliculitis Foreign body inflammatory facial skin disorder characterized by firm, hyperpigmented papules and barbae pustules that are painful and pruritic. Located on cheeks, jawline, and neck. Commonly occurs as a result of shaving ("razor bumps"), primarily affects African-American males.

Psoriasis Papules and plaques with silvery scaling H , especially on knees and elbows. Acanthosis with parakeratotic scaling (nuclei still in stratum corneum), Munro microabscesses. • stratum spinosum, • stratum granulosum. Auspitz sign (I)—pinpoint bleeding spots from exposure of dermal papillae when scales are scraped off. Associated with nail pitting and psoriatic arthritis.

Rosacea Inflammatory facial skin disorder characterized by erythematous papules and pustules J , but no comedones. May be associated with facial flushing in response to external stimuli (eg, alcohol, heat). Phymatous rosacea can cause rhinophyma (bulbous deformation of nose).

Seborrheic keratosis Flat, greasy, pigmented squamous epithelial proliferation of immature keratinocytes with keratin-filled cysts (horn cysts) K . Looks "stuck on." Lesions occur on head, trunk, and extremities. Common benign neoplasm of older persons. Leser-Trélat sign L

—rapid onset of multiple seborrheic keratoses, indicates possible malignancy (eg, GI adenocarcinoma).

Verrucae Warts; caused by low-risk HPV strains. Soft, tan-colored, cauliflower-like papules M. Epidermal hyperplasia, hyperkeratosis, koilocytosis. Condyloma acuminatum on anus or genitals N .

Urticaria Hives. Pruritic wheals that form after mast cell degranulation O . Characterized by superficial dermal edema and lymphatic channel dilation.

MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE `dERmatology SECTION III 478

Vascular tumors of skin

Glomus tumor Benign, painful, red-blue tumor, commonly under fingernails C . Arises from modified smooth muscle cells of the thermoregulatory glomus body.

MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE `dERmatology SECTION III 479

Cellulitis Acute, painful, spreading infection of deeper dermis and subcutaneous tissues. Usually from S pyogenes or S aureus. Often starts with a break in skin from trauma or another infection D .

Varicella zoster virus Causes varicella (chickenpox) and zoster (shingles). Varicella presents with multiple crops of lesions in various stages from vesicles to crusts. Zoster is a reactivation of the virus in dermatomal distribution (unless it is disseminated).

Hairy leukoplakia Irregular, white, painless plaques on lateral tongue that cannot be scraped off

J . EBV mediated. Occurs in HIV-positive patients, organ transplant recipients. Contrast with thrush (scrapable) and leukoplakia (precancerous).

MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE `dERmatology SECTION III 480
pathophysiology Potentially fatal. Most commonly seen in older adults. Type II hypersensitivity reaction. IgG antibodies against desmoglein-1 and/or desmoglein-3 (component of desmosomes, which connect keratinocytes in the stratum spinosum).

Less severe than pemphigus vulgaris. Most commonly seen in older adults. Type II hypersensitivity reaction.

IgG antibodies against hemidesmosomes (epidermal basement membrane; antibodies are “bullow” the epidermis).

gRoss moRphology Flaccid intraepidermal bullae A caused by Tense blisters C containing eosinophils; oral acantholysis (separation of keratinocytes, “row mucosa spared. Nikolsky sign ⊖. of tombstones” on H&E stain); oral mucosa is involved. Nikolsky sign ⊕.

immUnoFlUoREsCEnCE Reticular pattern around epidermal cells B . Linear pattern at epidermal-dermal junction D .

MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE `dERmatology SECTION III 481

D .

adverse drug reaction. Toxic epidermal necrolysis (TEN) EF is more severe form of SJS involving > 30% body surface area. 10–30% involvement denotes SJS-TEN.

MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE `dERmatology SECTION III 482

Acanthosis nigricans Epidermal hyperplasia causing symmetric, hyperpigmented thickening of skin, especially in axilla

AB . Associated with insulin resistance (eg, diabetes, obesity, Cushing syndrome,

PCOS), visceral malignancy (eg, gastric adenocarcinoma).

Actinic keratosis Premalignant lesions caused by sun exposure. Small, rough, erythematous or brownish papules or

CD . Risk of squamous cell carcinoma is proportional to degree of epithelial dysplasia. Rule of 9’s The extent of a burn injury can be estimated as a percentage of the body surface area.

H .

MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE `dERmatology SECTION III 483

Entire head 9% Entire torso 18% Entire arm (L) 9% Entire arm (R) 9% Entire abdomen 18% Perineum 1% Total 100% Entire leg (L) 18% Entire leg (R) 18% 4.5 4.5 4.5 4.5 1 9 9 9 9 4.5 9 9 9 9 4.5

MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE `dERmatology SECTION III 484

Skin cancer Basal cell carcinoma more common above upper lip Squamous cell carcinoma more common below lower lip Sun exposure strongly predisposes to skin cancer.

Basal cell carcinoma Most common skin cancer. Found in sun-exposed areas of body (eg, face). Locally invasive, but rarely metastasizes. Waxy, pink, pearly nodules, commonly with telangiectasias, rolled borders A , central crusting or ulceration. BCCs also appear as nonhealing ulcers with infiltrating growth B or as a scaling plaque (superficial BCC) C . Basal cell tumors have “palisading” (aligned) nuclei D .

Keratoacanthoma Seen in middle-aged and elderly individuals. Rapidly growing, resembles squamous cell carcinoma. Presents as dome-shaped nodule with keratin-filled center. Grows rapidly (4-6 weeks) and may spontaneously regress

E .

Melanoma Common tumor with significant risk of metastasis. S-100 tumor marker. Associated with dysplastic nevi; fair-skinned persons are at • risk. Depth of tumor (Breslow thickness) correlates with risk of metastasis. Look for the ABCDEs: Asymmetry, Border irregularity, Color variation, Diameter > 6 mm, and Evolution over time. At least 4 different types of melanoma, including superficial spreading F , nodular G , lentigo maligna H , and acral lentiginous (highest prevalence in African-Americans and Asians) I . Often driven by activating mutation in BRAF kinase. Primary treatment is excision with appropriately wide margins. Metastatic or unresectable melanoma in patients with BRAF V600E mutation may benefit from vemurafenib, a BRAF kinase inhibitor.

 vasodilation.

DinoprostoneEpoprostenol CarboprostAlprostadil COX-2 ONLY Celecoxib NF-˜B I˜B COX-1, COX-2 ENDOPEROXIDE SYNTHESIS (cyclooxygenase)KetorolacNaproxenGlucocorticoids (corticosteroids) COX-2 COX-1 Cyclic endoperoxides ThromboxaneProstaglandinsProstacyclin •platelet aggregation •vascular tone •uterine tone •uterine tone •platelet aggregation •vascular tone PGI2 PGE1 TXA2PGF2˜PGE2 •vascular tone Aspirin (irreversible) Other NSAIDs (reversible) Diclofenac Ketorolac Ibuprofen Naproxen Indomethacin is a neutrophil chemotactic agent. inhibits platelet aggregation and promotes Neutrophils arrive “B4” others. Platelet-Gathering Inhibitor.

mEChanism Reversibly inhibits cyclooxygenase, mostly in CNS. Inactivated peripherally.

CliniCal UsE Antipyretic, analgesic, but not anti-inflammatory. Used instead of aspirin to avoid Reye syndrome in children with viral infection.

adVERsE EFFECts Overdose produces hepatic necrosis; acetaminophen metabolite (NAPQI) depletes glutathione and forms toxic tissue byproducts in liver. N-acetylcysteine is antidote—regenerates glutathione.

 prostaglandins. • bleeding time. No effect on PT, PTT. Effect lasts until new platelets are produced.

CliniCal UsE Low dose (< 300 mg/day): • platelet aggregation. Intermediate dose (300–2400 mg/day): antipyretic and analgesic. High dose (2400–4000 mg/day): anti-inflammatory.

adVERsE EFFECts Gastric ulceration, tinnitus (CN VIII), allergic reactions (especially in patients with asthma or nasal polyps). Chronic use can lead to acute kidney injury, interstitial nephritis, GI bleeding.

Risk of Reye syndrome in children treated with aspirin for viral infection. Toxic doses cause respiratory alkalosis early, but transitions to mixed metabolic acidosis-respiratory alkalosis. Treatment of overdose: $NaHCO_3$.

mEChanism Reversibly and selectively inhibits the cyclooxygenase (COX) isoform 2 ("Selecoxib"), which is found in inflammatory cells and vascular endothelium and mediates inflammation and pain; spares COX-1, which helps maintain gastric mucosa. Thus, does not have the corrosive effects of other NSAIDs on the GI lining. Spares platelet function as TXA2 production is dependent on COX-1.

CliniCal UsE Rheumatoid arthritis, osteoarthritis.

adVERsE EFFECts • risk of thrombosis, sulfa allergy.

Nonsteroidal Ibuprofen, naproxen, indomethacin, ketorolac, diclofenac, meloxicam, piroxicam. anti-inflammatory drugs mEChanism Reversibly inhibit cyclooxygenase (both COX-1 and COX-2). Block prostaglandin synthesis.

CliniCal UsE Antipyretic, analgesic, anti-inflammatory. Indomethacin is used to close a PDA.

adVERsE EFFECts Interstitial nephritis, gastric ulcer (prostaglandins protect gastric mucosa), renal ischemia (prostaglandins vasodilate afferent arteriole), aplastic anemia.

mEChanism Reversibly inhibits dihydroorotate dehydrogenase, preventing pyrimidine synthesis. Suppresses T-cell proliferation.

CliniCal UsE Rheumatoid arthritis, psoriatic arthritis.

adVERsE EFFECts Diarrhea, hypertension, hepatotoxicity, teratogenicity.

Bisphosphonates Alendronate, ibandronate, risedronate, zoledronate.

mEChanism Pyrophosphate analogs; bind hydroxyapatite in bone, inhibiting osteoclast activity.

CliniCal UsE Osteoporosis, hypercalcemia, Paget disease of bone, metastatic bone disease, osteogenesis imperfecta.

adVERsE EFFECts Esophagitis (if taken orally, patients are advised to take with water and remain upright for 30 minutes), osteonecrosis of jaw, atypical femoral stress fractures.

MUSCULOSKELETAL, SKIN, AND CONNECTIVE TISSUE `phaRmaCology SECTION III 487 mEChanism Recombinant PTH analog. • osteoblastic activity when administered in pulsatile fashion.

CliniCal UsE Osteoporosis. Causes • bone growth compared to antiresorptive therapies (eg, bisphosphonates).

adVERsE EFFECts • risk of osteosarcoma (avoid use in patients with Paget disease of the bone or unexplained elevation of alkaline phosphatase). Avoid in patients who have had prior cancers or radiation therapy. Transient hypercalcemia.

Allopurinol Competitive inhibitor of xanthine oxidase □• conversion of hypoxanthine and xanthine to urate. Also used in lymphoma and leukemia to prevent tumor lysis–associated urate nephropathy. • concentrations of xanthine oxidase active metabolites, azathioprine, and 6-MP.

Pegloticase Recombinant uricase catalyzing uric acid to allantoin (a more water-soluble product).

Probenecid Inhibits reabsorption of uric acid in proximal Prevent APainful Flare. convoluted tubule (also inhibits secretion of penicillin). Can precipitate uric acid calculi.

Allopurinol, Febuxostat

Febuxostat Inhibits xanthine oxidase.

NSAIDs Any NSAID. Use salicylates with caution (may decrease uric acid excretion, particularly at

Diuretics,low doses). low-dose salicylates

Glucocorticoids Oral, intra-articular, or parenteral. Colchicine Binds and stabilizes tubulin to inhibit microtubule polymerization, impairing neutrophil chemotaxis and degranulation. Acute and prophylactic value. GI, neuromyopathic side effects.

Urine Probenecid, high-dose salicylates Tubular reabsorption

Etanercept Fusion protein (decoy receptor for TNF-α + IgG1 Fc), produced by recombinant DNA. Etanercept intercepts TNF.

Infliximab, adalimumab, certolizumab, golimumab

Anti-TNF-α monoclonal antibody.

Rheumatoid arthritis, psoriasis, ankylosing spondylitis

Inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, psoriasis Predisposition to infection, including reactivation of latent TB, since TNF is important in granuloma formation and stabilization.

Can also lead to drug-induced lupus.

“We are all now connected by the Internet, like neurons in a giant brain.” “Anything’s possible if you’ve got enough nerve.” —J.K. Rowling, Harry Potter and the Order of the Phoenix “I like nonsense; it wakes up the brain cells.” —Dr. Seuss “I believe in an open mind, but not so open that your brains fall out.” “The chief function of the body is to carry

the brain around." "Exactly how [the brain] operates remains one of the biggest unsolved mysteries, and it seems the more we probe its secrets, the more surprises we find."

Understand the difference between upper motor neuron (UMN) and lower motor neuron (LMN) findings and the underlying anatomy. Know the major motor, sensory, cerebellar and visual pathways and their respective locations in the CNS. Connect key neurological associations with certain pathologies (eg, cerebellar lesions, stroke manifestations, Brown-Séquard syndrome). Recognize common findings on MRI/ CT (eg, ischemic and hemorrhagic stroke) and on neuropathology (eg, neurofibrillary tangles and Lewy bodies). High-yield medications include those used to treat epilepsy, Parkinson disease, migraine, and pain (eg, opioids).

Neural development Notochord induces overlying ectoderm to differentiate into neuroectoderm and form neural plate.

Neural plate Neural plate gives rise to neural tube and neural crest cells.

Day 18 Notochord becomes nucleus pulposus of intervertebral disc in adults. Notochord Neural fold

Alar plate (dorsal): sensory; regulated by TGF-β (including bone morphogenetic protein [BMP])

Same orientation as spinal cord

Basal plate (ventral): motor; regulated by

Regional specification Telencephalon is the 1st part. Diencephalon is the 2nd part. The rest are arranged alphabetically: of developing brain mesencephalon, metencephalon, myelencephalon.

Neural tube defects Neuropores fail to fuse (4th week) persistent connection between amniotic cavity and spinal canal. Associated with maternal diabetes and folate deficiency. α-fetoprotein (AFP) in amniotic fluid and maternal serum (except spina bifida occulta = normal AFP). •acetylcholinesterase (AChE) in amniotic fluid is a helpful confirmatory test.

Spina bifida occulta Failure of caudal neuropore to close, but no herniation. Usually seen at lower vertebral levels. Dura is intact. Associated with tuft of hair or skin dimple at level of bony defect.

Meningocele Meninges (but no neural tissue) herniate through bony defect.

Myelomeningocele Meninges and neural tissue (eg, cauda equina) herniate through bony defect.

Myeloschisis Also called rachischisis. Exposed, unfused neural tissue without skin/meningeal covering.

Anencephaly Failure of rostral neuropore to close no forebrain, open calvarium. Clinical findings: polyhydramnios (no swallowing center in brain).

+/- Tuft of hair Skin defect/thinning Skin thin or absent Skin

Holoprosencephaly Failure of the embryonic forebrain (prosencephalon) to separate into 2 cerebral hemispheres; usually occurs during weeks 5–6. May be related to mutations in sonic hedgehog signaling pathway. Associated with other midline defects including cleft lip/palate (moderate form) and ★ cyclopia (severe form). •risk for pituitary dysfunction (eg, diabetes insipidus). Can be seen with Patau syndrome (trisomy 13). Monoventricle MRI reveals monoventricle A and fusion of basal ganglia (star in A).

Lissencephaly Failure of neuronal migration resulting in a "smooth brain" that lacks sulci and gyri. May be associated with microcephaly, ventriculomegaly.

Chiari I malformation Ectopia of cerebellar tonsils inferior to foramen magnum (1 structure) A . Congenital, usually asymptomatic in childhood, manifests in adulthood with headaches and cerebellar symptoms. Associated with spinal cavitations (eg, syringomyelia).

Chiari II malformation Herniation of cerebellar vermis and tonsils (2 structures) through foramen magnum with aqueductal stenosis noncommunicating hydrocephalus. Usually associated with lumbosacral myelomeningocele (may present as paralysis/sensory loss at and below the level of the lesion). More severe than Chiari I, usually presents early in life.

Dandy-Walker Agenesis of cerebellar vermis cystic enlargement of 4th ventricle (arrow in B) that fills the malformation enlarged posterior fossa. Associated with noncommunicating hydrocephalus, spina bifida.

Syringomyelia Cystic cavity (syrinx) within central canal of spinal cord (yellow arrows in A). Fibers crossing in anterior white commissure (spinothalamic tract) are typically damaged first. Results in a "capelike," bilateral, symmetrical loss of pain and temperature sensation in upper extremities (fine touch sensation is preserved). Associated with Chiari I malformation (red arrow in A shows low-lying cerebellar tonsils), scoliosis and other congenital malformations; acquired causes include trauma and tumors. Most common location cervical > thoracic >> lumbar. Syrinx = tube, as in "syringe."

Posterior fossa malformations A˜erent Lateral spinothalamic tract (pain, temperature) Posterior fossa malformations Posterior fossa malformations Posterior fossa malformations Posterior fossa malformations Posterior fossa malformations Posterior fossa malformations Posterior fossa malformations Posterior fossa malformations Posterior fossa malformations Posterior fossa malformations Posterior fossa malformations Posterior fossa malformations Posterior fossa malformations Posterior fossa malformations Posterior fossa malformations Posterior fossa malformations Posterior fossa malformations Expanding syrinx (can a˜ect multiple

dermatomes) Anterior white commissure compressed by syrinx Dorsal root Posterior fossa malformations Posterior fossa malformations ganglion

Loss of pain and temperature sensation at a˜ected dermatomes (C5-T4 shown here) 1st and 2nd pharyngeal arches form anterior 2/3 (thus sensation via CN V3, taste via CN VII).

3rd and 4th pharyngeal arches form posterior 1/3(thus sensation and taste mainly via CN IX, extreme posterior via CN X).

Motor innervation is via CN XII to hyoglossus (retracts and depresses tongue), genioglossus (protrudes tongue), and styloglossus (draws sides of tongue upward to create a trough for swallowing).

Motor innervation is via CN X to palatoglossus (elevates posterior tongue during swallowing).

Taste—CN VII, IX, X (solitary nucleus). Pain—CN V3, IX, X. Motor—CN X, XII.

The Genie comes out of the lamp in style.

Neurons Signal-transmitting cells of the nervous system. Permanent cells—do not divide in adulthood. Signal-relaying cells with dendrites (receive input), cell bodies, and axons (send output). Cell bodies and dendrites can be seen on Nissl staining (stains RER). RER is not present in the axon. Neuron markers: neurofilament protein, synaptophysin.

Astrocytes Most common glial cell type in CNS. Physical Derived from neuroectoderm.

support, repair, extracellular K+ buffer, removal Astrocyte marker: GFAP.

of excess neurotransmitter, component of blood-brain barrier, glycogen fuel reserve buffer. Reactive gliosis in response to neural injury.

Ependymal cells Ciliated simple columnar glial cells line the ventricles and central canal of spinal cord. Apical surfaces are covered in cilia (which circulate CSF) and microvilli (which help with CSF absorption). Specialized ependymal cells (choroid plexus) produce CSF.

Myelin • conduction velocity of signals transmitted down axons
 saltatory conduction of action potential at the nodes of Ranvier, where there are high concentrations of Na+ channels. In CNS (including CN II), myelin is synthesized by oligodendrocytes; in PNS (including CN III-XII), myelin is synthesized by Schwann cells.

Wraps and insulates axons (arrow in A): • space constant and • conduction velocity.

COPS: CNS = Oligodendrocytes, PNS = Schwann cells.

Schwann cells Promote axonal regeneration. Derived from Each “Schwone” cell myelinates only 1 PNS neural crest. axon. Injured in Guillain-Barré syndrome.

Oligodendrocytes Myelinate axons of neurons in CNS. Each Derived from neuroectoderm. oligodendrocyte can myelinate many axons “Fried egg” appearance histologically. (~ 30). Predominant type of glial cell in white Injured in multiple sclerosis, progressive matter. multifocal leukoencephalopathy (PML), leukodystrophies.

Pacinian corpuscles Large, myelinated fibers; adapt Deep skin layers, ligaments, High-frequency vibration, quickly joints pressure

Merkel discs Large, myelinated fibers; adapt Finger tips, superficial skin Pressure, deep static touch (eg, slowly shapes, edges), position sense

Endoneurium—thin, supportive connective Endo = inner tissue that ensheathes and supports individual Peri = around myelinated nerve fibers. Epi = outer

Perineurium (blood-nerve Permeability barrier)—surrounds a fascicle of nerve fibers.

Epineurium—dense connective tissue that surrounds entire nerve (fascicles and blood vessels).

Reaction of neuronal cell body to axonal injury. Changes reflect • protein synthesis in effort to repair the damaged axon. Characterized by:

Displacement of the nucleus to the periphery

Dispersion of Nissl substance throughout cytoplasm Wallerian degeneration—disintegration of the axon and myelin sheath distal to site of axonal injury with macrophages removing debris.

Proximal to the injury, the axon retracts, and the cell body sprouts new protrusions that grow toward other neurons for potential reinnervation. Serves as a preparation for axonal regeneration and functional recovery.

Neurotransmitter changes with disease

Acetylcholine Basal nucleus of Meynert

Three membranes that surround and protect the CSF flows in the subarachnoid space, located brain and spinal cord: between arachnoid and pia mater.

Dura mater—thick outer layer closest to Epidural space—potential space between skull. Derived from mesoderm. the dura mater and skull/vertebral column

Arachnoid mater—middle layer, contains containing fat and blood vessels. Site of blood web-like connections. Derived from neural collection associated with middle meningeal crest. artery injury.

Pia mater—thin, fibrous inner layer that firmly adheres to brain and spinal cord. Derived from neural crest.

Prevents circulating blood substances Circumventricular organs with fenestrated (eg, bacteria, drugs) from reaching the CSF/ capillaries and no blood-brain barrier CNS. Formed by 3 structures: allow molecules in blood to affect brain

Tight junctions between nonfenestrated function (eg, area postrema— vomiting after capillary endothelial cells chemotherapy; OVLT [organum vasculosum

Astrocyte foot processes neurosecretory products to enter circulation Glucose and amino acids cross slowly by carrier-(eg, neurohypophysis—ADH release). mediated transport mechanisms. Infarction and/or neoplasm destroys endothelial Nonpolar/lipid-soluble substances cross rapidly cell tight junctions • vasogenic edema.

via diffusion. Hyperosmolar agents (eg, mannitol) can disrupt the BBB □• permeability of medications.

Coordinated by nucleus tractus solitarius (NTS) in the medulla, which receives information from the chemoreceptor trigger zone (CTZ, located within area postrema in 4th ventricle), GI tract (via vagus nerve), vestibular system, and CNS.

CTZ and adjacent vomiting center nuclei receive input from 5 major receptors: muscarinic (M1), dopamine (D2), histamine (H1), serotonin (5-HT3), and neurokinin (NK-1) receptors.

5-HT3, D2, and NK-1 antagonists used to treat chemotherapy-induced vomiting.

H1 and M1 antagonists treat motion sickness; H1 antagonists treat hyperemesis gravidarum.

Sleep physiology Sleep cycle is regulated by the circadian rhythm, which is driven by suprachiasmatic nucleus (SCN) of the hypothalamus. Circadian rhythm controls nocturnal release of ACTH, prolactin, melatonin, norepinephrine: SCN • norepinephrine release □ pineal gland □• melatonin. SCN is regulated by environment (eg, light). Two stages: rapid-eye movement (REM) and non-REM. Alcohol, benzodiazepines, and barbiturates are associated with • REM sleep and N3 sleep; norepinephrine also • REM sleep. Benzodiazepines are useful for night terrors and sleepwalking by • N3 and REM sleep.

Thalamus Major relay for all ascending sensory information except olfaction. Limbic system Collection of neural structures involved in The famous 5 F’s.

emotion, long-term memory, olfaction, behavior modulation, ANS function.

Consists of hippocampus (red arrows in A), amygdalae, mammillary bodies, anterior thalamic nuclei, cingulate gyrus (yellow arrows in

A), entorhinal cortex. Responsible for Feeding, Fleeing, Fighting, Feeling, and Sex.

A .

Input: inferior cerebellar peduncle from spinal cord Output:

The only output of cerebellar cortex = Purkinje cells (always inhibitory) deep nuclei of cerebellum contralateral cortex via superior cerebellar peduncle

Deep nuclei (lateral medial)—Dentate, Emboliform, Globose, Fastigial

Lateral lesions—affect voluntary movement of extremities (lateral structures); when injured, propensity to fall toward injured (ipsilateral) side.

Medial lesions (eg, vermis, fastigial nuclei, flocculonodular lobe)—truncal ataxia (widebased cerebellar gait), nystagmus, head tilting. Generally result in bilateral motor deficits affecting axial and proximal limb musculature (medial structures).

Important in voluntary movements and adjusting posture A . D1 Receptor = D1Rect Receives cortical input, provides negative feedback to cortex to pathway.

modulate movement. Indirect (D2) = Inhibitory. Striatum = putamen (motor) + Caudate (cognitive). Lentiform = putamen + globus pallidus.

Direct (excitatory) pathway—SNc input to the striatum via the nigrostriatal dopaminergic pathway releases GABA, which inhibits GABA release from the GPi, disinhibiting the Thalamus via the GPi (• motion).

Indirect (inhibitory) pathway—SNc input to the striatum via the nigrostriatal dopaminergic pathway releases GABA that disinhibits STN via GPe inhibition, and STN stimulates GPi to inhibit the thalamus (• motion).

Dopamine binds to D1, stimulating the excitatory pathway, and to D2, inhibiting the inhibitory pathway •• motion.

Cerebral perfusion Relies on tight autoregulation. Primarily driven by Pco2 (Po2 also modulates perfusion in severe hypoxia).

Also relies on a pressure gradient between mean arterial pressure (MAP) and intracranial pressure (ICP). • blood pressure or • ICP •• cerebral perfusion pressure (CPP).

 vasoconstriction • cerebral blood flow • ICP. May be used to treat acute cerebral edema (eg, 2° to stroke) unresponsive to other interventions.

CPP = MAP − ICP. If CPP = 0, there is no cerebral perfusion • brain death. Hypoxemia increases CPP only if Po2 < 50 mm Hg. CPP is directly proportional to Pco2 until Pco2 > 90 mm Hg.

HipLeg HipTrunk NeckHeadShoulderArmElbow RingLittle MiddleIndexThumb ForearmWrist Toes Ankle KneeShoulder FingersFingers ElbowWristHandLittleRingMiddleIndexThumbNeckBrow Lips TongueJaw Swallowing Eyelid & eyeball TrunkEye Nose Face Upper lip Lower lipTeeth, gums Foot Toes TongueIntra-abdominalPharynx Genitals

Homunculus Topographic representation of motor and sensory areas in the cerebral cortex. Distorted appearance is due to certain body regions being more richly innervated and thus having • cortical representation.

Watershed zones Cortical border zones occur between anterior and middle cerebral arteries and posterior and middle cerebral arteries (blue areas in A). Internal border zones occur between the superficial and deep vascular territories of the middle cerebral artery (red areas in

A).

Infarct due to severe hypoperfusion • proximal upper and lower extremity weakness (“manin-the-barrel syndrome”), higher order visual dysfunction (if posterior cerebral/middle cerebral cortical border zone stroke).

Circle of Willis System of anastomoses between anterior and posterior blood supplies to brain.

Dural venous sinuses Large venous channels A that run through the periosteal and meningeal layers of the dura mater. Drain blood from cerebral veins (arrow) and receive CSF from arachnoid granulations. Empty into internal jugular vein.

Venous sinus thrombosis—presents with signs/symptoms of • ICP (eg, headache, seizures, papilledema, focal neurologic deficits). May lead to venous hemorrhage. Associated with hypercoagulable states (eg, pregnancy, OCP use, factor V Leiden).

(main location of CSF return via arachnoid granulations)

Superior ophthalmic vein Great cerebral vein of Galen

Confuence of the sinuses Sigmoid sinus

Lateral ventricles 3rd ventricle via right and left interventricular foramina of Monro. 3rd ventricle 4th ventricle via cerebral aqueduct of Sylvius. 4th ventricle subarachnoid space via:

Foramina of Luschka = Lateral.

Foramen of Magendie = Medial.

CSF made by choroid plexuses located in the lateral and fourth ventricles. Travels to subarachnoid space via foramina of Luschka and Magendie, is reabsorbed by arachnoid granulations, and then drains into dural venous sinuses.

Brain stem—ventral view 4 CN are above pons (I, II, III, IV). 4 CN exit the pons (V, VI, VII, VIII).

(CN I) 4 CN are in medulla (IX, X, XI, XII). Olfactory tract 4 CN nuclei are medial (III, IV, VI, XII). CN II "Factors of 12, except 1 and 2."

Middle cerebellar Anterior wall of peduncle fourth ventricle

Pineal gland—melatonin secretion, circadian rhythms.

Superior colliculi—direct eye movements to stimuli (noise/movements) or objects of interest.

Inferior colliculi—auditory.

Your eyes are above your ears, and the superior colliculus (visual) is above the inferior colliculus (auditory).

In adults, spinal cord ends at lower border of L1–L2 vertebrae. Subarachnoid Space (which contains the CSF) extends to lower border of S2 vertebra. Lumbar puncture is usually performed between L3–L4 or L4–L5 (level of cauda equina).

Goal of lumbar puncture is to obtain sample of CSF without damaging spinal cord. To keep the cord alive, keep the spinal needle between L3 and L5.

