

Treatment (*Lancet* 2013;381:484)

- Induction chemo followed by consolidation; if unfit, hypomethylating agents or clinical trial
- Induction chemo:** “7 + 3” = cytarabine \times 7 d + ida/daunorubicin \times 3 d. Daunorubicin dose: age <60 \rightarrow high (90 mg/m²); age >60 \rightarrow standard (60 or 45 mg/m²) (*NEJM* 2009;361:1249). Gemtuzumab ozogamicin (α -CD33) ? benefit in fav/int risk AML (*Lancet* 2012;379:1508).
- ✓ for complete remission (CR) = ANC >1000, plts >100, off RBC Rx, <5% BM blasts
CR \neq cure; \therefore must always f/u induction with **consolidation Rx**
- If \oplus CR: consolidation Rx per Pt risk (age, genetics, PS): chemo (eg, high-dose cytarabine, HiDAC) if favorable risk; poor risk \rightarrow allo-HSCT; int risk depends on mutat., donors, PS
- If \ominus CR: reinduce w/ altern. Rx [eg, MEC (mitoxantrone, etoposide, cytarabine)], HiDAC
- If relapse after CR: salvage chemo or clinical trial \rightarrow allogeneic HSCT
- Supportive care: hydration + allopurinol or rasburicase for tumor lysis prophylaxis; transfusions; antibiotics for fever and neutropenia; antifungals for prolonged fever & neutropenia; hydroxyurea \pm leukapheresis for leukostasis (avoid pheresis in APL)

Prognosis

- CR achieved in 70–80% of Pts <60 y and in 40–50% for Pts >60 y
- Overall survival variable, depends on prognostic factors: ranges from <10% of older Pts w/ poor risk tumor genetics to >75% for younger Pts w/ favorable prognostic factors
- Poor prog. factors: age >60, unfavorable cytogenetics, poor performance status, antecedent MDS/MPN, tAML; genetics (*NEJM* 2016;374:2209; *JAMA* 2015;314:811); residual dis. eg, persistent NPM 1-mut. transcripts a/w \uparrow relapse, \downarrow survival (*NEJM* 2016;374:422)

Acute promyelocytic leukemia (APL) (*Blood* 2009;113:1875)

- Rare disease, approx. 8% of total AML cases in U.S. but biologically and clinically distinct
- Atypical promyelocytes (large, granular cells; bilobed nuclei) in blood and bone marrow
- Defined by translocation of retinoic acid receptor: **t(15;17); PML-RAR α** (>95% of cases)
- Medical emergency** with **DIC** and **bleeding** common; supportive care measures crucial
- Remarkable responses to **all-trans-retinoic acid (ATRA)**, which induces differentiation, and **arsenic trioxide (ATO)**; early initiation of ATRA critical as soon as APL suspected; ATO highly active as first-line therapy or in treatment of refractory disease.
- Induction: ATRA + ATO \rightarrow CR ~100%, \uparrow 2-y event-free survival (*NEJM* 2013;362:111); anthracycline + ATRA \pm cytarabine \rightarrow CR in ~90%, favored in high-risk APL (WBC >10k)
- Differentiation (ATRA) syndrome: ~25% of Pts; fever, pulm infiltrates, SOB, edema, HoTN, AKI; tx w/ dexamethasone 10 mg bid, supportive care (eg, diuresis) (*Blood* 2008;113:775)
- Consolidation: daunorubicin + ATRA (*Blood* 2010;116:3751) or ATRA+ATO (*NEJM* 2013;369:111)
- Role of maintenance Rx (eg, ATRA + 6MP + MTX) controversial; not w/ ATRA/ATO Rx
- Best prognosis of all AMLs: >90% cure; WBC >10,000/ μ L = \downarrow prognosis (*Blood* 2000;96:1247)

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)**Classification**

- Lymphoblastic neoplasms may present as acute leukemia (ALL) with **>20% BM blasts** or as lymphoblastic lymphoma (LBL) w/ mass lesion & <20% BM blasts. ALL and LBL are considered the same disease with different clinical presentations.
- Morphology:** no granules (granules seen in myeloid lineage)
- Cytochemistry:** \oplus terminal deoxynucleotidyl transferase (TdT) in 95% of ALL
- Cytogenetics** (*Blood* 2010;115:206): t(9;22) = Philadelphia chrom (Ph) ~25% of adults w/ ALL; “Ph-like” ALL gene expression: worse prognosis, ? role of TKI (*NEJM* 2014;371:1005)
- Immunohistochem.: 2 major phenotypes (Burkitt's treated differently; see “Lymphoma”)

WHO Immunophenotype Classification of ALL (*Blood* 2016;127:2375)

WHO type	Adult freq.	Immunohistochemistry
B cell	75%	\oplus TdT, \oplus CD19; variable CD10, CD20
T cell	25%	\oplus TdT, \oplus T-cell Ag (CD2, cytoplasmic CD3, CD5, CD7)

Treatment (*JCO* 2011;29:532; *Leukemia* 2015;29:526)

- Induction chemo:** regimens typically include combination of anthracycline, vincristine, steroids, cyclophosphamide, \pm asparaginase; based on pediatric regimens
- CNS prophylaxis:** intrathecal MTX/cytarabine \pm cranial irradiation or systemic MTX
- Postremission therapy** options:
 consolidation/intensification chemo (~7 mo) followed by maintenance chemo (~2–3 y)
 high-dose chemo w/ allo HSCT considered for Pts in CR1 w/ available donor
 pediatric regimens in adults (*Leukemia* 2015;29:526); consider allo SCT if <50 (controversial)
- If relapse \rightarrow salvage (eg, chemo or CAR-T or inotuzumab), then allogeneic HSCT if able
- Ph \ominus t(9;22) primary refractory/relapsed B-cell ALL: blinatumomab (*Lancet Oncol* 2015;16:57)
- Ph \oplus t(9;22) \rightarrow add imatinib or dasatinib, followed by allogeneic HSCT

- MLL-AF4 t(4;11), hypodiploidy (<44 chromosomes), min residual disease → consider allo-HSCT
- Infusion of chimeric antigen receptor-modified T cells promising (NEJM 2014;371:1507)

Prognosis

- Morphologic CR in >80% of adults; but minimal residual disease (MRD) at CR = poor prog.
- Cure achieved in 50–60% if good prog. factors vs. 10–30% w/ poor prog. factors
- Good prognostic factors: younger age, WBC <30,000/ μ L, T-cell immunophenotype, absence of Ph chromosome or t(4;11), early attainment of CR w/ MRD negative

CHRONIC MYELOGENOUS LEUKEMIA (CML)

Definition (Blood 2009;114:937)

- **Myeloproliferative neoplasm** with clonal overproduction of hematopoietic myeloid stem cells that can differentiate
- **Philadelphia chromosome (Ph)** = t(9;22) → **BCR-ABL** fusion → ↑ Abl kinase activity **BCR-ABL required for Dx** (make via karyotyping or FISH; PCR useful but not adequate)
- “Atypical CML” (BCR-ABL \ominus) now considered a separate disease and reclassified as MDS/MPN (qv) w/ many Pts \oplus for CSF3R or SETBP1 mutations

Epidemiology and risk factors

- ~6600 new cases/y in U.S.; median age ~64 at presentation; ~15% of adult leukemias
- ↑ risk with irradiation; no clear relation to cytotoxic drugs

Clinical manifestations

- Triphasic clinical course: 85% present in the chronic phase
- **Chronic phase:** often asymptomatic but common features are fatigue, malaise, weight loss, night sweats, abdominal fullness (**splenomegaly** 50%)
- **Accelerated phase:** refractory leukocytosis, ↓ plt and worsening sx → fever, wt loss, ↑ splenomegaly, bone pain, bleeding, infections, pruritus (basophilia)
- **Blastic phase** = acute leukemia → severe constitutional symptoms, infection, bleeding, and possible **leukostasis** (see “Acute Leukemia”)

Diagnostic evaluation

- **Peripheral smear:** **leukocytosis**, left-shifted with all stages of myeloid maturation; anemia, thrombocytosis, **basophilia**
- **Bone marrow:** hypercellular, ↑ myeloid to erythroid ratio, ↓ leuk alkaline phosphatase
- **Chronic:** <10% blasts (peripheral or BM)
- **Accelerated:** 10–19% blasts, ≥20% basos, plts <100k, ↑ spleen size, karyotypic prog.
- **Blastic:** ≥20% blasts ($\frac{2}{3}$ myeloid, $\frac{1}{3}$ lymphoid), may see extramedullary leukemia

Treatment (Lancet 2015;385:1447)

- **Tyrosine kinase inhibitor (TKI):** imatinib, dasatinib, nilotinib, bosutinib, & ponatinib are selective inhibitors of BCR-ABL (JCO 2010;28:428; Blood 2012;120:1390). Imatinib, nilotinib, & dasatinib approved as initial Rx. Resistance = recurrent dis. on TKI, often result of BCR-ABL mutation or amplification. Nilotinib, dasatinib, bosutinib, & ponatinib approved for resistant disease, w/ only ponatinib effective on T315I resistance mutation (NEJM 2012;367:2075 & 2013;369:1783). Side effects: nausea, diarrhea, muscle cramps, cytopenias, ↓ PO₄, ↑ QT, rarely CHF; dasatinib: pericardial & pleural effusions and pulm HTN; nilotinib: ↑ bili & lipase, CV toxicity; ponatinib: thrombosis, pancreatitis and CV toxicity
- **Chronic phase:** TKI; continued indefinitely in responders (Blood 2012;120:1390)
- **Accelerated phase:** TKI upfront, consider allogeneic HSCT
- **Blastic phase:** TKI vs. TKI + either ALL or AML induction (based on cell type); then HSCT
- **Allogeneic HSCT:** possibility of cure, consider for Pts w/ available donor; Pts who present in accelerated or blastic phase; or Pts with relapsed/refractory disease to TKIs

Goals of TKI Therapy (Blood 2013;122:872)

Response	Definition	Optimal time
Hematologic	WBC <10k, plt <450k, no immature cells in blood, basophils <5%, spleen nonpalpable	3 mo
Cytogenetic	Absence of the Ph chromosome in metaphase cells	12 mo
Molecular	<0.1% BCR-ABL = 3-log reduction by quantitative PCR	12 mo

Prognosis (Cancer 2013;119:2620)

- Chronic phase CML Rx'd w/ imatinib: 89% 5-y overall survival, 95% survival free of CML-related deaths, 7% progression to blast phase at 5 y (NEJM 2006;355:2408)
- Accelerated phase CML Rx'd w/ imatinib: ~50% overall survival at 4 y (Cancer 2005;103:2099)
- Poor prognostic factors: ↑ age, ↑ platelet count, ↑ spleen size, ↑% of blasts/basophils

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Definition (NEJM 2005;352:804; Blood 2008;111:5446)

- Monoclonal accumulation of functionally incompetent mature B lymphocytes
- CLL (>5000/ μ L malignant cells) & small lymphocytic lymphoma (SLL; <5000/ μ L malignant cells, with + LAN \pm splenomegaly) classified as same disease
- Monoclonal B lymphocytosis (<5000/ μ L, nodes <1.5 cm, nl RBC and Plt counts): observe

Epidemiology and risk factors

- ~15,000 new cases/y; median age at dx is 71 y; most common adult leukemia
- \uparrow incidence in 1st-degree relatives; no known association with radiation, chemicals, drugs

Clinical manifestations

- Symptoms: often asx & identified when CBC reveals lymphocytosis; 10–20% p/w fatigue, malaise, night sweats, weight loss (ie, lymphoma "B" sx)
- Signs: **lymphadenopathy** (80%) and **hepatosplenomegaly** (50%)
- Autoimmune hemolytic anemia** (AIHA) (~10%) or **thrombocytopenia** (ITP) (~1–2%)
- Hypogammaglobulinemia \pm neutropenia \rightarrow \uparrow susceptibility to **infections**
- Bone marrow failure in ~13%; monoclonal gammopathy in ~5%
- Aggressive transformation: ~5% develop **Richter's syndrome** = transformation into high-grade lymphoma (usually DLBCL) and sudden clinical deterioration

Diagnostic evaluation (see "Lymphoma" for general approach)

- Peripheral smear:** **lymphocytosis** (>5000/ μ L, mature-appearing small cells) "smudge" cells from damage to abnl lymphs from shear stress of making blood smear
- Flow cytometry:** **clonality** with dim surface Ig (slg); CD5+, CD19+, CD20(dim), CD23+, CD38+ or ZAP70+ a/w unmutated Ig variable heavy chain region & worse prog.
- Bone marrow:** normo- or hypercellular; infiltrated w/ small B-cell lymphocytes (\geq 30%)
- Lymph nodes:** infiltrated w/ small lymphocytic or diffuse small cleaved cells = SLL
- Genetics:** del 11q22-23 & 17p13 unfavorable; trisomy 12 neutral; del 13q14 and mut IgVH favorable. Nine significantly mutated genes, including TP53, NOTCH1, MYD88 and SF3B1. Key role for spliceosome mutations (NEJM 2011;365:2497; JCI 2012;122:3432).

CLL Staging

Rai system		Median survival	Binet system	
Stage	Description		Description	Stage
0	Lymphocytosis only	>10 y	<3 node areas	A
I	\oplus lymphadenopathy	7–10 y	>3 node areas	B
II	\oplus hepatosplenomegaly			
III	\oplus anemia (not AIHA)	1–2 y	Anemia or thrombocytopenia	C
IV	\oplus thrombocytopenia (not ITP)			

Treatment (JAMA 2014;312:2265)

- Treatment is primarily **palliative** \rightarrow early stage disease can be followed w/o Rx
- Indications for treatment: Rai stages III/IV, Binet stage C, disease-related sx, progressive disease, AIHA or ITP refractory to steroids, recurrent infections
- Options: combo superior to monoRx (Lancet 2007;370:230), but comorbidities/age important
 - purine analogues:** fludarabine ("F"), pentostatin ("P")
 - alkylating agents:** cyclophosphamide ("C"), bendamustine ("B"), CVP, CHOP \pm **monoclonal Ab** against CD20 (**rituximab**, "R"; ofatumumab) or CD52 (alemtuzumab)
- Healthy/younger (<70y): FCR \uparrow survival vs. FC (Lancet 2010;376:1164); FR also acceptable
- Infirm/elderly: many options incl. ibrutinib (NEJM 2015;373:2425); chlorambucil + anti-CD20 [eg, obinutuzumab (NEJM 2014;370:1101) or ofatumumab (Lancet 2015;385:1873)], BR
- Refractory disease: ibrutinib > ofatumumab (NEJM 2014;371:213); acalabrutinib (BTK; NEJM 2016;374:323), idelalisib (PI3K; NEJM 2014;370:997); venetoclax (α -BCL2; NEJM 2016;374:311)
- 17p- or TP53 mutat.: venetoclax, idelalisib, or ibrutinib \pm rituximab (Lancet Oncol 2014;10:1090)
- Consider allo-HSCT in 17p-, TP53 mutation or refractory CLL (BJH 2012;158:174)
- Supportive care: PCP, HSV, VZV prophylaxis; CMV monitoring for Pts receiving anti-CD52; AIHA/ITP \rightarrow steroids; recurrent infections \rightarrow IVIg

Prognosis (NEJM 2004;351:893; JCO 2006;24:4634)

- Survival varies substantially. Median overall survival ~10 y (Am J Hematol 2011;12:985)
- Favorable prognosis: 13q14 deletion (~50% of CLL cases)
- Factors a/w worse prognosis include:
 - unfavorable cytogenetics: eg, 17p- or TP53 mutation (JCO 2010;28:4473)
 - unmutated (<2 c/w germline) IgVH gene (<8–10 y vs. >20–25 y if mutated)
 - high (>20–30%) Zap-70 expression (part of T cell receptor; correlated w/ unmutated IgVH)
 - CD38 >30% or CD49d <30%: correlated with unmutated IgVH (Blood 2008;111:865)
 - higher β_2 -microglobulin levels (correlate with disease stage and tumor burden)

Definition

- Malignant disorder of lymphoid cells that reside predominantly in lymphoid tissues
- Generally characterized as **Hodgkin lymphoma (HL)** or **non-Hodgkin lymphoma (NHL)**

Clinical manifestations

- Lymphadenopathy (nontender)
 - HL:** Reed-Sternberg (RS) cells; superficial (usually cervical/suprACLAVICULAR) ± mediastinal LAN; nodal disease with **orderly, anatomic spread** to adjacent nodes
 - NHL:** diffuse; **nodal and/or extranodal** disease with **noncontiguous spread**; symptoms reflect involved sites (abdominal fullness, bone pain)
- Constitutional ("B") symptoms: **fever** ($>38^\circ$), drenching **sweats**, \downarrow **weight** ($>10\%$ in 6 mo)
 - HL:** periodic, recurrent "Pel-Ebstein" fever; 10–15% have pruritus; ~35% "B" symptoms
 - NHL:** "B" symptoms vary between subtypes, ~15–50%

Diagnostic and staging evaluation

- Physical exam: lymph nodes, liver/spleen size, Waldeyer's ring, testes (~1% of NHL), skin
- Pathology: **excisional lymph node bx** (not FNA b/c need surrounding architecture) with immunophenotyping and cytogenetics; **BM bx** or **PET** (except in HL clinical stage IA/IIA w/ favorable features or CLL by flow); LP if CNS involvement clinically suspected
- Lab tests: CBC, BUN/Cr, LFTs, ESR, LDH, UA, Ca, alb; ✓ HBV & HCV (and must ✓ HBsAg & anti-HBC if planning rituximab Rx, as can lead to HBV reactivation); consider HIV, HTLV, & EBV serologies and connective tissue diseases autoAbs
- Imaging: PET-CT scans as CT alone does not reliably detect spleen/liver involvement (espec. in HL, DLBCL). PET response to Rx can be prognostic & possibly guide Rx (NEJM 2015;372:1598 & 2016;374:2419). Head CT/MRI only if neurologic symptoms.