Needle passes through: skin fascia and fat supraspinous ligament interspinous ligament ligamentum flavum epidural space (epidural anesthesia needle stops here) dura mater arachnoid mater subarachnoid space (CSF collection occurs here)

Spinal tract anatomy Ascending tracts synapse and then cross. and functions

Dorsal column Pressure, vibration, fine touch, proprioception

Spinothalamic tract Lateral: pain, temperature

Anterior: crude touch, pressure Sensory nerve ending bypasses pseudounipolar cell body in dorsal root ganglion enters spinal cord ascends ipsilaterally in dorsal columns

Sensory nerve ending (Aδ and C fibers) bypasses pseudounipolar cell body in dorsal root ganglion • enters spinal cord Nucleus gracilis, nucleus cuneatus (ipsilateral medulla) ascends contralaterally as the medial lemniscus

Decussates in spinal cord as the anterior white commissure

Clinical reflexes Reflexes count up in order (main nerve root in Additional reflexes: bold): Cremasteric reflex = L1, L2 (“testicles move”) Achilles reflex = S1, S2 (“buckle my shoe”) Anal wink reflex = S3, S4 (“winks galore”) C5, 6

Patellar reflex = L2–L4 (“kick the door”) C6, 7, 8 Biceps and brachioradialis reflexes = C5, C6 (“pick up sticks”)

L2, 3, 4

Triceps reflex = C6, C7, C8 (“lay them S1, 2 straight”)

Primitive reflexes CNS reflexes that are present in a healthy infant, but are absent in a neurologically intact adult. Normally disappear within 1st year of life. These primitive reflexes are inhibited by a mature/ developing frontal lobe. They may reemerge in adults following frontal lobe lesions loss of inhibition of these reflexes.

Moro reflex “Hang on for life” reflex—abduct/extend arms when startled, and then draw together

Rooting reflex Movement of head toward one side if cheek or mouth is stroked (nipple seeking)

Sucking reflex Sucking response when roof of mouth is touched

Palmar reflex Curling of fingers if palm is stroked

Plantar reflex Dorsiflexion of large toe and fanning of other toes with plantar stimulation Babinski sign—presence of this reflex in an adult, which may signify a UMN lesion

Galant reflex Stroking along one side of the spine while newborn is in ventral suspension (face down) causes lateral flexion of lower body toward stimulated side

C2 Posterior half of skull

C3 High turtleneck shirt Diaphragm and gallbladder pain referred to the right shoulder via phrenic nerve C3, 4, 5 keeps the diaphragm alive

T4 At the nipple T4 at the teat pore

T7 At the xiphoid process 7 letters in xiphoid

T10 At the umbilicus (belly butten) Point of referred pain in early appendicitis

L1 At the Inguinal Ligament

L4 Includes the kneecaps Down on ALL 4’s

S2, S3, S4 Sensation of penile and anal zones S2, 3, 4 keep the penis off the floor

Irreversible neuronal injury begins after 5 minutes of hypoxia. Most vulnerable: hippocampus, neocortex, cerebellum (Purkinje cells), watershed areas ("vulnerable hippos need pure water"). Stroke imaging: noncontrast CT to exclude hemorrhage (before tPA can be given). CT detects ischemic changes in 6–24 hr. Diffusion-weighted MRI can detect ischemia within 3–30 min.

Acute blockage of vessels disruption of blood flow and subsequent ischemia infarction necrosis. 3 types:

Thrombotic—due to a clot forming directly at site of infarction (commonly the MCA A), usually over a ruptured atherosclerotic plaque.

Embolic—embolus from another part of the body obstructs vessel. Can affect multiple vascular territories. Examples: atrial fibrillation, carotid artery stenosis, DVT with patent foramen ovale, infective endocarditis.

Hypoxic—due to hypoperfusion or hypoxemia. Common during cardiovascular surgeries, tends to affect watershed areas.

Treatment: tPA (if within 3–4.5 hr of onset and no hemorrhage/risk of hemorrhage) and/or thrombectomy (if large artery occlusion). Reduce risk with medical therapy (eg, aspirin, clopidogrel); optimum control of blood pressure, blood sugars, lipids; smoking cessation; and treat conditions that • risk (eg, atrial fibrillation, carotid artery stenosis).

Transient ischemic Brief, reversible episode of focal neurologic dysfunction without acute infarction (⊖ MRI), with the attack majority resolving in < 15 minutes; ischemia (eg, embolus, small vessel stenosis).

Bleeding into ventricles (arrow in coronal transcranial ultrasound A shows blood in right intraventricular space, extending into periventricular white matter). Increased risk in premature and low-birth-weight infants. Originates in germinal matrix, a highly vascularized layer within the subventricular zone. Due to reduced glial fiber support and impaired autoregulation of BP in premature infants. Can present with altered level of consciousness, bulging fontanelle, hypotension, seizures, coma.

Epidural hematoma Rupture of middle meningeal artery (branch of maxillary artery), often 2° to skull fracture (circle in A) involving the pterion (thinnest area of the lateral skull). Might present with transient loss of consciousness recovery ("lucid interval") rapid deterioration due to hematoma expansion. Scalp hematoma (arrows in

A) and rapid intracranial expansion (arrows in B) under systemic arterial pressure transtentorial herniation, CN III palsy. CT shows biconvex (lentiform), hyperdense blood collection B not crossing suture lines.

Subdural hematoma Rupture of bridging veins. Can be acute (traumatic, high-energy impact hyperdense on CT) or chronic (associated with mild trauma, cerebral atrophy, elderly, alcoholism hypodense on CT). Also seen in shaken babies. Predisposing factors: brain atrophy, trauma.

Crescent-shaped hemorrhage (red arrows in C and D) that crosses suture lines. Can cause midline shift (yellow arrow in C), findings of "acute on chronic" hemorrhage (blue arrows in D).

EF due to trauma, or rupture of an aneurysm (such as a saccular aneurysm E) or arteriovenous malformation. Rapid time course. Patients complain of "worst headache of my life." Bloody or yellow (xanthochromic) lumbar puncture. Vasospasm can occur due to blood breakdown ischemic infarct; nimodipine used to prevent/reduce vasospasm. • risk of developing communicating and/or obstructive hydrocephalus.

Most commonly caused by systemic hypertension. Also seen with amyloid angiopathy (recurrent lobar hemorrhagic stroke in elderly), vasculitis, neoplasm. May be 2° to reperfusion injury in ischemic stroke.

Hypertensive hemorrhages (Charcot-Bouchard microaneurysm) most often occur in putamen of basal ganglia (lenticulostriate vessels G), followed by thalamus, pons, and cerebellum

H .

Effects of strokes

Anterior circulation Middle cerebral artery Motor and sensory cortices A —upper limb and face. Temporal lobe (Wernicke area); frontal lobe (Broca area).

Contralateral paralysis and sensory loss—face and upper limb.

Aphasia if in dominant (usually left) hemisphere. Hemineglect if lesion affects nondominant (usually right) hemisphere.

Wernicke aphasia is associated with right superior quadrant visual field defect due to temporal lobe involvement.

Lenticulo-striate artery Striatum, internal capsule. Contralateral paralysis. Absence of cortical signs (eg, neglect, aphasia, visual field loss). Pure motor stroke. Common location of lacunar infarcts B , due to hyaline arteriosclerosis (lipohyalinosis) 2° to unmanaged hypertension. Posterior circulation

Lateral medulla: Nucleus ambiguus (CN IX, X, XI)

Vestibular nuclei Lateral spinothalamic tract, spinal trigeminal nucleus

Dysphagia, hoarseness, • gag reflex, hiccups.

Vomiting, vertigo, nystagmus • pain and temperature sensation from contralateral body, ipsilateral face.

Ipsilateral Horner syndrome. Ipsilateral ataxia, dysmetria.

Lateral medullary (Wallenberg) syndrome.

Nucleus ambiguus effects are specific to PICA lesions

C .

“Don’t pick a (PICA) horse (hoarseness) that can’t eat (dysphagia).”

Also supplies inferior cerebellar peduncle (part of cerebellum).

Lateral pons: Facial nucleus

Vestibular nuclei Spinothalamic tract, spinal trigeminal nucleus

Paralysis of face (LMN lesion vs UMN lesion in cortical stroke), • lacrimation, • salivation, • taste from anterior 2⁄3 of tongue. Vomiting, vertigo, nystagmus • pain and temperature sensation from contralateral body, ipsilateral face.

Ipsilateral Horner syndrome. Ipsilateral ataxia, dysmetria.

Ipsilateral sensorineural deafness, vertigo.

Lateral pontine syndrome. Facial nucleus effects are specific to AICA lesions. “Facial droop means AICA’s pooped.”

Also supplies middle and inferior cerebellar peduncles (part of cerebellum).

Effects of strokes (continued)

Basilar artery Pons, medulla, lower midbrain.

Corticospinal and corticobulbar tracts.

Ocular cranial nerve nuclei, paramedian pontine reticular formation.

If RAS spared, consciousness is preserved.

Quadriplegia; loss of voluntary facial, mouth, and tongue movements.

Loss of horizontal, but not vertical, eye movements.

Locked-in syndrome (locked in the basement).

Posterior cerebral artery Occipital lobe D . Contralateral hemianopia with macular sparing; alexia without agraphia (dominant hemisphere).

Diffuse axonal injury Caused by traumatic shearing forces during rapid acceleration and/or deceleration of the brain (eg, motor vehicle accident). Usually results in devastating neurologic injury, often causing coma or persistent vegetative state. MRI A shows multiple lesions (punctate hemorrhages) involving the white matter tracts.

Aphasia Aphasia—higher-order language deficit Good comprehension Poor comprehension (inability to understand/produce/use language appropriately); caused by pathology in dominant cerebral hemisphere (usually left). speech Dysarthria—motor inability to produce speech (movement deficit).

Broca (expressive) Broca area in inferior frontal gyrus of frontal lobe. Patient appears frustrated, insight intact. Broca = Broken Boca (boca = mouth in Spanish).

Wernicke (receptive) Wernicke area in superior temporal gyrus of temporal lobe. Patients do not have insight. Wernicke is a Word salad and makes no sense.

Conduction Can be caused by damage to arCuate fasciculus.

Global Broca and Wernicke areas affected.

Transcortical motor Affects frontal lobe around Broca area, but Broca area is spared.

Transcortical sensory Affects temporal lobe around Wernicke area, but Wernicke area is spared.

Transcortical mixed Broca and Wernicke areas and arcuate fasciculus remain intact; surrounding watershed areas affected.

Aneurysms Abnormal dilation of an artery due to weakening of vessel wall.

Also called berry aneurysm A . Occurs at bifurcations in the circle of Willis. Most common site is junction of ACom and ACA. Associated with ADPKD, Ehlers-Danlos syndrome. Other risk factors: advanced age, hypertension, smoking, race (• risk in African-Americans).

Usually clinically silent until rupture (most common complication) • subarachnoid hemorrhage (“worst headache of my life” or “thunderclap headache”) focal neurologic deficits. Can also cause symptoms via direct compression of surrounding structures by growing aneurysm.

ACom—compression bitemporal hemianopia (compression of optic chiasm); visual acuity deficits; rupture ischemia in ACA distribution • contralateral lower extremity hemiparesis, sensory deficits.

MCA—rupture ischemia in MCA distribution contralateral upper extremity and lower facial hemiparesis, sensory deficits.

PCom—compression ipsilateral CN III palsy • mydriasis (“blown pupil”); may also see ptosis, “down and out” eye.

Seizures Characterized by synchronized, high-frequency neuronal firing. Variety of forms.

Impaired consciousness?

Headaches Pain due to irritation of structures such as the dura, cranial nerves, or extracranial structures. More common in females, except cluster headaches.

Unilateral 15 min–3 hr; Excruciating periorbital pain repetitive ("suicide headache") with lacrimation and rhinorrhea. May present with Horner syndrome. More common in males.

Unilateral 4–72 hr Pulsating pain with nausea, photophobia, or phonophobia. May have "aura." Due to irritation of CN V, meninges, or blood vessels (release of vasoactive neuropeptides [eg, substance P, calcitonin gene-related peptide]).

Bilateral > 30 min Steady, "band-like" pain. No (typically 4–6 photophobia or phonophobia. hr); constant No aura.

Acute: sumatriptan, 100% O2. Prophylaxis: verapamil.

Acute: NSAIDs, triptans, dihydroergotamine.

Prophylaxis: lifestyle changes (eg, sleep, exercise, diet), β-blockers, amitriptyline, topiramate, valproate, botulinum toxin, anti-CGRP monoclonal antibodies.

POUND–Pulsatile, One-day duration, Unilateral, Nausea, Disabling.

Acute: analgesics, NSAIDs, acetaminophen.

Prophylaxis: TCAs (eg, amitriptyline), behavioral therapy.

Other causes of headache include subarachnoid hemorrhage ("worst headache of my life"), meningitis, hydrocephalus, neoplasia, giant cell (temporal) arteritis.

aCompare with trigeminal neuralgia, which produces repetitive, unilateral, shooting/shock-like pain in the distribution of CN V. Triggered by chewing, talking, touching certain parts of the face. Lasts (typically) for seconds to minutes, but episodes often increase in intensity and frequency over time. First-line therapy: carbamazepine.

Athetosis Slow, snake-like, writhing Basal ganglia. Seen in Huntington disease. movements; especially seen in the fingers.

Intention tremor Slow, zigzag motion when Cerebellar dysfunction. pointing/extending toward a target.

Hemiballismus Sudden, wild flailing of one Contralateral subthalamic
Pronounce “Half-of-body side of the body. nucleus (eg, lacunar stroke).
ballistic.”

Parkinson TRAPSS your body: Tremor (pill-rolling tremor at rest) Rigidity (cogwheel) Akinesia (or bradykinesia) Postural instability Shuffling gait Small handwriting (micrographia)

MPTP, a contaminant in illegal drugs, is metabolized to MPP+, which is toxic to substantia nigra.

• in cognitive ability, memory, or function with intact consciousness.

Must rule out depression as cause of dementia (called pseudodementia). Other reversible causes of dementia: hypothyroidism, vitamin B12 deficiency, neurosyphilis, normal pressure hydrocephalus.

Loss of dopaminergic neurons (ie, depigmentation) of substantia nigra pars compacta.

Lewy bodies: composed of α-synuclein (intracellular eosinophilic inclusions

A).

Autosomal dominant trinucleotide (CAG)n repeat expansion in the huntingtin (HTT) gene on chromosome 4 (4 letters). Symptoms manifest between ages 20 and 50: chorea, athetosis, aggression, depression, dementia (sometimes initially mistaken for substance abuse).

Anticipation results from expansion of CAG repeats. Caudate loses ACh and GABA.

Atrophy of caudate and putamen with ex vacuo ventriculomegaly.

• dopamine, • GABA, • ACh in brain. Neuronal death via NMDA-R binding and glutamate excitotoxicity.

Most common cause of dementia in elderly. Down syndrome patients have • risk of developing Alzheimer disease, as APP is located on chromosome 21.

ACh. Associated with the following altered proteins:

ApoE-2: • risk of sporadic form

ApoE-4: • risk of sporadic form • APP, presenilin-1, presenilin-2: familial forms (10%) with earlier onset

Widespread cortical atrophy (normal cortex B ; cortex in Alzheimer disease C), especially hippocampus (arrows in B and C). Narrowing of gyri and widening of sulci.

Senile plaques D in gray matter: extracellular β-amyloid core; may cause amyloid angiopathy intracranial hemorrhage; Aβ (amyloid-β) synthesized by cleaving amyloid precursor protein (APP).

E : intracellular, hyperphosphorylated tau protein = insoluble cytoskeletal elements; number of tangles correlates with degree of dementia.

Hirano bodies—intracellular eosinophilic proteinaceous rods in hippocampus.

Formerly called Pick disease. Early changes in Frontotemporal lobe degeneration

F . personality and behavior (behavioral variant), Inclusions of hyperphosphorylated tau (round or aphasia (primary progressive aphasia). Pick bodies

G) or ubiquitinated TDP-43.

May have associated movement disorders.

Lewy body dementia Visual hallucinations (“haLewycinations”), Intracellular Lewy bodies A primarily in cortex.

dementia with fluctuating cognition/ alertness, REM sleep behavior disorder, and parkinsonism. Called Lewy body dementia if apart, otherwise considered dementia 2° to

Parkinson disease.

Also called pseudotumor cerebri. • ICP with no obvious findings on imaging. Risk factors include female sex, Tetracyclines, Obesity, vitamin A excess, Danazol (female TOAD). Associated with cerebral venous sinus stenosis. Findings: headache, tinnitus, diplopia (usually from CN VI palsy), no change in mental status. Impaired optic nerve axoplasmic flow papilledema. Visual field testing shows enlarged blind spot and peripheral constriction. Lumbar puncture reveals • opening pressure and provides temporary headache relief.

Treatment: weight loss, acetazolamide, invasive procedures for refractory cases (eg, CSF shunt placement, optic nerve sheath fenestration surgery for visual loss).

Hydrocephalus • CSF volume ventricular dilation +/- • ICP.

Noncommunicating Caused by structural blockage of CSF circulation within ventricular system (eg, stenosis of hydrocephalus aqueduct of Sylvius, colloid cyst blocking foramen of Monro, tumor B).

Multiple sclerosis Autoimmune inflammation and demyelination of CNS (brain and spinal cord) with subsequent axonal damage. Can present with:

Acute optic neuritis (painful unilateral visual loss associated with Marcus Gunn pupil)

Brain stem/cerebellar syndromes (eg, diplopia, ataxia, scanning speech, intention tremor, nystagmus/INO [bilateral > unilateral])

Pyramidal tract demyelination (eg, weakness, spasticity)

Spinal cord syndromes (eg, electric shock-like sensation along cervical spine on neck flexion, neurogenic bladder, paraparesis, sensory manifestations affecting the trunk or one or more extremity)

Symptoms may exacerbate with increased body temperature (eg, hot bath, exercise). Relapsing and remitting is most common clinical course. Most often affects women in their 20s and 30s; more common in individuals living farther from equator and with low serum vitamin D levels.

Findings • IgG level and myelin basic protein in CSF. Oligoclonal bands are diagnostic. MRI is gold standard. Periventricular plaques A (areas of oligodendrocyte loss and reactive gliosis). Multiple white matter lesions disseminated in space and time.

treAtment Stop relapses and halt/slow progression with disease-modifying therapies (eg, β-interferon, glatiramer, natalizumab). Treat acute flares with IV steroids. Symptomatic treatment for neurogenic bladder (catheterization, muscarinic antagonists), spasticity (baclofen, GABAB receptor agonists), pain (TCAs, anticonvulsants).

Osmotic demyelination Also called central pontine myelinolysis. Massive axonal demyelination in pontine white matter syndrome A 2° to rapid osmotic changes, most commonly iatrogenic correction of hyponatremia but also rapid shifts of other osmolytes (eg, glucose). Acute paralysis, dysarthria, dysphagia, diplopia, loss of consciousness. Can cause "locked-in syndrome." Correcting serum Na+ too fast: "From low to high, your pons will die" (osmotic demyelination syndrome) "From high to low, your brains will blow" (cerebral edema/herniation)

Charcot-Marie-Tooth Also called hereditary motor and sensory neuropathy. Group of progressive hereditary nerve disease disorders related to the defective production of proteins involved in the structure and function of peripheral nerves or the myelin sheath. Typically autosomal dominant and associated with foot deformities (eg, pes cavus, hammer toe), lower extremity weakness (eg, foot drop), and sensory deficits. Most common type, CMT1A, is caused by PMP22 gene duplication.

Progressive multifocal Demyelination of CNS B due to destruction of oligodendrocytes (2° to reactivation of latent leukoencephalopathy JC virus infection). Seen in 2–4% of patients with AIDS. Rapidly progressive, usually fatal. Predominantly involves parietal and occipital areas; visual symptoms are common. • risk associated with natalizumab.

Other disorders Krabbe disease, metachromatic leukodystrophy, adrenoleukodystrophy.

Most common subtype of Guillain-Barré syndrome.

Autoimmune condition that destroys Schwann cells via inflammation and demyelination of motor fibers, sensory fibers, peripheral nerves (including CN III-XII). Likely facilitated by molecular mimicry and triggered by inoculations or stress. Despite association with infections (eg, Campylobacter jejuni, viruses [eg, Zika]), no definitive causal link to any pathogen.

Results in symmetric ascending muscle weakness/paralysis and depressed/absent DTRs beginning in lower extremities. Facial paralysis (usually bilateral) and respiratory failure are common. May see autonomic dysregulation (eg, cardiac irregularities, hypertension, hypotension) or sensory abnormalities. Almost all patients survive; majority recover completely after weeks to months.

• CSF protein with normal cell count (albuminocytologic dissociation).

Respiratory support is critical until recovery. Disease-modifying treatment: plasmapheresis or IV immunoglobulins. No role for steroids.

Congenital nonhereditary anomaly of neural crest derivatives. Somatic mosaicism of an activating mutation in one copy of the GNAQ gene.

B seizures/epilepsy; intellectual disability; episcleral hemangioma • IOP • early-onset glaucoma.

Also called encephalotrigeminal angiomatosis.

SSTURGGE-Weber: Sporadic, port-wine Stain, Tram track calcifications (opposing gyri), Unilateral, intellectual disability (Retardation), Glaucoma, GNAQ gene, Epilepsy.

Tuberous sclerosis AD, variable expression. Mutation in tumor suppressor genes TSC1 on chromosome 9 (hamartin), TSC2 on chromosome 16 (tuberin).

Hamartomas in CNS and skin, Angiofibromas

C , Mitral regurgitation, Ash-leaf spots D , cardiac Rhabdomyoma, (Tuberous sclerosis), autosomal dOminant; Mental retardation (intellectual disability), renal Angiomyolipoma

E , Seizures, Shagreen patches.

HAMARTOMASS.

• incidence of Subependymal giant cell astrocytomas and ungual fibromas.

AD, 100% penetrance.

Mutation in NF1 tumor suppressor gene on chromosome 17 (encodes neurofibromin, a negative RAS regulator).

Café-au-lait spots F , Intellectual disability, Cutaneous neurofibromas

G , Lisch nodules (pigmented iris hamartomas H), Optic gliomas, Pheochromocytomas, Seizures/focal neurologic Signs (often from meningioma), bone lesions (eg, sphenoid dysplasia).

Also called von Recklinghausen disease. 17 letters in “von Recklinghausen.” CICLOPSS.

cells D .

H .

Cingulate (subfalcine) herniation under Can compress anterior cerebral artery. Falx cerebri falx cerebri

Uncal transtentorial herniation Uncus = medial temporal lobe. Early herniation compression), contralateral hemiparesis. Late herniation coma, Kernohan phenomenon (misleading contralateral blown pupil and ipsilateral hemiparesis due to contralateral compression against Kernohan notch).

Central/downward transtentorial Caudal displacement of brain stem rupture of mass hemorrhages. Usually fatal.

Cerebellar tonsillar herniation into the Coma and death result when these herniations foramen magnum compress the brain stem.

(less muscle mass, • muscle tone, • reflexes,

Upper motor neuron = everything up (tone, Reflexes • DTRs, toes) Tone •

Fasciculations = muscle twitching Babinski +– Positive Babinski is normal in infants

Poliomyelitis Caused by poliovirus (fecal-oral transmission). Replicates in oropharynx and small intestine before spreading via bloodstream to CNS. Infection causes destruction of cells in anterior horn of spinal cord (LMN death). Signs of LMN lesion: asymmetric weakness (vs symmetric weakness in spinal muscular atrophy), hypotonia, flaccid paralysis, fasciculations, hyporeflexia, muscle atrophy. Respiratory muscle involvement leads to respiratory failure. Signs of infection: malaise, headache, fever, nausea, etc. CSF shows • WBCs (lymphocytic pleocytosis) and slight • of protein (with no change in CSF glucose). Virus recovered from stool or throat.

Hemisection of spinal cord. Findings: Ipsilateral loss of all sensation at level of lesion Ipsilateral LMN signs (eg, flaccid paralysis) at level of lesion Ipsilateral UMN signs below level of lesion (due to corticospinal tract damage) Ipsilateral loss of proprioception, vibration, light (2-point discrimination) touch, and tactile sense below level of lesion (due to dorsal column damage) Contralateral loss of pain, temperature, and crude (non-discriminative) touch below level of lesion (due to spinothalamic tract damage)

If lesion occurs above T1, patient may present with ipsilateral Horner syndrome due to damage of oculosympathetic pathway.

Level of lesion

Loss of sensation LMN signs

Impaired proprioception, vibration, light touch, tactile sense

Impaired pain, temperature, crude touch sensation

Autosomal recessive trinucleotide repeat disorder (GAA)n on chromosome 9 in gene that encodes frataxin (iron-binding protein). Leads to impairment in mitochondrial functioning. Degeneration of lateral corticospinal tract (spastic paralysis), spinocerebellar tract (ataxia), dorsal columns (• vibratory sense, proprioception), and dorsal root ganglia (loss of DTRs). Staggering gait, frequent falling, nystagmus, dysarthria, pes cavus, hammer toes, diabetes mellitus, hypertrophic cardiomyopathy (cause of death). Presents in Friedreich is Fratastic (frataxin): he's your favorite frat brother, always staggering and falling but has a sweet, big heart.

B .

Ataxic GAAit.

CN V motor lesion Jaw deviates toward side of lesion due to unopposed force from the opposite pterygoid muscle. CN X lesion Uvula deviates away from side of lesion. Weak side collapses and uvula points away. CN XI lesion Weakness turning head to contralateral side of lesion (SCM). Shoulder droop on side of lesion (trapezius). The left SCM contracts to help turn the head to the right. CN XII lesion LMN lesion. Tongue deviates toward side of lesion ("lick your wounds") due to weakened tongue muscles on affected side.

Facial nerve lesions Bell palsy is the most common cause of peripheral facial palsy A . Usually develops after HSV reactivation. Treatment: corticosteroids +/− acyclovir. Most patients gradually recover function, but aberrant regeneration can occur. Other causes of peripheral facial palsy include Lyme disease, herpes zoster (Ramsay Hunt syndrome), sarcoidosis, tumors (eg, parotid gland), diabetes mellitus.

lesion loCAtion Motor cortex, connection from motor cortex to Facial nucleus, anywhere along CN VII facial nucleus in pons musCles inVolVed Lower muscles of facial expression Upper and lower muscles of facial expression

ForeheAd inVolVed? Spared, due to bilateral UMN innervation Affected other symPtoms None Incomplete eye closure (dry eyes, corneal ulceration), hyperacusis, loss of taste sensation to anterior tongue

Face area of motor cortex

Outer ear Visible portion of ear (pinna), includes auditory canal and tympanic membrane. Transfers sound waves via vibration of tympanic membrane.

Middle ear Air-filled space with three bones called the ossicles (malleus, incus, stapes). Ossicles conduct and amplify sound from tympanic membrane to inner ear.

Inner ear Snail-shaped, fluid-filled cochlea. Contains basilar membrane that vibrates 2° to sound waves. Vibration transduced via specialized hair cells auditory nerve signaling • brain stem. Each frequency leads to vibration at specific location on basilar membrane (tonotopy):

Low frequency heard at apex near helicotrema (wide and flexible).

High frequency heard best at base of cochlea (thin and rigid).

Weber test Tuning fork on vertex of skull Rinne test Tuning fork in front of ear (air conduction, AC), Tuning fork on mastoid process (bone conduction, BC) No localization BC > AC Localizes to una˜ected ear ˜ transmission of all sound AC > BCAC > BC Localizes to a˜ected ear ˜ transmission of background noise

Types of hearing loss

Cholesteatoma Overgrowth of desquamated keratin debris within the middle ear space (A , arrows); may erode ossicles, mastoid air cells conductive hearing loss. Often presents with painless otorrhea.

Conjunctivitis Inflammation of the conjunctiva red eye A . Allergic— itchy eyes, bilateral. Bacterial—pus; treat with antibiotics. Viral—most common, often adenovirus; sparse mucous discharge, swollen preauricular node, • lacrimation; self-resolving.

Cataract Painless, often bilateral, opacification of lens A , often resulting in glare and • vision, especially at night. Acquired risk factors: • age, smoking, excessive alcohol use, excessive sunlight, prolonged corticosteroid use, diabetes mellitus, trauma, infection. Congenital risk factors: classic galactosemia, galactokinase deficiency, trisomies (13, 18, 21), TORCH infections (eg, rubella), Marfan syndrome, Alport syndrome, myotonic dystrophy, neurofibromatosis 2.

Iris Lens Suspended from ciliary body by zonule fbers. Muscular fbers and position. Iris Dilator muscle (α1) Sphincter muscle (M3) Ciliary body Trabecularmeshwork Cornea Sclera Canal of Schlemm Anterior chamber “Angle” of the eye Lens Trabecular outfow (90%) Drainage through trabecular meshwork canal of Schlemm episcleral vasculature agonist (eg, carbachol, pilocarpine) ↓↓↓Uveoscleral outfow (10%) Drainage into uvea and sclera with prostaglandin agonists (eg, latanoprost, bimatoprost) Aqueous humor Posterior chamber

Produced by nonpigmented epithelium on ciliary body and carbonic anhydrase inhibitors (eg, acetazolamide) by β-blockers (eg, timolol), α2-agonists (eg, brimonidine),

Glaucoma Optic disc atrophy with characteristic cupping (normal A versus thinning of outer rim of optic nerve head B), usually with elevated intraocular pressure (IOP) and progressive peripheral visual field loss if untreated. Treatment is through pharmacologic or surgical lowering of IOP.

Open-angle glaucoma Associated with • age, African-American race, family history. Painless, more common in US. Primary—cause unclear. Secondary—blocked trabecular meshwork from WBCs (eg, uveitis), RBCs (eg, vitreous hemorrhage), retinal elements (eg, retinal detachment).

Uveitis Inflammation of uvea; specific name based on location within affected eye. Anterior uveitis: iritis; posterior uveitis: choroiditis and/or retinitis. May have hypopyon (accumulation of pus in anterior chamber A) or conjunctival redness. Associated with systemic inflammatory disorders (eg, sarcoidosis, rheumatoid arthritis, juvenile idiopathic arthritis, HLA-B27–associated conditions).

Degeneration of macula (central area of retina). Causes distortion (metamorphopsia) and eventual loss of central vision (scotomas).

Dry (nonexudative, > 80%)—Deposition of yellowish extracellular material ("Drusen") in between Bruch membrane and retinal pigment epithelium A with gradual • in vision. Prevent progression with multivitamin and antioxidant supplements.

Wet (exudative, 10–15%)—rapid loss of vision due to bleeding 2° to choroidal neovascularization. Treat with anti-VEGF (vascular endothelial growth factor) injections (eg, bevacizumab, ranibizumab).

Diabetic retinopathy Retinal damage due to chronic hyperglycemia. Two types: (arrows in A) and macular edema. Treatment: blood sugar control.

Proliferative—chronic hypoxia results in new blood vessel formation with resultant traction on retina • retinal detachment. Treatment: anti-VEGF injections, peripheral retinal photocoagulation, surgery.

Hypertensive Retinal damage due to chronic uncontrolled HTN.

retinopathy Flame-shaped retinal hemorrhages, arteriovenous nicking, microaneurysms, macular star (exudate, red arrow in A), cotton-wool spots (blue arrow in A). Presence of papilledema requires immediate lowering of BP. Associated with • risk of stroke, CAD, kidney disease.

Retinal vein occlusion Blockage of central or branch retinal vein due to compression from nearby arterial atherosclerosis. Retinal hemorrhage and venous engorgement ("blood and thunder appearance"; arrows in A), edema in affected area.

Separation of neurosensory layer of retina (photoreceptor layer with rods and cones) from outermost pigmented epithelium (normally shields excess light, supports retina) degeneration of photoreceptors vision loss. May be 2° to retinal breaks, diabetic traction, inflammatory effusions.

Visualized on fundoscopy as crinkling of retinal tissue A and changes in vessel direction.

Breaks more common in patients with high myopia and/or history of head trauma. Often preceded by posterior vitreous detachment (“flashes” and “floaters”) and eventual monocular loss of vision like a “curtain drawn down.” Surgical emergency.

Central retinal artery Acute, painless monocular vision loss. Retina cloudy with attenuated vessels and “cherry-red” spot occlusion at fovea (center of macula) A . Evaluate for embolic source (eg, carotid artery atherosclerosis, cardiac vegetations, patent foramen ovale).

Retinitis pigmentosa Inherited progressive retinal degeneration. Nyctalopia (night blindness) peripheral vision loss. Bone spicule-shaped deposits

A .

Papilledema Optic disc swelling (usually bilateral) due to • ICP (eg, 2° to mass effect). Enlarged blind spot and elevated optic disc with blurred margins A .

Leukocoria Loss (whitening) of the red reflex. Important causes in children include retinoblastoma A , congenital cataract, toxocariasis.

Miosis Constriction, parasympathetic: 1st neuron: Edinger-Westphal nucleus to ciliary ganglion via CN III 2nd neuron: short ciliary nerves to sphincter pupillae muscles Short ciliary nerves shorten the pupil diameter.

Pupillary light reflex Light in either retina sends a signal via CN II to pretectal nuclei (dashed lines in image) in midbrain that activates bilateral Edinger-Westphal nuclei; pupils constrict bilaterally (direct and consensual reflex). Result: illumination of 1 eye results in bilateral pupillary constriction.

Mydriasis Dilation, sympathetic: 1st neuron: hypothalamus to ciliospinal center of Budge (C8–T2) 2nd neuron: exit at T1 to superior cervical ganglion (travels along cervical sympathetic chain near lung apex, subclavian vessels) 3rd neuron: plexus along internal carotid, through cavernous sinus; enters orbit as long ciliary nerve to pupillary dilator muscles. Sympathetic fibers also innervate smooth muscle of eyelids (minor retractors) and sweat glands of forehead and face.

Long ciliary nerves make the pupil diameter longer.

Marcus Gunn pupil Also called relative afferent pupillary defect (RAPD). When the light shines into a normal eye, constriction of the ipsilateral (direct reflex) and contralateral eye (consensual reflex) is observed. When the light is then swung to the affected eye, both pupils dilate instead of constrict due to impaired conduction of light signal along the injured optic nerve. Associated with optic neuritis, early multiple sclerosis.

Sympathetic denervation of face □: PAM is horny (Horner).

ƒ Ptosis (slight drooping of eyelid: superior

Hypothalamus Ophthalmic divisiontarsal muscle) of trigeminal nerve

Anhidrosis (absence of sweating) and Long ciliary nerve flushing of affected side of face To sweat glands of forehead

To smooth muscle of eyelid

Associated with lesions along the sympathetic chain: Internal carotid To sweat glands of face ƒ 1st neuron: pontine hemorrhage, lateral artery medullary syndrome, spinal cord lesion

Third neuron above T1 (eg, Brown-Séquard syndrome, First neuron 2nd neuron: stellate ganglion compression lateral horn 3rd neuron: carotid dissection (painful) Spinal cord

Superior Superior Superior CN VI innervates the Lateral Rectus. oblique rectus oblique

CN IV innervates the Superior Oblique.

CN III innervates the Rest.

Medial rectus The “chemical formula” LR6SO4R3. muscle

Obliques go Opposite (left SO and IO tested with patient looking right). IOU: IO tested looking Up.

CN III, IV, VI palsies

CN III damage CN III has both motor (central) and parasympathetic (peripheral) components. Common causes include:

Cavernous sinus thrombosis • proptosis, involvement of CNs IV, V1/V2, VI

Motor output to extraocular muscles—affected primarily by vascular disease (eg, diabetes mellitus: glucose □ sorbitol) due to • diffusion of oxygen and nutrients to the interior fibers from compromised vasculature that resides on outside of nerve. Signs: ptosis, “down-and-out” gaze.

Parasympathetic output—fibers on the periphery are first affected by compression (eg, PCom aneurysm, uncal herniation). Signs: diminished or absent pupillary light reflex, “blown pupil” often with “down-and-out” gaze

A .

Visual field defects 1. Right anopia (monocular vision loss) 4Opticchiasm7 Macula Opticnerve Optic tractVisual 13 52Dorsal optic radiation(parietallobe)Lt. Rt.Lateralgeniculatebody

Defect in visual feld of L eye R eye 2.

Bitemporal hemianopia (pituitary lesion, chiasm) 3.

4.

Left upper quadrantanopia (right temporal lesion, MCA) 5.

loop(right parietal lesion, MCA) (temporal 6. Left hemianopia with macular sparing (right occipital lesion, PCA) 7. Central scotoma (eg, macular degeneration) PCA infarct) 6 Calcarine cortex sulcus

Meyer Loop—Lower retina; Loops around inferior horn of Lateral ventricle.

Note: When an image hits 1° visual cortex, it is upsideDorsal optic radiation—superior retina; takes down and left-right reversed.

shortest path via internal capsule.

Cavernous sinus Collection of venous sinuses on either side of pituitary. Blood from eye and superficial cortex cavernous sinus internal jugular vein. CNs III, IV, V1, V2, and VI plus postganglionic sympathetic pupillary fibers en route to orbit all pass through cavernous sinus. Cavernous portion of internal carotid artery is also here.

Cavernous sinus syndrome—presents with variable ophthalmoplegia, • corneal sensation, Horner syndrome and occasional decreased maxillary sensation. 2° to pituitary tumor mass effect, carotid-cavernous fistula, or cavernous sinus thrombosis related to infection.

3rd ventricle Oculomotor n. (CN III) Trochlear n. (CN IV) Ophthalmic n. (CN V1) Optic chiasma (CN II) Maxillary n. (CN V2) Pituitary Pia Dura Arachnoid Sphenoid sinus Subarachnoid space Anterior cerebral a. Internal carotid a. Cavernous sinus Abducens n. (CN VI)

Medial longitudinal fasciculus (MLF): pair of tracts that allows for crosstalk between CN VI and CN III nuclei. Coordinates both eyes to move in same horizontal direction. Highly myelinated (must communicate quickly so eyes move at same time). Lesions may be unilateral or bilateral (latter classically seen in multiple sclerosis, stroke).

Lesion in MLF = internuclear ophthalmoplegia (INO), a conjugate horizontal gaze palsy. Lack of communication such that when CN VI nucleus activates ipsilateral lateral rectus, contralateral CN III nucleus does not stimulate medial rectus to contract. Abducting eye displays nystagmus (CN VI overfires to stimulate CN III). Convergence normal.

MLF in MS.

When looking left, the left nucleus of CN VI fires, which contracts the left lateral rectus and stimulates the contralateral (right) nucleus of CN III via the right MLF to contract the right medial rectus.

Directional term (eg, right INO, left INO) refers to the eye that is unable to adduct.

INO = Ipsilateral adduction failure, Nystagmus Opposite.

Sedation, tolerance,

Also for eclampsia seizures (1st dependence, respiratory line is MgSO4) depression

Diplopia, ataxia, blood 1st line for trigeminal neuralgia dyscrasias (agranulocytosis, aplastic anemia), liver toxicity, teratogenesis (cleft lip/palate, spina bifida), induction of cytochrome P-450, SIADH, SJS

Sucks to have Silent causes Fatigue, GI distress, (absence) Seizures Headache, Itching (and urticaria), SJS

PHENYTOIN: cytochrome P-450 induction, Hirsutism, Enlarged gums, Nystagmus, Yellow-brown skin, Teratogenicity (fetal hydantoin syndrome), Osteopenia, Inhibited folate absorption, Neuropathy. Rare: SJS, DRESS syndrome, SLE-like syndrome. Toxicity leads to diplopia, ataxia, sedation.

Sedation, slow cognition,

Also used for migraine kidney stones, skinny (weight prophylaxis loss), sight threatened (glaucoma), speech (wordfinding) difficulties

GI distress, rare but fatal

Also used for myoclonic seizures, bipolar disorder, hepatotoxicity (measure migraine prophylaxis

LFTs), pancreatitis, neural tube defects, tremor, weight gain, contraindicated in

Vision gone all bad with • GABA. Irreversible GABA * = Common use, ** = 1st line for acute, *** = 1st line for recurrent seizure prophylaxis.

Barbiturates Phenobarbital, pentobarbital, thiopental, secobarbital.

meChAnism Facilitate GABAA action by • duration of Cl− channel opening, thus □ neuron firing (barbidurates • duration).

CliniCAl use Sedative for anxiety, seizures, insomnia, induction of anesthesia (thiopental).

AdVerse eFFeCts Respiratory and cardiovascular depression (can be fatal); CNS depression (can be exacerbated by alcohol use); dependence; drug interactions (induces cytochrome P-450). Overdose treatment is supportive (assist respiration and maintain BP). Contraindicated in porphyria.

Benzodiazepines Diazepam, lorazepam, triazolam, temazepam, oxazepam, midazolam, chlordiazepoxide, alprazolam.

meChAnism Facilitate GABAA action by • frequency of Cl– channel opening ("frenzodiazepines" • frequency).

• REM sleep. Most have long half-lives and active metabolites (exceptions [ATOM]: Alprazolam, Triazolam, Oxazepam, and Midazolam are short acting higher addictive potential).

CliniCAl use Anxiety, panic disorder, spasticity, status epilepticus (lorazepam, diazepam, midazolam), eclampsia, detoxification (especially alcohol withdrawal– DTs), night terrors, sleepwalking, general anesthetic (amnesia, muscle relaxation), hypnotic (insomnia). Lorazepam, Oxazepam, and Temazepam can be used for those with liver disease who drink a LOT due to minimal first-pass metabolism.

AdVerse eFFeCts Dependence, additive CNS depression effects with alcohol and barbiturates (all bind the GABAA receptor). Less risk of respiratory depression and coma than with barbiturates. Treat overdose with flumazenil (competitive antagonist at GABA benzodiazepine receptor). Can precipitate seizures by causing acute benzodiazepine withdrawal.

Nonbenzodiazepine Zolpidem, Zaleplon, esZopiclone. "These ZZZs put you to sleep." hypnotics meChAnism Act via the BZ1 subtype of the GABA receptor. Effects reversed by flumazenil. Sleep cycle less affected as compared with benzodiazepine hypnotics.

CliniCAl use Insomnia.

AdVerse eFFeCts Ataxia, headaches, confusion. Short duration because of rapid metabolism by liver enzymes. Unlike older sedative-hypnotics, cause only modest day-after psychomotor depression and few amnestic effects. • dependence risk than benzodiazepines.

meChAnism Orexin (hypocretin) receptor antagonist. Suvorexant is an orexin antagonist.

CliniCAl use Insomnia.

AdVerse eFFeCts CNS depression (somnolence), headache, abnormal sleep-related activities. Contraindications: narcolepsy, combination with strong CYP3A4 inhibitors. Not recommended in patients with liver disease. Limited physical dependence or abuse potential.

AdVerse eFFeCts Dizziness, nausea, fatigue, headache. No dependence (not a controlled substance).

meChAnism 5-HT agonists. Inhibit trigeminal nerve A sumo wrestler trips and falls on his head.

activation, prevent vasoactive peptide release, induce vasoconstriction.

CliniCAl use Acute migraine, cluster headache attacks.

AdVerse eFFeCts Coronary vasospasm (contraindicated in patients with CAD or vasospastic angina), mild paresthesia, serotonin syndrome (in combination with other 5-HT agonists).

meChAnism • dopamine in brain. Unlike dopamine, l-DOPA can cross blood-brain barrier and is converted by dopa decarboxylase in the CNS to dopamine. Carbidopa, a peripheral DOPA decarboxylase inhibitor, is given with l-DOPA to • bioavailability of l-DOPA in the brain and to limit peripheral side effects.

CliniCAl use Parkinson disease.

AdVerse eFFeCts Nausea, hallucinations, postural hypotension. With progressive disease, l-DOPA can lead to "onoff" phenomenon with improved mobility during "on" periods, then impaired motor function during "off" periods when patient responds poorly to l-DOPA or medication wears off.

Selegiline, rasagiline meChAnism Selectively inhibit MAO-B (metabolize dopamine) □• dopamine availability. Selegiline selectively inhibits MAO-B and is more commonly found in the Brain than in the periphery.

CliniCAl use Adjunctive agent to l-DOPA in treatment of Parkinson disease.

AdVerse eFFeCts May enhance adverse effects of l-DOPA.

Inhaled anesthetics Desflurane, halothane, enflurane, isoflurane, sevoflurane, methoxyflurane, N2O.

meChAnism Mechanism unknown.

eFFeCts Myocardial depression, respiratory depression, postoperative nausea/vomiting, • cerebral blood flow, • cerebral metabolic demand.

AdVerse eFFeCts Hepatotoxicity (halothane), nephrotoxicity (methoxyflurane), proconvulsant (enflurane, epileptogenic), expansion of trapped gas in a body cavity (N2O).

Malignant hyperthermia—rare, life-threatening condition in which inhaled anesthetics or succinylcholine induce severe muscle contractions and hyperthermia. Susceptibility is often inherited as autosomal dominant with variable penetrance. Mutations in voltage-sensitive ryanodine receptor (RYR1 gene) cause • Ca2+ release from sarcoplasmic reticulum.

Treatment: dantrolene (a ryanodine receptor antagonist).

Local anesthetics Esters—procaine, tetracaine, benzocaine, chloroprocaine. Amides—lIdocaIne, mepIvacaIne, bupIvacaIne, ropIvacaIne (amIdes have 2 I's in name).

meChAnism Block Na+ channels by binding to specific receptors on inner portion of channel. Most effective in rapidly firing neurons. 3° amine local anesthetics penetrate membrane in uncharged form, then bind to ion channels as charged form. Can be given with vasoconstrictors (usually

epinephrine) to enhance local action—• bleeding, • anesthesia by • systemic concentration. In infected (acidic) tissue, alkaline anesthetics are charged and cannot penetrate membrane effectively need more anesthetic.

Order of nerve blockade: small-diameter fibers > large diameter. Myelinated fibers > unmyelinated fibers. Overall, size factor predominates over myelination such that small myelinated fibers > small unmyelinated fibers > large myelinated fibers > large unmyelinated fibers.

Order of loss: (1) pain, (2) temperature, (3) touch, (4) pressure.

CliniCAl use Minor surgical procedures, spinal anesthesia. If allergic to esters, give amides.

AdVerse eFFeCts CNS excitation, severe cardiovascular toxicity (bupivacaine), hypertension, hypotension, arrhythmias (cocaine), methemoglobinemia (benzocaine).

Spasmolytics, antispasmodics meChAnism Act as agonists at opioid receptors (μ = β-endorphin, δ = enkephalin, κ = dynorphin) to modulate synaptic transmission—close presynaptic Ca2+ channels, open postsynaptic K+ channels • synaptic transmission. Inhibit release of ACh, norepinephrine, 5-HT, glutamate, substance P.

eFFiCACy Full agonist: morphine, heroin, meperidine, methadone, codeine, fentanyl. Partial agonist: buprenorphine. Mixed agonist/antagonist: nalbuphine, pentazocine, butorphanol. Antagonist: naloxone, naltrexone, methylnaltrexone.

CliniCAl use Moderate to severe or refractory pain, diarrhea (loperamide, diphenoxylate), acute pulmonary edema, maintenance programs for heroin addicts (methadone, buprenorphine + naloxone).

AdVerse eFFeCts Nausea, vomiting, pruritus, addiction, respiratory depression, constipation, sphincter of Oddi spasm, miosis (except meperidine mydriasis), additive CNS depression with other drugs. Tolerance does not develop to miosis and constipation. Treat toxicity with naloxone (competitive opioid receptor antagonist) and prevent relapse with naltrexone once detoxified.

meChAnism Very weak opioid agonist; also inhibits the Tramadol is a Slight opioid agonist, and a reuptake of norepinephrine and serotonin. Serotonin and norepinephrine reuptake inhibitor. It is used for Stubborn pain, but

CliniCAl use Chronic pain.

can lower Seizure threshold, and may cause

AdVerse eFFeCts Similar to opioids; decreases seizure threshold;

Serotonin Syndrome.

serotonin syndrome.

Glaucoma therapy • IOP via • amount of aqueous humor (inhibit synthesis/secretion or • drainage). BAD humor may not be Politically Correct.

β-blockers Timolol, betaxolol, carteolol • aqueous humor synthesis No pupillary or vision changes α-agonists Epinephrine (α1), • aqueous humor synthesis via Mydriasis (α1); do not use in apraclonidine, vasoconstriction (epinephrine) closed-angle glaucoma brimonidine (α2) • aqueous humor synthesis Blurry vision, ocular (apraclonidine, brimonidine) hyperemia, foreign body sensation, ocular allergic reactions, ocular pruritus

Diuretics Acetazolamide • aqueous humor synthesis No pupillary or vision changes via inhibition of carbonic anhydrase

Prostaglandins Bimatoprost, latanoprost • outflow of aqueous humor via Darkens color of iris (PGF2α) • resistance of flow through (browning), eyelash growth uveoscleral pathway

Cholinomimetics (M3) Direct: pilocarpine, carbachol • outflow of aqueous humor via Miosis (contraction of pupillary Indirect: physostigmine, contraction of ciliary muscle sphincter muscles) and echothiophate and opening of trabecular cyclospasm (contraction of meshwork ciliary muscle) Use pilocarpine in acute angle closure glaucoma—very effective at opening meshwork into canal of Schlemm “Words of comfort, skillfully administered, are the oldest therapy known to man.” “All men should strive to learn before they die what they are running from, and to, and why.” “The sorrow which has no vent in tears may make other organs weep.” “It’s no use going back to yesterday, because I was a different person then.” —Lewis Carroll, Alice in Wonderland

This chapter encompasses overlapping areas in psychiatry, psychology, sociology, and psychopharmacology. High-yield topics include schizophrenia, mood disorders, eating disorders, personality disorders, somatic symptom disorders, substance abuse, and antipsychotic agents. Know the DSM-5 criteria for diagnosing common psychiatric disorders.

Operant conditioning Learning in which a particular action is elicited because it produces a punishment or reward. Usually elicits voluntary responses.

Reinforcement Target behavior (response) is followed by desired Skinner operant conditioning quadrants: reward (positive reinforcement) or removal of aversive stimulus (negative reinforcement).

Punishment Repeated application of aversive stimulus (positive punishment) or removal of desired reward (negative punishment) to extinguish unwanted behavior.

Extinction Discontinuation of reinforcement (positive or negative) eventually eliminates behavior. Can occur in operant or classical conditioning.

Transference Patient projects feelings about formative or other important persons onto physician (eg, psychiatrist is seen as parent).

Countertransference Doctor projects feelings about formative or other important persons onto patient (eg, patient reminds physician of younger sibling).

Ego defenses Thoughts and behaviors (voluntary or involuntary) used to resolve conflict and prevent undesirable feelings (eg, anxiety, depression).

Denial Avoiding the awareness of some painful reality. A patient with cancer plans a full-time work schedule despite being warned of significant fatigue during chemotherapy.

Mature adults wear a SASH.

Lack of basic trust

Reactive attachment disorder (infant withdrawn/unresponsive to comfort)

Disinhibited social engagement (child indiscriminately attaches to strangers)

Child neglect Failure to provide a child with adequate food, shelter, supervision, education, and/or affection. Most common form of child maltreatment. Signs: poor hygiene, malnutrition, withdrawal, impaired social/emotional development, failure to thrive. As with child abuse, suspected child neglect must be reported to local child protective services.

Onset before age 12. ≥ 6 months of limited attention span and/or poor impulse control. Characterized by hyperactivity, impulsivity, and/or inattention in ≥ 2 settings (eg, school, home, places of worship). Normal intelligence, but commonly coexists with difficulties in school. Often persists into adulthood. Commonly coexists with oppositional defiant disorder. Treatment: stimulants (eg, methylphenidate) +/− behavioral therapy; alternatives include atomoxetine, guanfacine, clonidine.

Conduct disorder Repetitive, pervasive behavior violating societal norms or the basic rights of others (eg, aggression toward people and animals, destruction of property, theft). After age 18, often reclassified as antisocial personality disorder. Treatment: psychotherapy (eg, cognitive behavioral therapy [CBT]).

Intellectual disability Global cognitive deficits (vs specific learning disorder) that affect reasoning, memory, abstract thinking, judgment, language, learning. Adaptive functioning is impaired, leading to major difficulties with education, employment, communication, socialization,

independence. Treatment: psychotherapy, occupational therapy, special education.

Oppositional defiant Enduring pattern of anger and irritability with argumentative, vindictive, and defiant behavior disorder toward authority figures. Treatment: psychotherapy (eg, CBT).

Selective mutism Onset before age 5. Anxiety disorder lasting ≥ 1 month involving refraining from speech in certain situations despite speaking in other, usually more comfortable situations. Development (eg, speech and language) not typically impaired. Interferes with social, academic, and occupational tasks. Commonly coexists with social anxiety disorder. Treatment: behavioral, family, and play therapy; SSRIs.

Tourette syndrome Onset before age 18. Sudden, Sudden, recurrent, nonrhythmic, stereotyped motor and vocal tics that persist for > 1 year. Coprolalia (involuntary obscene speech) found in some patients. Associated with OCD and ADHD. Treatment: psychoeducation, behavioral therapy. For intractable and distressing tics, high-potency antipsychotics (eg, haloperidol, fluphenazine), tetrabenazine, α2-agonists (eg, guanfacine, clonidine), or atypical antipsychotics.

Orientation Patients' ability to know the date and time, where they are, and who they are (order of loss: time □ place □ person). Common causes of loss of orientation: alcohol, drugs, fluid/electrolyte imbalance, head trauma, hypoglycemia, infection, nutritional deficiencies, hypoxia.

Depersonalization/ Persistent feelings of detachment or estrangement from one's own body, thoughts, perceptions, derealization and actions (depersonalization) or one's environment (derealization). Intact reality testing (vs disorder psychosis).

Delirium "Waxing and waning" level of consciousness with acute onset, • attention span, • level of arousal. Characterized by disorganized thinking, hallucinations (often visual), misperceptions (eg, illusions), disturbance in sleep-wake cycle, cognitive dysfunction, agitation. Reversible. Usually 2° to other identifiable illness (eg, CNS disease, infection, trauma, substance abuse/ withdrawal, metabolic/electrolyte disturbances, hemorrhage, urinary/fecal retention), or medications (eg, anticholinergics), especially in the elderly. Most common presentation of altered mental status in inpatient setting, especially in the ICU or during prolonged hospital stays. EEG may show diffuse background rhythm slowing.

Delirium = changes in sensorium.

Treatment: identification and management of underlying condition. Orientation protocols (eg, keeping a clock or calendar nearby), • sleep disturbances, and • cognitive stimulation to manage symptoms. Antipsychotics as needed. Avoid unnecessary restraints and drugs that may worsen delirium (eg, anticholinergics, benzodiazepines, opioids).

Psychosis Distorted perception of reality characterized by delusions, hallucinations, and/or disorganized thought/speech. Can occur in patients with medical illness, psychiatric illness, or both.

Delusions False, fixed, idiosyncratic beliefs that persist despite evidence to the contrary and are not typical of a patient's culture or religion (eg, a patient who believes that others are reading his thoughts). Types include erotomanic, grandiose, jealous, persecutory, somatic, mixed, and unspecified.

Disorganized thought Speech may be incoherent ("word salad"), tangential, or derailed ("loose associations").

Hallucinations Perceptions in the absence of external stimuli (eg, seeing a light that is not actually present). Contrast with misperceptions (eg, illusions) of real external stimuli. Types include:

Auditory—more commonly due to psychiatric illness (eg, schizophrenia) than medical illness.

Visual—more commonly due to medical illness (eg, drug intoxication, delirium) than psychiatric illness.

Tactile—common in alcohol withdrawal and stimulant use (eg, "cocaine crawlies," a type of delusional parasitosis).

Olfactory—often occur as an aura of temporal lobe epilepsy (eg, burning rubber) and in brain tumors.

Gustatory—rare, but seen in epilepsy.

Hypnagogic—occurs while going to sleep. Sometimes seen in narcolepsy.

Hypnopompic—occurs while waking from sleep ("get pomped up in the morning"). Sometimes seen in narcolepsy.

Schizophrenia Chronic illness causing profound functional impairment. Symptom categories include:

Positive—hallucinations, delusions, unusual thought processes, disorganized speech, bizarre behavior

Negative—flat or blunted affect, apathy, anhedonia, alogia, social withdrawal

Cognitive—reduced ability to understand or make plans, diminished working memory, inattention

Diagnosis requires ≥ 2 of the following active symptoms, including ≥ 1 from symptoms #1–3: 1.

2.

Hallucinations, often auditory 3.

4.

5.

Requires ≥ 1 month of active symptoms over the past 6 months; onset ≥ 6 months prior to diagnosis.

Associated with altered dopaminergic activity, • serotonergic activity, and • dendritic branching. Ventriculomegaly on brain imaging. Lifetime prevalence—1.5% (males > females). Presents earlier in men (late teens to early 20s) than in women (late 20s to early 30s). • suicide risk.

Heavy cannabis use in adolescence is associated with • incidence and worsened course of psychotic, mood, and anxiety disorders.

Treatment: atypical antipsychotics (eg, risperidone) are first line. Negative symptoms often persist after treatment, despite resolution of positive symptoms.

Brief psychotic disorder—≥ 1 positive symptom(s) lasting < 1 month, usually stress-related. Schizophreniform disorder—≥ 2 symptoms lasting 1–6 months.

Schizoaffective Shares symptoms with both schizophrenia and mood disorders (major depressive or bipolar disorder disorder). To differentiate from a mood disorder with psychotic features, patient must have > 2 weeks of psychotic symptoms without a manic or depressive episode.

Delusional disorder ≥ 1 delusion(s) lasting > 1 month, but without a mood disorder or other psychotic symptoms. Daily functioning, including socialization, may be impacted by the pathological, fixed belief but is otherwise unaffected. Can be shared by individuals in close relationships (folie à deux).

Schizotypal personality Cluster A personality disorder that also falls on the schizophrenia spectrum. May include brief disorder psychotic episodes (eg, delusions) that are less frequent and severe than in schizophrenia.

Mood disorder Characterized by an abnormal range of moods or internal emotional states and loss of control over them. Severity of moods causes distress and impairment in social and occupational functioning. Includes major depressive, bipolar, dysthymic, and cyclothymic disorders. Episodic superimposed psychotic features (delusions, hallucinations, disorganized speech/behavior) may be present.

Manic episode Distinct period of abnormally and persistently elevated, expansive, or irritable mood and • activity or energy lasting ≥ 1 week. Diagnosis requires hospitalization or marked functional impairment with ≥ 3 of the following (manics DIG FAST):

Distractibility • Flight of ideas—racing thoughts

Impulsivity/Indiscretion—seeks pleasure • • goal-directed
Activity/psychomotor without regard to consequences (hedonistic)
Agitation

Hypomanic episode Similar to a manic episode except mood disturbance is not severe enough to cause marked impairment in social and/or occupational functioning or to necessitate hospitalization. Abnormally • activity or energy usually present. No psychotic features. Lasts ≥ 4 consecutive days.

length of time). Bipolar II—a hypomanic and a depressive episode (no history of manic episodes). Patient's mood and functioning usually normalize between episodes. Use of antidepressants can destabilize mood. High suicide risk. Treatment: mood stabilizers (eg, lithium, valproic acid, carbamazepine, lamotrigine), atypical antipsychotics.

Cyclothymic disorder—milder form of bipolar disorder fluctuating between mild depressive and hypomanic symptoms. Must last ≥ 2 years with symptoms present at least half of the time, with any remission lasting ≤ 2 months.

Recurrent episodes lasting ≥ 2 weeks characterized by ≥ 5 of 9 diagnostic symptoms (must include depressed mood or anhedonia) (DIGS SPACE):

Guilt or feelings of worthlessness

Screen for previous manic or hypomanic episodes to rule out bipolar disorder. Treatment: CBT and SSRIs are first line. Also SNRIs, mirtazapine, bupropion, electroconvulsive therapy (ECT).

Persistent depressive Often milder than MDD; ≥ 2 depressive symptoms lasting ≥ 2 years (≥ 1 year in children), with any disorder (dysthymia) remission lasting ≤ 2 months.

MDD with seasonal Formerly called seasonal affective disorder. Major depressive episodes occurring only during a pattern particular season (usually winter) in ≥ 2 consecutive years and in most years across a lifetime. Atypical symptoms common.

Depression with atypical features

Characterized by mood reactivity (transient improvement in response to a positive event), hypersomnia, hyperphagia, leaden paralysis (heavy feeling in arms and legs), long-standing interpersonal rejection sensitivity. Most common subtype of depression. Treatment: CBT and SSRIs are first line. MAO inhibitors (MAOIs) are effective but not first line because of their risk profile.

MDD with peripartum 10–15% incidence rate. Formerly called postpartum depression. Meets MDD criteria with onset no onset later than 1 year after delivery. Treatment: CBT and SSRIs are first line.

Postpartum psychosis 0.1–0.2% incidence rate. Characterized by mood-congruent delusions, hallucinations, and thoughts of harming the baby or self. Risk factors include first pregnancy, family history, bipolar

disorder, psychotic disorder, recent medication change. Treatment: hospitalization and initiation of atypical antipsychotic; if insufficient, ECT may be used.