Ann Arbor Staging System with Cotswolds Modifications

Stage	Features
I	Single lymph node (LN) region
II	≥ 2 LN regions on the same side of the diaphragm
III	LN regions on both sides of the diaphragm
IV	Disseminated involvement of one or more extralymphatic organs

Modifiers: A = no symptoms; B = fever, night sweats or weight loss; X = bulky disease = greatest transverse diam. of mediastinal mass/max diam. of chest wall $>1/3$ on CXR or >10 cm if in abd; E = involves single contiguous extranodal site; H = hepatic; S = splenic

HODGKIN LYMPHOMA (HL) (NEJM 2010;363:653)**Epidemiology and risk factors**

- ~9,000 cases/y; bimodal distribution (15–35 & >50 y); $\uparrow \delta$; role of EBV in subsets of HL, esp. immunocompromised patients (eg, HIV)

Pathology

- Affected nodes show RS cells (<1%) in background of non-neoplastic inflammatory cells
- Classic RS cells: bilobed nucleus & prominent nucleoli with surrounding clear space ("owl's eyes"). RS cells are **clonal B-cells**: CD15+, CD30+, CD20- (rarely +).

WHO Histologic Classification of Classical HL

Nodular sclerosis	60–80%	Collagen bands; frequent mediastinal LAN; young adults; female predominance; usually stage I or II at dx
Mixed cellularity	15–30%	Pleomorphic; older age; male predominance; $\geq 50\%$ stage III or IV at presentation; intermediate prognosis
Lymphocyte rich	5%	Abundant normal-appearing lymphocytes; mediastinal LAN uncommon; male predominance; good prognosis
Lymphocyte depleted	<1%	Diffuse fibrosis and large numbers of RS cells; older, male patients; disseminated at dx; seen in HIV; worst prognosis

- Nonclassical** (5%): nodular lymphocyte predominant (NLP); involves peripheral LN 80% present in stages I-II and Rx can be RT alone or combination chemo + RT w/ 80% 10-y progression-free survival, 93% overall survival (JCO 1997;15:3060)
 - Consider rituximab as most NLP RS cells are CD20+
 - Stages III–IV treated with combination chemo (see below)

Treatment (*Lancet* 2012;380:836)

- Stages I-II: ABVD** (doxorubicin, bleomycin, vinblastine, dacarbazine) ± RT
Lower intensity regimens comparable efficacy if favorable prognosis (*NEJM* 2010;363:640)
- Stages III-IV: ABVD × 6 cycles or escalated BEACOPP** (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone)
- Refractory/relapsed disease: salvage chemo + auto HSCT, ± RT
brentuximab vedotin (CD30 antibody-drug conjugate): salvage (*NEJM* 2010;363:1812), or post-ASCT consolidation (*Lancet* 2015;385:1853)
- PD1/PDL1 blockade (eg, pembrolizumab or nivolumab) (*NEJM* 2015;372:311)
- Late effects include ↑ risk for:
 - second cancers:** ~4.6x risk for up to 40 y (*NEJM* 2015;373:2499)
breast (if RT), ∴ annual screening at age 40 or 8–10 y post RT
 - lung, ? role of screening CXR or CT (controversial)
 - acute leukemia/MDS; NHL
- cardiac disease** (if RT or anthracycline), ? role of echo/stress at 10 y (controversial)
- pulmonary toxicity** (if bleomycin)
- hypothyroidism** (if RT), ∴ annual TSH (if neck RT)

International Prognostic Score (IPS) (*JCO* 2012;30:3383)

Negative prognostic indicators	Total # of indicators	5-y PFS
Albumin <4 g/dL; Hb <10.5 g/dL	0	88%
Male; Age >45 y	1	84%
Stage IV	2	80%
WBC ≥15k/µL	3	74%
Lymphocytes <600/µL or <8% of differential	4	67%
	≥5	62%

Non-Hodgkin Lymphoma (NHL)

Epidemiology and risk factors

- ~70,000 new cases/y; median age at dx ~65 y; ♂ predominance; 85% B-cell origin
- Associated conditions: immunodeficiency (eg, HIV, posttransplant); autoimmune disorders (eg, Sjögren's, RA, SLE); infection (eg, EBV, HTLV-I, *H. pylori*)
- Burkitt lymphoma: (1) endemic or African (jaw mass, 80–90% EBV-related); (2) sporadic or American (20% EBV-related); (3) HIV-related

WHO Classification of Lymphoid Malignancies (*Blood* 2016;127:2375)

Type	Examples	Associated abnormalities
Mature B cell	Diffuse large B-cell lymphoma (DLBCL) Follicular lymphoma CLL/small lymphocytic lymphoma Mantle cell Marginal zone lymphoma (nodal, extranodal [MALT ✓ <i>H. pylori</i>], splenic) Burkitt's lymphoma Hairy cell leukemia (p/w fatigue, ↓ monos, massive splenomegaly; ⊕ TRAP)	BCL2, MYC, MLL2, CREBBP, etc. <i>IGH</i> -BCL2, MLL2 <i>IGVH</i> , ZAP70, TP53, SF3B1, etc. <i>t(11; 14)</i> BCL1-H _g H → cyclin D1 dysreg AP12-MALT1 & BCL-10-Ig enhancer 8q24, c-MYC BRAF V600E
Mature T cell & NK cell	Peripheral T-cell lymphoma Mycosis fungoïdes (cutaneous lymphoma)/Sézary syndrome (+ LAN) Anaplastic large-cell lymphoma Angioimmunoblastic T-cell lymphoma	<i>TET2</i> and <i>DNMT3A</i> Some ALK1 ⊕

Treatment (*Lancet* 2012;380:848)

- Treatment and prognosis determined by histopathologic classification rather than stage
- Rituximab (antibody to CD20; *NEJM* 2012;366:2008) if CD20+; no role if tumor is CD20-
- Indolent:** goal is sx mgmt (bulky dis., cytopenias, "B" sx); not curable (except allo HSCT)
 - Options include RT for localized disease, rituximab ± chemo (bendamustine, CVP, fludarabine), ibrutinib
 - For MALT → treat *H. pylori* if ⊕
 - Rituximab maintenance ↑ survival in relapsed disease (*JNCI* 2009;101:248); growing role for rituximab maintenance in indolent and aggressive disease (*Lancet* 2011;377:42)
 - Hairy cell: cladribine; oral BRAF inhibitor if relapsed/refractory (*NEJM* 2015;373:1733)
- Aggressive** (DLBCL, 30–40% of NHL): goal is cure (*JCO* 2005;23:6387)
 - R-CHOP** (rituximab, cyclophosphamide, doxorubicin = hydroxydaunorubicin, vincristine = Oncovin, prednisone) (*NEJM* 2002;346:235 & 2008;359:613)
 - 10-y progression-free survival = 45%; overall survival = 55% (*Blood* 2010;116:2040)

? R-ACVBP (ritux, doxorubicin = Adriamycin, cyclophosph, vindesine, bleo, prednisone) ↑ 3-y OS vs. R-CHOP, but ↑ adverse events (*Lancet* 2011;378:1858)

+ Radiation for localized or bulky disease

Consider **CNS prophylaxis** w/ intrathecal or systemic high-dose methotrexate if paranasal sinus, testicular, breast, periorbital, paravertebral, or bone marrow involved; ≥2 extranodal sites + ↑ LDH may also warrant

Refractory/relapsed disease: salvage chemo; high-dose chemo + auto-HSCT (*NEJM* 1995;333:1540); allo-HSCT if beyond 2nd relapse (*JCO* 2011;29:1342)

Mantle cell: ibrutinib for relapsed/refractory disease (*Lancet* 2016;387:770)

• Highly aggressive (Burkitt, lymphoblastic lymphoma, high-grade B-cell lymphoma w/ rearrangements of MYC and BCL2 and/or BCL6)

Burkitt: intensive short-course chemo (*Blood* 2004;104:3009) + rituximab (*BJH* 2014;165:102)

Low risk defined as nl LDH & single focus of disease <10 cm; all others high risk

Low-risk Rx: CODOX-M (cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate ± rituximab) (*Leuk Lymph* 2004;45:761)

High-risk Rx: CODOX-M/IVAC (above w/ ifosfamide, etoposide, high-dose cytarabine), hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone)

Dose-adjusted EPOCH-R w/ promise (see below; titrate to ANC) (*NEJM* 2013;369:1915)

All Pts receive CNS prophylaxis & tumor lysis syndrome prophylaxis

Addition of rituximab improves EFS (*Lancet* 2016;387:2402)

Lymphoblastic lymphoma (B or T cell): treated like ALL (see "Acute Leukemia")

High-grade B-cell lymphoma w/ rearrangements of MYC and BCL2 and/or BCL6: previously "double/triple-hit" lymphoma, assoc. w/ poor prognosis.

Prognosis

- Indolent: typically incurable, but long median survival

Follicular Lymphoma International Prognostic Index (FLIPI) (*Blood* 2004;104:1258)

Factors: age >60, stages III/IV, Hb <12 g/dL, >4 nodal areas, LDH >nl

# factors	5-y overall survival	10-y overall survival
0–1	90%	71%
2	78%	51%
≥3	52%	35%

- Aggressive: ↑ chance of cure, but overall worse prognosis

International Prognostic Index (IPI) for Aggressive NHL (*Blood* 2007;109:1857)

Factors: age >60, stage III/IV, ≥2 extranodal sites, performance status ≥2, LDH >nl

# factors	Complete response	5-y overall survival
0–1	87%	73%
2	67%	51%
3	55%	43%
4–5	44%	26%

Revised IPI Prognosis in Patients Rx'd with CHOP-R

Factors	% at dx	4-y overall survival
0	10%	94%
1–2	45%	79%
3–5	45%	55%

HIV-associated NHL (*Blood* 2006;107:13)

- HIV + imparts 60–100x relative risk
- NHL is an AIDS-defining malignancy along with Kaposi's, cervical CA, anal CA
- Concurrent HAART & chemotherapy likely provide survival benefit
- DLBCL & immunoblastic lymphoma (67%): CD4 <100, EBV-associated
Treat as immunocompetent (CHOP-R), but avoid rituximab if CD4 <100
Alternative regimens include R-EPOCH (etop, pred, vincristine, cyclophos, doxorubicin)
- Burkitt lymphoma (20%): can occur with CD4 >200
Treat as immunocompetent; prognosis is not significantly worse
- Primary CNS lymphoma (16%): CD4 <50, EBV-associated (also seen in Pts w/o HIV). Rx w/ high-dose MTX-based regimen + steroids ± temozolomide ± RT, consider auto HSCT.
- Primary effusion lymphoma (<5%): HHV8 driven; also can be seen in other immuno-supp. Pts such as s/p solid organ transplant or w/ chronic HBV. Treat with standard CHOP (often CD20-) or consider EPOCH, overall poor prognosis.

PLASMA CELL DYSCRASIAS

MULTIPLE MYELOMA (MM)

Definition and epidemiology (NEJM 2011;364:1046)

- Malignant neoplasm of **plasma cells** producing a monoclonal Ig = "**M protein**"
- ~27,000 new cases/y; median age at diagnosis 69 y; more common in African-Americans

Clinical manifestations (CRAB criteria and other less common features)

- Hyper**Calcemia** due to ↑ osteoclast activity
- Renal disease:** multiple mechanisms include toxic effect of filtered light chains → **renal failure** (cast nephropathy) or type II RTA; amyloidosis or light chain deposition disease → **nephrotic syndrome**; hypercalcemia, urate nephropathy, type I cryoglobulinemia
- Anemia** (normocytic) due to bone marrow involvement; rarely, may see AIHA
- Bone pain** due to ↑ osteoclast activity → lytic lesions, pathologic fx
- Recurrent infxns due to relative hypogammaglob. (clonal plasma cells suppress nl Ig)
- Neurologic: cord compression; POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes) syndrome
- Hyperviscosity: usually when IgM >4 g/dL, IgG >5 g/dL, or IgA >7 g/dL
- Coagulopathy: inhibition of or Ab against clotting factor; Ab-coated platelets
- AL Amyloidosis (see "Amyloidosis")

Diagnostic and staging evaluation (Lancet Onc 2014;15:e538)

- MM criteria:** clonal BM plasma cells ≥10% or bx-proven plasmacytoma and ≥1 myeloma-defining event:
 - myeloma-related organ or tissue impairment (**ROTI**) = lytic bone lesions, Ca >11 mg/dL, Cr >2 mg/dL, or Hb <10 g/dL
 - any of the following biomarkers: BM plasma cells ≥60%, serum free light chain (FLC) ratio ≥100:1, >1 focal lesion on MRI studies
- Variants**
 - smoldering MM: M protein >3 g/dL or plasmacytosis >10%, no myeloma-defining event or amyloidosis; risk of prog. 10%/y, depends on M protein concen., subtype, FLC ratio
 - solitary bone plasmacytoma: 1 lytic lesion w/o plasmacytosis or other ROTI
 - extramedullary (nonskeletal) plasmacytoma: usually upper respiratory tract
 - plasma cell leukemia: plasma cell count >2000/µL in peripheral blood
 - nonsecretory MM (~2% of MM Pts): no M protein, but marrow plasmacytosis & ROTI
- Ddx of M component: MM, MGUS (see below), CLL, lymphoma, sarcoidosis, RA.
- Polyclonal hypergam can be seen in inflammatory states: HIV, rheumatic dis., cirrhosis.
- Peripheral smear → rouleaux (see insert); ✓ Ca, alb, Cr; ↓ anion gap, ↑ globulin, ↑ ESR
- Protein electrophoresis and immunofixation**
 - serum protein electrophoresis (SPEP):** quantitates M component; + in >80% of Pts
 - urine protein electrophoresis (UPEP):** detects Pts who secrete only light chains (= Bence Jones proteins), which are filtered rapidly from the blood
 - immunofixation: shows component is monoclonal and identifies Ig type → IgG (50%), IgA (20%), IgD (2%), IgM (0.5%), light chain only (20%), nonsecretors (<5%)
- serum FLC assay:** important for dx (esp. ligh chain only Pts) and f/up response to Rx
- β₂-microglobulin and LDH levels reflect tumor burden
- BM bx cytogenetics:** normal karyotype better than abnl. **Standard risk** = hyperdiploidy or t(11;14); **high risk** = hypodiploidy, del. 17p13 (~10% of Pts), t(4;14) & t(4;16)
- Gene mutations include TP53, NRAS, KRAS, BRAF, & NK-κB pathway (Nature 2011;471:467)
- Skeletal survey** (plain radiographs) to identify lytic bone lesions and areas at risk for pathologic fracture; *bone scan is not useful for detecting lytic lesions*

Multiple Myeloma Staging Systems (OS does not account for cytogenetics)

Stage	ISS criteria*	Durie-Salmon (DS) criteria	ISS Median OS
I	β ₂ -microglobulin <3.5 mg/L and albumin >3.5 g/dL	all of the following: Hb >10 g/dL; Ca ≤12 mg/dL; 0–1 lytic bone lesions; IgG <5 g/dL or IgA <3 g/dL or urine light chain <4 g/24 h	62 mo
II	fulfilling criteria for neither I nor III		44 mo
III	β ₂ -microglobulin >5.5 mg/L	any of the following: Hb <8.5 g/dL; Ca >12 mg/dL; >5 lytic bone lesions; IgG >7 g/dL or IgA >5 g/dL or urine light chain >12 g/24 h	29 mo (30 mo if Cr < 2 mg/dL; 15 mo if Cr ≥ 2 mg/dL)

*Consider R-ISS incl chrom abnl & LDH (JCO 2005;23:3412 & 2015;61:2267).

Treatment (NEJM 2011;364:1046; Am J Hematol 2012;87:79)

- Decisions generally dictated by risk stratification and transplant eligibility
- Active drugs incl. **proteasome inhibitors**: bortezomib (V), carfilzomib (Cz), ixazomib (I); **immunomodulators**: lenalidomide (R), thalidomide (T), pomalidomide; **immunotherapy**: daratumumab (anti-CD38), elotuzumab (SLAMF7)
 - Other active drugs incl. prednisone (P), dexamethasone (D), melphalan (M), panobinostat, cyclophosphamide (Cy); CAR-T cells promising (NEJM 2015;373:621&1207; Lancet 2016;387:1551)
- Induction Rx regimens w/ best response rate combine proteasome inhib (V, Cz) & immunomod (R). Common induction regimens include doublets (RD, VD) or triplets (RVD, CyBorD), based on comorbidities and risk (NEJM 2014;371:906 & 2016;374:1621).
- If not transplant eligible: **induction chemo** ↑ survival, not curative; consider maint chemo
- If transplant eligible: induction chemo (eg, RVD, VCD, RD; Lancet 2010;376:2075) then **high-dose melphalan + auto-HSCT**. Not curative, but ↑ survival c/w chemo (NEJM 2014;371:895; Lancet Onc 2015;16:1617). Offer if good perf. status & no prohibitive comorbid. Maint Rx w/ R improves PFS/OS (NEJM 2014;371:10). Timing of HSCT (upfront vs. relapse) debatable. Tandem auto-HSCT & allo-HSCT ↑ survival for some (NEJM 2003;349:2495).
- Relapsed/refractory: based on prior response & HSCT eligibility: HSCT (if good prior response, no prior HSCT), RD, CVD, VRD, CzRD, IRD, pomalidomide+D, daratumumab
- Local radiation for solitary or extramedullary plasmacytoma
- Adjunctive Rx: bone: **bisphosphonates** (JCO 2007;25:2464), XRT for sx bony lesions renal: avoid NSAIDs & IV contrast; consider plasmapheresis for acute renal failure **hyperviscosity syndrome**: plasmapheresis; infxns: consider IVIg for recurrent infections
- Common **toxicities** of Rx: melphalan → myelosuppression; lenalidomide → low plt & thromboembolism; bortezomib → periph. neuropathy; steroids → hyperglycemia, infxn

MONOCLONAL GAMMOPATHY OF UNCERTAIN SIGNIFICANCE (MGUS)**Definition and epidemiology (NEJM 2006;355:2765)**

- M prot. <3 g/dL, marrow plasmacytosis <10%, neither myeloma ROTI nor amyloidosis
- Prevalence ~3% in population >50 y of age, ~5% in population >70 y of age, and 7.5% in population >85 y of age (NEJM 2006;354:1362)

Management

- ✓ CBC, Ca, Cr, SPEP, serum free light chains, UPEP w/ immunofixation (to exclude MM)
- Close observation: repeat SPEP in 6 mo, then yearly thereafter if stable

Prognosis (NEJM 2002;346:564)

- ~1%/y or ~25% lifetime risk → MM, WM, amyloidosis, or malign. lymphoproliferative dis.
- Abnormal serum free light chain ratio: ↑ risk of progression to MM (Blood 2005;105:812)

WALDENSTRÖM'S MACROGLOBULINEMIA (WM)**Definition (Blood 2009;114:2375)**

- B-cell neoplasm (lymphoplasmacytic lymphoma) that secretes monoclonal IgM
- 91% w/ MYD88 (NF-κB pathway) L265P mut, may distinguish from MM (NEJM 2012;367:826)
- No evidence of bone lesions (IgM M component + lytic bone lesions = "IgM myeloma")

Clinical manifestations

- Fatigue** from anemia is most common sx
- Tumor infiltration**: BM (cytopenias), hepatomegaly, splenomegaly, lymphadenopathy
- Circulating monoclonal IgM**
 - hyperviscosity syndrome** (~15%): Neurologic: blurred vision ("sausage" retinal veins), HA, dizziness, Δ MS. Cardiopulmonary: congestive heart failure, pulm. infiltrates.
 - type I cryoglobulinemia** → **Raynaud's phenomenon**
platelet dysfxn → mucosal bleeding
- IgM deposition** (skin, intestine, kidney); amyloidosis and glomerulopathy
- Autoantibody activity of IgM**: Chronic AIHA (prominent rouleaux; 10% Coombs' + = AIHA). Peripheral neuropathy: may be due to IgM against myelin-associated glycoprotein.