Grief The five stages of grief per the Kübler-Ross model are denial, anger, bargaining, depression, and acceptance (may occur in any order). Other normal grief symptoms include shock, guilt, sadness, anxiety, yearning, and somatic symptoms that usually occur in waves. Simple hallucinations of the deceased person are common (eg, hearing the deceased speaking). Any thoughts of dying are limited to joining the deceased (vs complicated grief). Duration varies widely; usually resolves within 6–12 months. Persistent complex bereavement disorder involves obsessive preoccupation with the deceased and causes functional impairment, lasting at least 12 months (6 months in children). Can also meet criteria for major depressive episode.

SAD PERSONS are more likely to complete suicide.

Most common method in US is firearms; access to guns • risk of suicide completion.

Women try more often; men complete more often.

Other risk factors include recent psychiatric hospitalization and family history of completed suicide.

Anxiety disorders Inappropriate experiences of fear/worry and their physical manifestations incongruent with the magnitude of the stressors. Symptoms are not attributable to another psychiatric disorder, medical condition (eg, hyperthyroidism), or substance abuse. Includes panic disorder, phobias, generalized anxiety disorder, and selective mutism.

Phobias Severe, persistent (≥ 6 months) fear or anxiety due to presence or anticipation of a specific object or situation. Person often recognizes fear is excessive. Treatment: CBT with exposure therapy.

Social anxiety disorder—exaggerated fear of embarrassment in social situations (eg, public speaking, using public restrooms). Treatment: CBT, SSRIs, venlafaxine. For performance type (eg, anxiety restricted to public speaking), use β-blockers or benzodiazepines as needed.

Agoraphobia—irrational fear/anxiety while facing or anticipating ≥ 2 specific situations (eg, open/ closed spaces, lines, crowds, public transport). If severe, patients may refuse to leave their homes. Associated with panic disorder. Treatment: CBT, SSRIs.

Trichotillomania Compulsively pulling out one’s hair. Causes significant distress and persists despite attempts to stop. Presents with areas of thinning hair or baldness on any area of the body, most commonly the scalp

A . Incidence highest in childhood but spans all ages. Treatment: psychotherapy.

Adjustment disorder Emotional or behavioral symptoms (eg, anxiety, outbursts) that occur within 3 months of an identifiable psychosocial stressor (eg, divorce, illness) lasting < 6 months once the stressor has ended. If symptoms persist > 6 months after stressor ends, it is GAD. Symptoms do not meet criteria for MDD. Treatment: CBT is first line; antidepressants and anxiolytics may be considered.

Schizoid Voluntary social withdrawal (Aloof), limited emotional expression, content with social isolation (vs avoidant).

Factitious disorders Symptoms are intentional, motivation is unconscious. Patient consciously creates physical and/or psychological symptoms in order to assume "sick role" and to get medical attention and sympathy (1° [internal] gain).

Conversion disorder Also called functional neurologic symptom disorder. Loss of sensory or motor function (eg, paralysis, blindness, mutism), often following an acute stressor; patient may be aware of but indifferent toward symptoms (la belle indifférence); more common in females, adolescents, and young adults.

Illness anxiety Preoccupation with acquiring or having a serious illness, often despite medical evaluation and disorder reassurance; minimal to no somatic symptoms.

Bulimia nervosa Recurring episodes of binge eating with compensatory purging behaviors at least weekly over the last 3 months. BMI often normal or slightly overweight (vs anorexia). Associated with parotid gland hypertrophy (may see • serum amylase), enamel erosion, Mallory-Weiss syndrome, electrolyte disturbances (eg, • K^+ , • Cl^-), metabolic alkalosis, dorsal hand calluses from induced vomiting (Russell sign). Treatment: psychotherapy, nutritional rehabilitation, antidepressants (eg, SSRIs). Bupropion is contraindicated due to seizure risk.

Sleep terror disorder Periods of inconsolable terror with screaming in the middle of the night. Most common in children. Occurs during slow-wave/deep (stage N3) non-REM sleep with no memory of the arousal episode, as opposed to nightmares that occur during REM sleep (remembering a scary dream). Triggers include emotional stress, fever, and lack of sleep. Usually self limited.

Enuresis Nighttime urinary incontinence ≥ 2 times/week for ≥ 3 months in person > 5 years old. First-line treatment: behavioral modification (eg, scheduled voids, nighttime fluid restriction) and positive reinforcement. For refractory cases: bedwetting alarm, oral desmopressin (ADH analog; preferred over imipramine due to fewer side effects).

Narcolepsy Excessive daytime sleepiness (despite awakening well-rested) with recurrent episodes of rapid-onset, overwhelming sleepiness ≥ 3 times/week for the last 3 months. Due to • orexin (hypocretin) production in lateral hypothalamus and dysregulated sleep-wake cycles. Associated with:

Hypnagogic (just before going to sleep) or hypnopompic (just before awakening; get pomped up in the morning) hallucinations.

Nocturnal and narcoleptic sleep episodes that start with REM sleep (sleep paralysis).

Cataplexy (loss of all muscle tone following strong emotional stimulus, such as laughter).

Treatment: good sleep hygiene (scheduled naps, regular sleep schedule), daytime stimulants (eg, amphetamines, modafinil) and/or nighttime sodium oxybate (GHB).

Stages of change in overcoming addiction

Maladaptive pattern of substance use involving ≥ 2 of the following in the past year:

Intense, distracting cravings

Using more, or longer, than intended

Persistent desire but inability to cut down

Time-consuming substance acquisition, use, or recovery

Impaired functioning at work, school, or home > 1 episode of use involving danger (eg, unsafe sex, driving while impaired)

Continued use despite awareness of harm 1.

2.

Contemplation—acknowledging problem, but unwilling to change 3.

4.

5.

6.

Relapse—(if applicable) returning to old behaviors and abandoning changes

Nonspecific: mood elevation, • anxiety, sedation, Nonspecific: anxiety, tremor, seizures, behavioral disinhibition, respiratory depression. insomnia.

Alcohol Emotional lability, slurred speech, ataxia, coma, blackouts. Serum γ-glutamyltransferase (GGT)—sensitive indicator of alcohol use. AST value is 2× ALT value (“ToAST 2 ALcohol”). Treatment: benzodiazepines.

Nonspecific: mood elevation, • appetite, Nonspecific: post-use “crash,” including psychomotor agitation, insomnia, cardiac depression, lethargy,

• appetite, sleep arrhythmias, tachycardia, anxiety. disturbance, vivid nightmares.

Alcohol use disorder Physiologic tolerance and dependence on alcohol with symptoms of withdrawal when intake is interrupted. Complications: vitamin B1 (thiamine) deficiency, alcoholic cirrhosis, hepatitis, pancreatitis, peripheral neuropathy, testicular atrophy. Treatment: naltrexone (reduces cravings), acamprosate, disulfiram (to condition the patient to abstain from alcohol use). Support groups such as Alcoholics Anonymous are helpful in sustaining abstinence and supporting patient and family.

Wernicke-Korsakoff Results from vitamin B1 deficiency. Symptoms can be precipitated by administering dextrose syndrome before vitamin B1. Triad of confusion, ophthalmoplegia, ataxia (Wernicke encephalopathy). May progress to irreversible memory loss, confabulation, personality change (Korsakoff syndrome). Treatment: IV vitamin B1 (before dextrose).

Behavioral therapy Teaches patients how to identify and change maladaptive behaviors or reactions to stimuli. Examples include systematic desensitization for treatment of phobia.

Cognitive behavioral Teaches patients to recognize distortions in their thought processes, develop constructive coping therapy skills, and • maladaptive coping behaviors • greater emotional control and tolerance of distress. Examples include recognizing triggers for alcohol consumption.

Dialectical behavioral Designed for use in borderline personality disorder, but can be used in other psychiatric conditions therapy as well (eg, depression).

Interpersonal therapy Focused on improving interpersonal relationships and communication skills.

Supportive therapy Utilizes empathy to help individuals during a time of hardship to maintain optimism or hope.

for selected ADHD Stimulants (methylphenidate, amphetamines) psychiatric conditions

Alcohol withdrawal Benzodiazepines (eg, chlordiazepoxide, lorazepam, diazepam)

Generalized anxiety disorder SSRIs, SNRIs

Obsessive-compulsive disorder SSRIs, venlafaxine, clomipramine

Panic disorder SSRIs, venlafaxine, benzodiazepines

PTSD SSRIs, venlafaxine

MEchaNisM • catecholamines in the synaptic cleft, especially norepinephrine and dopamine.

cliNical UsE ADHD, narcolepsy, binge-eating disorder.

aDVErsE EFFEcts Nervousness, agitation, anxiety, insomnia, anorexia, tachycardia, hypertension, weight loss, tics, bruxism.

Typical antipsychotics Haloperidol, pimozide, trifluoperazine, fluphenazine, thioridazine, chlorpromazine.

MEchaNisM Block dopamine D2 receptor (• cAMP).

cliNical UsE Schizophrenia (1° positive symptoms), psychosis, bipolar disorder, delirium, Tourette syndrome, Huntington disease, OCD. Use with caution in dementia.

PotENcy High potency: Haloperidol, Trifluoperazine, Fluphenazine (Hal Tries to Fly High)—more neurologic side effects (eg, extrapyramidal symptoms [EPS]). Low potency: Chlorpromazine, Thioridazine (Cheating Thieves are low)—more anticholinergic, antihistamine, α1-blockade effects.

aDVErsE EFFEcts Lipid soluble stored in body fat slow to be removed from body. Endocrine: dopamine receptor antagonism • hyperprolactinemia galactorrhea, oligomenorrhea, gynecomastia. Metabolic: dyslipidemia, weight gain, hyperglycemia. Antimuscarinic: dry mouth, constipation. Antihistamine: sedation. α1-blockade: orthostatic hypotension. Cardiac: QT prolongation. Ophthalmologic: Chlorpromazine—Corneal deposits; Thioridazine—reTinal deposits. Neuroleptic malignant syndrome. Extrapyramidal symptoms— ADAPT:

Hours to days: Acute Dystonia (muscle spasm, stiffness, oculogyric crisis). Treatment: benztropine, diphenhydramine.

Days to months:

Akathisia (restlessness). Treatment: β-blockers, benztropine, benzodiazepines.

Parkinsonism (bradykinesia). Treatment: benztropine, amantadine.

Months to years: Tardive dyskinesia (chorea, especially orofacial). Treatment: atypical antipsychotics (eg, clozapine), valbenazine, deutetrabenazine.

MAOIs AXON POSTSYNAPTIC NEURON Mirtazapine TCAs, SSRIs, SNRIs, trazodone MAO Metabolites ----NE NE reuptake ˜2 (autoreceptor) adrenergic receptor Metabolites 5-HT 5-HT reuptake 5-HT receptorNE receptor -MAO AXON -TCAs, SNRIs, bupropion

Selective serotonin reuptake inhibitors Fluoxetine, fluvoxamine, paroxetine, sertraline, escitalopram, citalopram.

MEchaNisM Inhibit 5-HT reuptake. It normally takes 4–8 weeks for antidepressants to show appreciable effect.

cliNical UsE Depression, generalized anxiety disorder, panic disorder, OCD, bulimia, binge-eating disorder, social anxiety disorder, PTSD, premature ejaculation, premenstrual dysphoric disorder.

aDVErsE EFFEcts Fewer than TCAs. Serotonin syndrome, GI distress, SIADH, sexual dysfunction (anorgasmia, • libido).

Serotoninnorepinephrine reuptake inhibitors Venlafaxine, desvenlafaxine, duloxetine, levomilnacipran, milnacipran.

MEchaNisM Inhibit 5-HT and NE reuptake.

cliNical UsE Depression, generalized anxiety disorder, diabetic neuropathy. Venlafaxine is also indicated for social anxiety disorder, panic disorder, PTSD, OCD. Duloxetine and milnacipran are also indicated for fibromyalgia.

aDVErsE EFFEcts • BP, stimulant effects, sedation, nausea.

Tricyclic Amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, doxepin, amoxapine. antidepressants

MEchaNisM TCAs inhibit 5-HT and NE reuptake.

cliNical UsE MDD, peripheral neuropathy, chronic neuropathic pain, migraine prophylaxis, OCD (clomipramine), nocturnal enuresis (imipramine, although adverse effects may limit use).

aDVErsE EFFEcts Sedation, α1-blocking effects including postural hypotension, and atropine-like (anticholinergic) side effects (tachycardia, urinary retention, dry mouth). 3° TCAs (amitriptyline) have more anticholinergic effects than 2° TCAs (nortriptyline). Can prolong QT interval. Tri-CyCliC's: Convulsions, Coma, Cardiotoxicity (arrhythmia due to Na+ channel inhibition); also respiratory depression, hyperpyrexia. Confusion and hallucinations are more common in the elderly due to anticholinergic side effects (2° amines [eg, nortriptyline] better tolerated). Treatment: NaHCO3 to prevent arrhythmia.

Monoamine oxidase Tranylcypromine, Phenelzine, Isocarboxazid, Selegiline (selective MAO-B inhibitor). inhibitors (MAO Takes Pride In Shanghai).

MEchaNisM Nonselective MAO inhibition □• levels of amine neurotransmitters (norepinephrine, 5-HT, dopamine).

cliNical UsE Atypical depression, anxiety. Parkinson disease (selegiline).

aDVErsE EFFEcts CNS stimulation; hypertensive crisis, most notably with ingestion of tyramine. Contraindicated with SSRIs, TCAs, St. John's wort, meperidine, dextromethorphan, linezolid (to avoid precipitating serotonin syndrome). Wait 2 weeks after stopping MAOIs before starting serotonergic drugs or stopping dietary restrictions.

Bupropion Inhibits NE and DA reuptake. Also used for smoking cessation. Toxicity: stimulant effects (tachycardia, insomnia), headache, seizures in patients with bulimia and anorexia nervosa. Favorable sexual side effect profile.

Mirtazapine α2-antagonist (• release of NE and 5-HT), potent 5-HT2 and 5-HT3 receptor antagonist, and H1 antagonist. Toxicity: sedation (which may be desirable in depressed patients with insomnia), • appetite, weight gain (which may be desirable in underweight patients), dry mouth.

Trazodone Primarily blocks 5-HT2, α1-adrenergic, and H1 receptors; also weakly inhibits 5-HT reuptake. Used primarily for insomnia, as high doses are needed for antidepressant effects. Toxicity: sedation, nausea, priapism, postural hypotension. Think traZZZobone due to sedative and male-specific side effects.

Varenicline Nicotinic ACh receptor partial agonist. Used for smoking cessation. Toxicity: sleep disturbance, depressed mood, suicidal ideation. Varenicline helps nicotine cravings decline.

Methadone Long-acting oral opiate used for heroin detoxification or long-term maintenance therapy.

Buprenorphine Sublingual form (partial agonist) used to prevent relapse.

Naloxone Short-acting opioid antagonist given IM, IV, or as a nasal spray to treat acute opioid overdose, particularly to reverse respiratory and CNS depression.

Naltrexone Long-acting oral opioid antagonist used after detoxification to prevent relapse. Use naltrexone for the long trex back to sobriety.

“But I know all about love already. I know precious little still about kidneys.” —Aldous Huxley, Antic Hay “This too shall pass. Just like a kidney stone.” “I drink too much. The last time I gave a urine sample it had an olive in it.”

Being able to understand and apply renal physiology will be critical for the exam. Important topics include electrolyte disorders, acid-base derangements, glomerular disorders (including histopathology), acute and chronic kidney disease, urine casts, diuretics, ACE inhibitors, and AT-II receptor blockers. Renal anomalies associated with various congenital defects are also high-yield associations to think about when evaluating pediatric vignettes.

Kidney embryology Pronephros—week 4; then degenerates. Mesonephros—functions as interim kidney for 1st trimester; later contributes to male genital system. Metanephros—permanent; first appears in 5th week of gestation; nephrogenesis continues through weeks 32–36 of gestation.

Ureteric bud (metanephric diverticulum)— derived from caudal end of mesonephric duct; gives rise to ureter, pelvises, calyces, collecting ducts; fully canalized by 10th week

Metanephric mesenchyme (ie, metanephric blastema)—ureteric bud interacts with this tissue; interaction induces differentiation and formation of glomerulus through to distal convoluted tubule (DCT)

Aberrant interaction between these 2 tissues may result in several congenital malformations of the kidney (eg, renal agenesis, multicystic dysplastic kidney)

Ureteropelvic junction—last to canalize congenital obstruction. Most common cause of prenatal hydronephrosis. Detected by prenatal ultrasound.

Oligohydramnios compression of developing fetus limb deformities, facial anomalies (eg, low-set ears and retrognathia A , flattened nose), compression of chest and lack of amniotic fluid aspiration into fetal lungs pulmonary hypoplasia (cause of death).

Causes include ARPKD, obstructive uropathy (eg, posterior urethral valves), bilateral renal agenesis, chronic placental insufficiency.

Babies who can't "Pee" in utero develop Potter sequence.

POTTER sequence associated with: Pulmonary hypoplasia Oligohydramnios (trigger) Twisted face Twisted skin Extremity defects Renal failure (in utero)

Inferior poles of both kidneys fuse abnormally A . As they ascend from pelvis during fetal development, horseshoe kidneys get trapped under inferior mesenteric artery and remain low in the abdomen. Kidneys function normally. Associated with hydronephrosis (eg, ureteropelvic junction obstruction), renal stones, infection, • risk of renal cancer.

Higher incidence in chromosomal aneuploidy (eg, Turner syndrome, trisomies 13, 18, 21).

*Components of glomerular fltration barrier.

Cross-section of glomerulus

Left kidney is taken during living donor transplantation because it has a longer renal vein.

Afferent = Arriving.

Efferent = Exiting.

Renal blood flow: renal artery segmental artery • interlobar artery arcuate artery

A • efferent arteriole vasa recta/peritubular capillaries • venous outflow. Left renal vein receives two additional veins: left suprarenal and left gonadal veins.

Despite high overall renal blood flow, renal medulla receives significantly less blood flow than renal cortex very sensitive to hypoxia vulnerable to ischemic damage.

Course of ureters Course of ureter A : arises from renal pelvis, Water (ureters) flows over the iliacs and under travels under gonadal arteries • over common the bridge (uterine artery or vas deferens).

(retroperitoneal).

Gynecologic procedures (eg, ligation of ureteral obstruction or leak. (in female)

Bladder contraction compresses the intravesical ureter, preventing urine reflux.

Blood supply to ureter:

Middle—gonadal artery, aorta, common and internal iliac arteries 3 common points of ureteral obstruction: ureteropelvic junction, pelvic inlet, ureterovesical junction.

Body mass: 70 kg HIKIN': HIgh K+ INtracellularly.

60–40–20 rule (% of body weight for average 60% of body mass = 42 kg 42 L 40% of body mass = 28 kg person): 40% ICF, mainly composed of K+, Mg2+, organic phosphates (eg, ATP) 20% ECF, mainly composed of Na+, Cl−,

Extracellular fuid (ECF)~ 14 kg (20% of 70 kg) Intracellular fuid (ICF)~ 28 kg (40% of 70 kg) Interstitial fuid = 75% ECF 10.5 L 10.5 kg Blood volume 6 L Plasma = 25% ECF 3.5 L 3.5 kg RBC volume 2.8 L

HCO3−, albumin Normal Hct = 45% Plasma volume can be measured by Hct (%) 3 [Hb] in g/dL radiolabeling albumin.

or mannitol. Serum osmolality = 285–295 mOsm/kg H2O. Plasma volume = TBV × (1 − Hct).

Glomerular filtration Responsible for filtration of plasma according to Charge barrier—all 3 layers contain ⊖ charged barrier size and charge selectivity. glycoproteins that prevent entry of ⊖ charged

Composed of:

Basement membrane with type IV collagen chains and heparan sulfate

Visceral epithelial layer consisting of podocyte foot processes (FPs) molecules (eg, albumin).

Size barrier—fenestrated capillary endothelium (prevents entry of > 100 nm molecules/blood cells); podocyte foot processes interpose with glomerular basement membrane (GBM); slit diaphragm (prevents entry of molecules > 50–60 nm).

Glomerular filtration Inulin clearance can be used to calculate GFR 14 rate because it is freely filtered and is neither reabsorbed nor secreted. 12

Creatinine clearance is an approximate measure of GFR. Slightly overestimates GFR because 2 creatinine is moderately secreted by renal tubules.

coefficient). Normal GFR ≈ 100 mL/min.

Filtration Filtration fraction (FF) = GFR/RPF. GFR can be estimated with creatinine Normal FF = 20%. clearance. Filtered load (mg/min) = GFR (mL/min) RPF is best estimated with PAH clearance.

× plasma concentration (mg/mL). Prostaglandins Dilate Afferent arteriole (PDA). Angiotensin II Constricts Efferent arteriole (ACE).

Prostaglandins preferentially dilate aferent arteriole Bowman capsule GFR, so no ˜ FF) (parietal layer)

RPF,

RPF,

GFR, so

Calculation of Filtered load = GFR × P.

reabsorption and Excretion rate = V × Ux.

secretion rate Reabsorption rate = filtered − excreted. Secretion rate = excreted − filtered. FeNa = fractional excretion of sodium.

Glucose clearance Glucose at a normal plasma level (range 60–120 mg/dL) is completely reabsorbed in proximal convoluted tubule (PCT) by Na+/glucose cotransport. In adults, at plasma glucose of ~ 200 mg/dL, glucosuria begins (threshold). At rate of ~ 375 mg/min, all transporters are fully saturated (Tm). Normal pregnancy is associated with • GFR. With • filtration of all substances, including glucose, the glucose threshold occurs at lower plasma glucose concentrations glucosuria at normal plasma glucose levels. Sodium-glucose cotransporter 2 (SGLT2) inhibitors (eg, -flozin drugs) result in glucosuria at plasma concentrations < 200 mg/dL.

Glucosuria is an important clinical clue to diabetes mellitus.

Splay phenomenon—Tm for glucose is reached gradually rather than sharply due to the heterogeneity of nephrons (ie, different Tm points); represented by the portion of the titration curve between threshold and T .

Early PCT—contains brush border. Reabsorbs all glucose and amino acids and most HCO_3^-, Na^+, Cl^-, PO_4^{3-}, K^+, H_2O, and uric acid. Isotonic

absorption. Generates and secretes NH3, which enables the kidney to secrete more H+.

PTH—inhibits Na+/PO43− cotransport •• PO43− excretion.

AT II—stimulates Na+/H+ exchange •• Na+, H2O, and HCO3− reabsorption (permitting contraction alkalosis).

65–80% Na+ and H2O reabsorbed.

Thin descending loop of Henle—passively reabsorbs H2O via medullary hypertonicity (impermeable to Na+). Concentrating segment. Makes urine hypertonic.

Mg2+, Ca2+ Interstitium blood

Diusion down the electrochemical gradient

Thick ascending loop of Henle—reabsorbs Na+, K+, and Cl−. Indirectly induces paracellular reabsorption of Mg2+ and Ca2+ through ˜ lumen potential generated by K+ backleak. Impermeable to H2O. Makes urine less concentrated as it ascends.

10–20% Na+ reabsorbed.

Early DCT—reabsorbs Na+, Cl−. Impermeable to H2O.

Makes urine fully dilute (hypotonic). PTH—• Ca2+/Na+ exchange •• Ca2+ reabsorption. 5–10% Na+ reabsorbed.

Collecting tubule—reabsorbs Na+ in exchange for secreting K+ and H+ (regulated by aldosterone). Aldosterone—acts on mineralocorticoid receptor • mRNA • protein synthesis. In principal cells: • apical K+ conductance, • Na+/K+ pump, • epithelial Na+ channel (ENaC) activity • lumen negativity • K+ secretion. In ˜-intercalated cells: lumen negativity •• H+ ATPase activity •• H+ secretion •• HCO3−/Cl− exchanger activity.

ADH—acts at V2 receptor • insertion of aquaporin H2O channels on apical side. 3–5% Na+ reabsorbed.

Renal tubular defects Order: Fanconi’s BaGeLS Gitelman syndrome Bartter syndrome Liddle syndrome, SAME

Syndrome of Apparent Mineralocorticoid Excess

Treatment: K+-sparing diuretics (• mineralocorticoid effects) or corticosteroids (exogenous corticosteroid • endogenous cortisol production □• mineralocorticoid receptor activation) 0% 25% 50% 75% 100% % Distance along PCT length PAH Creatinine Inulin clearance = GFR Urea Cl−Glucose Amino acids HCO3 − K+ Osmolarity, Na+ 1.90 1.85 when solute is reabsorbed less quickly 1.80

Tubular inulin • in concentration (but not amount) along the PCT as a result of water reabsorption. Cl− reabsorption occurs at a slower rate than Na+ in early PCT and then matches the rate of Na+ reabsorption more distally. Thus, its relative concentration • before it plateaus.

Renal cells ↑BP ↑activity Na+ , HCOƒ , and H⁄O H+ secretion ↑receptor type I Vasoconstriction ↑FF arteriole Na+ reabsorption H⁄O reabsorption secretion pituitary) Preserves GFR (when RBF) PCT cell α-intercalated cell Principal cell

Na+/K+ ATPase, and ENaC activity)

Renin Secreted by JG cells in response to • renal perfusion pressure (detected by renal baroreceptors in afferent arteriole), • renal sympathetic discharge (β1 effect), and • NaCl delivery to macula densa cells.

AT II Helps maintain blood volume and blood pressure. Affects baroreceptor function; limits reflex bradycardia, which would normally accompany its pressor effects.

ANP, BNP Released from atria (ANP) and ventricles (BNP) in response to • volume; inhibits renin-angiotensinaldosterone system; relaxes vascular smooth muscle via cGMP □□ GFR, • renin. Dilates afferent arteriole, promotes natriuresis.

ADH Primarily regulates serum osmolality; also responds to low blood volume states. Stimulates reabsorption of water in collecting ducts. Also stimulates reabsorption of urea in collecting ducts to maximizes corticopapillary osmotic gradient.

Aldosterone Primarily regulates ECF volume and Na+ content; • release in • blood volume states. Responds to hyperkalemia by • K+ excretion.

contraction alkalosis) activity) (K+ conductance,

JGA maintains GFR via renin-angiotensinaldosterone system.

In addition to vasodilatory properties, β-blockers can decrease BP by inhibiting β1-receptors of the JGA □• renin release.

Calciferol (vitamin D) PCT cells convert 25-OH vitamin D to 1,25-25-OH D (OH)2 vitamin D3 (calcitriol, active form). (calcidiol) 1˜-hydroxylase (calcitriol) 1,25-(OH) D

Secreted in response to ° atrial pressure. Causes ° GFR and ° Na+ fltration with no compensatory Na+ reabsorption + loss and volume loss.

Synthesized in response to reabsorption in proximal and distal nephron. Net e˜ect: BP. Causes e˜erent arteriole˜ ° GFR and ° FF but with compensatory Na+ preservation of renal function (° FF) in low-volume state with simultaneous Na+ reabsorption (both proximal and distal) to maintain circulating volume. Glomerulus Proximal convoluted tubule Loop of Henle Ascending limb, loop of Henle (permeable to salts) Collecting

duct convoluted tubule Cortex Medulla Sugars Amino acids Na+ Na+ K+ 2CI− Ca2+ Mg2+ Mg2+ Na+ CI− H Ca2+ Parathyroid hormone Secreted in response to ˜ plasma [Ca2+], ° plasma [PO43−], or ˜ plasma 1,25-(OH)2 D3. Causes ° [Ca2+] reabsorption (DCT), ˜ [PO43−] reabsorption (PCT), and ° 1,25-(OH)2 D3 production (° Ca2+ and PO43− absorption from gut via vitamin D). Aldosterone Secreted in response to ˜ blood volume (via AT II) and ° plasma [K+]; causes ° Na+ reabsorption, ° K+ secretion, ° H+ secretion. ADH (vasopressin) Secreted in response to ° plasma osmolarity and ˜ blood volume. Binds to receptors on principal cells, causing ° number of aquaporins and ° H2O reabsorption. ° reabsorption of urea in collecting ducts to maximize corticopapillary osmotic gradient. K+ H+ Na+

Features of renal disorders

Key: □• = compensatory response.

[HCO3 −]Henderson-Hasselbalch equation: pH = 6.1 + log 0.03 P2

Predicted respiratory compensation for a simple metabolic acidosis can be calculated using the Winters formula. If measured Pco2 > predicted Pco2 □ concomitant respiratory acidosis; if measured Pco2 < predicted Pco2 • concomitant respiratory alkalosis:

Pco2 = 1.5 [HCO3−] + 8 ± 2

Acidosis and alkalosis Check arterial pH pH < 7.35 Pco2 > 44 mm Hg HCO3 − < 20 mEq/L Acidemia Respiratory acidosis Metabolic acidosis Hypoventilation Airway obstruction Acute lung disease Chronic lung disease Opioids, sedatives Weakening of respiratory muscles •Anion gap MUDPILES: Normal anion gap Check anion gap Methanol (formic acid) Uremia Diabetic ketoacidosis Propylene glycol Iron tablets or INH Lactic acidosis Ethylene glycol (oxalic acid) Salicylates (late) HARDASS:= Na+ − (CI + HCO3)− _

Anxiety/panic attack Hypoxemia (eg, high altitude) Salicylates (early) Tumor Pulmonary embolism pH > 7.45 6.97.0 7.17.2 7.37.4 7.57.6 7.77.8 7.9

Renal tubular Disorder of the renal tubules that causes normal anion gap (hyperchloremic) metabolic acidosis. acidosis

Distal renal Inability of > 5.5 • Amphotericin B toxicity, • risk for calcium tubular acidosis α-intercalated cells to analgesic nephropathy, phosphate kidney (type 1) secrete H+ □ no new congenital anomalies stones (due to • urine

HCO3 is generated (obstruction) of urinary pH and • bone • metabolic acidosis tract, autoimmune turnover related to diseases (eg, SLE) buffering)

Defect in PCT > 5.5 when

HCO3 reabsorption resorptive □• excretion of threshold

Urine can be acidified by exceeded; α-intercalated cells in < 5.5 when collecting duct, but not HCO3 enough to overcome depleted • Fanconi syndrome, • risk for multiple myeloma, hypophosphatemic carbonic anhydrase rickets (in Fanconi inhibitors syndrome) (eg, diabetic hyporeninism, ACE inhibitors, ARBs, NSAIDs, heparin, cyclosporine, adrenal insufficiency) or aldosterone resistance (eg, K+-sparing diuretics, nephropathy due to obstruction, TMP-SMX)

Casts in urine Presence of casts indicates that hematuria/pyuria is of glomerular or renal tubular origin. Bladder cancer, kidney stones hematuria, no casts. Acute cystitis pyuria, no casts.