Diagnostic evaluation

- SPEP + immunofixation with IgM >3 g/dL; 24-h urine for UPEP (only 20% have + UPEP)
- Bone marrow biopsy: ↑ plasmacytoid lymphocytes; β₂-microglobulin for prognostic eval
- Relative serum viscosity**: defined as ratio of viscosity of serum to H₂O (nl ratio 1.8) hyperviscosity syndrome when relative serum viscosity >5–6

Treatment

- Hyperviscosity: **plasmapheresis**
- Sx (eg, prog. anemia): rituximab ± chemo (eg, bendamustine, Cy, etc.); ibrutinib esp. in MYD88 mut/CXCR4 wt (NEJM 2015;372:1430). Everolimus or HSCT in salvage.

HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

Transplantation of donor pluripotent cells that can reconstitute all recipient blood lineages

Categories of Stem Cell Transplantation

Feature	Allogeneic (Allo)	Autologous (Auto)
Donor-recipient relationship	Immunologically distinct	Donor is also recipient
Graft-vs.-host disease	Yes	No
Graft-vs.-tumor effect	Yes	No
Risk of graft contam. w/ tumor	No	Yes
Relapse risk (leukemia)	Lower	Higher
Transplant-related mortality	Higher	Lower

- **Types of Allo HSCT:** based on donor/recipient matching of major HLA antigens on Chr. 6 (4 principal genes for serotyping: HLA-A, -B, -C, & -DR; each w/ 2 alleles ∴ 8 major Ag). **Matched related** (sibling matched at 8/8 major Ag): lowest risk of GVHD; preferred donor. **Mismatched related** (eg, 1/8 Ag mismatch) or **haploidentical** (mismatch at 4/8 Ag): easiest to find, but ↑ risk of GVHD, rejection; ∴ need additional immunosuppression. **Matched unrelated:** ↑ risk of GVHD; ∴ matching of 10 HLA alleles (DQ also) to ↓ risk; chance of match correlates w/ ethnicity (NEJM 2014;371:339). **Umbilical cord blood:** HSC processed at birth & stored; ↓ risk of GVHD; tolerate mismatch but much slower immune reconstitution (Blood 2010;116:4693).
- **Graft-vs.-host disease (GVHD):** undesirable side effect of allo HSCT. allogeneic T cells view host cells as foreign; ↑ incid. w/ mismatch or unrelated donors.
- **Graft-vs.-tumor (GVT):** desired effect in allo-SCT; graft T cells attack host tumor cells

Indications (BBMT 2015;21:1863; BMT 2015;50:1037)

- **Malignant disease:**
 - Auto HSCT** allows **higher ablative chemo doses** and then rescues the hematopoietic system (used for lymphoma, multiple myeloma, testicular cancer, neuroblastoma)
 - Allo HSCT** produces **graft-vs.-tumor (GVT)** effect, in addition to hematopoietic rescue (used for AML, ALL > CML, CLL, MDS, lymphoma)
- **Nonmalignant disease:** allo HSCT replaces abnl lymphohematopoietic system w/ one from nl donor (eg, immunodef., aplastic anemia, hemoglobinopathies, ? autoimmune dis.)

Transplantation procedure

- **Preparative regimen:** chemotherapy and/or immunosuppression prior to transplantation. **myeloablative conditioning ("MAC"):** chemotherapy and/or total body irradiation. Goal is **eradication** of underlying disease for which transplant is being performed. **reduced intensity conditioning ("RIC" or "mini"):** lower dose conditioning → ↓ toxicity to allow Pts w/ comorbidities or ↑ age to tolerate HSCT. Goal = transplant when in remission. Depends mostly on GVT; ↓ transplant-related mortality, but ↑ relapse (Blood 2015;126:23). Otherwise eligible candidates should have MAC.
- **Sources of stem cells:**
 - bone marrow (BM):** original source of HSCT, now less commonly used than PBSC
 - peripheral blood stem cells (PBSC):** easier to collect, more commonly used. BM vs. PBSC ≈ survival; BM ↓ chronic GVHD, PBSC ↓ graft failure, faster engraftment (NEJM 2012;367:1487)
 - umbilical cord blood (UCB):** less stringent HLA-matching requirements, but fewer cells per donor (∴ 2 donors combined); slower engraftment, delayed immune recovery
 - haploidentical:** most available; new conditioning makes safer/more common
- **Engraftment:** absolute neutrophil count (ANC) recovers to 500/µL w/in ~2 wk w/ PBSC, ~2.5 wk w/ BM, ~4 wk w/ UCB. G-CSF accelerates recovery by 3–5 d in all scenarios. **Engraftment syndrome:** fever, rash, noncardiogenic pulm edema, abnl LFTs, AKI, wt gain. Dx of exclusion: r/o infection, GVHD; Rx w/ 1 mg/kg steroids, rapid taper over 3–4 d.

Complications

- Either **direct chemoradiotoxicities** associated with preparative regimen or consequences of interaction between donor and recipient immune systems
- **Sinusoidal obstruction syndrome (SOS):** incidence ~10%, mortality ~30%. Previously known as **veno-occlusive disease (VOD)** (BBMT 2016;22:400). Mechanism: direct cytotoxic injury to hepatic venules → *in situ* thrombosis. Symptoms: tender hepatomegaly, ascites, jaundice, fluid retention with severe disease → liver failure, encephalopathy, hepatorenal syndrome. Diagnosis: ↑ ALT/AST, ↑ bilirubin; ↑ PT with severe disease; Doppler U/S may show reversal of portal vein flow; ↑ hepatic wedge pressure; abnl liver bx. Treatment: supportive; prophylaxis with **ursodiol**; treat w/ defibrotide (Blood 2016;127:1656).

- Idiopathic pneumonia syndrome (IPS):** 5–25% of Pts, >50% mortality (*Blood* 2003;102:2777)
Alveolar injury 2/2 direct toxicity → fever, hypoxia, diffuse infiltrates; occult infxn frequent
- Diffuse alveolar hemorrhage (DAH):** Diagnosis: bronchoscopy to exclude infection;
↑ bloody lavage fluid seen with DAH. Treatment: pulse 500–1000 mg Solu-Medrol × 3 d ± etanercept (*BBMT* 2015;1:67).
- Acute GVHD** (usually within 6 mo of transplant; *Lancet* 2009;373:1550)
 - Clinical grades I–IV based on scores for **skin** (severity of maculopapular rash), **liver** (bilirubin level) and **GI** (volume of diarrhea); bx supports diagnosis
 - Prevention: **immunosuppression** (MTX + CsA or tacrolimus) or T-cell depletion of graft
 - Treatment: grade I → topical Rx grades II–IV → associated with ↓ survival and ∴ treated with immunosuppressants (corticosteroids, CsA, tacrolimus, rapamycin, MMF)
- Chronic GVHD** (developing or persisting beyond 3 mo posttransplant; *BMT* 2009;43:149)
 - Clinical: malar rash, sicca syndrome, arthritis, obliterative bronchiolitis, bile duct degeneration, cholestasis and many others. More common w/ PBSC than BM.
 - Treatment: immunosuppression; rituximab; photopheresis
- Graft failure**
 - Primary = persistent neutropenia without evidence of engraftment
 - Secondary = delayed pancytopenia after initial engraftment; either immune mediated via immunocompetent host cells (**graft rejection**) or non-immune mediated (eg. CMV)
- Infectious complications**
 - due to regimen-induced pancytopenia and immunosuppression
 - auto HSCT recipients: no immunosuppression ∴ at ↑ risk only pre-/postengraftment both primary infections and reactivation events occur (eg. CMV, HSV, VZV)

Timing of Complications following Allogeneic HSCT

	Time after transplant and associated risk factors		
	Days 0–30	Days 30–90	>90 days
Viral infection	Mucositis Organ dysfunction Neutropenia	Acute GVHD ↓ cellular immunity	Chronic GVHD ↓ cellular & humoral immunity
	Respiratory and enteral viruses, BK virus HSV*	CMV*, HHV 6 & 7 EBV-related lymphoma	VZV*, JC
Bacterial infection	Gram + cocci (coagulase-negative Staph., <i>S. aureus</i> , <i>S. viridans</i>) GNRs (Enterobacteriaceae, <i>Pseudomonas</i> , <i>Legionella</i> , <i>S. maltophilia</i>)		Encapsulated bacteria
Fungal infection	<i>Candida</i> spp.	<i>Aspergillus</i> spp.	
Parasitic infection		<i>T. gondii</i> <i>P. carinii</i> <i>S. stercoralis</i>	<i>T. gondii</i> <i>P. carinii</i>
Regimen-related	Pancytopenia		Growth failure
	Mucositis, rash, alopecia		Hypogonadism/infertility
	Nausea, vomiting, diarrhea		Hypothyroidism
	Peripheral neuropathies		Cataracts
	Hemorrhagic cystitis		Avascular necrosis of bone
	Veno-occlusive disease		2 nd malignancy
Immune-mediated	IPS/Interstitial pneumonitis		
	Acute GVHD		Chronic GVHD
	Primary graft failure	Secondary graft failure	

*Primarily among persons who are seropositive before transplant.

Prophylaxis/Supportive Medications during HSCT

Medication	Prophylaxis against	Duration
Fluconazole or posaconazole	<i>Candida</i>	75 d
Acyclovir	HSV/VZV	365 d
Valganciclovir or ganciclovir if CMV +	CMV	100 d or when no longer immunosuppressed
Antibiotics (eg, fluoroquinolone)	Bacterial infxn	While neutropenic
TMP-SMX	PCP	365 d or when off immunosupp.
Allopurinol	Hyperuricemia	Until d –1
Ursodiol	SOS/VOD	60 d

LUNG CANCER

Pathology and Genetics

	Pathology	%	Type locat.	Genetic mutations in
Non-small cell	Adeno-carcinoma (incl. bronchioalveolar)	40	Peripheral	KRAS (20–30%), EGFR (15–20%, esp. ♀, Asian, never smokers), HER2 (6%) or rearrang. in ALK (~4%), ROS 1 (~2%) and RET (~1%)
	Squamous	20	Central	FGFR 1, SOX, PIK3CA, PTEN, TP53, SOX2, DDR2, BRAF
	Large cell	5	Peripheral	
	Other/not classifiable	20		
Small cell	15	Central		Complex; most have inactiv. of TP53 and RB 1

(NEJM 2008;359:1367; JCO 2012;30:863; J Thorac Oncol 2012;7:924; Nature 2011;489:519; Cell 2012;150:1107)

Epidemiology and risk factors

- Most common cause of cancer-related death for both men and women in the U.S.
- Cigarette smoking:** 85% of lung cancers occur in smokers; risk \propto total pack-yrs, \downarrow risk after quitting/reducing but not to baseline (Int J Cancer 2012;131:1210)
squamous & small cell almost exclusively in smokers
adenocarcinoma most common type in nonsmokers
bronchioalveolar carcinoma associated with women, nonsmokers, EGFR mutations
- Asbestos: when combined with smoking, synergistic \uparrow in risk of lung cancer
- Radon: risk to general population unclear

Clinical manifestations

- ~10% are asx at presentation and are detected incidentally by imaging
- Endobronchial growth** of 1° tumor: **cough, hemoptysis, dyspnea**, wheezing, post-obstructive pneumonia; more common with squamous or small cell (central location)
- Regional spread**
pleural effusion, pericardial effusion, hoarseness (recurrent laryngeal nerve palsy), dysphagia (esophageal compression), stridor (tracheal obstruction)
- Pancoast's syndrome:** apical tumor \rightarrow brachial plexus involvement (C8,T1,T2) \rightarrow Horner's syndrome, shoulder pain, rib destruction, atrophy of hand muscles
- SVC syndrome** (NEJM 2007;356:1862): central tumor \rightarrow SVC compression \rightarrow face or arm swelling (>80%), venous distention of neck & chest wall (~60%), dyspnea/cough (~50%), HA (~10%); Rx = steroids & diuretics, RT \pm chemo after tissue dx, SVC stent for severe sx, fibrinolytic + anticoag if thrombus
- Extrathoracic metastases:** brain, bone, liver, adrenal
- Paraneoplastic syndromes**
 - Endocrine:**
ACTH (SCLC) \rightarrow **Cushing's syndrome**; ADH (SCLC) \rightarrow **SIADH**
PTH-rP (squamous cell) \rightarrow **hypercalcemia**
 - Skeletal:** digital clubbing (non-small cell), **hypertrophic pulmonary osteoarthropathy** (adenocarcinoma) = symmetric polyarthritis and proliferative periostitis of long bones
 - Neurologic** (SCLC): **Eaton-Lambert**, peripheral neuropathy, cerebellar degeneration, limbic encephalitis
 - Cutaneous:** acanthosis nigricans, dermatomyositis
 - Hematologic:** hypercoagulable state (adenocarcinoma), DIC, marantic endocarditis

Screening (Lancet 2014;382:732)

- No benefit to CXR or sputum cytology, even in high-risk Pts
- Annual low-dose chest CT in ≥ 30 pack-y in current or former (quit w/in 15 y) smokers, age 55–74 y \rightarrow 20% \downarrow in lung cancer-related mortality (NEJM 2011;365:395 & USPSTF)
number needed to screen = 320; high false \oplus rate
consider risk scores to target screening (NEJM 2013;369:245 & 910; JAMA 2016;315:2300)

Diagnostic and staging evaluation (NCCN Guidelines v.2.2016)

- Initial imaging:** chest CT (include liver and adrenal glands) w/ contrast if possible
- Tissue:** **bronchoscopy** (central lesions) or **CT-guided needle bx** (peripheral lesions or accessible sites of suspected metastasis); mediastinoscopy (LN bx), VATS (eval. of pleura peripheral lesions), thoracentesis (cell block for cytology) or sputum cytology (central lesions)
- Staging**
 - Intrathoracic:** **mediastinoscopy** (\pm preceded by U/S-guided transesoph. or transbronch. needle aspiration; JAMA 2010;304:2245) or **VATS**; thoracentesis if pleural effusion

- Extrathoracic:** **PET-CT** more Se than CT alone for detecting mediastinal and distant mets as well as bone mets (NEJM 2009;361:32); **brain MRI** for all Pts (except IA)
- Genetics:** ✓ EGFR mut. & ALK, ROS1 or RET rearrang. for stage IV nonsquam NSCLC
 - PFTs w/ quantitative V/Q if planned treatment includes surgical resection; need to have 30% of normal, predicted lung fxn after resection

TNM Staging System for NSCLC (7th Edition)

T/M stage	N stage	N0	N1	N2	N3
	Definition	no + nodes	ipsilat. hilar	ipsilat. mediast.	contralat. or supraclav.
T1	T ≤ 2 cm (T1a) or T > 2–3 cm (T1b)	IA	IIA		
T2	T ≤ 5 cm (T2a) or T 5–7 cm (T2b)	IB/IIA	IIA/B		
T3	T > 7 cm or invasion of chest wall, diaph., mediast. pleura, pericard.	IIB	IIIA		
T4	Invasion of mediast., heart, great vessels, trachea, esoph, vertebrae; separate tumor nodule ipsilat. lobe				IIIB
M1a	Nodules contralat lobe; pleural nodules or malignant effusion			IV	
M1b	Distant metastasis				

NSCLC treatment (NCCN Guidelines v.2.2016)

- Stages I & II:** **surgical resection + adjuvant chemo** (surgery alone for stage IA) (NEJM 2004;350:351 & 2005;352:2589)
- Stage III:** **chemoradiation** is main treatment modality
IIIA viewed as potentially resectable (Lancet 2009;374:379) and IIIB as unresectable neoadjuvant chemoradiation may convert unresectable → resectable
- Stage IV:** **chemotherapy** ↑ survival; early palliative care also ↑ survival (NEJM 2010;363:733)
backbone of therapy is platinum-based doublet; cisplatin/pemetrexed better for adenocarcinoma; cisplatin/gemcitabine better for squamous (JCO 2008;26:3543)
PD-1 inhib (eg, nivolumab, pembrolizumab, atezolizumab) if progression on chemo (NEJM 2015;373:123; Lancet 2016;387:1540 & 1837); immune-related adverse events include pneumonitis, consider Rx w/ high-dose corticosteroids
bevacizumab (anti-VEGF mAb) + chemo ↑ survival by 2 mo; ↑ bleeding risk, ∴ avoid if untreated, brain mets (JCO 2009;27:5255), hemoptysis or squamous (NEJM 2006;355:2542)
if EGFR mut.: EGFR tyrosine kinase inhibitor (TKI, eg, erlotinib) 1st-line Rx; next-gen EGFR TKI for those who develop resistance mutations (NEJM 2015;372:1689 & 1700)
if ALK rearrang.: ALK TKI (crizotinib 1st-line Rx; NEJM 2014;371:2167); ceritinib 2nd-line TKI toxicities: rash & diarrhea (common); lung & liver injury (rare but potentially serious)
palliative radiation used to control local sx caused by tumor or metastasis
solitary brain metastasis: surgical resection + brain radiation may ↑ survival