A Glomerulonephritis, hypertensive emergency.

B Tubulointerstitial inflammation, acute pyelonephritis, transplant rejection.

Nomenclature of glomerular disorders Glomerular diseases GBM damage loss of RBCs into urine • hematuria Hematuria, RBC casts in urine oliguria, azotemia, release, HTN

Proteinuria often in the subnephrotic range (< 3.5 g/ day) but in severe cases may be in nephrotic range

Massive proteinuria (> 3.5 g/ day) with hypoalbuminemia, edema

Frothy urine with fatty casts

Associated with hypercoagulable state due to antithrombin III loss in urine and • risk of infection (loss of IgGs in urine and soft tissue compromise by edema) May be 1° (eg, direct podocyte damage) or 2° (podocyte damage from systemic process):

Kidney Can lead to severe complications such as hydronephrosis, pyelonephritis, and acute kidney injury. Obstructed stones stone presents with unilateral flank tenderness, colicky pain radiating to groin, hematuria. Treat and prevent by encouraging fluid intake.

Calcium Calcium Radiopaque Radiopaque Shaped like oxalate: envelope

Calcium Radiopaque Radiopaque Wedge-phosphate: shaped • pH prism Calcium stones most common (80%); calcium oxalate more common than calcium phosphate stones.

Can result from ethylene glycol (antifreeze) ingestion, vitamin C abuse, hypocitraturia (associated with • urine pH), malabsorption (eg, Crohn disease).

Treatment: thiazides, citrate, low-sodium diet. Treatment: low-sodium diet, thiazides.

B Account for 15% of stones. Caused by infection magnesium with urease ⊕ bugs (eg, Proteus mirabilis, phosphate Staphylococcus saprophyticus,

Klebsiella) (struvite) that hydrolyze urea to ammonia urine alkalinization. Commonly form staghorn calculi

C . Treatment: eradication of underlying infection, surgical removal of stone.

D About 5% of all stones. Risk factors: • urine visible or rosettes volume, arid climates, acidic pH.

Strong association with hyperuricemia (eg, gout). Often seen in diseases with • cell turnover (eg, leukemia).

Treatment: alkalinization of urine, allopurinol.

opaque radiopaque which Cystine-reabsorbing PCT transporter loses function, causing cystinuria. Transporter defect also results in poor reabsorption of Ornithine, Lysine, Arginine (COLA). Cystine is poorly soluble, thus stones form in urine. Usually begins in childhood. Can form staghorn calculi. Sodium cyanide nitroprusside test ⊕.

“SIXtine” stones have SIX sides.

Treatment: low sodium diet, alkalinization of urine, chelating agents (eg, penicillamine) if refractory.

Hydronephrosis Distention/dilation of renal pelvis and calyces A . Usually caused by urinary tract obstruction (eg, renal stones, severe BPH, congenital obstructions, cervical cancer, injury to ureter); other causes include retroperitoneal fibrosis, vesicoureteral reflux. Dilation occurs proximal to site of pathology. Serum creatinine becomes elevated if obstruction is bilateral or if patient has an obstructed solitary kidney. Leads to compression and possible atrophy of renal cortex and medulla.

Urinary incontinence Mixed incontinence has features of both stress and urgency incontinence.

Acute cystitis Inflammation of urinary bladder. Presents as suprapubic pain, dysuria, urinary frequency, urgency. Systemic signs (eg, high fever, chills) are usually absent. Risk factors include female sex (short urethra), sexual intercourse, indwelling catheter, diabetes mellitus, impaired bladder emptying. Causes:

Staphylococcus saprophyticus—seen in sexually active young women (E coli is still more common in this group)

Proteus mirabilis—urine has ammonia scent Labs: ⊕ leukocyte esterase. ⊕ nitrites (indicate gram ⊖ organisms). Sterile pyuria (pyuria with ⊖ urine cultures) could suggest urethritis by Neisseria gonorrhoeae or Chlamydia trachomatis. Treatment: antibiotics (eg, TMP-SMX, nitrofurantoin).

Acute pyelonephritis Neutrophils infiltrate renal interstitium A . Affects cortex with relative sparing of glomeruli/vessels. Presents with

fevers, flank pain (costovertebral angle tenderness), nausea/vomiting, chills. Causes include ascending UTI (E coli is most common), hematogenous spread to kidney. Presents with WBCs in urine +/- WBC casts. CT would show striated parenchymal enhancement B . Risk factors include indwelling urinary catheter, urinary tract obstruction, vesicoureteral reflux, diabetes mellitus, pregnancy. Complications include chronic pyelonephritis, renal papillary necrosis, perinephric abscess, urosepsis. Treatment: antibiotics.

Also called tubulointerstitial nephritis. Acute interstitial renal inflammation. Pyuria (classically eosinophils) and azotemia occurring after administration of drugs that act as haptens, inducing hypersensitivity (eg, diuretics, NSAIDs, penicillin derivatives, proton pump inhibitors, rifampin, quinolones, sulfonamides). Less commonly may be 2° to other processes such as systemic infections (eg, Mycoplasma) or autoimmune diseases (eg, Sjögren syndrome, SLE, sarcoidosis).

Associated with fever, rash, hematuria, pyuria, and costovertebral angle tenderness, but can be asymptomatic.

Remember these 5P’S:

Acute tubular necrosis Most common cause of acute kidney injury in hospitalized patients. Spontaneously resolves in many cases. Can be fatal, especially during initial oliguric phase. • FENa. Key finding: granular casts (often muddy brown in appearance) A . 3 stages: 1.

2.

Maintenance phase—oliguric; lasts 1–3 weeks; risk of hyperkalemia, metabolic acidosis, uremia 3.

Recovery phase—polyuric; BUN and serum creatinine fall; risk of hypokalemia and renal wasting of other electrolytes and minerals Can be caused by ischemic or nephrotoxic injury:

Ischemic—2° to • renal blood flow (eg, hypotension, shock, sepsis, hemorrhage, HF). Results in death of tubular cells that may slough into tubular lumen B (PCT and thick ascending limb are highly susceptible to injury).

Nephrotoxic—2° to injury resulting from toxic substances (eg, aminoglycosides, radiocontrast agents, lead, cisplatin, ethylene glycol), crush injury (myoglobinuria), hemoglobinuria. Proximal tubules are particularly susceptible to injury.

Diffuse cortical Acute generalized cortical infarction of both Associated with obstetric catastrophes (eg, necrosis kidneys. Likely due to a combination of abruptio placentae), septic shock. vasospasm and DIC.

Renal papillary Sloughing of necrotic renal papillae A • gross Associated with: Sickle cell disease or trait, necrosis hematuria and proteinuria. May be triggered Acute pyelonephritis, Analgesics (NSAIDs), by recent

infection or immune stimulus. Diabetes mellitus (SAAD papa with papillary necrosis).

Consequences of renal failure

Decline in renal filtration can lead to excess retained nitrogenous waste products and electrolyte disturbances.

Consequences (MAD HUNGER):

Uremia—clinical syndrome marked by:

Na+/H2O retention (HF, pulmonary edema, hypertension) 2 forms of renal failure: acute (eg, ATN) and chronic (eg, hypertension, diabetes mellitus, congenital anomalies).

Incremental reductions in GFR define the stages of chronic kidney disease.

Renal osteodystrophy Hypocalcemia, hyperphosphatemia, and failure of vitamin D hydroxylation associated with chronic kidney disease 2° hyperparathyroidism 3° hyperparathyroidism (if 2° poorly managed). High serum phosphate can bind with Ca2+ tissue deposits •serum Ca2+. • 1,25-(OH)2D3 •intestinal Ca2+ absorption. Causes subperiosteal thinning of bones.

Autosomal recessive Cystic dilation of collecting ducts B . Often presents in infancy. Associated with congenital polycystic kidney hepatic fibrosis. Significant oliguric renal failure in utero can lead to Potter sequence. Concerns disease beyond neonatal period include systemic hypertension, progressive renal insufficiency, and portal hypertension from congenital hepatic fibrosis.

Autosomal dominant Also called medullary cystic kidney disease. Causes tubulointerstitial fibrosis and progressive renal tubulointerstitial insufficiency with inability to concentrate urine. Medullary cysts usually not visualized; smaller kidney disease kidneys on ultrasound. Poor prognosis.

Renal cell carcinoma Polygonal clear cells A filled with accumulated lipids and carbohydrate. Often golden-yellow

B due to • lipid content. Originates from PCT invades renal vein (may develop varicocele if left sided) IVC • hematogenous spread metastasis to lung and bone. Manifests with hematuria, palpable masses, 2° polycythemia, flank pain, fever, weight loss.

Treatment: surgery/ablation for localized disease. Immunotherapy (eg, aldesleukin) or targeted therapy for metastatic disease, rarely curative. Resistant to chemotherapy and radiation therapy.

C . Most common in men 50–70 years old, • incidence with smoking and obesity.

Associated with paraneoplastic syndromes, eg, PTHrP, Ectopic EPO, ACTH, Renin ("PEAR"-aneoplastic).

Clear cell (most common subtype) associated with gene deletion on chromosome 3 (sporadic, or inherited as von Hippel-Lindau syndrome).

RCC = 3 letters = chromosome 3.

Benign epithelial cell tumor arising from collecting ducts (arrows in A point to well-circumscribed mass with central scar). Large eosinophilic cells with abundant mitochondria without perinuclear clearing

B (vs chromophobe renal cell carcinoma). Presents with painless hematuria, flank pain, abdominal mass.

Often resected to exclude malignancy (eg, renal cell carcinoma).

Also called Wilms tumor. Most common renal malignancy of early childhood (ages 2–4). Contains embryonic glomerular structures. Presents with large, palpable, unilateral flank mass A and/or hematuria and possible HTN.

"Loss of function" mutations of tumor suppressor genes WT1 or WT2 on chromosome 11. May be a part of several syndromes:

WAGR complex—Wilms tumor, Aniridia (absence of iris), Genitourinary malformations, mental Retardation/intellectual disability (WT1 deletion)

Denys-Drash syndrome—Wilms tumor, Diffuse mesangial sclerosis (early-onset nephrotic syndrome), Dysgenesis of gonads (male pseudohermaphroditism), WT1 mutation

Beckwith-Wiedemann syndrome—Wilms tumor, macroglossia, organomegaly, hemihyperplasia (WT2 mutation), omphalocele

Urothelial carcinoma Also called transitional cell carcinoma. Most of the bladder common tumor of urinary tract system (can occur in renal calyces, renal pelvis, ureters, and bladder) A B . Can be suggested by painless hematuria (no casts).

Associated with problems in your Pee SAC: Phenacetin, Smoking, Aniline dyes, and Cyclophosphamide.

Diuretics site of action 5Glomerulus A°erent Mannitol Acetazolamide Loop diuretics Thiazide diuretics K+ sparing diuretics Proximal convoluted tubule Loop of Henle Descending limb, loop of Henle (permeable to water) Ascending limb, loop of Henle (permeable to salts) Collecting duct Distal convoluted tubule Cortex Medulla 1234Sugars Amino acids Na+ Na+ K+ 2CI– Ca2+ Mg2+ Na+ CI– Na+ Na+ HCO3 – Ca2+ 34K+ H+ 5521E°erent H2O mEChANism Osmotic diuretic. • tubular fluid osmolarity □• urine flow, • intracranial/intraocular pressure.

CLiNiCAL UsE Drug overdose, elevated intracranial/intraocular pressure.

ADVERsE EFFECts Pulmonary edema, dehydration, hypoor hypernatremia. Contraindicated in anuria, HF.

mEChANism Carbonic anhydrase inhibitor. Causes self-limited NaHCO3 diuresis and □ total body HCO3 – stores. Alkalinizes urine.

CLiNiCAL UsE Glaucoma, metabolic alkalosis, altitude sickness, idiopathic intracranial hypertension.

ADVERsE EFFECts Proximal renal tubular acidosis, paresthesias, "Acid"azolamide causes Acidosis. NH3 toxicity, sulfa allergy, hypokalemia. Promotes calcium phosphate stone formation (insoluble at high pH).

Furosemide, bumetanide, torsemide mEChANism Sulfonamide loop diuretics. Inhibit cotransport system (Na+/K+/2Cl−) of thick ascending limb of loop of Henle. Abolish hypertonicity of medulla, preventing concentration of urine. Associated with • PGE (vasodilatory effect on afferent arteriole); inhibited by NSAIDs. • Ca2+ excretion. Loops Lose Ca2+.

CLiNiCAL UsE Edematous states (HF, cirrhosis, nephrotic syndrome, pulmonary edema), hypertension, hypercalcemia.

CLiNiCAL UsE Diuresis in patients allergic to sulfa drugs.

ADVERsE EFFECts Similar to furosemide, but more ototoxic. Loop earrings hurt your ears.

Thiazide diuretics Hydrochlorothiazide, chlorthalidone, metolazone.

mEChANism Inhibit NaCl reabsorption in early DCT □• diluting capacity of nephron. • Ca2+ excretion.

CLiNiCAL UsE Hypertension, HF, idiopathic hypercalciuria, nephrogenic diabetes insipidus, osteoporosis.

ADVERsE EFFECts Hypokalemic metabolic alkalosis, hyponatremia, hyperGlycemia, hyperLipidemia, hyperUricemia, hyperCalcemia. Sulfa allergy.

HyperGLUC.

Potassium-sparing Spironolactone, Eplerenone, Amiloride, Keep your SEAT diuretics Triamterene.

mEChANism Spironolactone and eplerenone are competitive aldosterone receptor antagonists in cortical collecting tubule. Triamterene and amiloride block Na+ channels at the same part of the tubule.

CLiNiCAL UsE Hyperaldosteronism, K+ depletion, HF, hepatic ascites (spironolactone), nephrogenic DI (amiloride), antiandrogen.

ADVERsE EFFECts Hyperkalemia (can lead to arrhythmias), endocrine effects with spironolactone (eg, gynecomastia, antiandrogen effects).

Diuretics: electrolyte changes

Urine NaCl • with all diuretics (strength varies based on potency of diuretic effect). Serum NaCl may decrease as a result.

Urine Ca2+ • with loop diuretics: • paracellular Ca2+ reabsorption □ hypocalcemia.

• with thiazides: enhanced Ca2+ reabsorption.

Angiotensin-Captopril, enalapril, lisinopril, ramipril. converting enzyme inhibitors mEChANism Inhibit ACE □• AT II □• GFR by preventing constriction of efferent arterioles. • renin due to loss of negative feedback. Inhibition of ACE also prevents inactivation of bradykinin, a potent vasodilator.

CLiNiCAL UsE Hypertension, HF, proteinuria, or chronic kidney disease (eg, diabetic nephropathy) with intolerance to ACE inhibitors (eg, cough, angioedema).

ADVERsE EFFECts Hyperkalemia, • GFR, hypotension; teratogen.

mEChANism Direct renin inhibitor, blocks conversion of angiotensinogen to angiotensin I. Aliskiren Kills Renin.

CLiNiCAL UsE Hypertension.

ADVERsE EFFECts Hyperkalemia, • GFR, hypotension, angioedema. Relatively contraindicated in patients already taking ACE inhibitors or ARBs and contraindicated in pregnancy.

“Artificial insemination is when the farmer does it to the cow instead of the bull.”

Make no mistake about why these babies are here they are here to replace us.

“Whoever called it necking was a poor judge of anatomy.” “See, the problem is that God gives men a brain and a penis, and only enough blood to run one at a time.”

The reproductive system can be intimidating at first but is manageable once you organize the concepts into the pregnancy, endocrinologic, embryologic, and oncologic aspects of reproduction. Study the endocrine and reproductive chapters together, because mastery of the hypothalamic-pituitary-gonadal axis is key to answering questions on ovulation, menstruation, disorders of sexual development, contraception, and many pathologies.

Embryology is a nuanced subject that covers multiple organ systems. Approaching it from a clinical perspective will allow for better understanding. For instance, make the connection between the presentation

of DiGeorge syndrome and the 3rd/4th pharyngeal pouch, and between the Müllerian/Wolffian systems and disorders of sexual development.

As for oncology, don't worry about remembering screening or treatment guidelines. It is more important to know how these cancers present (eg, signs and symptoms) and their associated labs, histopathology, and risk factors. In addition, some of the testicular and ovarian cancers have distinct patterns of hCG, AFP, LH, or FSH derangements that serve as helpful clues in exam questions.

Important genes of embryogenesis

Types of errors in morphogenesis

Deformation Extrinsic disruption (eg, multiple gestations crowding foot deformities); occurs after embryonic period.

Malformation Intrinsic disruption; occurs during embryonic period (weeks 3–8).

Sequence Abnormalities result from a single 1° embryologic event (eg, oligohydramnios Potter sequence).

Teratogens Most susceptible in 3rd–8th weeks (embryonic period—organogenesis) of pregnancy. Before week 3, "all-or-none" effects. After week 8, growth and function affected.

ACE inhibitors Renal failure, oligohydramnios, hypocalvaria.

Lithium Ebstein anomaly.

Methimazole Aplasia cutis congenita (congenital absence of skin, particularly on scalp).

Alcohol Fetal alcohol syndrome.

Iodine (lack or excess) Congenital goiter or hypothyroidism (cretinism).

Maternal diabetes Caudal regression syndrome, cardiac defects (eg, VSD), neural tube defects, macrosomia, neonatal hypoglycemia (due to islet cell hyperplasia), polycythemia.

Methylmercury Neurotoxicity. Highest in swordfish, shark, tilefish, king mackerel.

Vitamin A excess Extremely high risk for spontaneous abortions and birth defects (cleft palate, cardiac).

X-rays Microcephaly, intellectual disability. Minimized by lead shielding.

One of the leading preventable causes of intellectual disability in the US. Newborns of mothers who consumed alcohol during any stage of pregnancy have • incidence of congenital abnormalities, including preand

postnatal developmental retardation, microcephaly, facial abnormalities A (eg, smooth philtrum, thin vermillion border, small palpebral fissures), limb dislocation, heart defects. Heart-lung fistulas and holoprosencephaly in most severe form. One mechanism is due to impaired migration of neuronal and glial cells.

Twinning Dizygotic ("fraternal") twins arise from 2 eggs that are separately fertilized by 2 different sperm (always 2 zygotes) and will have 2 separate amniotic sacs and 2 separate placentas (chorions).

Monozygotic ("identical") twins arise from 1 fertilized egg (1 egg + 1 sperm) that splits in early pregnancy. The timing of cleavage determines chorionicity (number of chorions) and amnionicity (number of amnions) (SCAB):

Cleavage 0–4 days: Separate chorion and amnion

Cleavage 4–8 days: shared Chorion

Cleavage 8–12 days: shared Amnion

Cleavage 13+ days: shared Body (conjoined) 2 eggs, 1 egg, 1 sperm 2 sperm

Placenta 1° site of nutrient and gas exchange between mother and fetus.

Decidua basalis Derived from endometrium. Maternal blood in lacunae.

Branch villus Umbilical vein (O2 rich) Umbilical arteries (O2 poor) Endometrial vein Maternal circulation Chorionic plate Maternal blood Amnion Maternal circulation Fetal circulation CO2 H2O Urea, waste products Hormones Endometrial artery Decidua basalis Endothelial cell Syncytiotrophoblast Cytotrophoblast O2 H2O, electrolytes Nutrients Hormones IgG Drugs Viruses

Urachus Allantois forms from hindgut and extends into urogenital sinus. Allantois becomes the urachus, a duct between fetal bladder and umbilicus. Failure of urachus to involute can lead to anomalies that may increase risk of infection and/or malignancy (eg, adenocarcinoma) if not treated. Obliterated urachus is represented by the median umbilical ligament after birth, which is covered by median umbilical fold of the peritoneum.

Vesicourachal Slight failure of urachus to obliterate □ outpouching of bladder. diverticulum

Vitelline duct 7th week—obliteration of vitelline duct (omphalomesenteric duct), which connects yolk sac to midgut lumen.

Vitelline fistula Vitelline duct fails to close □ meconium discharge from umbilicus.

Meckel diverticulum Partial closure of vitelline duct, with patent portion attached to ileum (true diverticulum, white arrow in B). May be

asymptomatic. May have heterotopic gastric and/or pancreatic tissue melena, hematochezia, abdominal pain.

Aortic arch derivatives Develop into arterial system.

1st Part of maxillary artery (branch of external 1st arch is maximal carotid) 3rd Common Carotid artery and proximal part of C is 3rd letter of alphabet internal Carotid artery 4th On left, aortic arch; on right, proximal part of 4th arch (4 limbs) = systemic right subclavian artery 6th Proximal part of pulmonary arteries and (on left only) ductus arteriosus 6th arch = pulmonary and the pulmonary-tosystemic shunt (ductus arteriosus)

Pharyngeal apparatus Composed of pharyngeal clefts, arches, CAP covers outside to inside: pouches. Clefts = ectoderm Pharyngeal clefts—derived from ectoderm. Also Arches = mesoderm + neural crest called pharyngeal grooves. Pouches = endoderm Pharyngeal arches—derived from mesoderm (muscles, arteries) and neural crest (bones, cartilage). Pharyngeal pouches—derived from endoderm.

• Maxilla, zygoMatic Mandible,

Malleus and incus, sphenoMandibular ligament

Reichert cartilage: Stapes, Styloid process, leSSer horn of hyoid, Stylohyoid ligament Muscles of Mastication (temporalis, Masseter, lateral and Medial pterygoids), Mylohyoid, anterior belly of digastric, tensor tympani, anterior 2/3 of tongue, tensor veli palatini

Muscles of facial expression, Stapedius, Stylohyoid, platySma, posterior belly of digastric

CN V3 chew Pierre Robin sequence— micrognathia, glossoptosis, cleft palate, airway obstruction

CN VII (facial • craniofacial expression) abnormalities (eg, smile zygomatic bone and mandibular hypoplasia), hearing loss, airway compromise 3rd pharyngeal Greater horn of hyoid Stylopharyngeus (think CN IX (styloarch of stylopharyngeus pharyngeus) innervated by swallow stylishly glossopharyngeal nerve) 4th and 6th Arytenoids, Cricoid, pharyngeal Corniculate, arches Cuneiform, Thyroid (used to sing and ACCCT) 4th arch: most pharyngeal 4th arch: CN Arches 3 and 4 form constrictors; cricothyroid, X (superior posterior 1/3 of tongue levator veli palatini laryngeal branch) Arch 5 makes no 6th arch: all intrinsic simply swallow major developmental muscles of larynx except 6th arch: CN contributions cricothyroid X (recurrent/ inferior laryngeal branch) speak aSensory and motor nerves are not pharyngeal arch derivatives. They grow into the arches and are derived from neural crest (sensory) and neuroectoderm (motor).

When at the restaurant of the golden arches, children tend to first chew (1), then smile (2), then swallow stylishly (3) or simply swallow (4), and then speak (6).

1st pharyngeal pouch Middle ear cavity, eustachian 1st pouch contributes to Ear, tonsils, bottom-to-top: tube, mastoid air cells endoderm-lined structures 1 (ear) of ear 2 (tonsils) 3 dorsal (bottom for inferior 2nd pharyngeal pouch Epithelial lining of palatine 3rd pharyngeal pouch Dorsal wings • inferior 3rd pouch contributes to 3 parathyroids structures (thymus, left and (C) cells of thyroid

Cleft lip and cleft Distinct, multifactorial etiologies, but often occur together. palate

Cleft lip Due to failure of fusion of the maxillary and merged medial nasal processes (formation of 1° palate).

Cleft palate Due to failure of fusion of the two lateral palatine shelves or failure of fusion of lateral palatine shelf with the nasal septum and/or 1° palate (formation of 2° palate).

Intermaxillary segment Roof of mouth (1° palate) Nasal septum Maxillary prominence Palatine shelves (2° palate)

Female Default development. Mesonephric duct degenerates and paramesonephric duct develops.

Metanephric kidney Ureter Uterus Vagina Vas deferens Degenerated paramesonephric duct Degenerated mesonephric duct Oviduct Urinary bladder Testis Ovary Epididymis Testis-determining factor Androgens MIF Gubernaculum Mesonephros Paramesonephric duct Mesonephric duct Urogenital sinus No androgens (Müllerian) duct fallopian tubes, uterus, upper portion of vagina (lower portion from urogenital sinus). Male remnant is appendix testis. Müllerian agenesis (Mayer-Rokitansky-Küster-Hauser syndrome)—may present 2° sexual characteristics (functional ovaries). (Wolffian) duct prostate)—Seminal vesicles, Epididymis, Ejaculatory duct, Ductus deferens (SEED). Female remnant is Gartner duct.

determining factor • testes development.

Sertoli cells secrete Müllerian inhibitory factor (MIF, also called antimullerian hormone) that suppresses development of paramesonephric ducts.

Leydig cells secrete androgens that stimulate development of mesonephric ducts. Paramesonephric Develops into female internal structures— as 1° amenorrhea (due to a lack of uterine development) in females with fully developed

Absence of Sertoli cells or lack of Müllerian inhibitory factor develop both male and sexual differentiation. Sertoli Shuts down female (internal) sexual differentiation.

genitalia, ambiguous external genitalia until

In the testes: Leydig Leads to male (internal and external)

Septate uterus Common anomaly vs normal uterus A . Incomplete resorption of septum B . • fertility and early miscarriage/pregnancy loss. Treat with septoplasty.

Opening of sinus Scrotum Opening of Anus

Hypospadias Abnormal opening of penile urethra on ventral Hypospadias is more common than surface of penis due to failure of urethral folds epispadias. Associated with inguinal hernia, to fuse. cryptorchidism, chordee (downward or upward bending of penis).

Hypo is below.

Can be seen in 5α-reductase deficiency.

Epispadias Abnormal opening of penile urethra on dorsal Exstrophy of the bladder is associated with surface of penis due to faulty positioning of Epispadias. genital tubercle. When you have Epispadias, you hit your Eye when you pEE.

Descent of testes and ovaries

Adnexal torsion Twisting of ovary and fallopian tube around infundibulopelvic ligament and ovarian ligament compression of ovarian vessels in infundibulopelvic ligament blockage of lymphatic and venous outflow. Continued arterial perfusion ovarian edema complete blockage of arterial inflow necrosis, local hemorrhage.

Associated with ovarian masses. Presents with acute pelvic pain, adnexal mass, nausea/vomiting.

Vagina Stratified squamous epithelium, nonkeratinized

Ectocervix Stratified squamous epithelium, nonkeratinized

Uterus Simple columnar epithelium with long tubular glands in proliferative phase; coiled glands in secretory phase

Pathway of sperm during ejaculation—

SEVEN UP: Seminiferous tubules Epididymis Vas deferens Ejaculatory ducts (Nothing) Urethra Penis

Autonomic innervation of male sexual response

Occurs almost exclusively in men. Suspect if blood seen at urethral meatus. Urethral catheterization is relatively contraindicated.

If Buck fascia is torn, urine escapes into perineal space Blood at urethral meatus and scrotal hematoma Blood at urethral meatus and high-riding prostate

Erection—Parasympathetic nervous system (pelvic splanchnic nerves, S2-S4):

NO □• cGMP □ smooth muscle relaxation □ vasodilation □ proerectile.

antierectile. Emission—Sympathetic nervous system (hypogastric nerve, T11-L2).

Expulsion—visceral and Somatic nerves (pudendal nerve).

Point, Squeeze, and Shoot.

S2, 3, 4 keep the penis off the floor.

PDE-5 inhibitors (eg, sildenafil) □• cGMP breakdown.

local levels of testosterone Produce MIF Tight junctions between adjacent Sertoli cells • inhibin B with • temperature Line seminiferous tubules Non-germ cells Convert testosterone and androstenedione to estrogens via aromatase Sertoli cells are inSide Seminiferous tubules, Support Sperm Synthesis, and inhibit FSH Homolog of female granulosa cells • temperature seen in varicocele, cryptorchidism

Leydig cells Secrete testosterone in the presence of LH; Interstitium temperature Homolog of female theca interna cells

Spermatogenesis Begins at puberty with spermatogonia. Full "Gonium" is going to be a sperm; "Zoon" is development takes 2 months. Occurs in "Zooming" to egg. seminiferous tubules. Produces spermatids Tail mobility impaired in ciliary dyskinesia/ that undergo spermiogenesis (loss of Kartagener syndrome □ infertility. cytoplasmic contents, gain of acrosomal cap) Tail mobility normal in cystic fibrosis (in CF, to form mature spermatozoa.

Spermatogonium 1° spermatocyte 2° spermatocyte Diploid Diploid Haploid (2N, 2C) (2N, 4C) (1N, 2C) absent vas deferens □ infertility).

Mature spermatozoon Haploid Haploid (1N, 1C) (1N, 1C)

SOURCE Ovary (17β-estradiol), placenta (estriol), adipose Potency: estradiol > estrone > estriol. tissue (estrone via aromatization).

FUNCTION Development of genitalia and breast, female fat distribution. Growth of follicle, endometrial proliferation, • myometrial excitability.

Upregulation of estrogen, LH, and progesterone receptors; feedback inhibition of FSH and LH, then LH surge; stimulation of prolactin secretion.

• transport proteins, SHBG; • HDL; • LDL.

Pregnancy: 1000-fold • in estriol (indicator of fetal wellbeing)

Estrogen receptors expressed in cytoplasm; translocate to nucleus when bound by estrogen.

SOURCE Corpus luteum, placenta, adrenal cortex, testes. Fall in progesterone after delivery disinhibits

FUNCTION During luteal phase, prepares uterus for implantation of fertilized egg:

Stimulation of endometrial glandular secretions and spiral artery development

Production of thick cervical mucus

Prevention of endometrial hyperplasia • • body temperature • • estrogen receptor expression • • gonadotropin (LH, FSH) secretion

During pregnancy: • Maintenance of pregnancy • • myometrial excitability □• contraction frequency and intensity • • prolactin action on breasts prolactin □ lactation. • progesterone is indicative of ovulation. Progesterone is pro-gestation. Prolactin is pro-lactation.