NSCLC Simplified Staging Schema, Treatment and 5-y Survival

Stage	% at dx	Definition	Treatment	5-y (%)
I	10–20	Isolated lesion	Surgery + chemo	>60
II	10–20	Hilar node spread	Surgery ± radiation ± chemo	40–50
IIIA	15	Mediast. spread but resectable	Chemoradiation ± surgical resection	25–30
IIIB	15	Unresectable	Chemoradiation ± biologic ± surgery (selected cases)	10–20
IV	40	Metastatic	Chemo ± bevacizumab or tyrosine kinase inhibitor and/or supportive care	4

SCLC treatment (NCCN Guidelines v.1.2016)

- SCLC usually disseminated at presentation but can be very responsive to chemoradiation
- Chemotherapy** (platinum + etoposide) is primary treatment modality
- Thoracic radiation** added to chemotherapy improves survival in limited-stage disease
- Prophylactic cranial irradiation (PCI)** ↑ survival for limited disease in complete remission (NEJM 1999;341:476) & ↓ symptomatic brain mets in extensive disease (NEJM 2007;357:664)

SCLC Staging Schema and Treatment

Stage	% at dx	Definition	Treatment	Median survival
Limited	30–40	Confined to ipsilat. hemithorax w/in 1 radiation port	Radiation + chemotherapy ± PCI	1–2 y
Extensive	60–70	Beyond 1 radiation port	Chemotherapy ± PCI	~1 y

BREAST CANCER

Epidemiology and genetics (risk assessment tool: www.cancer.gov/bcrisktool/)

- In U.S., most common cancer in women; 2nd leading cause of cancer death in women
- Age: incidence rates ↑ with age, with possible ↓ in slope after menopause
- **Genetics** (*Nature* 2012;490:61): mutations in *TP53*, *PIK3CA*, and *GATA3*; *HER2* amplified. 15–20% have ⊕ FHx → 2x ↑ risk; ~45% of familial cases a/w known germline mutation
- **BRCA1/2:** 35–85% lifetime risk of breast cancer & ↑ risk of **ovarian cancer**; ? ↑ colon & prostate cancer; prog not worse than in noncarriers w/ breast cancer (*NEJM* 2007;357:115); *BRCA2*: a/w ↑ male breast cancer & pancreatic cancer. Germline loss-of-function mutations in *PALB2* a/w 35% ↑ risk of breast cancer by age 70 (*NEJM* 2014;371:497).
- **Estrogen:** ↑ risk with early menarche, late menopause, late parity or nulliparity (*NEJM* 2006;354:270); ↑ risk with prolonged HRT (RR = 1.24 after 5.6 y; *JAMA* 2003;289:3243); no ↑ risk shown with OCP use (*NEJM* 2002;346:2025)
- Benign breast conditions: ↑ risk w/ atypia (atypical ductal or lobular hyperplasia; *NEJM* 2015;372:78) & proliferative (ductal hyperplasia, papilloma, radial scar, or sclerosing adenosis) features; no ↑ risk w/ cysts, fibroadenoma, or columnar changes
- ↑ risk with h/o ionizing radiation to chest for treatment of Hodgkin lymphoma

Prevention (with selective estrogen receptor modulator or AI; *Annals* 2013;159:698)

- Tamoxifen: ↓ risk contralat. breast CA as adjuvant Rx. Approved for 1° prevent. if ↑ risk ↓ invasive breast cancer, but ↑ DVT & uterine CA; ? ↑ in mortality (*Lancet* 2002;360:817).
- Raloxifene: ↓ risk of invasive breast cancer & vertebral fx, ↑ risk of stroke & DVT/PE (*NEJM* 2006;355:125); ≈ tamoxifen in prevention of breast cancer w/ ↓ risk of DVT/PE & cataracts, trend toward ↓ uterine cancer (*JAMA* 2006;295:2727)
- AIs in high-risk postmeno ↓ breast cancer by >50% (*NEJM* 2011;364:2381; *Lancet* 2014;383:1041)
- **BRCA 1/2 ⊕:** intensified surveillance. Prophylactic bilat. mastectomy → ~90% ↓ risk; bilat. salpingo-oophorectomy ↓ risk of ovarian and breast cancer (*NEJM* 2016;374:454).

Clinical manifestations

- Breast mass (hard, irregular, fixed, nontender), nipple discharge (higher risk if unilateral, limited to 1 duct, bloody, associated with mass)
- Special types: **Paget's disease** → unilateral nipple eczema + nipple discharge; **inflammatory** breast cancer → skin erythema and edema (*peau d'orange*)
- Metastases: lymph nodes, bone, liver, lung, brain

Screening (*JAMA* 2015;314:1599; *Annals* 2016;164:279)

- **Mammography:** ~20–30% ↓ in breast cancer mortality (smaller abs. benefit in women <50 y) (*Lancet* 2006;368:2053; *Annals* 2009;151:727); 75% of all abnl findings benign; suspicious: clustered **microcalcifications**, **spiculated**, **enlarging**
- ACS recommends annual mammo beginning at age 45 (consider biennial after age 54)
- USPSTF recommends beginning at 50 and biennially (some may want to begin at age 40)
- ↑ risk: screen earlier w/ CBE and mammo (age 25 in *BRCA 1/2* carrier, 5–10 y before earliest FHx case, 8–10 y after thoracic RT, upon dx of ↑ risk benign disease)
- **MRI:** superior to mammo in high-risk Pts; consider annually if >20% lifetime risk (eg, ⊕⊕ FHx, *BRCA 1/2*, prior chest RT) (*Lancet* 2011;378:1804)
- **Genetic testing** should be considered in women with strong FHx

Diagnostic evaluation

- **Palpable breast mass:** age <30 y → observe for resolution over 1–2 menstrual cycles; age <30 y, unchanging mass → **U/S** → aspiration if mass not simple cyst; age >30 y or solid mass on U/S or bloody aspirate or recurrence after aspiration → **mammo** (detect other lesions) and either **fine-needle asp.** or **core-needle bx** clearly cancerous on exam or indeterminate read or atypia on bx → **excisional bx**
- **Suspicious mammogram** with normal exam: stereotactically guided bx
- **MRl:** detects contralateral cancer in 3% of Pts w/ recently dx breast cancer & ⊖ contralateral mammo (but PPV only 21%) (*NEJM* 2007;356:1295); utility remains unclear

Staging

- **Anatomic:** tumor size, chest wall invasion, axillary LN mets (strongest prognostic factor)
- **Histopathologic:** type (little prognostic relevance) & grade; lymphatic/vascular invasion

In situ carcinoma: no invasion of surrounding stroma

Ductal (DCIS): ↑ risk of invasive cancer in ipsilateral breast (~30%/10 y)

Lobular (LCIS): marker of ↑ risk of invasive cancer in either breast (~1%/y)

Invasive carcinoma: infiltrating ductal (70–80%); invasive lobular (5–10%); tubular, medullary and mucinous (10%, better prognosis); papillary (1–2%); other (1–2%)

Inflammatory breast cancer (see above): not a histologic type but a clinical reflection of tumor invasion of dermal lymphatics; very poor prognosis

Paget disease: ductal cancer invading nipple epidermis ± associated mass

- Biomarkers:** ✓ estrogen, progesterone receptor (ER/PR) and HER2/neu status
- Oncotype DX 21-gene risk recurrence score has predictive and prognostic value in ER \oplus , HER2 \ominus , and node \ominus Pts (NEJM 2015;373:2005)
- Circulating tumor DNA may serve as biomarker of met tumor burden (NEJM 2013;368:1199)

Simplified Staging System for Breast Cancer

Stage	Characteristics	Description	5-y surv.
I	Tumor ≤ 2 cm	Operable	90%
IIA	Tumor > 2 cm or mobile axillary nodes	locoregional	80%
IIB	Tumor > 5 cm		65%
IIIA	Internal mammary or fixed axillary nodes	Locally advanced	50%
IIIB	Direct extension to chest wall or skin	Inoperable	45%
IIIC	Infraclavicular or supraclavicular nodes	locoregional	40%
IV	Distant metastases	Metastatic	25%

Treatment

• Local control: surgery and radiation therapy (RT)

Breast-conserving usual approach w/ lumpectomy + breast RT + axillary node dissection (ALND), unless multicentric dis., diffuse microCa²⁺, BRCA1/2 \oplus , prior RT, pregnant, ? tumor > 5 cm; cavity shaving \downarrow risk of need for re-excision (NEJM 2015;373:503)

Sentinel lymph node dissection (SLND) prior to ALND preferred if w/o palp axillary LNs; T1-2 w/ \oplus SLND & Rx w/ lumpect./RT/chemo may not need ALND (JAMA 2011;305:569)

Radiation therapy (RT) after mastectomy for ≥ 4 \oplus LN, tumor > 5 cm, or \oplus surgical margins $\rightarrow \downarrow$ locoregional recurrence and \uparrow survival (Lancet 2011;378:1707); regional nodal RT \downarrow recurrence and breast cancer mortality (NEJM 2015;373:307 & 317)

• Systemic therapy: for stage I-III except tumors < 1 cm (complex risk assessment needed).

<http://www.adjuvantonline.com/index.jsp> can guide use of chemo and/or hormonal Rx.

Chemotherapy: neoadjuvant (to \uparrow breast conservation; path complete response a/w \uparrow disease-free survival; Lancet 2014;384:164) or adjuvant (anthracycline-based).

Addition of taxane (eg. paclitaxel) \rightarrow small \uparrow survival (NEJM 2010;362:2053 & 2010;363:2200). Consider platinum in triple \ominus cancers (JCO 2015;33:13).

Anti-HER2 therapy (growing list of agents) in HER2 \oplus tumors (NEJM 2012;366:176)

trastuzumab (anti-HER2 mAb) \uparrow survival (NEJM 2011;365:1273); 1 y = 2 yr (Lancet 2013;382:1021); after anthracycline or w/ taxane to \downarrow cardiotox (JCO 2002;20:1215)

lapatinib (tyrosine kinase inhib. of HER2 & EGFR) + trastuzumab \uparrow survival after failing trastuzumab (JCO 2012;30:2585); dual inhib. initial Rx \uparrow response (Lancet 2012;379:633)

pertuzumab (anti-HER2 mAb, prevents dimerization) \uparrow progression-free survival when added to trastuzumab as 1st-line Rx for metastatic dis. (NEJM 2015;372:724)

trastuzumab emtansine (T-DM1, HER2 mAb conjugated to microtubule inhibitor) \uparrow survival compared to 2nd-line lapatinib + capecitabine (NEJM 2012;367:1783)

Bevacizumab (anti-VEGF): ? in neoadjuvant Rx if HER2 \ominus (NEJM 2012;366:299 & 310)

Hormonal (in ER/PR \oplus or unknown status)

tamoxifen: 39% \downarrow recurrence and 30% \downarrow breast cancer mortality in pre- and postmenopausal patients; 10 y of Rx superior to 5 y (Lancet 2011; 378:771 & 2013;381:805)

aromatase inhibitors (AI) (anastrozole, letrozole, exemestane): ~18% \downarrow recurrence vs. tamoxifen in postmenopausal Pts (NEJM 2005;353:2747 & 2016;375:209)

2nd-line: ovarian ablation with LHRH agonists (goserelin) or oophorectomy if premenopausal; pure antiestrogens (fulvestrant) if postmenopausal

Cell proliferation inhibitors (if postmenopausal & failed hormonal Rx)

palbociclib (CDK 4/6 inhib): \uparrow progression-free survival (NEJM 2015;373:209)

everolimus (mTOR inhib): \uparrow progression-free survival (NEJM 2012;366:520)

Treatment of Carcinoma *in situ* and Invasive Carcinoma of the Breast

LCIS	Close surveillance \pm chemoprevention; ? prophylactic bilat. mastectomy
DCIS	Mastect. or lump. + RT; ALND not indic.; + chemoprev (Lancet 2016;387:849 & 866)
	Surgery + RT
I	+ Adjuvant chemo if \uparrow risk: tumor > 1 cm or \oplus LN or ER/PR \ominus (Lancet 1998;352:930)
II	+ Hormonal therapy if ER/PR \oplus (or unknown status) (Lancet 2009;374:2055) + anti-HER2 Rx if HER2 \oplus and tumor ≥ 1 cm or \oplus LN
	Neoadjuvant chemo \rightarrow surgery + RT \pm adjuvant chemotherapy
III	+ Hormonal therapy for ER/PR \oplus (or unknown status) tumors + anti-HER2 Rx if HER2 \oplus
	ER/PR \oplus : hormonal Rx (NEJM 2012;367:435) or chemo \pm everolimus/palbociclib
IV	ER/PR \ominus : HER2 \oplus \rightarrow chemo + anti-HER2 therapy; HER2 \ominus \rightarrow chemotherapy Bony mets: bisphosphonates & denosumab \downarrow fractures (Cochrane 2012;CD003474)

PROSTATE CANCER

Epidemiology and risk factors (NEJM 2003;349:366)

- Most common cancer in U.S. men; 2nd most common cause of cancer death in men
- Lifetime risk of prostate cancer dx ~16%; lifetime risk of dying of prostate cancer ~3%
- ↑ risk with ↑ age (rare if <45 y), in African Americans, + FHx, BRCA mutations

Clinical manifestations (usually asymptomatic at presentation)

- Obstructive sx** (more common with BPH): hesitancy, ↓ stream, retention, nocturia
- Irritative sx** (also seen with prostatitis): frequency, dysuria, urgency
- Periprostatic spread: hematuria, hematospermia, new-onset erectile dysfunction
- Metastatic disease: bone pain, spinal cord compression, cytopenias

Screening (NEJM 2012;367:e11; JAMA 2014;311:1143; Lancet 2014;384:2027)

- Digital rectal exam (DRE)**: size, consistency, lesions
- PSA**: 4 ng/mL cut point neither Se nor Sp; can ↑ with BPH, prostatitis, acute retention, after bx or TURP, and ejaculation (*no significant ↑ after DRE, cystoscopy*); 15% of men >62 y w/ PSA <4 & nl DRE have bx-proven T1 cancer (NEJM 2004;350:2239)
- ACS rec: ≥50 y (or ≥ 45 y if African-Am or + FHx) should discuss PSA screening w/ MD; USPSTF rec. against screening in asx males (no ↓ in prostate cancer-related mort.)

Diagnostic and staging evaluation

- Transrectal ultrasound (TRUS) guided biopsy**, with 6–12 core specimens
- Histology: Gleason grade** (2–10; low grade ≤6) = sum of the differentiation score (1 = best, 5 = worst) of the 2 most prevalent patterns in the bx; correlates with prognosis
- Imaging**: to evaluate extraprostatic spread
bone scan: for PSA >10 ng/mL, high Gleason grade or clinically advanced tumor
abdomen-pelvis CT: inaccurate for detecting extracapsular spread and lymph node mets
endorectal coil MRI: improves assessment of extracapsular spread

TNM Staging & Treatment of Prostate Cancer (Lancet 2015;387:70)

Stage	Tumor	Nodes, Mets	Treatment
I	T1a = non-palp., not visible on imaging	N0, M0, Gleason 2–4	Surveillance : consider if life expect. <10 y. Dutasteride ↓ risk of progression (Lancet 2012;379:1103).
II	T1/T2 = w/ in prostate	N0, M0	Radiation (external or brachy; NEJM 2006;355:1583). Short-term androgen deprivation ↓ mort. (NEJM 2011;365:107)
III	T3 = extends thru capsule	N0, M0	Radical prostatectomy (± RT and/or hormonal Rx if high-risk features): ↓ prostate cancer mortality, espec. if <65 y and not low risk (NEJM 2014;370:932)
	T4 = invades adjacent structures	N0, M0	Radiation + androgen deprivation (see below) (Lancet 2011;378:2104)
		N1, M0	Radiation (for M0 disease)
IV	Any T	Any N, M1	Androgen deprivation Rx (ADT) (NEJM 2009;360:2516) GnRH analogues (leuprolide, goserelin) antiandrogens (flutamide, bicalutamide) Docetaxel added to ADT improves overall survival in metastatic disease (NEJM 2015;373:737) If castrate resistant : chemo (eg, docetaxel); androgen synthesis inhib. (abiraterone; NEJM 2011;364:1995) or receptor signaling inhib. (enzalutamide; NEJM 2012;367:1187) ↓ mort.; immuno Rx (NEJM 2010;363:411); olaparib (PARP inhib) if BRCA + (NEJM 2015;373:1697) Bone mets: bisphosph or denosumab, latter ↓ bone mets & fx (NEJM 2009;361:745; Lancet 2011;377:813 & 2012;379:39); radium-223 ↓ mortality by 30% (NEJM 2013;369:213)

Prognosis

- PSA level, Gleason grade and age are predictors of metastatic disease
- In surgically treated Pts, 5-y relapse-free survival >90% if disease confined to organ, ~75% if extension through capsule, and ~40% if seminal vesicle invasion
- PSA doubling time, Gleason, & time to biochemical recurrence predict mortality following recurrence. For local recurrence following RP, salvage RT may be beneficial if low PSA.
- Metastatic disease: median survival ~44–57 mo (NEJM 2015;373:737); all become castrate resistant (in 15–20% discontinuation of antiandrogens results in paradoxical ↓ in PSA)

Prevention

- Finasteride and dutasteride ↓ prostate cancers detected by bx, but ↑ # of high Gleason grade tumors; no Δ in overall mortality (NEJM 2003;349:215; 2010;362:1192; 2013;369:603)

COLORECTAL CANCER (CRC)

Epidemiology and risk factors (*Lancet* 2010;375:1030; *CA Cancer J Clin* 2011;61:212)

- 4th most common cancer in U.S. men & women; 2nd leading cause of all cancer death
- Rare before age 40, w/ 90% of cases occurring after age 50. ~75% are sporadic.

- **Family history:** up to 25% of Pts have \oplus FHx. Risk depends on # of 1st-degree relatives (w/ CRC or polyp) and their age at dx; ~5% have an identifiable germline mutation

Familial adenomatous polyposis (FAP): mutation in APC gene \rightarrow 1000s of polyps at young age \rightarrow ~100% lifetime risk; \uparrow risk of thyroid, stomach, small bowel cancers

Hereditary nonpolyposis colorectal cancer (HNPCC): most common hereditary CRC (~3% of all CRC); mutations in DNA mismatch repair genes (eg, MSH2, MLH1) \rightarrow microsatellite instability (MSI) \rightarrow \uparrow tumor progression \rightarrow ~80% lifetime risk.

Predom. **right-sided** tumors; \uparrow risk of **endometrial**, ovarian, stomach, urothelial, small bowel and pancreatic cancers.

Amsterdam criteria: ≥ 3 family members w/ HNPCC-related cancer, one of which is dx before age 50, affecting 2 successive generations.

MAP (MYH-assoc polyposis): autosomal recessive; consider if mult. polyps but \ominus for FAP

- **Inflammatory bowel disease:** \uparrow risk with \uparrow extent and duration of disease
- **COX-2:** \downarrow risk of adenomas w/ ASA & NSAIDs. ASA a/w \downarrow CRC incidence, mets and mort (*Lancet* 2010;376:1741; 2012;379:1591 & 1602). ASA effect limited to PIK3CA-mut CRC (*NEJM* 2012;367:1596). ASA rec for 1^o prevention if age 50–59 (69?) y & $\geq 10\%$ 10-y risk of CRC.

Pathology and genetics (*NEJM* 2009;361:2449; *Nature* 2012;487:330)

- **Adenoma \rightarrow carcinoma sequence** reflects accumulation of multiple genetic mutations.
 - \uparrow risk of malig. w/ large (>2.5 cm), villous, sessile adenomatous polyps. Adenomas typically observed ~10 y prior to onset of cancer (both sporadic & familial).
- Genetic profile in sporadic CRC: APC (~80%), KRAS (~40%), TP53 (50–70%), DCC or SMAD4, or BRAF (~15%); chrom instability (majority) or mismatch repair defic (10–15%)
- Upfront genotyping may guide Rx; eg, benefit of anti-EGFR Ab cetuximab greater in KRAS wild-type than KRAS mutant (*NEJM* 2008;359:1757). BRAF mutation may guide clinical trials. Lack of CDX2 a/w \uparrow benefit from chemo (*NEJM* 2016;374:211).

Clinical manifestations

- Distal colon: Δ **bowel habits, obstruction**, colicky abdominal pain, **hematochezia**
- Proximal colon: **iron defic. anemia**, dull vague abd pain; obstruction atypical due to larger lumen, liquid stool and polypoid tumors (vs. annular distal tumors)
- Metastases: nodes, **liver**, lung, peritoneum \rightarrow RUQ tenderness, ascites, supraclavicular LN
- Associated with *Streptococcus bovis* bacteremia and *Clostridium septicum* sepsis

Screening (*JAMA* 2016;315:2564)

- **Average risk:** colonoscopy starting at age 50 & repeat q10y strongly preferred method
- \uparrow **risk:** earlier and/or more frequent screening. \oplus FHx: age 40 or 10 y before index dx, then q5y. IBD: 8–10 y after dx, then q1–2y. Known or suspected familial syndrome: genetic counseling & very early screening (eg, age 20–25 y), then q1–2y.

Imaging

Colonoscopy: test of choice as examines entire colon; 90% Se for lesions >1 cm. Flex sig less Se vs. colo and CTC (*Gut* 2009;58:241). If polyp found, re \checkmark in 3–5 y. Removal of adenomatous polyps associated with lower CRC mortality (*NEJM* 2012;366:687).

Sigmoidoscopy: 21% \downarrow incidence in CRC & 26% \downarrow mortality in distal CRC (*NEJM* 2012;366:2345). Benefit may also be seen w/ 1-time flex-sig (*Lancet* 2010;375:9726).

CT colonography (CTC): c/w colonoscopy, ~90% Se for lesions ≥ 1 cm but considerably less for smaller lesions (*NEJM* 2008;359:1207). In high-risk Pts, Se only 85% for advanced neoplasia ≥ 6 mm (*JAMA* 2009;301:2453). At population level, \uparrow participation w/ CTC, but \downarrow yield vs. colonoscopy; \therefore similar screening overall (*Lancet* 2012;13:55).

Biochemical fecal testing

Occult blood (FOBT): \downarrow mortality (*NEJM* 1993;328:1365 & 2000;343:1603); 3 card home testing more Se (24% vs. 5%) than DRE/FOBT (*Annals* 2005;142:81). Repeat q1y.

DNA: \uparrow Se, \approx Sp c/w FOBT but less Se than colonoscopy (*NEJM* 2004;351:2704). Combo DNA + Hb immunoassay w/ ~90% Se & Sp (*NEJM* 2014;370:1287).

Staging (AJCC Cancer Staging Manual, 7th ed, 2010)

- TNM staging: Size/depth of primary (T), locoregional nodes (N), distant metastases (M). Staging is complex and based on pathologic correlation with observed survival data.
- **Colonoscopy + biopsy/polypectomy + intraoperative and pathologic** staging essential for evaluating extracolonic spread
- CT scans of chest and abdomen/pelvis (inaccurate for depth of invasion & malignant LN)
- Baseline **CEA** in Pt with known CRC has prognostic significance and is useful to follow response to therapy and detect recurrence; not a screening tool

Treatment Based on TNM and Modified Dukes Staging of Colorectal Cancer				
TNM	Dukes	Path. criteria	5-y surv.	Treatment
I	A	Into submucosa or muscularis	94–97%	Surgery alone (resection and analysis of ≥12 LN)
IIA	B	Into serosa	83%	Surgery; no established role for adjuvant chemo for colon cancer ^a
IIB	B	Into peritoneum	74%	Preop RT or 5-FU/RT added for rectal cancer → postop chemo
IIC	B	Direct invasion	56%	
IIIA	C	≤6 + LNs	86%	Surgery + chemotherapy ^b
IIIB	C	Varying # + LNs & local invasion	51–77%	Preop RT or chemorad added for rectal cancer (NEJM 2006;355:1114)
IIIC	C		15–47%	
IV	D	Distant metastases	5%	Chemotherapy ± surgical resection for isolated mets (~30% 5-y surv) Consider resection of 1° tumor if perf, obstruction or bleeding

NCCN Clinical Practice Guidelines, www.nccn.org. 5-y survival data are approx. equivalent for colon and rectal cancers, shown as average, w/ ranges for TNM substaging, adapted from SEER data (JCO 2010;28:256 & 264).

^aConsider adjuvant chemo for high-risk stage II (obstruction, perf, adherence to adjacent structures, inadequate nodal sampling, lymphovasc invasion, poorly differentiated). MSI-high CRC benefit less from adjuvant chemo (NEJM 2003;349:247). ^bAdjuvant FOLFOX (see below) is standard of care chemo (NEJM 2004;350:2343).

- Chemotherapy (Lancet 2014;383:1490)

FOLFOX (5-FU + leucovorin + oxaliplatin), FOLFIRI or CapeOx (NEJM 2004;350:2343)
± Bevacizumab (anti-VEGF, NEJM 2004;350:2335) or cetuximab/panitumumab (anti-EGFR mAb, NEJM 2004;351:337; benefit limited to Pts w/o RAS mutations; NEJM 2013;369:1023)

Consider FOLFOXIRI-bevacizumab particularly if BRAF+ mutations or needing response for potentially curative resection (NEJM 2014;371:1609)

Regorafenib (multikinase inhib.) and TAS102 (trifluridine + tipiracil) ↑ survival in progressive metastatic CRC (Lancet 2013;381:303; NEJM 2015;372:1909)

CHEMOTHERAPY SIDE EFFECTS

Nausea & vomiting common (NEJM 2016;374:1356; 375:134 & 177)

Select Adverse Effects from Chemotherapy

Toxicity	Common Agents	Comments
Cardiotoxicity (JCO 2005;23:7685; NEJM 2013;368:1154) Stop agent if adverse event; ? role for ACEI in prevention (Circ 2006;114:2474).	Anthracyclines 5-FU Trastuz. & PD-1 inhib Tyrosine kinase inhib. (TKI) Cyclophosphamide Cisplatin Busulfan Bleomycin TKI (esp. dasatinib) Cyclophosphamide (<1%) Bevacizumab Anti-PD1 (eg, nivolumab) Anti-CTLA-4 (ipilimumab) Platinum Rx (cisplatin) Methotrexate Cyclophosphamide Platinum Rx (cisplatin) Cytarabine Methotrexate (esp. intrathecal) Ifosfamide	Dose-dependent CMP; ✓ EF pre-Rx; via topoisomerase IIb (Nat Med 2012;18:1639) Spasm → ischemia; CCB may prevent CMP, esp. w/ concom anthracycline QTc prolongation, CMP, angina Myopericarditis (esp. in BMT) HypoMg → arrhythmia, ischemia ~8% fibrosis or DAH; if severe → steroids ~10% IPF; d/c drug, Rx w/ steroids Pulmonary effusion Pneumonitis, progressive fibrosis; d/c drug Pulm hemorrhage (esp. NSCLC) Pneumonitis Organizing pneumonia, sarcoidosis Esp. proximal tubule; pretreat w/ IV saline Rx deposition; alkalinize urine, hydration Hemorrhagic cystitis; give Mesna “Stocking-glove;” vit. E Ppx (JCO 2003;21:927) Cerebellar toxicity (irreversible 5–10%) Late leukoenceph, meningitis; reverse w/ intrathecal glucarpidase, leucovorin Enceph (10–30%); ? Rx w/ methylene blue, thiamine, dexmedetomidine Sensorimotor long fiber neuropathy
Pulmonary (Sem Oncol 2006;33:98)		
Nephrotoxicity/urologic toxicity		
Neurotoxicity (Sem Oncol 2006;33:324)		
Hepatotoxicity (Sem Oncol 2006;33:50)		
Dermatologic	TKI (eg, imatinib)	Dermatitis, can be severe (eg, SJS)

PANCREATIC TUMORS

Pathology and genetics (Ann Rev Pathol 2008;3:157; Nature 2012;491:399)

- Histologic types: adenocarcinoma, acinar cell carcinoma, endocrine tumors, cystic neoplasms (eg, IPMN, see below); rarely, mets to pancreas (eg, lung, breast, renal cell)
- Pancreatic adenocarcinoma accounts for majority of pancreatic cancer (~85%)
- Location: ~60% in head, 15% in body, 5% in tail; in 20% diffuse infiltration of pancreas
- Mutations in adenoca.: KRAS (>90%), p16 (80–95%), p53 (50–75%), SMAD4 (~55%)

Epidemiology and risk factors (NEJM 2014;371:1039; Lancet 2016;388:73)

- Pancreatic adenocarcinoma 4th leading cause of cancer death in U.S. men and women
- 80% of pancreatic adenocarcinomas occur in Pts 60–80 y
- Acquired risk factors: **smoking** (RR ~1.5; 20% Pts), obesity, chronic pancreatitis, ? diabetes
- Hereditary risk factors: genetic susceptibility may play a role in 5–10% of cases
 - Hereditary chronic pancreatitis: mutation in cationic trypsinogen gene (PRSS 1), SPINK 1
 - Familial cancer syndromes and gene mutations with ↑ risk: familial atypical multiple mole melanoma (CDKN2A/p16), familial breast and ovarian cancer (BRCA2), Peutz-Jeghers (LKB 1), ataxia-telangiectasia (ATM), ? hereditary colorectal cancer (HNPCC and FAP)

Clinical manifestations

- Painless jaundice** (w/ pancreatic head mass), **pain** radiating to back, ↓ **appetite & wt**
- New-onset atypical diabetes mellitus (25%); unexplained malabsorption or pancreatitis
- Migratory thrombophlebitis (Trousseau's sign), not specific to panc cancer (JCO 1986;4:509)
- Exam: abd mass; nontender, palpable gallbladder (Courvoisier's sign, but more often seen w/ biliary tract cancers); hepatomegaly; ascites; left supraclavicular (Virchow's) node & palpable rectal shelf (both nonspecific signs of carcinomatosis)
- Laboratory tests may show ↑ bilirubin, ↑ alk phos, anemia

Diagnostic and staging evaluation (NCCN Guidelines v.2.2012)

- Pancreatic protocol CT scan** (I⁺ w/ arterial & venous phase imaging) **or MRI**
- If no lesion seen, → EUS, ERCP, MRI/MRCP may reveal mass or malignant ductal strictures
- Biopsy pancreatic lesion via EUS-guided FNA (preferred in potential surgical candidates) or CT-guided (potential risk of seeding) or biopsy of possible metastasis
- ↑ CA19-9 (nb, also ↑ in benign liver/biliary disease); may be useful to follow dis. postop

Clinical (Radiologic) Staging & Prognosis of Pancreatic Adenocarcinoma		
Stage (% at dx)	Criteria	Median Survival
Resectable , 15–20%	No extrapancreatic dis. or bulky LN Patent SMV & portal vein; celiac axis & SMA not involved	10–20 mo (favorable: tumor <3 cm, ⊖ marg., well-different.) 5-y ~30% node ⊖ vs. ~10% if +
Locally advanced (unresect.), 40%	Extensive PV/SMV, celiac axis or SMA involvement	8–12 mo
Metastatic , 40%	Usually liver & peritoneum; occ lung	Up to 11 mo w/ FOLFIRINOX

Treatment of pancreatic adenocarcinoma (NEJM 2014;371:1039; Lancet 2016;388:73)

- Resectable: surgery ± adjuvant (neoadjuvant or postoperative) therapy
 - pancreaticoduodenectomy = **Whipple procedure** = resection of pancreatic head, duodenum, CBD and gallbladder ± partial gastrectomy
 - adjuvant therapy: ↑ survival, but choice of regimen controversial (chemo vs. chemo/RT and gemcitabine vs. 5-FU (J Surg Oncol 2013;107:78; JAMA 2013;310:1473))
- Locally advanced: optimal strategy controversial. Gemcitabine alone vs. gemcitabine + RT (JCO 2008;26:214s; Ann Oncol 2008;19:1592; JCO 2011;29:4105).
- Metastatic: **FOLFIRINOX** (5-FU + leucovorin, irinotecan, oxaliplatin) if good perform. status (NEJM 2011;364:1817); **gemcitabine** + nab-paclitaxel (NEJM 2013;369:1691) or gemcitabine monotherapy if poor performance status (JCO 1997;15:2403). Offer clinical trials.
- Palliative and supportive care:
 - obstructive jaundice or gastric outlet obstruction: endoscopic stenting or surgical bypass
 - pain: opiates, celiac plexus neurolysis, radiation therapy
 - weight loss: pancreatic enzyme replacement, nutrition consult, end-of-life discussions

Cystic lesions of the pancreas (NEJM 2004;351:1218; Oncologist 2009;14:125)

- <10% of pancreatic neoplasms. Dx w/ CT, ERCP, MRCP, or EUS.
- Serous cystadenoma**: usually benign; central scar or honeycomb appearance on imaging
- Mucinous cystic neoplasm (MCN)**: predominantly young females; multiloculated tumors in body or tail w/ ovarian-type stroma and mucin-rich fluid w/ ↑ CEA levels; precancerous
- Intraductal papillary mucinous neoplasm (IPMN)**: neoplasm arising in main pancreatic duct or a branch; a/w ductal dilation w/ extrusion of mucinous material. Uncertain progression to cancer (? 5–20 y). Surgery based on age, size, location, & dysplasia.

FEVER AND NEUTROPENIA (FN)

Definition

- Fever: single oral temp $\geq 38.3^{\circ}\text{C}$ (101°F) or $\geq 38^{\circ}\text{C}$ (100.4°F) for ≥ 1 h
- Neutropenia:** ANC $< 500 \text{ cells}/\mu\text{L}$ or $< 1000 \text{ cells}/\mu\text{L}$ with predicted nadir $< 500 \text{ cells}/\mu\text{L}$

Pathophysiology and microbiology

- Predisposing factors: catheters, skin breakdown, GI mucositis, obstruction (lymphatics, biliary tract, GI, urinary tract), immune defect a/w malignancy
- Most episodes thought to result from seeding of bloodstream by GI flora
- Neutropenic enterocolitis (typhlitis): RLQ pain, watery/bloody diarrhea, cecal wall thickening
- GNRs (esp. *P. aeruginosa*) were historically most common
- Gram \oplus infections have recently become more common (60–70% of identified organisms)
- Fungal superinfection often results from prolonged neutropenia & antibiotic use
- Infection with atypical organisms and bacterial meningitis is rare

Prevention

- Levofloxacin (500 mg qd) \downarrow febrile episodes & bacterial infections in chemo-related high-risk neutropenic patients; no difference in mortality (NEJM 2005;353:977 & 988)

Diagnostic evaluation

- Exam: skin, oropharynx, lung, perirectal area, surgical & catheter sites; avoid DRE
- Labs: CBC with differential, electrolytes, BUN/Cr, LFTs, U/A
- Micro: blood (peripheral & through each indwelling catheter port), urine, & sputum cx; for localizing s/s $\rightarrow \checkmark$ stool (*C. difficile*, cx), peritoneal fluid, CSF (rare source)
- Imaging: CXR; for localizing s/s \rightarrow CNS, sinus, chest or abdomen/pelvis imaging
- Caveats: neutropenia \rightarrow impaired inflammatory response \rightarrow exam and radiographic findings may be subtle; absence of neutrophils by Gram stain does not r/o infection

Risk stratification (factors that predict lower risk)

- History: age < 60 y, no symptoms, no major comorbidities, cancer in remission, solid tumor, no h/o fungal infection or recent antifungal Rx
- Exam: temp $< 39^{\circ}\text{C}$, no tachypnea, no hypotension, no Δ MS, no dehydration
- Studies: ANC $> 100 \text{ cells}/\mu\text{L}$, anticipated duration of neutropenia < 10 d, normal CXR

Initial antibiotic therapy (Clin Infect Dis 2011;52:e56, NCCN Guidelines v.2.2015)

- Empiric regimens including drug w/ **antipseudomonal activity**; consider VRE coverage if colonized; OR 3.8 for VRE if VRE \oplus (BBMT 2010;16:1576)
- PO abx may be used in low-risk Pts (<10 d neutropenia, nl hep/renal fxn, no N/V/D, no active infxn, stable exam): cipro + amoxicillin-clavulanate (NEJM 1999;341:305)
- IV antibiotics: no clearly superior regimen; monotherapy or 2-drug regimens can be used
Monotherapy: ceftazidime, cefepime, imipenem, or meropenem
2-drug therapy: aminoglycoside + antipseudomonal β -lactam
PCN-allergic: levofloxacin + aztreonam or aminoglycoside
- Vancomycin** in select cases (HoTN, PNA, clinically apparent catheter-related or soft-tissue infxn, MRSA colonization, gram \oplus BCx, h/o quinolone ppx); d/c when cultures $\ominus \times 48$ h