Oogenesis 1° oocytes begin meiosis I during fetal life and complete meiosis I just prior to ovulation. Meiosis I is arrested in prOphase I for years until Ovulation (1° oocytes). Meiosis II is arrested in metaphase II until fertilization (2° oocytes). "An egg met a sperm." If fertilization does not occur within 1 day, the 2° oocyte degenerates.

Oogonium 1° oocyte 2° oocyte Ovum Diploid Diploid Haploid Haploid (2N, 2C) (2N, 4C) (1N, 2C) (1N, 1C)

N = ploidy C = # of chromatids

Menstrual cycle Follicular phase can vary in length. Luteal phase is 14 days. Ovulation day + 14 days = menstruation. Follicular growth is fastest during 2nd week of the follicular phase. Estrogen stimulates endometrial proliferation. Progesterone maintains endometrium to support implantation.

• progesterone □• fertility.

Abnormal uterine Characterized as either heavy menstrual Terms such as dysfunctional uterine bleeding, bleeding bleeding (AUB/HMB) or intermenstrual menorrhagia, oligomenorrhea are no longer bleeding (AUB/IMB). recommended. These are further subcategorized by PALM

COEIN:

Structural causes (PALM): Polyp, Adenomyosis, Leiomyoma, or Malignancy/ hyperplasia

Non-structural causes (COEIN): Coagulopathy, Ovulatory, Endometrial, Iatrogenic, Not yet classified

Pregnancy Fertilization most commonly occurs in upper end of fallopian tube (the ampulla). Occurs within 1 day of ovulation.

Implantation within the wall of the uterus occurs 6 days after fertilization.

Syncytiotrophoblasts secrete hCG, which is conception. Gestational age—calculated from date of last menstrual period.

Physiologic adaptations in pregnancy:

Weeks of pregnancy • • GFR □• BUN and creatinine, Placental hormone secretion generally increases • glucosuria threshold over the course of pregnancy, but hCG peaks at • • cardiac output (• preload, • afterload, 8–10 weeks.

Anemia (•• plasma, • RBCs) • • lipolysis and fat utilization (due to maternal hypoglycemia and insulin resistance) □ preserves glucose and amino acids for utilization by the fetus

SOURCE Syncytiotrophoblast of placenta. FUNCTION Maintains corpus luteum (and thus progesterone) for first 8–10 weeks of pregnancy by acting like LH (otherwise no luteal cell stimulation □ abortion). After 8–10 weeks, placenta synthesizes its own estriol and progesterone and corpus luteum degenerates. Used to detect pregnancy because it appears early in urine (see above). Has identical α subunit as LH, FSH, TSH (states of • hCG can cause hyperthyroidism). β subunit is unique (pregnancy tests detect β subunit). hCG is • in multiple gestations, hydatidiform moles, choriocarcinomas, and Down syndrome; hCG is • in ectopic/failing pregnancy, Edwards syndrome, and Patau syndrome.

Human placental Also called chorionic somatomammotropin. lactogen

SOURCE Syncytiotrophoblast of placenta.

FUNCTION Stimulates insulin production; overall • insulin resistance. Gestational diabetes can occur if maternal pancreatic function cannot overcome the insulin resistance.

Assessment of newborn vital signs following delivery via a 10-point scale evaluated at 1 minute and 5 minutes. Apgar score is based on Appearance, Pulse, Grimace,

Activity, and Respiration. Apgar scores < 7 may require further evaluation. If Apgar score remains low at later time points, there is • risk the child will develop long-term neurologic damage.

Milestone dates are ranges that have been approximated and vary by source. Children not meeting milestones may need assessment for potential developmental delay.

Cruises, takes first steps (by = age (yr) × 3 Cutlery—feeds self with fork and spoon (by 20 mo) Kicks ball (by 24 mo)

Defined as < 2500 g. Caused by prematurity or intrauterine growth restriction (IUGR). Associated with • risk of sudden infant death syndrome (SIDS) and with • overall mortality.

Lactation After parturition and delivery of placenta, rapid • in progesterone disinhibits prolactin • initiation of lactation. Suckling is required to maintain milk production and ejection, since • nerve stimulation □• oxytocin and prolactin. Prolactin—induces and maintains lactation and • reproductive function. Oxytocin—assists in milk letdown; also promotes uterine contractions. Breast milk is the ideal nutrition for infants < 6 months old. Contains maternal immunoglobulins (conferring passive immunity; mostly IgA), macrophages, lymphocytes. Breast milk reduces infant infections and is associated with • risk for child to develop asthma, allergies, diabetes mellitus, and obesity. Guidelines recommend exclusively breastfed infants get vitamin D and possibly iron supplementation. Breastfeeding • maternal risk of breast and ovarian cancer and facilitates mother-child bonding.

Menopause Diagnosed by amenorrhea for 12 months.

• estrogen production due to age-linked decline in number of ovarian follicles. Average age at onset is 51 years (earlier in smokers).

Usually preceded by 4–5 years of abnormal menstrual cycles. Source of estrogen (estrone) after menopause becomes peripheral conversion of androgens, • androgens □ hirsutism.

•• FSH is specific for menopause (loss of negative feedback on FSH due to • estrogen).

Hormonal changes: • estrogen, •• FSH, • LH (no surge), • GnRH.

Causes HAVOCS: Hot flashes, Atrophy of the Vagina, Osteoporosis, Coronary artery disease, Sleep disturbances.

Menopause before age 40 suggests 1° ovarian insufficiency (premature ovarian failure); may occur in women who have received chemotherapy and/or radiation therapy.

Androgens Testosterone, dihydrotestosterone (DHT), androstenedione.

SOURCE DHT and testosterone (testis), AnDrostenedione Potency: DHT > testosterone > (ADrenal) androstenedione.

FUNCTION Testosterone:

Differentiation of epididymis, vas deferens, seminal vesicles (internal genitalia, except prostate)

Growth spurt: penis, seminal vesicles, sperm, muscle, RBCs

Deepening of voice

Closing of epiphyseal plates (via estrogen converted from testosterone)

Libido DHT:

Early—differentiation of penis, scrotum, prostate

Late—prostate growth, balding, sebaceous gland activity

Testosterone is converted to DHT by 5α-reductase, which is inhibited by finasteride.

In the male, androgens are converted to estrogen by cytochrome P-450 aromatase (primarily in adipose tissue and testis).

Aromatase is the key enzyme in conversion of androgens to estrogen.

Androgenic steroid abuse—abuse of anabolic steroids to • fat-free mass, muscle strength, and performance. Suspect in men who present with changes in behavior (eg, aggression), acne, gynecomastia, • Hb and Hct, small testes (exogenous testosterone • hypothalamic-pituitary-gonadal axis inhibition □• intratesticular testosterone □□ testicular size, □ sperm count, azoospermia). Women may present with virilization (eg, hirsutism, acne, breast atrophy, male pattern baldness).

Tanner stages of sexual development

Tanner stage is assigned independently to genitalia, pubic hair, and breast (eg, a person can have Tanner stage 2 genitalia, Tanner stage 3 pubic hair). Earliest detectable secondary sexual characteristic is breast bud development in girls, testicular enlargement in boys.

Coarsening of pubic Coarse hair across pubis, Coarse hair across pubis and Flat-appearing chest with (pubarche) hair

Breast enlarges, raised adult size (thelarche), mound forms areola, mound on mound Adult breast contour, areola fattens

Pre-pubertal ~ 811.5 years ~ 11.5–13 years ~ 13–15 years Usually > 15 years

Precocious puberty Appearance of 2° sexual characteristics (eg, adrenarche, thelarche, menarche) before age 8 years in girls and 9 years in boys. • sex hormone exposure or production □• linear growth, somatic and skeletal maturation (eg, premature closure of epiphyseal plates □ short stature). Types include:

Central precocious puberty (• GnRH secretion): idiopathic (most common; early activation of hypothalamic-pituitary gonadal axis), CNS tumors.

Peripheral precocious puberty (GnRH-independent; • sex hormone production or exposure to exogenous sex steroids): congenital adrenal hyperplasia, estrogen-secreting ovarian tumor (eg, granulosa cell tumor), Leydig cell tumor, McCune-Albright syndrome.

Sex chromosome disorders Aneuploidy most commonly due to meiotic nondisjunction.

Klinefelter syndrome Male, 47,XXY. Dysgenesis of seminiferous tubules

Testicular atrophy, eunuchoid body shape, □• inhibin B □• FSH.

tall, long extremities, gynecomastia, female Abnormal Leydig cell function □• testosterone

A . May present with □• LH □• estrogen.

developmental delay. Presence of inactivated

X chromosome (Barr body). Common cause of hypogonadism seen in infertility work-up.

Double Y males 47, XYY. Phenotypically normal (usually undiagnosed), very tall. Normal fertility. May be associated with severe acne, learning disability, autism spectrum disorders.

Female, 45,XO.

Short stature (associated with SHOX gene, preventable with growth hormone therapy), ovarian dysgenesis (streak ovary), shield chest B , bicuspid aortic valve, coarctation of the aorta (femoral < brachial pulse), lymphatic defects (result in webbed neck or cystic hygroma; lymphedema in feet, hands), horseshoe kidney, high-arched palate, shortened 4th metacarpals.

Most common cause of 1° amenorrhea. No Barr body.

Menopause before menarche.

• estrogen leads to • LH, FSH. Sex chromosome (X, or rarely Y) loss often due to nondisjunction during meiosis or mitosis. Meiosis errors usually occur in paternal gametes □ sperm missing the sex chromosome.

Mitosis errors occur after zygote formation □ loss of sex chromosome in some but not all cells □ mosaic karyotype (eg. 45,X/46XX). (45,X/46,XY) mosaicism associated with increased risk for gonadoblastoma.

Pregnancy is possible in some cases (IVF, exogenous estradiol-17β and progesterone).

•• Defective androgen receptor □• Testosterone-secreting tumor, exogenous ⊕⊖ Hypergonadotropic hypogonadism (eg, Turner syndrome, genetic mosaicism, pure gonadal dysgenesis) Hypogonadotropic hypogonadism (eg, CNS lesions, Kallmann syndrome)

Kallmann syndrome Failure to complete puberty; a form of hypogonadotropic hypogonadism. Defective migration of neurons and subsequent failure of olfactory bulbs to develop □• synthesis of GnRH in the hypothalamus; hyposmia/anosmia; • GnRH, FSH, LH, testosterone. Infertility (low sperm count in males; amenorrhea in females).

Abruptio placentae Premature separation (partial or complete) of placenta from uterine wall before delivery of infant. Risk factors: trauma (eg,

motor vehicle accident), smoking, hypertension, preeclampsia, cocaine abuse. Presentation: abrupt, painful bleeding (concealed or apparent) in third trimester; possible DIC (mediated by tissue factor activation), maternal shock, fetal distress. May be life threatening for mother and fetus.

Complete abruption with Partial abruption (blue arrow) concealed hemorrhage with apparent hemorrhage (red arrow)

Defective decidual layer abnormal attachment and separation after delivery. Risk factors: prior C-section or uterine surgery involving myometrium, inflammation, placenta previa, advanced maternal age, multiparity. Three types distinguishable by the depth of penetration:

Placenta accreta—placenta attaches to myometrium without penetrating it; most common type.

Placenta increta—placenta penetrates into myometrium.

Placenta percreta—placenta penetrates (“perforates”) through myometrium and into uterine serosa (invades entire uterine wall); can result in placental attachment to rectum or bladder (can result in hematuria).

Presentation: often detected on ultrasound prior to delivery. No separation of placenta after delivery postpartum bleeding (can cause Sheehan syndrome).

Placenta previa Attachment of placenta over internal cervical os. Risk factors: multiparity, prior C-section. Associated with painless third-trimester bleeding. A “preview” of the placenta is visible through cervix. Low-lying placenta (< 2 cm from internal cervical os, but not over it) is managed differently from placenta previa.

Implantation of fertilized ovum in a site other Isthmus (highest riskInterstitium than the uterus, most often in ampulla of

Fallopian tube of tubal rupture) fallopian tube

A . Suspect with history of amenorrhea, lower-than-expected rise in hCG based on dates, and sudden lower abdominal pain; confirm with ultrasound, which may show extraovarian adnexal mass. Often clinically mistaken for appendicitis.

Pain +/- bleeding. Risk factors:

History of infertility

Hydatidiform mole Cystic swelling of chorionic villi and proliferation of chorionic epithelium (only trophoblast). Presents with vaginal bleeding, emesis, uterine enlargement more than expected, pelvic pressure/ pain. Associated with hCG-mediated sequelae: early preeclampsia (before 20 weeks), theca-lutein cysts, hyperemesis gravidarum, hyperthyroidism. Treatment: dilation and curettage and methotrexate. Monitor hCG.

Rare; can develop during or after pregnancy in mother or baby. Malignancy of trophoblastic tissue

A (cytotrophoblasts, syncytiotrophoblasts); no chorionic villi present. • frequency of bilateral/ multiple theca-lutein cysts. Presents with abnormal • hCG, shortness of breath, hemoptysis. Hematogenous spread to lungs

B . Treatment: methotrexate.

Incidence (US)—endometrial > ovarian > cervical; cervical cancer is more common worldwide due to lack of screening or HPV vaccination.

Prognosis: Cervical (best prognosis, diagnosed < 45 years old) > Endometrial (middleaged, about 55 years old) > Ovarian (worst prognosis, > 65 years).

CEOs often go from best to worst as they get older.

Bartholin cyst and Due to blockage of Bartholin gland duct causing accumulation of gland fluid. May lead to abscess abscess 2° to obstruction and inflammation A . Usually in reproductive-age females.

Lichen sclerosus Thinning of epidermis with fibrosis/sclerosis of dermis. Presents with porcelain-white plaques with a red or violet border. Skin fragility with erosions can be observed B . Most common in postmenopausal women. Benign, but slightly increased risk for SCC.

Lichen simplex Hyperplasia of vulvar squamous epithelium. Presents with leathery, thick vulvar skin with chronicus enhanced skin markings due to chronic rubbing or scratching. Benign, no risk of SCC. Neoplastic

Vulvar carcinoma Carcinoma from squamous epithelial lining of vulva C . Rare. Presents with leukoplakia, biopsy often required to distinguish carcinoma from other causes. HPV-related vulvar carcinoma—associated with high-risk HPV types 16, 18. Risk factors: multiple partners, early coitarche. Usually in reproductive-age females. Non-HPV vulvar carcinoma—usually from long-standing lichen sclerosus. Females > 70 years old.

Imperforate hymen Incomplete degeneration of the central portion of the hymen. Accumulation of vaginal mucus at birth □ self-resolving bulge in introitus. If untreated, leads to 1° amenorrhea, cyclic abdominal pain, hematocolpos (accumulation of menstrual blood in vagina □ bulging and bluish hymenal membrane).

Vaginal squamous cell Usually 2° to cervical SCC; 1° vaginal carcinoma rare. carcinoma

Disordered epithelial growth; begins at basal layer of squamocolumnar junction (transformation zone) and extends outward. Classified as CIN 1, CIN 2, or CIN 3 (severe, irreversible dysplasia or carcinoma in situ), depending on extent of dysplasia. Associated with HPV-16 and HPV-18, which produce both the E6 gene product (inhibits TP53) and E7 gene product (inhibits pRb) (6 before 7; P before R). Koilocytes A are

pathognomonic of HPV infection. May progress slowly to invasive carcinoma if left untreated. Typically asymptomatic (detected with Pap smear) or presents as abnormal vaginal bleeding (often postcoital).

Risk factors: multiple sexual partners, HPV, smoking, early coitarche, DES exposure, immunocompromise (eg, HIV, transplant).

Invasive carcinoma Often squamous cell carcinoma. Pap smear can detect cervical dysplasia before it progresses to invasive carcinoma. Diagnose via colposcopy and biopsy. Lateral invasion can block ureters • hydronephrosis • renal failure.

Most common causes Pregnancy, polycystic ovarian syndrome, obesity, HPO axis abnormalities/immaturity, premature of anovulation ovarian failure, hyperprolactinemia, thyroid disorders, eating disorders, competitive athletics, Cushing syndrome, adrenal insufficiency, chromosomal abnormalities (eg, Turner syndrome).

Also called exercise-induced amenorrhea. Severe caloric restriction, • energy expenditure, and/or stress functional disruption of pulsatile GnRH secretion • LH, FSH, estrogen. Pathogenesis includes • leptin (due to • fat) and • cortisol (stress, excessive exercise).

Associated with eating disorders and "female athlete triad" (• calorie availability/excessive exercise, • bone mineral density, menstrual dysfunction).

Hyperinsulinemia and/or insulin resistance hypothesized to alter hypothalamic hormonal feedback response • LH:FSH, androgens (eg, testosterone) from theca interna cells, • rate of follicular maturation unruptured follicles (cysts) + anovulation. Common cause of • fertility in women.

Enlarged, bilateral cystic ovaries A ; presents with amenorrhea/oligomenorrhea, hirsutism, acne, • fertility. Associated with obesity, acanthosis nigricans. • risk of endometrial cancer 2° to unopposed estrogen from repeated anovulatory cycles.

Treatment: cycle regulation via weight reduction (• peripheral estrone formation), OCPs (prevent endometrial hyperplasia due to unopposed estrogen); clomiphene (ovulation induction); spironolactone, finasteride, flutamide to treat hirsutism.

Primary dysmenorrhea Painful menses, caused by uterine contractions to • blood loss • ischemic pain. Mediated by prostaglandins. Treatment: NSAIDs.

TyPE mAlIgNANT? CHARACTERISTICS arrow in E). Tumor marker: •AFP.

Endometriosis Endometrium-like glands/stroma outside endometrial cavity, most commonly in the ovary (frequently bilateral), pelvis, peritoneum (yellow-brown "powder burn" lesions). In ovary, appears as endometrioma (blood-filled "chocolate cysts" [oval structures above and below asterisks in A]). May be due to retrograde flow, metaplastic

transformation of multipotent cells, transportation of endometrial tissue via lymphatic system. Characterized by cyclic pelvic pain, bleeding, dysmenorrhea, dyspareunia, dyschezia (pain with defecation), infertility; normal-sized uterus. Treatment: NSAIDs, OCPs, progestins, GnRH agonists, danazol, laparoscopic removal.

Endometritis Inflammation of endometrium B associated with retained products of conception following delivery, miscarriage, abortion, or with foreign body (eg, IUD). Retained material is nidus for bacteria from vagina or GI tract. Chronic endometritis shows plasma cells on histology. Treatment: gentamicin + clindamycin +/− ampicillin.

Commonly postmenopausal. Often presents as a palpable hard mass A most often in the upper outer quadrant. Invasive cancer can become fixed to pectoral muscles, deep fascia, Cooper ligaments, and overlying skin nipple retraction/skin dimpling.

Usually arises from terminal duct lobular unit. Amplification/overexpression of estrogen/ progesterone receptors or c-erbB2 (HER2, an EGF receptor) is common; triple negative (ER ⊖, PR ⊖, and HER2/neu ⊖) form more aggressive.

Risk factors in women: • age; history of atypical hyperplasia; family history of breast cancer; race (Caucasians at highest risk, African Americans at • risk for triple ⊖ breast cancer); BRCA1/BRCA2 mutations; • estrogen exposure (eg, nulliparity); postmenopausal obesity (adipose tissue converts androstenedione to estrone); • total number of menstrual cycles; absence of breastfeeding; later age of first pregnancy; alcohol intake. In men: BRCA2 mutation, Klinefelter syndrome.

Axillary lymph node metastasis most important prognostic factor in early-stage disease.

Invasive ductal Firm, fibrous, “rock-hard” mass with sharp margins and small, glandular, duct-like cells in desmoplastic stroma.

aAll types of invasive breast carcinoma can be either of tubular subtype (well-differentiated tubules that lack myoepithelium) or mucinous subtype (abundant extracellular mucin, seen in older women).

Peyronie disease Abnormal curvature of penis A due to fibrous plaque within tunica albuginea. Associated with erectile dysfunction. Can cause pain, anxiety. Consider surgical repair or treatment with collagenase injections once curvature stabilizes. Distinct from penile fracture (rupture of corpora cavernosa due to forced bending).

Ischemic priapism Painful sustained erection lasting > 4 hours. Associated with sickle cell disease (sickled RBCs block venous drainage of corpus cavernosum vascular channels), medications (eg, sildenafil, trazodone). Treat immediately with corporal aspiration, intracavernosal phenylephrine, or surgical decompression to prevent ischemia.

Squamous cell Seen in the US, but more common in Asia, Africa, South America. Precursor in situ lesions: carcinoma Bowen disease (in penile shaft, presents as leukoplakia “white plaque”), erythroplasia of Queyrat

B (carcinoma in situ of the glans B , presents as erythroplakia “red plaque”). Bowenoid papulosis (carcinoma in situ of unclear malignant potential, presenting as reddish papules). Associated with uncircumcised males and HPV.

Cryptorchidism Descent failure of one A or both testes; impaired spermatogenesis (since sperm develop best at temperatures < 37°C); can have normal testosterone levels (Leydig cells are mostly unaffected by temperature); associated with • risk of germ cell tumors. Prematurity • risk of cryptorchidism.

• inhibin B, • FSH, • LH; testosterone • in bilateral cryptorchidism, normal in unilateral. Most cases resolve spontaneously; otherwise, orchiopexy performed before 2 years of age.

Testicular torsion Rotation of testicle around spermatic cord and vascular pedicle. Commonly presents in males 12–18 years old. May occur after an inciting event (eg, trauma) or spontaneously. Characterized by acute, severe pain, high-riding testis, and absent cremasteric reflex. Treatment: surgical correction (orchiopexy) within 6 hours, manual detorsion if surgical option unavailable in timeframe. If testis is not viable, orchiectomy. Orchiopexy, when performed, should be bilateral because the contralateral testis is at risk for subsequent torsion.

Varicocele Dilated veins in pampiniform plexus due to • venous pressure; most common cause of scrotal enlargement in adult males; most often on left side because of • resistance to flow from left gonadal vein drainage into left renal vein; can cause infertility because of • temperature; diagnosed by standing clinical exam/Valsalva maneuver (distension on inspection and “bag of worms” on palpation; augmented by Valsalva) or ultrasound A ; does not transilluminate. Treatment: consider surgical ligation or embolization if associated with pain or infertility.

Extragonadal germ cell Arise in midline locations. In adults, most commonly in retroperitoneum, mediastinum, pineal, and tumors suprasellar regions. In infants and young children, sacrococcygeal teratomas are most common.

Scrotal masses Benign scrotal lesions present as testicular masses that can be transilluminated (vs solid testicular tumors).

Congenital hydrocele Common cause of scrotal swelling A in infants, Transilluminating swelling. due to incomplete obliteration of processus vaginalis. Most spontaneously resolve within 1 year.

Germ cell tumors account for ~ 95% of all testicular tumors. Arise from germ cells that produce sperm. Most often occur in young men. Risk factors: cryptorchidism, Klinefelter syndrome. Can present as a mixed germ cell tumor. Do not transilluminate. Usually not biopsied (risk of seeding scrotum), removed via radical orchiectomy.

Sex cord stromal tumors develop from embryonic sex cord (develops into Sertoli and Leydig cells of seminiferous tubules, theca and granulosa cells of follicle) derivatives. 5% of all testicular tumors. Mostly benign.

Orchitis Inflammation of testis. Presents with testicular pain and swelling. Mumps orchitis • infertility risk. Rare in boys < 10 years old.

Prostatitis Characterized by dysuria, frequency, urgency, low back pain. Warm, tender, enlarged prostate. Acute bacterial prostatitis—in older men most common bacterium is E coli; in young men consider C trachomatis, N gonorrhoeae. Chronic prostatitis—either bacterial or nonbacterial (eg, 2° to previous infection, nerve problems, chemical irritation).

Common in men > 50 years old. Characterized by smooth, elastic, firm nodular enlargement (hyperplasia not hypertrophy) of periurethral (lateral and middle) lobes, which compress the urethra into a vertical slit. Not premalignant.

Often presents with • frequency of urination, nocturia, difficulty starting and stopping urine stream, dysuria. May lead to distention and hypertrophy of bladder, hydronephrosis, UTIs.

• free prostate-specific antigen (PSA).

Treatment: α1-antagonists (terazosin, tamsulosin), which cause relaxation of smooth muscle; 5α-reductase inhibitors (eg, finasteride); PDE-5 inhibitors (eg, tadalafil); surgical resection (eg, TURP, ablation).

Control of reproductive hormones

Goserelin, leuprolide mECHANISm GnRH analogs. When used in pulsatile Leuprolide can be used in lieu of GnRH.

fashion act as GnRH agonists. When used in continuous fashion first transiently act as

GnRH agonists (tumor flare), but subsequently act as GnRH antagonists (downregulate • LH).

ClINICAl USE Uterine fibroids, endometriosis, precocious puberty, prostate cancer, infertility.

ADVERSE EFFECTS Hypogonadism, • libido, erectile dysfunction, nausea, vomiting.

mECHANISm GnRH antagonist. No start-up flare.

ClINICAl USE Prostate cancer.

ADVERSE EFFECTS Hot flashes, liver toxicity.

Estrogens Ethinyl estradiol, DES, mestranol.

mECHANISm Bind estrogen receptors.

ClINICAl USE Hypogonadism or ovarian failure, menstrual abnormalities (combined OCPs), hormone replacement therapy in postmenopausal women.

ADVERSE EFFECTS • risk of endometrial cancer (when given without progesterone), bleeding in postmenopausal women, clear cell adenocarcinoma of vagina in females exposed to DES in utero, • risk of thrombi. Contraindications—ER ⊕ breast cancer, history of DVTs, tobacco use in women > 35 years old.

Raloxifene Antagonist at breast, uterus; agonist at bone; • risk of thromboembolic events (especially with smoking) but no increased risk of endometrial cancer (vs tamoxifen); used primarily to treat osteoporosis.

Aromatase inhibitors Anastrozole, letrozole, exemestane.

mECHANISm Inhibit peripheral conversion of androgens to estrogen.

ClINICAl USE ER ⊕ breast cancer in postmenopausal women.

mECHANISm Bind progesterone receptors, • growth and • vascularization of endometrium, thicken cervical mucus.

ClINICAl USE Contraception (forms include pill, intrauterine device, implant, depot injection), endometrial cancer, abnormal uterine bleeding. Progestin challenge: presence of withdrawal bleeding excludes anatomic defects (eg, Asherman syndrome) and chronic anovulation without estrogen.

Antiprogestins Mifepristone, ulipristal.

mECHANISm Competitive inhibitors of progestins at progesterone receptors.

ClINICAl USE Termination of pregnancy (mifepristone with misoprostol); emergency contraception (ulipristal).

mECHANISm Produces local inflammatory reaction toxic to sperm and ova, preventing fertilization and implantation; hormone free.

ClINICAl USE Long-acting reversible contraception. Most effective emergency contraception.

ADVERSE EFFECTS Heavier or longer menses, dysmenorrhea. Risk of PID with insertion (contraindicated in active pelvic infection).

Tocolytics Medications that relax the uterus; include terbutaline (β2-agonist action), nifedipine (Ca^{2+} channel blocker), indomethacin (NSAID). Used to • contraction frequency in preterm labor and allow time for administration of steroids (to promote fetal lung maturity) or transfer to appropriate medical center with obstetrical care.

mECHANISm Synthetic androgen that acts as partial agonist at androgen receptors.

ClINICAl USE Endometriosis, hereditary angioedema.

ADVERSE EFFECTS Weight gain, edema, acne, hirsutism, masculinization, • HDL levels, hepatotoxicity, idiopathic intracranial hypertension.

Testosterone, methyltestosterone mECHANISm Agonists at androgen receptors.

ClINICAl USE Treat hypogonadism and promote development of 2° sex characteristics; stimulate anabolism to promote recovery after burn or injury.

ADVERSE EFFECTS Masculinization in females; • intratesticular testosterone in males by inhibiting release of LH (via negative feedback) gonadal atrophy. Premature closure of epiphyseal plates. • LDL, • HDL.

Finasteride 5α-reductase inhibitor (• conversion of Testosterone

DHT (more potent). testosterone to DHT). Used for BPH and male-pattern baldness. Adverse effects: gynecomastia and sexual dysfunction.

Tamsulosin α -antagonist used to treat BPH by inhibiting smooth muscle contraction. Selective for α receptors (found on prostate) vs vascular α1B receptors.

mECHANISm Direct arteriolar vasodilator.

ClINICAl USE Androgenetic alopecia (pattern baldness), severe refractory hypertension.

“There’s so much pollution in the air now that if it weren’t for our lungs, there’d be no place to put it all.” “Freedom is the oxygen of the soul.” “Whenever I feel blue, I start breathing again.” —L. Frank Baum “Life is not the amount of breaths you take; it’s the moments that take your breath away.” —Will Smith, Hitch

Group key respiratory, cardiovascular, and renal concepts together for study whenever possible. Know obstructive vs restrictive lung disorders, $\dot{V}/\dot{Q}$ mismatch, lung volumes, mechanics of respiration, and hemoglobin physiology. Lung cancers and other causes of lung masses are high yield. Be comfortable reading basic chest x-rays, CT scans, and PFTs.

Club cells Nonciliated; low columnar/cuboidal with secretory granules. Located in bronchioles. Degrade toxins; secrete component of surfactant; act as reserve cells.

Type I pneumocytes Squamous. 97% of alveolar surfaces. Thinly line the alveoli (two black arrows in A) for optimal gas exchange.

A . 2 (surface tension) 2 functions: radius

A . (≥ 2 is healthy; < 1.5 predictive of NRDS), foam

Risk factors: prematurity, maternal diabetes (due stability index, surfactant-albumin ratio. to • fetal insulin), C-section delivery (• release Persistently low O2 tension risk of PDA. of fetal glucocorticoids; less stressful than vaginal delivery).

Treatment: maternal steroids before birth; exogenous surfactant for infant.

Retinopathy of prematurity, Intraventricular hemorrhage, Bronchopulmonary dysplasia (RIB).

Conducting zone Large airways consist of nose, pharynx, larynx, trachea, and bronchi. Airway resistance highest in the largeto medium-sized bronchi. Small airways consist of bronchioles that further divide into terminal bronchioles (large numbers in parallel least airway resistance).