Modification to initial antibiotic regimen

- Low-risk Pts who become afebrile w/in 3–5 d can be switched to PO antibiotics
- Empiric antibiotics changed for fever > 3 –5 d or progressive disease (eg, add vancomycin)
- Antifungal therapy is added for neutropenic fever > 5 d
liposomal amphotericin B, caspofungin, micafungin, anidulafungin, voriconazole, & posaconazole are all options (NEJM 2002;346:225; 2007;356:348)

Duration of therapy

- Known source: complete standard course (eg, 14 d for bacteremia)
- Unknown source: continue antibiotics until afebrile and ANC $> 500 \text{ cells}/\mu\text{L}$
- Less clear when to d/c abx when Pt is afebrile but prolonged neutropenia

Role of hematopoietic growth factors (NEJM 2013;368:1131)

- Granulocyte (G-CSF) and granulocyte-macrophage (GM-CSF) colony-stimulating factors can be used as 1 $^{\circ}$ prophylaxis when expected FN incidence $> 20\%$ or as 2 $^{\circ}$ prophylaxis after FN has occurred in a previous cycle (to maintain dose-intensity for curable tumors). CSFs \downarrow rate of FN but have not been shown to impact mortality.
- Colony-stimulating factors can be considered as adjuvant therapy in high-risk FN Pts

SPINAL CORD COMPRESSION

Clinical manifestations (Lancet Neuro 2008;7:459)

- Metastases located in vertebral body extend and cause epidural spinal cord compression

- **Prostate, breast and lung** cancers are the most common causes, followed by renal cell carcinoma, NHL and myeloma
- **Site of involvement: thoracic** (60%), lumbar (25%), cervical (15%)
- Signs and symptoms: **pain** (>95%, precedes neuro Δ s), **weakness, autonomic dysfunction** (urinary retention, ↓ anal sphincter tone), **sensory loss**

Diagnostic evaluation

- Always take back pain in Pts with solid tumors very seriously
- Do not wait for neurologic signs to develop before initiating evaluation b/c duration & severity of neurologic dysfunction before Rx are best predictors of neurologic outcome
- Urgent **whole-spine MRI** (Se 93%, Sp 97%); CT myelogram if unable to get MRI

Treatment

- **Dexamethasone** (10 mg IV \times 1 stat, then 4 mg IV or PO q6h) initiate immediately while awaiting imaging if back pain + neurologic deficits
- Emergent RT or surgical decompression if confirmed compression/neuro deficits
- Surgery + RT superior to RT alone for neuro recovery in solid tumors (*Lancet* 2005;366:643)
- If pathologic fracture causing compression → surgery; if not surgical candidate → RT

TUMOR LYSIS SYNDROME

Clinical manifestations (NEJM 2011;364:1844; BJH 2010;149:578)

- Large tumor burden or a rapidly proliferating tumor → spontaneous or chemotherapy-induced release of intracellular electrolytes and nucleic acids
- Most common w/ Rx of high-grade lymphomas (**Burkitt's**) and leukemias (**ALL, AML, CML in blast crisis**); rare with solid tumors; rarely due to spontaneous necrosis
- Electrolyte abnormalities: ↑ K, ↑ uric acid, ↑ PO₄ → ↓ Ca
- **Renal failure** (urate nephropathy)

Prophylaxis

- Allopurinol 300 mg qd to bid PO or 200–400 mg/m² IV (adjusted for renal fxn) & aggressive hydration prior to beginning chemotherapy or RT
- Rasburicase (recombinant urate oxidase) 0.15 mg/kg or 6-mg fixed dose (except in obese Pts) & aggressive hydration prior to beginning chemotherapy or RT (see below)

Treatment

- Avoid IV contrast and NSAIDs
- Allopurinol + aggressive IV hydration ± diuretics to ↑ UOP for goal 80–100 cc/h
- Consider alkalinization of urine w/ isotonic NaHCO₃ to ↑ UA solubility, ↓ urate nephropathy risk (controversial: avoid w/ rasburicase; may cause met. alkalosis or Ca₃(PO₄)₂ precip.)
- Rasburicase (0.1–0.2 mg/kg \times 1, repeat as indicated) for ↑↑ UA, esp. in aggressive malig; UA level must be drawn on ice to quench ex vivo enzyme activity (JCO 2003;21:4402; Acta Haematol 2006;115:35). Avoid in G6PD deficiency as results in hemolytic anemia.
- Treat hyperkalemia, hyperphosphatemia and symptomatic hypocalcemia
- Hemodialysis may be necessary; early renal consultation for Pts w/ renal insuffic. or ARF

CANCER OF UNKNOWN PRIMARY SITE

Evaluation of Cancer of Unknown Primary (Lancet 2012;379:1428)

Path	Possible sources	Markers	Imaging	Additional path
Adeno.	Colon, upper GI, panc. HCC Breast Ovarian, prostate Lung	CEA, CA19-9 AFP CA15-3 CA125, PSA	Endoscopy/EUS Abd/pelvic CT Mammography Pelvic U/S Chest CT	CDX1, CK7/20 ER/PR, GCDFP CA125, PSAP TTF1, CK7
Squam.	Lung Head & neck Esophageal Cervix, anus	None	Chest CT Laryngoscopy Endoscopy	TTF1, CK7
Poorly Differen.	Germ cell Lymphoma Thyroid GIST, sarcoma Neuroendocrine	hCG, AFP LDH Thyroglob.	Testicular U/S PET Thyroid U/S Abd/pelvic CT	PLAP, isochrom 12p LCA, flow, cytogenetics Thyroglobulin c-KIT, desmin, vimentin NSE, chromogranin Consider EM for all

Additional studies for each possible source listed in same row.

- Bony mets: common primary tumors include breast, lung, thyroid, kidney, prostate

PNEUMONIA

Microbiology of Pneumonia

Clinical setting	Etiologies
Community-acquired (CAP) (NEJM 2014;371:1619 & 373:415; Lancet 2015;386:1097)	No pathogen identified in 50–60%, virus alone in ~25%, bacteria alone in ~10%, virus-bacteria coinfection in <5% Viruses: influenza, RSV, hMPV, rhinovirus (unknown significance), parainfluenza virus, coronavirus <i>S. pneumoniae</i> (most common bacterial cause) <i>S. aureus</i> (esp. postinfluenza) <i>Mycoplasma, Chlamydia</i> (esp. in young & healthy) <i>H. influenzae, M. catarrhalis</i> (esp. in COPD) <i>Legionella</i> (esp. in elderly, smokers, ↓ immunity, TNF inhibitors) <i>Klebsiella</i> & other GNR (esp. in alcoholics & aspiration)
Hospital-acquired or health care-assoc (HAP/HCAP)	<i>S. aureus, Pseudo., Klebsiella, E. coli, Enterobacter, Acinetobacter</i> (HCAP risk factors: hosp or abx w/in 90 d, nursing home, home infusion Rx or dialysis w/in 30 d, home wound care, family member w/ MDR pathogen, immunosuppr)
Immunosuppressed	Above + PCP, fungi, <i>Nocardia</i> , non-TB mycobacteria (NTM), CMV
Aspiration (NEJM 2001;334:665; Curr Opin Pulm Med 2011;17:148)	Chemical pneumonitis due to aspiration of gastric contents Bacterial pneumonia ≥24–72 h after aspiration event outPt: oral flora (strep, <i>S. aureus</i> , anaerobes) inPt or chronically ill: GNR (<i>Pseudomonas</i>) and <i>S. aureus</i>

Clinical manifestations

- Presenting features are variable and depend upon several host factors (esp. age)
- Classically (eg, w/ *S. pneumo*): fever, cough w/ purulent sputum, consolidation on CXR
- Atypical pathogens (*Legionella, Mycoplasma, Chlamydia, virus*): historically classified as “atypical” b/c they failed to grow on routine cx. Presentation varies from insidious to acute; imaging features vary from interstitial infiltrates to tree-in-bud opacities, to dense consolid.
- Clinical and imaging features do NOT distinguish “typical” from “atypical”
- Aspiration pneumonitis/PNA: can be infectious or non-infectious; may p/w acute inflammatory syndrome (fever, ↑ WBC, etc.) or insidious course (typically w/ putrid breath)

Diagnostic studies

- Sputum Gram stain/Cx:** reliable if high quality (ie, sputum not spit; <10 squamous cells/lpf) & if PNA should be purulent (>25 PMNs/lpf). Yield ↓ >10 h after abx (CID 2014;58:1782).
- Blood cultures (before antibiotics!): + in ~10% of inPts, depending on pathogen
- CXR** (PA & lateral; see Radiology inserts) → tap effusions if >5 cm or severe PNA
- Other: S_aO_2 or P_aO_2 , arterial pH (if severe), CBC w/ diff, Chem-20; HIV test (if unknown)
- Other micro based on clinical suspicion (paired serologies available for most atypicals):
Mycoplasma: PCR of throat or sputum/BAL before first dose abx
Legionella urinary Ag (detects *L. pneumophila* L1 serotype, 60–70% of clinical disease)
S. pneumoniae urinary Ag (Se 70%, Sp >90%)
MTb: induced sputum for AFB stain and mycobacterial cx (*empiric respiratory isolation while pending*); avoid quinolones if suspect TB; request rapid DNA probe if stain +
Induced sputum for PCP if HIV + or known ↓ cell-mediated immunity
- Viral testing (DFA or PCR) on nasopharyngeal swab or sputum
- Bronchoscopy: consider if immunosupp., critically ill, failing to respond, or chronic pneumonia. Also if suspected TB or PCP, or inadequate or - sputum cx. Some pathogens need specific cx media (eg, *Legionella* on BCYE).
- Reasons for failure to improve on initial Rx:
Insufficient time: may take ≥72 h to see improvement (fever persists >4 d in ~20%)
Insufficient drug levels for lung penetration (eg, vanco trough <15–20 µg/mL)
Resistant organisms (or superinfxn): eg, MRSA, Pseudo.; consider **bronchoscopy**
Wrong dx: fungal/viral, chemical pneumonitis, PE, CHF, ARDS, DAH, ILD; **consider CT**
Parapneumonic effusion/empyema/abscess: if CXR -, **consider CT** (dx tap ± chest tube if effusion present, esp. if loculated)
Metastatic infection (eg, endocarditis, meningitis, septic arthritis)

Prevention

- Pneumococcal vaccine (PPSV23): all persons >65 y of age. If high-risk comorbidity, give at younger age and consider additional vaccination with PCV13.
- VAP precautions: HOB >30°, chlorhexidine rinse; aspiration precautions in high-risk Pts
- Tdap booster: 1-time dose in adults with uncertain vaccination history (MMWR 2012; 61:468)

Prognosis

- For low-risk Pts, can discharge immediately after switching to PO abx (CID 2007;44:S27)

CXR resolves in most by 6 wk; consider f/u to r/o underlying malig (esp. if >50 y or smoker)

Class	Score	Mortality	Suggested Triage
I & II	≤70	<1%	Outpatient
III	71–90	3%	? Brief inpatient
IV	91–130	8%	Inpatient
V	>130	29%	ICU

Variables	Points
Demograph.	Men (age in y), women (age – 10), nursing home resident (+10)
Coexist. probs	Neoplasm (+30), liver dis. (+20), CHF (+10), CVA (+10), renal dis. (+10)
Exam	Δ MS (+20), RR >30 (+20), SBP <90 (+20), T <35°/≥40° (+15), HR >125 (+10)
Laboratory	pH <7.35 (+30), BUN >30 (+20), Na <130 (+20), glc >250 (+10), Hct <30 (+10), PaO ₂ <60 or SaO ₂ <90 (+10), pleural effusion (+10)

Treatment (CID 2007;44 Suppl:S27;JAMA 2016;315:593)

Scenario	Regimen	Special considerations
CAP (outPt)	Azithro or doxy	Recent abx or multiple comorbidities: respiratory FQ or [azithro + amox/clav]
CAP (ward)	Resp FQ or [3 rd -gen ceph + azithro]	Doxy can replace azithro
CAP (ICU)	Resp FQ + [3 rd -gen ceph or amp-sulbactam]	Only cover MRSA or Pseudomonas if risk factors. If resp FQ contraindic., use azithro
HCAP (incl. VAP)	[Pip-tazo or ceftazidime or carbapen.] + [vanco or linezolid]	May add resp FQ (or azithro) when concerned re: atypicals
Aspiration	Clindamycin, amox-clav, or β-lactam + metronidazole	

- Consider TMP-SMX if PCP suspected in immunosupp. host. Consider oseltamivir for flu.
- Steroids (pred 50 mg × 7 d or methylpred 0.5 mg/kg q12h × 5 d) may speed clinical stabilization and ↓ late resp failure (*Lancet* 2015;385:1511; *JAMA* 2015;313:677; *Annals* 2015;163:519), but not well studied in flu and not widely embraced yet
- Duration: CAP: 5–7 d if stable & afebrile for 48–72 h
HCAP: 8 d (exception: 15 d for *Pseudomonas* or other nonfermenting GNR)
- When possible, de-escalate abx based on sensitivities

VIRAL RESPIRATORY INFECTIONS

URI, bronchitis, bronchiolitis, pneumonia (*Lancet* 2011;377:1264)Microbiology & epidemiology (<http://www.cdc.gov/flu/weekly>)

- Typical pathogens: short, mild = rhinovirus, coronavirus; longer, more severe or complicated = influenza, parainfluenza, respiratory syncytial virus (RSV), adenovirus, metapneumovirus. Can be esp. severe in immunosupp.
- Seasonal flu: 365,000 hosp, 51,000 deaths per y in U.S.; most >65 y (NEJM 2008;359:2579)
- Pandemic 2009 H1N1 (swine): more severe in younger and obese Pts (JAMA 2009;302:1896)
- Sporadic 2011 H3N2: adults exposed to swine (also human-to-human) (MMWR 2011;60:1615)
- H5N1 influenza (avian): ongoing small outbreaks globally

Diagnosis

- Primarily clinical: **cough, fever, myalgias**, arthralgias, rhinorrhea, pharyngitis (in contrast, viral bronchitis p/w cough ± low-grade temp; usually benign & self-limited)
- Respiratory viral panel on nasal washing or sputum/BAL
- Rapid influenza test on nasal swab: Se ~50–70% (? lower for pandemic flu), Sp >95%
- DFA (Se ~85%), RT-PCR (gold standard) avail. for influenza (PCR distinguishes type)

Treatment (NEJM 2008;359:2579; Lancet 2015;385:1729)

- Seasonal influenza: treat with neuraminidase inhib. (oseltamivir, zanamivir), which are effective vs. A & B (shortens sx by ~1 d), but resistance emerging. M2 inhib. (amantadine, rimantadine) not recommended due to widespread resistance (MMWR 2011;60:1).
- Pandemic H1N1: nearly 100% sens. to **oseltamivir**. H5N1: Uncertain resistance pattern. H7N9: newly emerging in Asia (NEJM 2013;368:1888)
- Oseltamivir dosed 75 mg PO bid × 5 d. Must start w/in 48 h of sx for low-risk; for critically ill or immunosupp., start ASAP even if >48 h.
- Consider inhaled ribavirin for RSV in immunosupp. (eg, BMT, lung tx); limited adult data

Prevention

- Inactivated **influenza vaccine**: incl. H1N1. Rec for all >6 mo of age and esp. if pregnant, >50 y, immunosupp., or HCW (MMWR 2012;61:613)
- Isolation, droplet precautions for inPts strongly recommended
- Prophylaxis for high-risk contacts of confirmed influenza: oseltamivir 75 mg PO daily × 10 d

FUNGAL INFECTIONS

Candida species

- Microbiology:** normal GI flora; *C. albicans* & nonalbicans spp. (consider azole resistance if h/o Rx or nonalbicans; *C. parapsilosis* ↑ echinocandin resistant). Sensi testing available.
- Risk factors:** neutropenia, immunosupp., broad-spectrum abx, intravascular catheters (esp. if TPN), IVDU, abd surgery, DM, renal failure, age >65
- Clinical manifestations**
 - Mucocutaneous: cutaneous (eg, red, macerated lesions in intertriginous zones); oral thrush (exudative, erythematous or atrophic; if unexplained, r/o HIV); esophageal (odynophagia; ± oral thrush); vulvovaginal, balanitis
 - Candiduria: typically colonization due to broad-spectrum abx and/or indwelling catheter
 - Candidemia: r/o retinal involvement (ophtho consult in all cases, req ↑ Rx duration); endocarditis rare but serious (esp. w/ nonalbicans & prosthetic valve). May present with erythematous papules or pustules in immunocompromised.
 - Hepatosplenic: occurs w/ neutrophil recovery

Treatment (CID 2016;62:409)

Mucocutaneous	Clotrimazole, nystatin, fluconazole, itraconazole
Candiduria (must determine colonization vs. infection)	Fluconazole or intravesical ampho* if sx, severely immunosupp. or will undergo GU procedure
Candidemia w/o neutropenia	Echinocandin or fluconazole or ampho, remove any intravascular catheters if possible
Febrile neutropenia	Echinocandin or ampho

*See IDSA guidelines for ampho dosing. Liposomal preparation preferred, if available.

Cryptococcus (CID 2010;50:291)

- Epidemiology:** immunosupp. (esp. AIDS) most susceptible; can occur in healthy host, esp. elderly, EtOH, DM. Consider *C. gattii* (typically in healthy host).
- Clinical manifestations**
 - CNS** (meningitis): HA, fever, meningismus, ↑ ICP, CN abnl, ± stupor, often subacute. Dx: CSF CrAg, India ink stain, fungal cx. Cell counts vary; serum CrAg >1:8 Se/Sp in AIDS. Other sites: pulm, GU, cutaneous, CNS cryptococcoma. With any crypto dx, LP all Pts.
- Treatment**
 - CNS: If ↑ ICP, repeat large-volume LPs or temp. lumbar drain; few require VP shunt. In HIV + or immunosupp. Pts, CNS Rx has induction (ampho ± flucytosine), consolidation and maintenance (fluconazole) phases (NEJM 2013;368:1291). If r/o CNS disease, then fluconazole. Dosing and duration vary by host.
 - Non-CNS disease in healthy Pts: fluconazole vs. observation, based on clinical setting

Histoplasmosis (CID 2007;45:807)

- Hyperendemic to central & SE US, but sporadic cases throughout U.S.
- Clinical manifestations**
 - Acute: often subclinical, but may see mild to severe PNA ± cavitary & hilar LAN
 - Chronic pulm: ↑ productive cough, wt loss, night sweats, apical infiltrates, cavitation
 - Disseminated (typically in immunosupp.): fever, wt loss, HSM, LAN, oral ulcers, skin lesion, fibrosing mediastinitis, reactive arthritis, pericarditis
- Treatment:** itraconazole (monitor levels); ampho ± steroids if severe or immunosupp.