Warms, humidifies, and filters air but does not participate in gas exchange "anatomic dead space." Cartilage and goblet cells extend to the end of bronchi. Pseudostratified ciliated columnar cells primarily make up epithelium of bronchus and extend to beginning of terminal bronchioles, then transition to cuboidal cells. Clear mucus and debris from lungs (mucociliary escalator). Airway smooth muscle cells extend to end of terminal bronchioles (sparse beyond this point).

Respiratory zone Lung parenchyma; consists of respiratory bronchioles, alveolar ducts, and alveoli. Participates in gas exchange.

Mostly cuboidal cells in respiratory bronchioles, then simple squamous cells up to alveoli. Cilia terminate in respiratory bronchioles. Alveolar macrophages clear debris and participate in immune response.

Right lung has 3 lobes; Left has Less Lobes (2) and Lingula (homolog of right middle lobe). Instead of a middle lobe, left lung has a space occupied by the heart A .

Relation of the pulmonary artery to the bronchus at each lung hilum is described by RALS—Right Anterior; Left Superior. Carina is posterior to ascending aorta and anteromedial to descending aorta B .

Right lung is a more common site for inhaled foreign bodies because right main stem bronchus is wider, more vertical, and shorter than the left. If you aspirate a peanut:

While supine—usually enters superior segment of right lower lobe.

While lying on right side—usually enters right upper lobe.

While upright—usually enters right lower lobe.

Structures perforating diaphragm:

At T8: IVC, right phrenic nerve

At T10: esophagus, vagus (CN 10; 2 trunks)

At T12: aorta (red), thoracic duct (white), azygos vein (blue) ("At T-1-2 it's the red, white, and blue")

Diaphragm is innervated by C3, 4, and 5 (phrenic nerve). Pain from diaphragm irritation (eg, air, blood, or pus in peritoneal cavity) can be referred to shoulder (C5) and trapezius ridge (C3, 4).

Number of letters = T level: T8: vena cava (IVC) T10: (O)esophagus T12: aortic hiatus

I ate (8) ten eggs at twelve. C3, 4, 5 keeps the diaphragm alive. Other bifurcations:

The common carotid bifourcates at C4.

The trachea bifourcates at T4.

The abdominal aorta bifourcates at L4.

Lung volumes Note: a capacity is a sum of ≥ 2 physiologic volumes.

6.0

Tidal volume Air that moves into lung with each quiet inspiration, typically 500 mL 2.7 2.2 1.2 FRC

Determination of physiologic dead space

VD = physiologic dead space = anatomic dead space of conducting airways plus alveolar dead space; apex of healthy lung is largest contributor of alveolar dead space. Volume of inspired air that does not take part in gas exchange.

VT = tidal volume. Paco2 = arterial Pco2. Peco = expired air Pco 2 2.

Taco, Paco, Peco, Paco (refers to order of variables in equation)

Physiologic dead space—approximately equivalent to anatomic dead space in normal lungs. May be greater than anatomic dead space in lung diseases with $\dot{V}/\dot{Q}$ defects.

Minute ventilation Total volume of gas entering lungs per minute Normal values: VE = VT × RR Respiratory rate (RR) = 12–20 breaths/min

Alveolar ventilation Volume of gas that reaches alveoli each minute T V = 150 mL/breath

Elastic recoil Tendency for lungs to collapse inward and chest wall to spring outward.

At FRC, airway and alveolar pressures equal atmospheric pressure (called zero), and intrapleural pressure is negative (preventing atelectasis).

The inward pull of the lung is balanced by the outward pull of the chest wall. System pressure is atmospheric. Pulmonary vascular resistance (PVR) is at a minimum.

0.5 0.0 +2

Compliance Change in lung volume for a change in pressure (ΔV/ΔP). Inversely proportional to wall stiffness and increased by surfactant. 6 • • compliance = lung easier to fill (eg, emphysema, aging) • • compliance = lung harder to fill (eg, 4 pulmonary fibrosis, pneumonia, ARDS, pulmonary edema)

Hysteresis Lung inflation follows a different pressure-2 volume curve than lung deflation due to need to overcome surface tension forces in inflation.

Hemoglobin Oxygen content of blood

O2 content = (1.34 × Hb × Sao2) + (0.003 × Pao2) Hb = hemoglobin concentration; Sao2 = arterial O2 saturation Pao2 = partial pressure of O2 in arterial blood

Normally 1 g Hb can bind 1.34 mL O2; normal Hb amount in blood is 15 g/dL. O2 binding capacity ≈ 20 mL O2/dL of blood. With • Hb there is • O2 content of arterial blood, but no change in O2 saturation and Pao2. O2 delivery to tissues = cardiac output × O2 content of blood.

ODC has sigmoidal shape due to positive cooperativity (ie, tetrameric Hb molecule can 100 bind 4 O2 molecules and has higher affinity for each subsequent O2 molecule bound). 80 Myoglobin is monomeric and thus does 70 not show positive cooperativity; curve lacks 60 sigmoidal appearance.

Shifting ODC to the right □• Hb affinity for O2 (facilitates unloading of O2 to tissue) □• P50 (higher Po2 required to maintain 50% saturation).

Shifting ODC to the left □• O2 unloading compensatory erythrocytosis.

Fetal Hb (2 α and 2 γ subunits) has higher affinity for O2 than adult Hb (due to • affinity for 2,3-BPG) □ dissociation curve is shifted left, driving diffusion of O2 across the placenta from mother to fetus.

Cyanide vs carbon Both inhibit aerobic metabolism via inhibition of complex IV (cytochrome c oxidase) □ hypoxia monoxide poisoning that does not fully correct with supplemental O2 and • anaerobic metabolism.

Both can lead to pink or cherry red skin (usually postmortem finding), seizures, and coma.

SOURCE Byproduct of synthetic product combustion, Odorless gas from fires, car exhaust, or gas ingestion of amygdalin (cyanogenic glucoside heaters. found in apricot seeds) or cyanide.

TREATmENT Hydroxocobalamin (binds cyanide 100% O2, hyperbaric O2.

• cyanocobalamin • renal excretion).

Nitrites (oxidize Hb • methemoglobin binds cyanide • cyanomethemoglobin less toxicity).

Sodium thiosulfate (• cyanide conversion to thiocyanate • renal excretion).

SIgNS/SYmPTOmS Breath has bitter almond odor; cardiovascular Headache, dizziness. collapse. Multiple individuals may be involved (eg, family with similar symptoms in winter). Classically associated with bilateral globus pallidus lesions on MRI A , although rarely seen with cyanide toxicity as well.

normal initially.

Left shift in curve • affinity for O2 • O2 unloading in tissues.

Binds competitively to Hb with 200× greater affinity than O2 to form carboxyhemoglobin • %O2 saturation of Hb.

O2 bound to Hb (mL O2 /100 mL)

Normally a low-resistance, high-compliance system. A • in Pao2 causes a hypoxic vasoconstriction that shifts blood away from poorly ventilated regions of lung to well-ventilated regions of lung.

Perfusion limited—O2 (normal health), CO2, N2O. Gas equilibrates early along the length of the capillary. Exchange can be • only if blood flow •.

Diffusion limited—O2 (emphysema, fibrosis, exercise), CO. Gas does not equilibrate by the time blood reaches the end of the capillary.

A consequence of pulmonary hypertension is cor pulmonale and subsequent right ventricular failure.

P − P Diffusion: V˙ gas = A × Dk × 1 2 where Δ

A = area, Δ x = alveolar wall thickness, Dk = diffusion coefficient of gas, P1 − P2 = difference in partial pressures.

A • in emphysema.

Δ x • in pulmonary fibrosis.

DLCO is the extent to which CO passes from air sacs of lungs into blood.

Ventilation/perfusion Ideally, ventilation is matched to perfusion (ie, mismatch V˙/Q˙ = 1) for adequate gas exchange. Lung zones:

V˙/Q˙ at apex of lung = 3 (wasted ventilation) Q

V˙/Q˙ at base of lung = 0.6 (wasted perfusion) Both ventilation and perfusion are greater at the base of the lung than at the apex of the lung.

With exercise (• cardiac output), there is vasodilation of apical capillaries □ V˙/Q˙ ratio approaches 1.

Certain organisms that thrive in high O2 (eg, TB) flourish in the apex.

□V ˜˜ V˙/Q˙ = 0 = "oirway" obstruction (shunt). In □□Q shunt, 100% O2 does not improve Pao2 (eg, foreign body aspiration). V˙/Q˙ = ∞ = blood flow obstruction (physiologic dead space). Assuming < 100% dead space, 100% O2 improves Pao2 (eg, pulmonary embolus).

CO2 is transported from tissues to lungs in 3 forms: HCO3 − (70%). Carbaminohemoglobin or HbCO2 (21–25%). CO2 bound to Hb at N-terminus of globin (not heme). CO2 favors deoxygenated form (O2 unloaded). Dissolved CO2 (5–9%).

In lungs, oxygenation of Hb promotes dissociation of H+ from Hb. This shifts equilibrium toward CO2 formation; therefore, CO2 is released from RBCs (Haldane effect).

In peripheral tissue, • H+ from tissue metabolism shifts curve to right, unloading O2 (Bohr effect).

Majority of blood CO2 is carried as HCO3 − in the plasma.

Response to high altitude sickness. Chronic • in ventilation.

erythropoietin □• Hct and Hb (due to chronic hypoxia).

2,3-BPG (binds to Hb causing rightward shift of the ODC so that Hb releases more O2). Cellular changes (• mitochondria).

renal excretion of HCO3 − to compensate for respiratory alkalosis (can augment with acetazolamide). Chronic hypoxic pulmonary vasoconstriction results in pulmonary hypertension and RVH.

Response to exercise • CO2 production. • O2 consumption. Right shift of ODC.

ventilation rate to meet O2 demand. V˙/Q˙ ratio from apex to base becomes more uniform.

pulmonary blood flow due to • cardiac output.

pH during strenuous exercise (2° to lactic acidosis). No change in Pao2 and Paco2, but • in venous CO2 content and • in venous O2 content.

Obstruction of sinus drainage into nasal cavity □ inflammation and pain over affected area. Typically affects maxillary sinuses, which drain against gravity due to ostia located superomedially (red arrow points to fluid-filled right maxillary sinus in A).

Superior meatus—drains sphenoid, posterior ethmoid; middle meatus—drains frontal, maxillary, and anterior ethmoid; inferior meatus—drains nasolacrimal duct.

Most common acute cause is viral URI; may lead to superimposed bacterial infection, most commonly H influenzae, S pneumoniae, M catarrhalis.

Paranasal sinus infections may extend to the orbits, cavernous sinus, and brain, causing complications (eg, orbital cellulitis, cavernous sinus syndrome, meningitis).

Head and neck cancer Mostly squamous cell carcinoma. Risk factors include tobacco, alcohol, HPV-16 (oropharyngeal), EBV (nasopharyngeal). Field cancerization: carcinogen damages wide mucosal area • multiple tumors that develop independently after exposure.

Blood clot within a deep vein swelling, redness

A , warmth, pain. Predisposed by Virchow triad (SHE):

Stasis (eg, post-op, long drive/flight)

Hypercoagulability (eg, defect in coagulation cascade proteins, such as factor V Leiden; oral contraceptive use; pregnancy)

Most pulmonary emboli arise from proximal deep veins of lower extremity.

d-dimer lab test used clinically to rule out DVT in low-to-moderate risk patients (high sensitivity, low specificity).

Imaging test of choice is compression ultrasound with Doppler.

Use unfractionated heparin or low-molecular weight heparins (eg, enoxaparin) for prophylaxis and acute management.

Use oral anticoagulants (eg, rivaroxaban, apixaban) for treatment and long-term prevention.

Pulmonary emboli $\dot{V}/\dot{Q}$ mismatch, hypoxemia, respiratory alkalosis. Sudden-onset dyspnea, pleuritic chest pain, tachypnea, tachycardia. Large emboli or saddle embolus A may cause sudden death due to electromechanical dissociation (pulseless electrical activity). CT pulmonary angiography is imaging test of choice for PE (look for filling defects) B . May have S1Q3T3 abnormality on ECG. Lines of Zahn C are interdigitating areas of pink (platelets, fibrin) and red (RBCs) found only in thrombi formed before death; help distinguish preand postmortem thrombi. Types: Fat, Air, Thrombus, Bacteria, Amniotic fluid, Tumor. An embolus moves like a FAT BAT. Fat emboli—associated with long bone fractures and liposuction; classic triad of hypoxemia, neurologic abnormalities, petechial rash. Air emboli—nitrogen bubbles precipitate in ascending divers (caisson disease/decompression sickness); treat with hyperbaric O2; or, can be iatrogenic 2° to invasive procedures (eg, central line placement). Amniotic fluid emboli—typically occurs during

labor or postpartum, but can be due to uterine trauma. Can lead to DIC. Rare, but high mortality.

Mediastinal pathology Normal mediastinum contains heart, thymus, lymph nodes, esophagus, and aorta.

Mediastinal masses Some pathologies (eg, lymphoma, lung cancer, abscess) can occur in any compartment, but there are common associations:

Anterior—4T's: Thyroid (substernal goiter), Thymic neoplasm, Teratoma, "Terrible" lymphoma.

Middle—esophageal carcinoma, metastases, hiatal hernia, bronchogenic cysts.

Posterior—neurogenic tumor (eg, neurofibroma), multiple myeloma.

Mediastinitis Inflammation of mediastinal tissues. Commonly due to postoperative complications of cardiothoracic procedures (≤ 14 days), esophageal perforation, or contiguous spread of odontogenic/retropharyngeal infection. Chronic mediastinitis—also known as fibrosing mediastinitis; due to • proliferation of connective tissue in mediastinum. Histoplasma capsulatum is common cause. Clinical features: fever, tachycardia, leukocytosis, chest pain, and sternal wound drainage.

Pneumomediastinum Presence of gas (usually air) in the mediastinum (black arrows show air around the aorta, red arrow shows air dissecting into the neck A). Can either be spontaneous (due to rupture of pulmonary bleb) or 2° (eg, trauma, iatrogenic, Boerhaave syndrome). Ruptured alveoli allow tracking of air into the mediastinum via peribronchial and perivascular sheaths. Clinical features: chest pain, dyspnea, voice change, subcutaneous emphysema, ⊕ Hamman sign (crepitus on cardiac auscultation).

Emphysema ("pink puffer") Normal Centriacinar emphysema Panacinar emphysema Findings: barrel-shaped chest D , exhalation through pursed lips (increases airway pressure and prevents airway collapse).

Centriacinar—affects respiratory bronchioles while sparing distal alveoli, associated with

B . Frequently in upper lobes (smoke rises up).

Panacinar—affects respiratory bronchioles and alveoli, associated with α1-antitrypsin deficiency. Frequently in lower lobes.

Enlargement of air spaces recoil, • compliance, from destruction of alveolar walls (arrow in

C) and • blood volume in pulmonary capillaries.

Imbalance of proteases and antiproteases □• elastase activity □□ loss of elastic fibers □• lung compliance.

CXR: • AP diameter, flattened diaphragm, • lung field lucency.

Asthma Findings: cough, wheezing, tachypnea, dyspnea, hypoxemia, • inspiratory/ expiratory ratio, pulsus paradoxus, mucus plugging

E . Triggers: viral URIs, allergens, stress.

Hyperresponsive bronchi • reversible bronchoconstriction. Smooth muscle hypertrophy and hyperplasia, Curschmann spirals

F (shed epithelium forms whorled mucous plugs), and Charcot-Leyden crystals

G (eosinophilic, hexagonal, double-pointed crystals formed from breakdown of eosinophils in sputum). DLCO normal or •.

Type I hypersensitivity reaction.

Diagnosis supported by spirometry and methacholine challenge.

NSAID-exacerbated respiratory disease is a combination of COX inhibition (leukotriene overproduction • airway constriction), chronic sinusitis with nasal polyps, and asthma symptoms.

TYPE PRESENTATION PAThOlOgY OThER Bronchiectasis Findings: purulent sputum, recurrent infections (most often P aeruginosa), hemoptysis, digital clubbing. Chronic necrotizing infection of bronchi or obstruction permanently dilated airways. Associated with bronchial obstruction, poor ciliary motility (eg, smoking, Kartagener syndrome), cystic fibrosis H , allergic bronchopulmonary aspergillosis. A B C D E G HF

Restricted lung expansion causes • lung volumes (• FVC and TLC). PFTs: • FEV1/FVC ratio. Patient presents with short, shallow breaths.

Types:

Poor breathing mechanics (extrapulmonary, normal DLCO, normal A-a gradient):

Poor muscular effort—polio, myasthenia gravis, Guillain-Barré syndrome

Poor structural apparatus—scoliosis, morbid obesity

Interstitial lung diseases (pulmonary, • DLCO, • A-a gradient):

Pneumoconioses (eg, coal workers’ pneumoconiosis, silicosis, asbestosis)

Sarcoidosis: bilateral hilar lymphadenopathy, noncaseating granulomas; • ACE and Ca2+

Idiopathic pulmonary fibrosis (repeated cycles of lung injury and wound healing with • collagen deposition, “honeycomb” lung appearance [red

arrows in A], traction bronchiectasis [blue arrow in A] and digital clubbing).

Granulomatosis with polyangiitis (Wegener)

Drug toxicity (eg, bleomycin, busulfan, amiodarone, methotrexate)

Hypersensitivity pneumonitis—mixed type III/IV hypersensitivity reaction to environmental antigen. Causes dyspnea, cough, chest tightness, fever, headache. Often seen in farmers and those exposed to birds. Reversible in early stages if stimulus is avoided.

Sarcoidosis Characterized by immune-mediated, widespread noncaseating granulomas A , elevated serum ACE levels, and elevated CD4/CD8 ratio in bronchoalveolar lavage fluid. More common in African-American females. Often asymptomatic except for enlarged lymph nodes. CXR shows bilateral adenopathy and coarse reticular opacities B ; CT of the chest better demonstrates the extensive hilar and mediastinal adenopathy C . Associated with Bell palsy, Uveitis, Granulomas (noncaseating epithelioid, containing microscopic Schaumann and asteroid bodies), Lupus pernio (skin lesions on face resembling lupus), Interstitial fibrosis (restrictive lung disease), Erythema nodosum, Rheumatoid arthritis-like arthropathy, hypercalcemia (due to • 1α-hydroxylase–mediated vitamin D activation in macrophages). A facial droop is UGLIER. Treatment: steroids (if symptomatic).

Complication of inhalation of noxious stimuli (eg, smoke). Caused by heat, particulates (< 1 µm diameter), or irritants (eg, NH3) □ chemical tracheobronchitis, edema, pneumonia, ARDS. Many patients present 2° to burns, CO inhalation, cyanide poisoning, or arsenic poisoning. Singed nasal hairs or soot in oropharynx common on exam.

Bronchoscopy shows severe edema, congestion of bronchus, and soot deposition (A , 18 hours after inhalation injury; B , resolution at 11 days after injury).

Pneumoconioses Asbestos is from the roof (was common in insulation), but affects the base (lower lobes). Silica and coal are from the base (earth), but affect the roof (upper lobes).

Asbestosis Associated with shipbuilding, roofing, plumbing. “Ivory white,” calcified, supradiaphragmatic A and pleural B plaques are pathognomonic of asbestosis. Risk of bronchogenic carcinoma > risk of mesothelioma. • risk of Caplan syndrome (rheumatoid arthritis and pneumoconioses with intrapulmonary nodules).

Affects lower lobes.

Asbestos (ferruginous) bodies are golden-brown fusiform rods resembling dumbbells

C , found in alveolar sputum sample, visualized using Prussian blue stain, often obtained by bronchoalveolar lavage.

• risk of pleural effusions.

Berylliosis Associated with exposure to beryllium in Affects upper lobes. aerospace and manufacturing industries. Granulomatous (noncaseating) D on histology and therefore occasionally responsive to steroids. • risk of cancer and cor pulmonale.

Mesothelioma Malignancy of the pleura associated with Psammoma bodies seen on histology. asbestosis. May result in hemorrhagic pleural Calretinin and cytokeratin 5/6 ⊕ in almost all effusion (exudative), pleural thickening A . mesotheliomas, ⊖ in most carcinomas. Smoking not a risk factor.

PAThOPhYSIOlOgY Alveolar insult release of pro-inflammatory cytokines neutrophil recruitment, activation, and release of toxic mediators (eg, reactive oxygen species, proteases, etc) capillary endothelial damage and • vessel permeability leakage of protein-rich fluid into alveoli • formation of intra-alveolar hyaline membranes (arrows in A) and noncardiogenic pulmonary edema (normal PCWP). Loss of surfactant also contributes to alveolar collapse.

CAUSES Sepsis (most common), aspiration, pneumonia, trauma, pancreatitis.

DIAgNOSIS Diagnosis of exclusion with the following criteria (ARDS):

Respiratory failure within 1 week of alveolar insult

Decreased Pao2/Fio2 (ratio < 300, hypoxemia due to • intrapulmonary shunting and diffusion abnormalities)

Symptoms of respiratory failure are not due to HF/fluid overload

CONSEQUENCES Impaired gas exchange, • lung compliance; pulmonary hypertension.

mANAgEmENT Treat the underlying cause. Mechanical ventilation: • tidal volume, • PEEP.

Sleep apnea Repeated cessation of breathing > 10 seconds during sleep disrupted sleep daytime somnolence. Diagnosis confirmed by sleep study. Nocturnal hypoxia • systemic/pulmonary hypertension, arrhythmias (atrial fibrillation/flutter), sudden death. Hypoxia • EPO release • erythropoiesis.

Central sleep apnea Impaired respiratory effort due to CNS injury/toxicity, HF, opioids. May be associated with Cheyne-Stokes respirations (oscillations between apnea and hyperpnea). Think 3 C’s: Congestive HF, CNS toxicity, Cheyne-Stokes respirations. Treat with positive airway pressure.

Obesity Obesity (BMI ≥ 30 kg/m2) hypoventilation • Paco2 during waking hours (retention); • Pao2 hypoventilation and • Paco2 during sleep. Also known as Pickwickian syndrome. syndrome

Normal mean pulmonary artery pressure = 10–14 mm Hg; pulmonary hypertension ≥ 25 mm Hg at rest. Results in arteriosclerosis, medial hypertrophy, intimal fibrosis of pulmonary arteries, plexiform lesions. Course: severe respiratory distress • cyanosis and RVH • death from decompensated cor pulmonale.

Pleural effusion • Dull • None if small Away from side of lesion if large

Atelectasis • Dull • Toward side of lesion

Tension • Hyperresonant • Away from side of lesion pneumothorax

Atelectasis Alveolar collapse (right upper lobe collapse against mediastinum in A). Multiple causes:

Obstructive—airway obstruction prevents new air from reaching distal airways, old air is resorbed (eg, foreign body, mucous plug, tumor)

Compressive—external compression on lung decreases lung volumes (eg, space-occupying lesion, pleural effusion)

Contraction (cicatrization)—scarring of lung parenchyma that distorts alveoli (eg, sarcoidosis)

Adhesive—due to lack of surfactant (eg, NRDS in premature babies)

Pleural e˜usion, Scarring air, tumor

Pleural effusions Excess accumulation of fluid A between pleural layers restricted lung expansion during inspiration. Can be treated with thoracentesis to remove/reduce fluid B .

Lymphatic Also known as chylothorax. Due to thoracic duct injury from trauma or malignancy. Milkyappearing fluid; • triglycerides.

Exudate • protein content (> 2.9 g/dL), cloudy (cellular). Due to malignancy, inflammation/infection (eg, pneumonia, collagen vascular disease), trauma (occurs in states of • vascular permeability). Must be drained due to risk of infection.

Transudate • protein content (< 2.5 g/dL), clear (hypocellular). Due to • hydrostatic pressure (eg, HF, Na+ retention) or • oncotic pressure (eg, nephrotic syndrome, cirrhosis).

Pneumothorax Accumulation of air in pleural space A . Dyspnea, uneven chest expansion. Chest pain, • tactile fremitus, hyperresonance, and diminished breath sounds, all on the affected side.

Primary spontaneous Due to rupture of apical subpleural bleb or cysts. Occurs most frequently in tall, thin, young males pneumothorax and smokers.

Traumatic Caused by blunt (eg, rib fracture), penetrating (eg, gunshot), or iatrogenic (eg, central line pneumothorax placement, lung biopsy, barotrauma due to mechanical ventilation) trauma.

Can be from any of the above. Air enters pleural space but cannot exit. Increasing trapped air • tension pneumothorax. Trachea deviates away from affected lung B . May lead to increased intrathoracic pressure • mediastinal displacement kinking of IVC • venous return • cardiac output. Needs immediate needle decompression and chest tube placement.

Lobar pneumonia S pneumoniae most frequently, also Legionella, Intra-alveolar exudate • consolidation A ; may Klebsiella involve entire lobe

B or the whole lung.

Etiology unknown. Secondary organizing pneumonia is caused by chronic inflammatory diseases (eg, rheumatoid arthritis) or medication side effects (eg, amiodarone). ⊖ sputum and blood cultures, often responds to steroids but not to antibiotics.

Formerly known as bronchiolitis obliterans organizing pneumonia (BOOP). Noninfectious pneumonia characterized by inflammation of bronchioles and surrounding structure.

Natural history of lobar pneumonia

Lung cancer Leading cause of cancer death. Presentation: cough, hemoptysis, bronchial obstruction, wheezing, pneumonic "coin" lesion on CXR or noncalcified nodule on CT. Sites of metastases from lung cancer: Liver (jaundice, hepatomegaly), Adrenals, Bone (pathologic fracture), Brain; "Lung 'mets' Love Affective Boneheads and Brainiacs." In the lung, metastases (usually multiple lesions) are more common than 1° neoplasms. Most often from breast, colon, prostate, and bladder cancer.

SPHERE of complications: Superior vena cava/thoracic outlet syndromes Pancoast tumor Horner syndrome Endocrine (paraneoplastic) Recurrent laryngeal nerve compression

Risk factors include smoking, secondhand smoke, radon, asbestos, family history. Squamous and Small cell carcinomas are Sentral (central) and often caused by Smoking.

TYPE lOCATION ChARACTERISTICS hISTOlOgY Small cell Small cell (oat cell) carcinoma Central Undifferentiated very aggressive. May produce ACTH (Cushing syndrome), ADH (SIADH), or Antibodies against presynaptic Ca2+ channels (Lambert-Eaton myasthenic syndrome) or neurons (paraneoplastic myelitis, encephalitis, subacute cerebellar degeneration). Amplification of myc oncogenes common. Managed with chemotherapy +/− radiation. Neoplasm of neuroendocrine Kulchitsky cells small dark blue cells A . Chromogranin A ⊕, neuron-specific enolase ⊕, synaptophysin ⊕. Non-small cell

Adenocarcinoma Peripheral Most common 1° lung cancer. More common in women than men, most likely to arise in nonsmokers. Activating mutations

include KRAS, EGFR, and ALK. Associated with hypertrophic osteoarthropathy (clubbing). Bronchioloalveolar subtype (adenocarcinoma in situ): CXR often shows hazy infiltrates similar to pneumonia; better prognosis.

Glandular pattern on histology, often stains mucin ⊕

B .

Bronchioloalveolar subtype: grows along alveolar septa apparent "thickening" of alveolar walls. Tall, columnar cells containing mucus.

Squamous cell carcinoma Central Hilar mass C arising from bronchus; Cavitation; Cigarettes; hyperCalcemia (produces PTHrP). Keratin pearls D and intercellular bridges. Large cell carcinoma Peripheral Highly anaplastic undifferentiated tumor; poor prognosis. Less responsive to chemotherapy; removed surgically. Strong association with smoking. Pleomorphic giant cells E .

Localized collection of pus within parenchyma

A . Caused by aspiration of oropharyngeal contents (especially in patients predisposed to loss of consciousness [eg, alcoholics, epileptics]) or bronchial obstruction (eg, cancer).

B often seen on CXR; presence suggests cavitation. Due to anaerobes (eg, Bacteroides, Fusobacterium, Peptostreptococcus) or S aureus.

Treatment: antibiotics, drainage, or surgery.

Lung abscess 2° to aspiration is most often found in right lung. Location depends on patient's position during aspiration: RLL if upright, RUL or RML if recumbent.

Pancoast tumor Also known as superior sulcus tumor. Carcinoma that occurs in the apex of lung A may cause Pancoast syndrome by invading/compressing local structures. Compression of locoregional structures may cause array of findings:

Stellate ganglion • Horner syndrome (ipsilateral ptosis, miosis, anhidrosis)

An obstruction of the SVC that impairs blood drainage from the head ("facial plethora"; note blanching after fingertip pressure in A), neck (jugular venous distention), and upper extremities (edema). Commonly caused by malignancy (eg, mediastinal mass, Pancoast tumor) and thrombosis from indwelling catheters B . Medical emergency. Can raise intracranial pressure (if obstruction is severe) • headaches, dizziness, • risk of aneurysm/ rupture of intracranial arteries.

Histamine-1 blockers Reversible inhibitors of H1 histamine receptors.

First generation Diphenhydramine, dimenhydrinate, Names usually contain "-en/-ine" or "-en/-ate." chlorpheniramine, doxylamine.

ClINICAl USE Allergy, motion sickness, sleep aid.

ADVERSE EFFECTS Sedation, antimuscarinic, anti-α-adrenergic.

Second generation Loratadine, fexofenadine, desloratadine, Names usually end in "-adine." cetirizine.

ClINICAl USE Allergy.

ADVERSE EFFECTS Far less sedating than 1st generation because of • entry into CNS.

Guaifenesin Expectorant—thins respiratory secretions; does not suppress cough reflex.

N-acetylcysteine Mucolytic—liquifies mucus in chronic bronchopulmonary diseases (eg, COPD, CF) by disrupting disulfide bonds. Also used as an antidote for acetaminophen overdose.

Dextromethorphan Antitussive (antagonizes NMDA glutamate receptors). Synthetic codeine analog. Has mild opioid effect when used in excess. Naloxone can be given for overdose. Mild abuse potential. May cause serotonin syndrome if combined with other serotonergic agents.

Pseudoephedrine, phenylephrine mEChANISm α-adrenergic agonists.

ClINICAl USE Reduce hyperemia, edema (used as nasal decongestants); open obstructed eustachian tubes.