Coccidioidomycosis (CID 2005;41:1217)

- Endemic:** SW U.S. (San Joaquin or "Valley" fever)
- Clinical manifestations**
 - Acute: 50–67% subclinical; PNA w/ cough, chest pain, fever, arthralgias, fatigue
 - Chronic pulm: nodule(s), cavity or progressive fibrocavitary PNA (can be asx or sx)
 - Disseminated (typically in immunosupp.): fever, malaise, diffuse pulmonary process, bone, skin, & meningeal involvement
- Treatment:** monitor mild disease closely q3–6mo; for severe disease: fluconazole, itraconazole or amphotericin

Blastomycosis (CID 2008;46:1801)

- Endemic:** south central, SE and Midwest U.S.
- Clinical manifestations**
 - Acute: 50% subclinical; cough, multilobar PNA; can progress to ARDS
 - Chronic pulm: cough, wt loss, malaise, CT w/ masses & fibronodular infiltrates
 - Disseminated: (25–40% of all but ↑ in immunosupp.): verrucous & ulcerated skin lesions, bone, & GU involvement; CNS rare unless immunosupp.
- Treatment:** itraconazole (monitor levels); ampho B if severe, disseminated or immunosupp.

Aspergillosis (CID 2008;46:327; NEJM 2009;360:1870)

- ABPA; hypersensitivity pneumonitis:** see "Interstitial Lung Disease"
- Aspergilloma:** usually in pre-existing cavity (from TB, etc.); most asx, but can lead to hemoptysis; sputum cx \oplus in <50%; CT \rightarrow mobile intracavitary mass with air crescent Rx: antifungals w/o benefit; embolization or surgery for persistent hemoptysis
- Necrotizing tracheitis:** white necrotic pseudomembranes in Pts w/ AIDS or lung Tx
- Chronic necrotizing:** mild immunosupp.; sputum production, fever, wt loss; CT: infiltrate \pm nodule \pm thick pleura; lung bx \rightarrow invasion
- Invasive:** seen if immunosupp. (neutropenia for >10 d, transplant, high-dose corticosteroids, AIDS); s/s PNA w/ chest pain & hemoptysis; CT: nodules, halo sign (cavities w/ Rx \rightarrow air crescent sign); dx w/ galactomannan >0.5 (serum or BAL)
- Rx (necrotizing/invasive): voriconazole (or isavuconazole) superior to amphi; ✓ drug levels

Zygomycetes (eg, *Mucor*, *Rhizopus*)

- Epidemiology: diabetes** (70%, esp. DKA), heme malignancy, s/p transplant, chronic steroids, deferoxamine or iron overload, trauma, h/o voriconazole Rx or Ppx
- Clinical manifestations: rhinocerebral** = periorbital/forehead pain (more extensive than orbital cellulitis), \pm fever (may appear nontoxic at first), exophthalmos, \downarrow EOM, CNs (V > VII); nasal turbinates \pm black eschar but exam can be quite nl. Also, **pulmonary** (PNA w/ infarct & necrosis); **cutaneous** (indurated painful cellulitis \pm eschar); **GI** (necrotic ulcers).
- Treatment:** debridement + Rx (amphi, posaconazole, or isavuconazole); high mortality

Fungal diagnostics

- Culture:** *Candida* grows in blood/urine Cx, but \downarrow Se of BCx in deep tissue infection; others (eg, *Crypto*, *Histo*) $\downarrow\downarrow$ Se of BCx; if suspect *Coccidio* alert lab (biohazard)
- Antibody detection:** only clinically useful for *Coccidio*
- Antigen detection**
 - Histo urine/serum Ag:** Se of urine Ag 90% (serum 80%) if disseminated; Sp limited by X-react
 - Crypto Ag** (serum, CSF): serum Ag >90% Se & Sp in invasive infxn, less for pulm only
 - 1,3-β-D-glucan:** Se for many fungal infxns (*Candida*, *Aspergillus*, *Histo*, *Coccidio*, *Fusarium*, *Pneumocystis*, *Sporothrix*), but not *Crypto*, *Blasto*, *Mucor*, *Rhizopus*; not Sp
 - Galactomannan:** serum levels Se ~65%, Sp ~90% for invasive aspergillosis. BAL levels in Pts w/ hematologic malignancy \uparrow Se, but \downarrow Sp (false \oplus seen w/ colonization)
 - Blastomyces:** urine > serum Ag, high Se but modest Sp given X-react w/other fungi
- Biopsy** (ie, histopathology): nb, no grinding of tissue if Zygomycetes suspected

INFXNS IN IMMUNOSUPPRESSED HOSTS**Overview**

- Many Pts have ≥ 1 risk (eg, DM, ESRD, transplant, extremes of age)
- The following is not an exhaustive list, but a delineation of common or classic etiologies

Predisposition	Classic Infectious Etiologies
Humoral immune dysfunction (eg, CVID, myeloma) and asplenia	Encapsulated bacteria: <i>S. pneumo</i> , <i>H. flu</i> , <i>N. meningitidis</i> (vaccinate against these 3, ideally prior to splenectomy) Other bacteria: <i>E. coli</i> and other GNRs, <i>Capnocytophaga</i> Parasites: <i>Babesia</i> , <i>Giardia</i> ; Viruses: VZV, echovirus, enterovirus
Granulocytopenia or neutropenia (includes DM, ESRD → functional impairment)	Bacteria: Gram positive: coag \ominus staph, <i>S. aureus</i> , viridans strep, <i>S. pneumo</i> , other strep; <i>Corynebacterium</i> spp., <i>Bacillus</i> spp. Gram negative: <i>E. coli</i> , <i>Klebsiella</i> , <i>Pseudomonas</i> Fungi: Yeast: <i>Candida albicans</i> and other <i>Candida</i> spp. Molds: <i>Aspergillus</i> , <i>Mucor</i> spp., endemic fungi and others Viruses: VZV, HSV1 and 2, CMV
Impaired cell-mediated immunity (CMI) (eg, HIV, chronic steroids, posttransplant, DM, ESRD)	Bacteria: <i>Salmonella</i> spp., <i>Campylobacter</i> , <i>Listeria</i> , <i>Yersinia</i> , <i>Legionella</i> (Lancet 2016;387:376), <i>Rhodococcus</i> , <i>Nocardia</i> , TB, non-TB mycobacteria Fungi: <i>Candida</i> , <i>Crypto</i> , <i>Histo</i> , <i>Coccidio</i> , <i>Aspergillus</i> , <i>Pneumocystis</i> , Zygomycetes spp. and other molds Viruses: HSV, VZV, CMV, EBV, JC virus, BK virus Parasites: <i>Toxoplasma</i> , <i>Cryptosporidium</i> , <i>Isospora</i> , <i>Microsporidia</i> , <i>Babesia</i> ; <i>Strongyloides</i>
Organ dysfunction	Liver (esp. cirrhosis): <i>Vibrio</i> spp., encapsulated bacteria ESRD: impaired granulocyte fxn and CMI as above Iron overload (or deferoxamine Rx): <i>Yersinia</i> , Zygomycetes
Biologics (eg, TNF inhibitors, anti-B-cell Rx; ✓ for TB before starting)	Bacteria: sepsis, septic arthritis, TB, NTM, <i>Listeria</i> , <i>Legionella</i> Fungi: <i>Pneumocystis</i> , <i>Histo</i> , <i>Coccidio</i> , <i>Aspergillus</i> , endemic fungi Viruses: JC virus (PML), EBV, HSV, VZV, HBV Parasites: <i>Strongyloides</i> reactivation

URINARY TRACT INFECTIONS

UTI
6-5

Definitions

- Anatomic
 - lower:** urethritis, cystitis (superficial infection of bladder)
 - upper:** pyelonephritis (inflam of renal parenchyma), renal/perinephric abscess, prostatitis
- Clinical
 - uncomplicated:** cystitis in immunocompetent ♀ w/o underlying structural/neuro disease
 - complicated:** upper tract infection in women or any UTI in men or pregnant women or UTI with underlying structural/neuro disease, bladder dysfxn or immunosuppression

Microbiology

- Uncomplicated UTI: **E. coli** (80%), *Proteus*, *Klebsiella*, *S. saprophyticus* (CID 2004;39:75). In healthy, nonpregnant women, lactobacilli, enterococci, Group B strep and coag-neg staph (except *S. saprophyticus*) usually contaminants (Annals 2012;156:ITC3).
- Complicated UTI: *E. coli* (30%), enterococci (20%), *PsA* (20%), *S. epi* (15%), other GNR
- Catheter-associated UTI: **yeast** (30%), *E. coli* (25%), other GNR, enterococci, *S. epi*
- Urethritis: *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Ureaplasma urealyticum*, *Trichomonas vaginalis*, *Mycoplasma genitalium*, HSV
- S. aureus*: uncommon primary urinary pathogen in absence of catheter or recent instrumentation; ∴ consider bacteremia w/ hematogenous seeding

Clinical manifestations

- Cystitis:** **dysuria**, **urgency**, **frequency**, hematuria, suprapubic pain; fever usually absent. R/o vaginitis if symptoms of cystitis and urethritis.
- Urethritis:** similar to cystitis except *urethral discharge* can be present
- Prostatitis**
 - chronic:** similar to cystitis except *symptoms of obstruction* (hesitancy, weak stream)
 - acute:** perineal pain, fever, tenderness on prostate exam
- Pyelonephritis:** fever, chills, flank or back pain, nausea, vomiting, diarrhea
- Renal abscess** (intrarenal, perinephric): identical to pyelonephritis w/ persistent fever despite appropriate antibiotics

Diagnostic studies (NEJM 2016;374:562)

- Urinalysis:** **pyuria** + **bacteriuria** ± hematuria ± nitrites
- Urine Cx** (clean-catch midstream or straight-cath): obtain cx only if sx
 - Significant bacterial counts: typically $\geq 10^5$ CFU/mL in women, $\geq 10^3$ CFU/mL in men or catheterized Pts. Counts may vary depending on dilution & stage of infxn; interpret in context of sx and host.
 - Pyuria & \ominus UCx = sterile pyuria → urethritis, nephritis, renal tuberculosis, foreign body
- Blood cultures: obtain in febrile Pts; consider in complicated UTIs
- DNA detection/cx for *C. trachomatis*/*N. gonorrhoeae* in high-risk Pts or sterile pyuria
- If ? prostatitis: 1st void, midstream, prostatic expressage & postprostatic massage UCx
- Abdominal CT: r/o abscess in Pts with pyelo who fail to defervesce after 72 h
- Urologic w/u (renal U/S w/ PVR, abd CT, voiding cystography) if recurrent UTIs in men

Treatment of UTIs

Scenario	Empiric treatment guidelines ^a
Cystitis (JAMA 2014;16:1677)	Uncomp: nitrofurantoin ^b 100 mg × 5 d or TMP-SMX DS PO × 3 d or fosfomycin (3 g × 1). Refer to dosing guidelines for ↑ Cr. Complicated: FQ or TMP-SMX PO × 7–14 d Asx bacteriuria in pregnancy or prior to urologic surgery → abx × 3 d
Catheterized	Abx as above & remove catheter . Exchange if removal impossible.
Urethritis	Treat for both <i>Neisseria</i> and <i>Chlamydia</i> <i>Neisseria</i> : CTX 250 mg IM × 1 and 1 g azithro PO × 1 <i>Chlamydia</i> : doxy 100 mg PO bid × 7 d or azithro 1 g PO × 1 <i>M. genitalium</i> : 1 g azithro PO × 1
Prostatitis	FQ or TMP-SMX PO × 14–28 d (acute) or 6–12 wk (chronic)
Pyelonephritis	OutPt: FQ × 7 d or TMP-SMX PO × 14 d (Lancet 2012;380:452) InPt: CTX or amp/sulbactam or aminoglycoside × 14 d (Δ IV → PO when clinically improved & afebrile 24–48 h)
Renal abscess	Drainage + antibiotics as for pyelonephritis

^aChoice of agent individualized based on h/o allergies and adherence, local practice patterns, community prevalence and uropathogen resistance patterns, availability, cost, and Pt and provider threshold for failure. For empiric outPt Rx, community resistance to abx should be <20% for cystitis or <10% for pyelonephritis. Beta-lactams have less efficacy than other abx for UTI (CID 2011;52:e103; NEJM 2012;366:1028)

^bNote risk of pulmonary fibrosis with prolonged or recurrent use.

SOFT TISSUE AND BONE INFECTIONS

SKIN AND SOFT TISSUE INFECTIONS (SSTI; CID 2014;59:e10)

Clinical

- Cellulitis: infxn of dermis/sc fat, w/ erythema, edema, warmth, pain (rubor, tumor, calor, dolor)
- Erysipelas: infxn of upper dermis (more superficial than cellulitis), often caused by strep, w/ raised erythematous lesion w/ clear demarcation from normal skin
- Impetigo: infxn of superficial layers, often caused by staph, typically in children, w/ purulent lesions, often on face/extrem, ± bullae, ± gold crust
- Lymphangitis: proximal red streaking ± regional lymphadenopathy
- Toxic shock syndrome** can occur w/ staph or strep infxn. Fever, HA, N/V, diarrhea, myalgias, pharyngitis, diffuse rash w/ desquamation, HoTN, shock. BCx may be \ominus .

Microbiology (CID 2014;59:e10)

- Primarily strep and staph, including MRSA; may include GNRs in diabetics/immunosupp.
- MRSA** (NEJM 2005;352:1485 & 2006;355:666) causes up to 75% of purulent skin/soft tissue infxns, depending on local epi (rapidly increasing), often assoc. w/ purulent drainage or exudate. Often TMP-SMX sensitive; variably clindamycin sensitive (may falsely appear susceptible on lab testing, requires confirmation w/ D-test; NEJM 2007;357:380).
- Bites: skin and oral flora (incl anaerobes) + special exposures:

Feature	Microbiology	Clinical
Cat bite	<i>P. multocida</i>	Rapid onset
Dog bite	<i>P. multocida</i> <i>C. canimorsus</i>	Sepsis w/ symmetric, peripheral gangrene in asplenic/cirrhosis and other immunosupp.
Penetrating injury	<i>Pseudomonas</i>	Can be a/w deep tissue abscess
Gardening	<i>Sporothrix</i>	Ulcerating nodules, lymphatic spread
Salt H ₂ O or raw oysters/fish	<i>V. vulnificus</i>	Hemorrhagic bullae & sepsis (esp. in cirrhotics). If suspected, Rx w/ doxy + ceftaz.
	<i>Erysipelothrix</i>	Rapid onset, endocarditis can develop
Fresh H ₂ O	<i>Aeromonas</i>	Myonecrosis/rhabdo can occur. If suspected, Rx w/ doxy + cipro.

Diagnosis

- Largely clinical diagnosis; BCx low yield (~5–10%) but useful if \oplus
- Aspirate of bulla or pus from furuncle or pustule may provide microbiologic dx

Cellulitis Treatment (NEJM 2014;370:2238; CID 2014;59:e10; JAMA 2016;316:325)

Purulent	Micro	Severity	Treatment
No	β -hemolytic Strep > <i>S. aureus</i>	Mild	PCN, diclo, cephalosporin or clinda
		Mod	PCN, CTX, cefazolin or clinda
		Severe	Vanc + pip/tazo
Yes	<i>S. aureus</i> (incl. MRSA) >> β -hemolytic Strep.	Mild	I&D only
		Mod	TMP-SMX or doxy; some data for clinda (NEJM 2015;372:1093), but MRSA sensitivity variable
		Severe	Vanc, dapt, linezolid, ceftaroline, or telavancin

Mild: no systemic signs of infection; moderate: systemic signs; severe: SIRS or immunocompromised
Narrow abx per Cx data. Dalbavancin & oritavancin being studied (NEJM 2014;370:2169 & 2180).

- Limb elevation;** erythema may worsen after starting abx b/c bacterial killing \rightarrow inflam.
- In obese Pts, adequate drug dosing important to avoid treatment failure (J Infect 2012;2:128)

NECROTIZING FASCIITIS

Definition

- Infection and necrosis of superficial fascia, subcutaneous fat and deep fascia (necrosis of arteries and nerves in subcutaneous fat \rightarrow gangrene)
- Fournier's gangrene: necrotizing fasciitis of the male genitalia or female perineum

Epidemiology

- Affects healthy individuals but ↑ risk: DM, PVD, EtOH abuse, IVDU, immunosupp., cirrhosis

Microbiology

- Type I (after abd/perineal surgery or trauma; in DM, PVD): polymicrobial (w/ anaerobes)
- Type II (usually extremities): Strep pyogenes ± MRSA, often healthy w/o obvious portal of entry; up to $\frac{1}{2}$ have toxic shock syndrome (TSS)

Clinical manifestations

- Need high degree of clinical suspicion because of nonspecific physical exam
- Most common sites: extremities, abdominal wall, and perineum, but can occur anywhere
- **Cellulitic skin Δs** with poorly defined margins + **rapid spread + systemic toxicity**
- **Pain out of proportion** to apparent cellulitis; skin hyperesthetic and later anesthetic
- **Bullae, darkening of skin to bluish-gray ± crepitus** or radiographically visible gas

Diagnostic signs

- Clinical dx sufficient to initiate **urgent surgical exploration**
- Aspiration of necrotic center; BCx; Gram stain; ✓ CK for tissue necrosis
- Imaging: **noncontrast CT**, but do not delay therapy (*Arch Surg* 2010;145:452)
- Microbiologic dx from Gram stain and culture of surgical specimens

Treatment

- Definitive treatment is **surgical débridement** of necrotic tissue and fasciotomy
- Type I: empiric Tx w/vanc + pip-tazo
- Type II: PCN + clinda. If ↑ risk of CA-MRSA, + vanco. If concern for strep, IVIG.