ADVERSE EFFECTS Hypertension. Rebound congestion if used more than 4–6 days. Can also cause CNS stimulation/ anxiety (pseudoephedrine).

therapy IgE and blocks binding to FcεRI. Used in allergic asthma with • IgE levels resistant to inhaled steroids and long-acting β2-agonists.

(leukotrienes, histamine, interleukins, etc) due to • cAMP hydrolysis. Limited use due to narrow therapeutic index (cardiotoxicity, neurotoxicity); metabolized by cytochrome ˜-agonists

P-450. Blocks actions of adenosine.

Muscarinic Chromones Cromolyn—prevents mast cell degranulation. antagonists Prevents acute asthma symptoms. Rarely used.

Anti-IL-5 monoclonal Prevents eosinophil differentiation, maturation, therapy activation, and survival mediated by IL-5 Early response: Late response: stimulation. For maintenance therapy in severe eosinophilic asthma.

Mepolizumab, reslizumab—against IL-5.

Benralizumab—against IL-5 receptor α.

“Study without thought is vain: thought without study is dangerous.” “It is better, of course, to know useless things than to know nothing.” “For every complex problem there is an answer that is clear, simple, and wrong.” —H. L. Mencken

The following tables represent a collection of high-yield associations between diseases and their clinical findings, treatments, and key associations. They can be quickly reviewed in the days before the exam.

Gout, intellectual disability, self-mutilating behavior in a Lesch-Nyhan syndrome (HGPRT deficiency, X-linked 37 boy recessive)

Arachnodactyly, lens dislocation (upward and temporal), Marfan syndrome (fibrillin defect) 52 aortic dissection, hyperflexible joints

Calf pseudohypertrophy Muscular dystrophy (most commonly Duchenne, due to 61 X-linked recessive frameshift mutation of dystrophin gene)

Child uses arms to stand up from squat Duchenne muscular dystrophy (Gowers sign) 61

Slow, progressive muscle weakness in boys Becker muscular dystrophy (X-linked non-frameshift 61 deletions in dystrophin; less severe than Duchenne)

Infant with cleft lip/palate, microcephaly or Patau syndrome (trisomy 13) 63 holoprosencephaly, polydactyly, cutis aplasia

Infant with microcephaly, rocker-bottom feet, clenched Edwards syndrome (trisomy 18) 63 hands, and structural heart defect

Dilated cardiomyopathy, edema, alcoholism or Wet beriberi (thiamine [vitamin B1] deficiency) 66 malnutrition

Dermatitis, dementia, diarrhea Pellagra (niacin [vitamin B3] deficiency) 67

Swollen gums, mucosal bleeding, poor wound healing, Scurvy (vitamin C deficiency: can’t hydroxylate proline/ 69 petechiae lysine for collagen synthesis)

Chronic exercise intolerance with myalgia, fatigue, McArdle disease (skeletal muscle glycogen phosphorylase 87 painful cramps, myoglobinuria deficiency)

Infant with hypoglycemia, hepatomegaly Cori disease (debranching enzyme deficiency) or Von 87 Gierke disease (glucose-6-phosphatase deficiency, more severe)

Myopathy (infantile hypertrophic cardiomyopathy), Pompe disease (lysosomal α-1,4-glucosidase deficiency) 88 (sphingomyelin accumulation), central retinal artery occlusion

Hepatosplenomegaly, pancytopenia, osteoporosis, Gaucher disease (glucocerebrosidase [β-glucosidase] avascular necrosis of femoral head, bone crises deficiency)

Male child, recurrent infections, no mature B cells Bruton disease (X-linked agammaglobulinemia)

Recurrent cold (noninflamed) abscesses, eczema, high Hyper-IgE syndrome (Job syndrome: neutrophil 116 serum IgE, • eosinophils chemotaxis abnormality) "Strawberry tongue" Scarlet fever 136, Kawasaki disease 314

Abdominal pain, diarrhea, leukocytosis, recent antibiotic Clostridium difficile infection

Back pain, fever, night sweats Pott disease (vertebral TB)

Adrenal hemorrhage, hypotension, DIC Waterhouse-Friderichsen syndrome (meningococcemia) 142, 349

Large rash with bull's-eye appearance Erythema migrans from Ixodes tick bite (Lyme disease: 146 Borrelia)

Ulcerated genital lesion Nonpainful, indurated: chancre (1° syphilis, Treponema 147, pallidum) 184 Painful, with exudate: chancroid (Haemophilus ducreyi)

Smooth, moist, painless, wart-like white lesions on Condylomata lata (2° syphilis) 147 genitals

Fever, chills, headache, myalgia following antibiotic Jarisch-Herxheimer reaction (rapid lysis of spirochetes 148 treatment for syphilis results in endotoxin-like release)

Dog or cat bite resulting in infection Pasteurella multocida (cellulitis at inoculation site) 149 Rash on palms and soles Coxsackie A, 2° syphilis, Rocky Mountain spotted fever 150 Black eschar on face of patient with diabetic ketoacidosis Mucor or Rhizopus fungal infection 153

Chorioretinitis, hydrocephalus, intracranial calcifications Congenital toxoplasmosis 156

Child with fever later develops red rash on face that Erythema infectiosum/fifth disease ("slapped cheeks" 164 spreads to body appearance, caused by parvovirus B19)

Fever, cough, conjunctivitis, coryza, diffuse rash Measles 170

Small, irregular red spots on buccal/lingual mucosa with Koplik spots (measles [rubeola] virus) 170 blue-white centers

Bounding pulses, wide pulse pressure, diastolic heart Aortic regurgitation 291 murmur, head bobbing

Continuous “machine-like” heart murmur PDA (close with indomethacin; keep open with PGE

Chest pain on exertion Angina (stable: with moderate exertion; unstable: with 304 Chest pain, pericardial effusion/friction rub, persistent Dressler syndrome (autoimmune-mediated post-MI

Chest pain with ST depressions on ECG Angina (⊖ troponins) or NSTEMI (⊕ troponins) 307 fever following MI fibrinous pericarditis, 2 weeks to several months after acute episode)

Painful, raised red lesions on pads of fingers/toes Osler nodes (infective endocarditis, immune complex

Painless erythematous lesions on palms and soles Janeway lesions (infective endocarditis, septic emboli/ 311 microabscesses)

Retinal hemorrhages with pale centers Roth spots (bacterial endocarditis)

Distant heart sounds, distended neck veins, hypotension Beck triad of cardiac tamponade

Cervical lymphadenopathy, desquamating rash, coronary Kawasaki disease (mucocutaneous lymph node syndrome, 314 aneurysms, red conjunctivae and tongue, hand-foot treat with IVIG and aspirin) changes

Palpable purpura on buttocks/legs, joint pain, abdominal Immunoglobulin A vasculitis (Henoch-Schönlein 315 pain (child), hematuria purpura, affects skin and kidneys)

Telangiectasias, recurrent epistaxis, skin discoloration, Hereditary hemorrhagic telangiectasia (Osler-Weber-316 arteriovenous malformations, GI bleeding, hematuria Rendu syndrome)

Skin hyperpigmentation, hypotension, fatigue 1° adrenocortical insufficiency □• ACTH, • α-MSH (eg, 349 Addison disease)

Cutaneous flushing, diarrhea, bronchospasm Carcinoid syndrome (right-sided cardiac valvular lesions, 352 • 5-HIAA)

Cold intolerance, weight gain, brittle hair Hypothyroidism 341

Cutaneous/dermal edema due to deposition of Myxedema (caused by hypothyroidism, Graves disease 340 mucopolysaccharides in connective tissue [pretibial])

No lactation postpartum, absent menstruation, cold Sheehan syndrome (postpartum hemorrhage leading to 339 intolerance pituitary infarction)

Deep, labored breathing/hyperventilation Diabetic ketoacidosis (Kussmaul respirations) 347 Pancreatic, pituitary, parathyroid tumors MEN 1 (autosomal dominant) 351

Thyroid tumors, pheochromocytoma, MEN 2B (autosomal dominant RET mutation) 351 ganglioneuromatosis, Marfanoid habitus

Thyroid and parathyroid tumors, pheochromocytoma MEN 2A (autosomal dominant RET mutation) 351 Jaundice, palpable distended non-tender gallbladder Courvoisier sign (distal malignant obstruction of biliary 398 tree)

Vomiting blood following gastroesophageal lacerations Mallory-Weiss syndrome (alcoholic and bulimic patients) 377 Dysphagia (esophageal webs), glossitis, iron deficiency Plummer-Vinson syndrome (may progress to esophageal 377 anemia squamous cell carcinoma)

Enlarged, hard left supraclavicular node Virchow node (abdominal metastasis) 379

Arthralgias, adenopathy, cardiac and neurological Whipple disease (Tropheryma whipplei) symptoms, diarrhea

Severe RLQ pain with palpation of LLQ Rovsing sign (acute appendicitis)

Severe RLQ pain with deep tenderness McBurney sign (acute appendicitis)

Hamartomatous GI polyps, hyperpigmented macules on Peutz-Jeghers syndrome (inherited, benign polyposis can 387 mouth, feet, hands, genitalia cause bowel obstruction; • cancer risk, mainly GI)

Multiple colon polyps, osteomas/soft tissue tumors, Gardner syndrome (subtype of FAP)

Abdominal pain, ascites, hepatomegaly Budd-Chiari syndrome (posthepatic venous thrombosis) 392

Hyperphagia, hypersexuality, hyperorality Klüver-Bucy syndrome (bilateral amygdala lesion)

Resting tremor, athetosis, chorea Basal ganglia lesion “Worst headache of my life” Subarachnoid hemorrhage

Resting tremor, rigidity, akinesia, postural instability, Parkinson disease (loss of dopaminergic neurons in

Chorea, dementia, caudate degeneration Huntington disease (autosomal dominant CAG repeat 520 expansion)

Nystagmus, intention tremor, scanning speech, bilateral Multiple sclerosis 523 internuclear ophthalmoplegia

Café-au-lait spots, Lisch nodules (iris hamartoma), Neurofibromatosis type I 525 cutaneous neurofibromas, pheochromocytomas, optic gliomas

Vascular birthmark (port-wine stain) of the face Nevus flammeus (benign, but associated with Sturge-525 Weber syndrome)

Renal cell carcinoma (bilateral), hemangioblastomas, von Hippel-Lindau disease (dominant tumor suppressor 525 angiomatosis, pheochromocytoma gene mutation)

Hyperreflexia, hypertonia, Babinski sign present UMN damage 529

Hyporeflexia, hypotonia, atrophy, fasciculations LMN damage 529

Spastic weakness, sensory loss, bowel/bladder dysfunction Spinal cord lesion 530

Unilateral facial drooping involving forehead LMN facial nerve (CN VII) palsy; UMN lesions spare the 532 forehead

Episodic vertigo, tinnitus, hearing loss Ménière disease 534

Ptosis, miosis, anhidrosis Horner syndrome (sympathetic chain lesion) 540

Conjugate horizontal gaze palsy, horizontal diplopia Internuclear ophthalmoplegia (damage to MLF; may be 543 unilateral or bilateral)

Polyuria, renal tubular acidosis type II, growth failure, Fanconi syndrome (multiple combined dysfunction of the 586 electrolyte imbalances, hypophosphatemic rickets proximal convoluted tubule)

Athlete with polycythemia 2° to erythropoietin injection

Periorbital and/or peripheral edema, proteinuria (> 3.5g/ Nephrotic syndrome day), hypoalbuminemia, hypercholesterolemia

Hereditary nephritis, sensorineural hearing loss, Alport syndrome (mutation in collagen IV) retinopathy, lens dislocation

Streak ovaries, congenital heart disease, horseshoe kidney, Turner syndrome (45,XO) 638 cystic hygroma at birth, short stature, webbed neck, lymphedema

Red, itchy, swollen rash of nipple/areola Paget disease of the breast (sign of underlying neoplasm) 650

Fibrous plaques in tunica albuginea of penis with Peyronie disease (connective tissue disorder) 651 abnormal curvature

Hypoxemia, polycythemia, hypercapnia Chronic bronchitis (hyperplasia of mucous cells, “blue

Pink complexion, dyspnea, hyperventilation Emphysema (“pink puffer,” centriacinar [smoking] or

Bilateral hilar adenopathy, uveitis Sarcoidosis (noncaseating granulomas) • AFP in amniotic fluid/maternal serum Down syndrome, Edwards syndrome 63

Large granules in phagocytes, immunodeficiency Chédiak-Higashi disease (congenital failure of 117 phagolysosome formation)

Recurrent infections, eczema, thrombocytopenia Wiskott-Aldrich syndrome 117

Optochin sensitivity Sensitive: S pneumoniae; resistant: viridans streptococci 134 (S mutans, S sanguis)

Novobiocin response Sensitive: S epidermidis; resistant: S saprophyticus 134 Bacitracin response Sensitive: S pyogenes (group A); resistant: S agalactiae 134 (group B)

Branching gram ⊕ rods with sulfur granules Actinomyces israelii 139

Hilar lymphadenopathy, peripheral granulomatous lesion Ghon complex (1° TB: Mycobacterium bacilli) 140 in middle or lower lung lobes (can calcify)

Cardiomegaly with apical atrophy Chagas disease (Trypanosoma cruzi) 158

Enlarged cells with intranuclear inclusion bodies "Owl eye" appearance of CMV 165

Eosinophilic globule in liver Councilman body (viral hepatitis, yellow fever), represents 168 hepatocyte undergoing apoptosis

Eosinophilic inclusion bodies in cytoplasm of Negri bodies of rabies

Ring-enhancing brain lesion on CT/MRI in AIDS Toxoplasma gondii, CNS lymphoma

Psammoma bodies Meningiomas, papillary thyroid carcinoma, 211 mesothelioma, papillary serous carcinoma of the

Sheets of medium-sized lymphoid cells with scattered Burkitt lymphoma (t[8:14] c-myc activation, associated 430 pale, tingible body–laden macrophages ("starry sky" with EBV; "starry sky" made up of malignant cells) histology) • Monoclonal gammopathy of undetermined significance (MGUS consequence of aging)

Stacks of RBCs Rouleaux formation (high ESR, multiple myeloma) 423 Azurophilic peroxidase ⊕ granular inclusions in Auer rods (AML, especially the promyelocytic [M3] type) 432 granulocytes and myeloblasts "Brown" tumor of bone Hyperparathyroidism or osteitis fibrosa cystica (deposited 464 hemosiderin from hemorrhage gives brown color) "Soap bubble" in femur or tibia on x-ray Giant cell tumor of bone (generally benign) 464

Raised periosteum (creating a "Codman triangle") Aggressive bone lesion (eg, osteosarcoma, Ewing 465 sarcoma, osteomyelitis) "Onion skin" periosteal reaction Ewing sarcoma (malignant small blue cell tumor) 465 Anti-IgG antibodies Rheumatoid arthritis (systemic inflammation, joint 466 pannus, boutonniere and swan neck deformities)

Rhomboid crystals, ⊕ birefringent Pseudogout (calcium pyrophosphate dihydrate crystals) 467 Needle-shaped, ⊖ birefringent crystals Gout (monosodium urate crystals) 467 • uric acid levels Gout, Lesch-Nyhan syndrome, tumor lysis syndrome, 467 loop and thiazide diuretics "Bamboo spine" on x-ray Ankylosing spondylitis (chronic inflammatory arthritis: 469 HLA-B27)

Antinuclear antibodies (ANAs: anti-Smith and anti-SLE (type III hypersensitivity) 470 dsDNA)

Anti-histone antibodies Drug-induced SLE (eg, hydralazine, isoniazid, 250 phenytoin, procainamide)

Bloody or yellow tap on lumbar puncture Xanthochromia (due to subarachnoid hemorrhage) 513 Eosinophilic cytoplasmic inclusion in neuron Lewy body (Parkinson disease and Lewy body dementia) 520 Extracellular amyloid deposition in gray matter of brain Senile plaques (Alzheimer disease)

Depigmentation of neurons in substantia nigra Parkinson disease (basal ganglia disorder: rigidity, resting 520 tremor, bradykinesia)

Silver-staining spherical aggregation of tau proteins in Pick bodies (Pick disease: progressive dementia, changes 520 neurons in personality)

Streptococcus pneumoniae Penicillin/cephalosporin (systemic infection, pneumonia), 187, vancomycin (meningitis) 190

Staphylococcus aureus MSSA: nafcillin, oxacillin, dicloxacillin 188, (antistaphylococcal penicillins); MRSA: vancomycin, 190, daptomycin, linezolid, ceftaroline 195

Enterococci Vancomycin, aminopenicillins/cephalosporins 189, 190

Rickettsia rickettsii Doxycycline, chloramphenicol 192

Clostridium difficile Oral metronidazole; if refractory, oral vancomycin 190, 195

Mycobacterium tuberculosis RIPE (rifampin, isoniazid, pyrazinamide, ethambutol) 196

Influenza Oseltamivir, zanamivir 201

CMV Ganciclovir, foscarnet, cidofovir 202

Patent ductus arteriosus Close with indomethacin; keep open with PGE analogs 282 Stable angina Sublingual nitroglycerin 304

Kawasaki disease IVIG, aspirin 314

Granulomatosis with polyangiitis (Wegener) Cyclophosphamide, corticosteroids 315

Arrhythmia in damaged cardiac tissue Class IB antiarrhythmic (lidocaine, mexiletine) 322 Prolactinoma Cabergoline/bromocriptine (dopamine agonists) 330 Diabetes insipidus Desmopressin (central); hydrochlorothiazide, 338 indomethacin, amiloride (nephrogenic)

SIADH Fluid restriction, IV hypertonic saline, conivaptan/ 338 tolvaptan, demeclocycline

Diabetic ketoacidosis Fluids, insulin, K+ 347

Diabetes mellitus type 2 Dietary intervention, oral hypoglycemics, and insulin (if 347 refractory)

Pheochromocytoma α-antagonists (eg, phenoxybenzamine)

Crohn disease Corticosteroids, infliximab, azathioprine

Ulcerative colitis 5-ASA preparations (eg, mesalamine), 6-mercaptopurine, 382 infliximab, colectomy

Acute promyelocytic leukemia (M3) All-trans retinoic acid, arsenic trioxide

Drug of choice for anticoagulation in pregnancy or renal Low-molecular-weight heparin

Long-term anticoagulation Warfarin, dabigatran, rivaroxaban and apixaban 436, 437

Warfarin reversal Fresh frozen plasma (acute), vitamin K (non-acute) 436

Osteoporosis Calcium/vitamin D supplementation (prophylaxis); 462 bisphosphonates, PTH analogs, SERMs, calcitonin, denosumab (treatment)

Chronic gout Xanthine oxidase inhibitors (eg, allopurinol, febuxostat); 467 pegloticase; probenecid

Acute gout attack NSAIDs, colchicine, glucocorticoids 467

Migraine Abortive therapies (eg, sumatriptan, NSAIDs); prophylaxis 518 (eg, propranolol, topiramate, CCBs, amitriptyline)

Multiple sclerosis Disease-modifying therapies (eg, β-interferon, 523 natalizumab); for acute flares, use IV steroids

Tonic-clonic seizures Levetiracetam, phenytoin, valproate, carbamazepine 544

Anorexia Nutrition, psychotherapy, SSRIs 567

Alcoholism Disulfiram, acamprosate, naltrexone, supportive care 571 ADHD Methylphenidate, amphetamines, CBT, atomoxetine, guanfacine, clonidine

Bipolar disorder Mood stabilizers (eg, lithium, valproic acid, carbamazepine), atypical antipsychotics

Generalized anxiety disorder SSRIs, SNRIs (first line); buspirone (second line)

Benign prostatic hyperplasia α1-antagonists, 5α-reductase inhibitors, PDE-5 inhibitors 654

Infertility Leuprolide, GnRH (pulsatile), clomiphene

Prostate adenocarcinoma/uterine fibroids Leuprolide, GnRH (continuous)

Erectile dysfunction Sildenafil, tadalafil, vardenafil 686

Pulmonary arterial hypertension (idiopathic) Sildenafil, bosentan, epoprostenol 686

Mitochondrial inheritance Disease occurs in both males and females, inherited 59 through females only

Intellectual disability Down syndrome, fragile X syndrome 62, 63

Vitamin deficiency (USA) Folate (pregnant women are at high risk; body stores only 68 3to 4-month supply; prevents neural tube defects)

Bacterial meningitis (newborns and kids) Group B streptococcus/E coli/Listeria monocytogenes 180 (newborns), S pneumoniae/N meningitidis (kids/teens)

HLA-DR3 Diabetes mellitus type 1, SLE, Graves disease, Hashimoto 100 thyroiditis (also associated with HLA-DR5), Addison disease

HLA-DR4 Diabetes mellitus type 1, rheumatoid arthritis, Addison 100 disease

Bacteria associated with gastritis, peptic ulcer disease, and H pylori 146 gastric malignancies (eg, adenocarcinoma, MALToma)

Infection 2° to blood transfusion Hepatitis C

Food poisoning (exotoxin mediated) S aureus, B cereus

Osteomyelitis with IV drug use Pseudomonas, Candida, S aureus

UTI E coli, Staphylococcus saprophyticus (young women) 181 Sexually transmitted disease C trachomatis (usually coinfected with N gonorrhoeae)

Nosocomial pneumonia S aureus, Pseudomonas, other enteric gram ⊖ rods

Pelvic inflammatory disease C trachomatis, N gonorrhoeae

Infections in chronic granulomatous disease S aureus, E coli, Aspergillus (catalase ⊕)

Metastases to bone Prostate, breast > kidney, thyroid, lung

Metastases to brain Lung > breast > melanoma, colon, kidney

Metastases to liver Colon >> stomach > pancreas 223

S3 heart sound • ventricular filling pressure (eg, mitral regurgitation, 287 HF), common in dilated ventricles

S4 heart sound Stiff/hypertrophic ventricle (aortic stenosis, restrictive 287 cardiomyopathy)

Constrictive pericarditis TB (developing world); idiopathic, viral illness (developed 287 world)

Holosystolic murmur VSD, tricuspid regurgitation, mitral regurgitation 291

Heart murmur, congenital Mitral valve prolapse 291

Chronic arrhythmia Atrial fibrillation (associated with high risk of emboli) 295 Cyanosis (early; less common) Tetralogy of Fallot, transposition of great vessels, truncus 298 arteriosus, total anomalous pulmonary venous return, tricuspid atresia

Late cyanotic shunt (uncorrected left to right becomes Eisenmenger syndrome (caused by ASD, VSD, PDA; 299 right to left) results in pulmonary hypertension/polycythemia)

Hypertension, 2° Renal artery stenosis, chronic kidney disease (eg, 300 polycystic kidney disease, diabetic nephropathy),

Aortic aneurysm, thoracic Marfan syndrome (idiopathic cystic medial degeneration) 302 Aortic aneurysm, abdominal Atherosclerosis, smoking is major risk factor 302

Aortic aneurysm, ascending or arch 3° syphilis (syphilitic aortitis), vasa vasorum destruction 303 Sites of atherosclerosis Abdominal aorta > coronary artery > popliteal artery

Right heart failure due to a pulmonary cause Cor pulmonale

Heart valve in bacterial endocarditis Mitral > aortic (rheumatic fever), tricuspid (IV drug abuse) 310 Endocarditis presentation associated with bacterium S aureus (acute, IVDA, tricuspid valve), viridans 310 streptococci (subacute, dental procedure), S bovis (colon cancer), culture negative (Coxiella, Bartonella, HACEK)

Temporal arteritis Risk of ipsilateral blindness due to occlusion of

Recurrent inflammation/thrombosis of small/medium Buerger disease (strongly associated with tobacco) 314 vessels in extremities

Cardiac 1° tumor (kids) Rhabdomyoma, often seen in tuberous sclerosis

Cardiac tumor (adults) Metastasis, myxoma (90% in left atrium; "ball valve")

Congenital adrenal hyperplasia, hypotension 21-hydroxylase deficiency 1° hyperparathyroidism Adenomas, hyperplasia, carcinoma 345 2° hyperparathyroidism Hypocalcemia of chronic kidney disease 345 • Paraneoplastic (due to ACTH secretion by tumors)

Tumor of the adrenal medulla (kids) Neuroblastoma (malignant) 350

Tumor of the adrenal medulla (adults) Pheochromocytoma (usually benign) 350

Refractory peptic ulcers and high gastrin levels Zollinger-Ellison syndrome (gastrinoma of duodenum or 351, pancreas), associated with MEN1 352

Acute gastric ulcer associated with CNS injury Cushing ulcer (• intracranial pressure stimulates vagal 379 gastric H+ secretion)

Acute gastric ulcer associated with severe burns Curling ulcer (greatly reduced plasma volume results in 379 sloughing of gastric mucosa)

Bilateral ovarian metastases from gastric carcinoma Krukenberg tumor (mucin-secreting signet ring cells) 379 Chronic atrophic gastritis (autoimmune) Predisposition to gastric carcinoma (can also cause 379 pernicious anemia)

Alternating areas of transmural inflammation and normal Skip lesions (Crohn disease) 382 colon

Site of diverticula Sigmoid colon 383

Hepatocellular carcinoma Cirrhotic liver (associated with hepatitis B and C, alcoholism, and hemochromatosis) 1° liver cancer Hepatocellular carcinoma (chronic hepatitis, cirrhosis, 392 hemochromatosis, α1-antitrypsin deficiency, Wilson disease)

Congenital conjugated hyperbilirubinemia (black liver) Dubin-Johnson syndrome (inability of hepatocytes to

Hemochromatosis Multiple blood transfusions or hereditary HFE mutation 395 (can result in heart failure, "bronze diabetes," and • risk of hepatocellular carcinoma)

Pancreatitis (acute) Gallstones, alcohol

Pancreatitis (chronic) Alcohol (adults), cystic fibrosis (kids)

Bleeding disorder with GpIb deficiency Bernard-Soulier syndrome (defect in platelet adhesion to 427 von Willebrand factor)

DIC Severe sepsis, obstetric complications, cancer, burns, 428 trauma, major surgery, acute pancreatitis, APL

Malignancy associated with noninfectious fever Hodgkin lymphoma 429

Type of Hodgkin lymphoma Nodular sclerosis (vs mixed cellularity, lymphocytic 429 predominance, lymphocytic depletion) t(14;18) Follicular lymphomas (BCL-2 activation, anti-apoptotic 430 oncogene) t(8;14) Burkitt lymphoma (c-myc fusion, transcription factor 430 oncogene)

Type of non-Hodgkin lymphoma Diffuse large B-cell lymphoma 430

Age ranges for patient with ALL/CLL/AML/CML ALL: child, CLL: adult > 60, AML: adult ~ 65, CML: 432, adult 45–85 433

Malignancy (kids) Leukemia, brain tumors 432, 526 t(9;22) Philadelphia chromosome, CML (BCR-ABL oncogene, 434 tyrosine kinase activation), more rarely associated with ALL

Vertebral compression fracture Osteoporosis (type I: postmenopausal woman; type II: 462 elderly man or woman)

HLA-B27 Psoriatic arthritis, ankylosing spondylitis, IBD-associated 469 arthritis, reactive arthritis (formerly Reiter syndrome)

Tumor of infancy Strawberry hemangioma (grows rapidly and regresses

Actinic (solar) keratosis Precursor to squamous cell carcinoma

Atrophy of the mammillary bodies Wernicke encephalopathy (thiamine deficiency causing ataxia, ophthalmoplegia, and confusion) “Some books are to be tasted, others to be swallowed, and some few to be chewed and digested.” “Always read something that will make you look good if you die in the middle of it.” —P.J. O’Rourke “So many books, so little time.” “If one cannot enjoy reading a book over and over again, there is no use in reading it at all.” to Use the Database 712 `Anatomy,

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LA left atrial, left atrium

LM lateral meniscus, left main coronary artery, light microscopy

LT labile toxin, leukotriene

LV left ventricle, left ventricular

MAC membrane attack complex, minimum alveolar concentration

MAP mean arterial pressure, mitogen-activated protein

Med cond* medial condyle MELAS mitochondrial encephalopathy, lactic acidosis, and stroke-syndrome like episodes

MGUS monoclonal gammopathy of undetermined significance MHC major histocompatibility complex

MIRL membrane inhibitor of reactive lysis

MMR measles, mumps, rubella [vaccine]

MR medial rectus [muscle], mitral regurgitation

NPH neutral protamine Hagedorn, normal pressure hydrocephalus 1,25-OH D3 calcitriol (active form of vitamin D) 25-OH D3 storage form of vitamin D

OVLT organum vasculosum of the lamina terminalis

P-450 cytochrome P-450 family of enzymes

PA posteroanterior, pulmonary artery

Pao2 partial pressure of oxygen in arterial blood

Pao2 partial pressure of oxygen in alveolar blood

PAP Papanicolaou [smear], prostatic acid phosphatase

PC platelet count, pyruvate carboxylase

Pco2 partial pressure of carbon dioxide

PCP phencyclidine hydrochloride, Pneumocystis jirovecii pneumonia

PDA patent ductus arteriosus, posterior descending artery

Pi plasma interstitial osmotic pressure, inorganic phosphate PICA posterior inferior cerebellar artery

PIP2 phosphatidylinositol 4,5-bisphosphate

PIP3 phosphatidylinositol 3,4,5-bisphosphate

Po2 partial pressure of oxygen

PV plasma volume, venous pressure

R correlation coefficient, right, R variable [group]

R3 Registration, Ranking, & Results [system]

RANK-L receptor activator of nuclear factor-κ B ligand

RR relative risk, respiratory rate

RV residual volume, right ventricle, right ventricular

SE standard error [of the mean]

SIADH syndrome of inappropriate [secretion of] antidiuretic hormone

SV splenic vein, stroke volume

TCA tricarboxylic acid [cycle], tricyclic antidepressant

V1, V2 vasopressin receptors

Vd volume of distribution

V(D)J variable, (diversity), joining gene segments rearranged to form Ig genes

VH variable region, heavy chain [antibody]

VL variable region, light chain [antibody]

VPL ventral posterior nucleus, lateral

VPM ventral posterior nucleus, medial

VPN vancomycin, polymyxin, nystatin [media] $\dot{V}$ /$\dot{Q}$ ventilation/perfusion [ratio]

XR X-linked recessive XX/XY normal complement of sex chromosomes for female/male ZDV zidovudine [formerly AZT]