Prognosis

- Generally fatal if untreated; reported mortality 20–50%

CLOSTRIDIAL MYONECROSIS (GAS GANGRENE)

Definition

- Life-threatening, fulminant clostridial infection of skeletal muscle
- **Wound contamination** w/ clostridial spores after **trauma** (penetrating or crush injury)
- Most commonly *C. perfringens*; *C. septicum* assoc w/ cancer (GI, heme), even w/o trauma

Clinical manifestations

- Incubation period 6 h to 2–3 d
- Sense of heaviness/pain, often at site of trauma; rapid worsening; marked systemic toxicity
- Bronze skin discoloration, tense bullae, serosanguineous or dark fluid and necrotic areas
- **Crepitus** present but not prominent (gas is in muscle), may be obscured by edema

Diagnostic studies

- Gram stain: **large, Gram ⊕ rod w/ blunt ends** (can be Gram-variable), few polys
- Bacteremia in ~15%
- Plain radiographs: gas dissecting into muscle

Treatment

- **Surgical exploration with débridement**, fasciotomies and amputation if necessary
- **Antibiotics**: high-dose **penicillin G** 24 MU IV divided q2–3h + **clinda** 900 mg IV q8h

NEUROPATHIC FOOT ULCER

Leading cause of DM-related hosp. days & nontrauma amputations

Microbiology

- **Mild** (superficial, no bone or joint involvement): usually *S. aureus* or aerobic streptococci
- **Limb- or life-threatening** = deep, bone/joint involvement, systemic tox., limb ischemia
- Mono- or polymicrobial with aerobes + anaerobes
 - aerobes = *S. aureus*, strep, enterococci and GNR (including *Pseudomonas*)
 - anaerobes = anaerobic streptococci, *Bacteroides*, *Clostridium* (rare)

Clinical manifestations

- Clinical dx: ≥2 classic s/s of inflammation (erythema, warmth, tenderness [may be absent in neuropathy], pain or induration) or purulent secretions ± crepitus (indicating gas and/or mixed infection w/ GNR & anaerobes or *Clostridium*)
- Complications: osteomyelitis, systemic toxicity (fever, chills, leukocytosis, hyperglycemia)

Diagnostic studies

- Avoid superficial swabs (only helpful if ⊕ for *S. aureus* and suspect infxn); **wound cx** (eg, deep tissue sample or curettage at ulcer base after débridement) has ↑ Se
- Blood cx should be obtained in all Pts, ⊕ in 10–15%
- **Osteomyelitis should always be ruled out**: probe to bone test for all open wounds in a diabetic foot (high Sp but low Se); imaging (see below); **bone biopsy** best

Treatment (CID 2012;54:e132)

Severity of Infxn	Empiric Antibiotics
Mild	PCNase-resistant PCN or 1 st -gen. ceph. (TMP-SMX if ? MRSA)
Chronic, previously treated or serious	(FQ or ceftriaxone + clinda) or amp-sulbactam or ticar-clav or ertapenem. If MRSA, add vanco or TMP-SMX or linezolid or telavancin or daptomycin or ceftazidime.
Limb or life-threatening	Vanco + anti- <i>Pseudomonal</i> agent: imipenem or pip-tazo or (aztreonam + metronidazole)

- Elevation, non-weight-bearing status, **wound care**, glycemic control
- Evaluation and treatment for venous insufficiency and arterial ischemia
- Many require surgery:** early, aggressive and repeated débridement; revascularization or amputation may be necessary
- Management by multidisciplinary team improves outcomes

OSTEOMYELITIS

Infection of bone due to hematogenous seeding or direct spread from contiguous focus

Microbiology (NEJM 1997;336:999; Lancet 2004;364:369)

- Hematogenous:** *S. aureus*; mycobacterial infection of vertebral body = Pott's disease
- Contiguous focus** (may be acute or chronic)
 - open fracture, orthopedic surgery, etc.: *S. aureus* and *S. epidermidis*
 - skin breakdown + vasc. insuffic. (eg, diabetic foot): **polymicrobial**
 - GU source (GNR, Enterococcus)

Clinical manifestations

- Surrounding soft tissue compromise ± fistula to superficial skin
- ± Fever, malaise and night sweats (more common in hematogenous than contiguous)
- Vertebral osteomyelitis (esp. IVDU): unremitting, focal back pain, usually febrile (NEJM 2010;362:1022)

Diagnostic studies (JAMA 2008;299:806)

- Identification of the causative organism is key
- Tissue cx** (aspiration bx Se 30–74%) unless ⊕ blood Cx. Do not rely on swabs of ulcers or fistulae drainage.
- High suspicion in diabetic foot (see above) if can probe ulcer to bone or ulcer >2 cm²
- Blood cultures** (more often ⊕ with acute hematogenous osteomyelitis)
- ESR >70** greatly increases likelihood of osteo (JAMA 2008;299:806)
- Imaging
 - Plain radiographs: normal early in disease; lytic lesions seen after 2–6 wk
 - MRI:** most sensitive imaging study (overall Se 90%, Sp 82%; Archives 2007;167:125)
 - CT: can demonstrate periosteal reaction and cortical and medullary destruction
 - CT & MRI very Se but ↓ Sp; false ⊕ if contig focus w/ periosteal reaction, Charcot Δs
 - Radionuclide imaging: very Se but non-Sp (false ⊕ if soft tissue inflammation)

Treatment

- Antibiotics:** based on cx data. Duration depends on Rx strategy/goals of Rx management (eg, 6 wks for vertebral osteo; Lancet 2015;385:875).
- Surgery** should be considered for any of the following: acute osteo that fails to respond to medical Rx, chronic osteo, complications of pyogenic vertebral osteo (eg, neurologic compromise, spinal instability, epidural abscess) or infected prosthesis

EPIDURAL ABSCESS

Etiology

- Hematogenous spread ($\frac{2}{3}$): skin infection, soft tissue (dental abscess) or endocarditis
- Direct extension ($\frac{1}{3}$): vertebral osteo, sacral ulcer, spinal anesthesia or surgery, LP
- Risk factors: diabetes, renal failure, alcoholism, IVDU, immunosupp.
- S. aureus* most common pathogen, increasing incidence of MRSA

Clinical manifestations

- Back pain** (unremitting including midline) + often **fever** ± nerve root or cord signs

Diagnostic studies

- MRI**
- Aspiration of abscess fluid for Gram stain & cx or operative Gram stain & cx
- Blood cx (frequently ⊖)

Treatment

- Antibiotics ± surgery** (decompressive laminectomy and débridement) for failure to improve on medical Rx. Emergent surgery for early s/s of cord compression (w/ vertebral osteo and epidural abscess, may see paraplegia 48–72 h after first signs)

INFECTIONS OF THE NERVOUS SYSTEM

ACUTE BACTERIAL MENINGITIS

Clinical manifestations (NEJM 2006;354:44; Lancet 2012;380:1684)

- Fever (77%), headache (87%), stiff neck (31%), photosensitivity, Δ MS (69%) (defined as GCS <14), seizures (5%); 2 of 4 (fever, HA, stiff neck, Δ MS) present in 95%
- Presentation may be atypical (eg, lethargy w/o fever) in elderly and immunosupp.

Physical exam

- **Nuchal rigidity** (Se 31%), **Kernig's sign** (Pt supine, hip flexed at 90°, knee flexed at 90°; \oplus if passive extension of knee \rightarrow resistance), **Brudzinski's sign** (Pt supine and limbs supine; \oplus if passive neck flexion \rightarrow involuntary hip and/or knee flexion)
nb, Kernig's or Brudzinski's signs \oplus in only ~10% of Pts (Lancet 2012;380:1684)
- \pm Focal neuro findings (~30%; hemiparesis, aphasia, visual field cuts, CN palsies)
- \pm Funduscopic findings: papilledema, absent venous pulsations
- \pm HEENT findings: sinus tenderness, clear rhinorrhea (CSF leak)
- \pm Skin findings: petechial rash (*N. meningitidis*), genital or oral ulcers (HSV)

Microbiology in Bacterial Meningitis (NEJM 2011;364:2016)

Etiology	Comments
<i>S. pneumoniae</i> (30–60%)	Assess for distant infxn (eg, Osler's triad = meningitis, PNA, IE) <i>Drug-resistant S. pneumoniae</i> : -40% PCN-resistant (even intermediate resistance problematic) -<10% 3 rd -gen. cephalosporin-resistant Vaccine may have reduced rate of invasive disease
<i>N. meningitidis</i> (10–35%)	Primarily in those <30 y; may be a/w petechiae or purpura. Deficiencies in terminal complement predispose to recurrent meningococcemia & rarely meningitis. Vaccine rec for all adolescents, college freshmen living in dorm, military recruits, s/p splenectomy or C5-9 deficiency
<i>H. influenzae</i> (<5%)	\downarrow Incidence in children b/c vaccine. Look for risk factors in adults (eg, CSF leak, neurosurgical procedure, trauma, mastoiditis).
<i>L. monocytogenes</i> (5–10%)	\uparrow Incid in elderly, alcoholics or Pts w/ cancer, immunosupp. or iron overload. Outbreaks a/w contaminated dairy & raw vegetables. Despite name, a/w poly-predominant pleocytosis.
GNRs (1–10%)	Usually health care associated, postprocedure or in elderly or immunosuppressed
Staphylococci (5%)	Seen with indwelling CSF shunt (<i>S. epidermidis</i>) or following neurosurgery or head trauma (<i>S. aureus</i>)
Mixed infection	Suspect parameningeal focus or CSF leak
Fungal	Seen if immunosuppressed or after neurosurgery

Sequential approach to bacterial meningitis

- (1) Stat BCx \rightarrow antibiotics + corticosteroids (see below)
- (2) CT head (if indicated, see below)
- (3) LP (if not contraindicated); yield of CSF cx unlikely to be changed if obtained w/in ~4 h of initiation of abx

Diagnostic studies (Lancet 2012;380:1684)

- **Blood cultures $\times 2$ before abx**
- **WBC count:** >10,000 in >90% of bacterial meningitis in healthy hosts
- Consider head CT to r/o mass effect before LP if ≥ 1 high-risk feature (age >60 y, immunosupp., h/o CNS disease, new-onset seizure, Δ MS, focal neuro findings, papilledema); absence of all these has NPV 97%; however, in Pts w/ mass effect, herniation may occur w/o LP and may not occur even w/ LP (NEJM 2001;345:1727)
- **Lumbar puncture** (NEJM 2006;355:e12)
 - CSF Gram stain** has 30–90% Se; cx 80–90% Se if LP done prior to abx
 - opening pressure typically \uparrow in bact meningitis; must measure w/ Pt's legs extended
 - rule of 2s: CSF WBC >2k, glc <20, & TP >200 has >98% Sp for bacterial meningitis
 - repeat LP only if no clinical response after 48 h of appropriate abx or CSF shunt
- Additional CSF studies based on clinical suspicion: AFB smear & cx, India ink prep, cryptococcal Ag, fungal cx, VDRL, PCR (HSV, VZV, enteroviral), cytology

Typical CSF Findings in Meningitis

Type	Appearance	Pressure (cm H ₂ O)	WBC/mm ³ Predom type	Glc (mg/dL)	TP (mg/dL)
Normal	Clear	9–18	0–5 lymphs	50–75	15–40
Bacterial	Cloudy	18–30	100–10,000 polys	<45	100–1000
TB	Cloudy	18–30	<500 lymphs	<45	100–200
Fungal	Cloudy	18–30	<300 lymphs	<45	40–300
Aseptic	Clear	9–18	<300 polys → lymphs	50–100	50–100

Treatment of Bacterial Meningitis (*Lancet* 2012;380:1693)

Clinical scenario	Empiric treatment guidelines*
Normal adult	Ceftriaxone 2 g IV q12h + Vancomycin 15–20 mg/kg IV q12h If >50 y or alcoholic: add ampicillin 2 g IV q4h for <i>Listeria</i> β-lactam allergy: substitute cipro 400 mg q8h or aztreonam 2 g q6h for CTX. Substitute TMP/SMX for amp.
Immunosuppressed	Ampicillin + ceftazidime 2 g IV q8h + vancomycin
CSF shunts, recent neurosurgery or head trauma	Vancomycin + ceftazidime 2 g IV q8h (<i>NEJM</i> 2010;362:146)
Corticosteroids: dexamethasone 10 mg IV q6h × 4 d → ↓ neuro disability & mortality by ~50% w/ <i>S. pneumo</i> & GCS 8–11. Consider steroids in all bacterial meningitis prior to organism identification. Must start before or w/ 1st dose of abx (<i>NEJM</i> 2002;347:1549). Nb, do <i>not</i> give steroids in cryptococcal meningitis (<i>NEJM</i> 2016;374:542).	
Prophylaxis: rifampin (600 mg PO bid × 2 d) or ciprofloxacin (500 mg PO × 1) or ceftriaxone (250 mg IM × 1) for close contacts of Pt w/ <i>N. meningitidis</i> meningitis	
Precautions: droplet precautions until <i>N. meningitidis</i> is r/o	

*When possible, organism-directed Rx, guided by sensitivities or local patterns of drug resistance should be used

Prognosis

- For community-acquired *S. pneumo* mort. 19–37%; 30% have long-term neuro sequelae

ASEPTIC MENINGITIS

Definition

- CSF pleocytosis w/ ⊖ blood & CSF cx; typically lymphocyte predominant
- Less likely to be bacterial, but can be infectious or noninfectious

Etiologies (*Neurology* 2006;66:75)

- Viral:** enteroviruses (most common), HIV, HSV (type 2 > 1), VZV, mumps, lymphocytic choriomeningitis virus, encephalitis viruses, adenovirus, polio, CMV, EBV, WNV
- Parameningeal focus of infection** (eg, brain abscess, epidural abscess, septic thrombophlebitis of dural venous sinuses or subdural empyema)
- Partially treated bacterial meningitis**
- TB, fungal, spirochetal** (Lyme, syphilis, leptospirosis), **rickettsial**, *Coxiella*, *Ehrlichia*
- Medications:** TMP/SMX, NSAIDs, IVIG, PCN, INH, lamotrigine
- Systemic illness:** SLE, sarcoidosis, Behcet's, Sjögren's syndrome, RA
- Neoplasm:** intracranial tumors (or cysts), lymphomatous or carcinomatous meningitis (CSF cytology or flow may be reactive and dx may require meningeal bx)

Empiric treatment

- No abx if suspect viral (cell count <500 w/ >50% lymphs, TP <80–100 mg/dL, normal glc, ⊖ Gram stain, not elderly/immunosupp.); o/w start empiric abx, wait for cx data
- If suspect MTb: antimycobacterial Rx + dexamethasone (*NEJM* 2004;351:1741)
- If suspect fungal: amphotericin B lipid formulation, ± 5-fluorouracil

Definition

- Infection of brain parenchyma with evidence of neurologic dysfunction

Etiologies (specific etiology found in <20% of cases; Neurology 2006;66:75; CID 2008;47:303)

- HSV-1** (~9%): all ages/seasons; MRI: temporal lobe lesions/edema; EEG: temporal focus
- VZV** (~9%): 1° or reactivation; ± vesicular rash; all ages (favors elderly), all seasons
- Arboviruses** (~9%): Eastern/Western equine, St. Louis, Japanese, Powassan, W. Nile (NEJM 2005;353:287); fever, HA, **flaccid paralysis**, rash. Risk factors for severe dis: renal dis., cancer, EtOH, DM, HTN (Am J Trop Med Hyg 2012;87:179).
- Enteroviruses** (coxsackie, echo): viral syndrome; peaks in late summer/early fall
- Others: CMV, EBV, HIV, JC virus (PML), measles, mumps, rubella, rabies, flu, adenovirus
- Nonviral mimics: autoimmune/paraneoplastic (anti-NMDAR, anti-Hu, anti-Ma2, anti-CRMP5), bacterial endocarditis, brain abscess, toxoplasmosis, TB, toxins, vasculitis, Whipple's disease, subdural hematoma, encephalomyelitis (eg, ADEM), seizure

Clinical manifestations

- Fever, HA, Δ MS**, ± seizures and focal neuro findings (latter atypical for viral meningitis)

Diagnostic studies (CID 2013; 57:1114)

- Lumbar puncture:** lymphocytic pleocytosis; PCR for HSV (95% Se & Sp at 2–3 d), VZV, CMV, EBV, HIV, JC, adeno/enterovirus, W. Nile (<60% Se); W. Nile CSF IgM 80% Se
- Consider testing for autoimmune etiologies (anti-NMDAR, etc.) in approp. setting
- MRI** (CT if MRI unavailable); HSV w/temporal lobe involvement, W. Nile w/ thalamic hyperintensity
- EEG to r/o seizure; findings in encephalitis are nonspecific

Treatment

- HSV, VZV: acyclovir 10 mg/kg IV q8h (often empiric Rx given frequency of HSV/VZV)
- CMV: ganciclovir ± foscarnet; supportive care for most other etiologies

BELL'S PALSY**Definition & etiology**

- Acute idiopathic unilat. **facial nerve palsy** (CN VII), often presumed HSV-1 reactivation

Clinical manifestations

- Unilateral **facial muscle weakness, hyperacusis**, ↓ taste/lacrimation/salivation

Diagnosis

- Dx of exclusion: r/o brainstem lesion, Lyme (often bilateral), zoster (incl sine herpete), HIV/AIDS, sarcoid (often bilateral)

Treatment (NEJM 2007;357:1598; JAMA 2009;302:985)

- ~80% recover spontaneously by 9 mo (much lower rate in DM)
- Corticosteroids (prednisolone 25 mg PO bid × 10 d) started w/in 72 h of sx onset improve odds of recovery (note: no conclusive data for use in DM, immunosupp.)
- No conclusive data to support the use of acyclovir or valacyclovir

ZOSTER**Definition & etiology**

- Zoster = herpes zoster = shingles: acute, unilat., **painful dermatomal skin eruption**
- VZV reactivation in peripheral nerve distribution from latency in dorsal root ganglion

Clinical manifestations

- Neuritic pain in a dermatomal distribution**, then acute **dermatomal eruption of clustered rash** (vesicles > papules/pustules > macules) in varying stages of evolution
- Consecutive dermatomes may be seen in all Pts; more widespread in immunosupp.
- Lesions in V1 distribution of facial nerve require urgent ophthalmologic evaluation
- Post-herpetic neuralgia (PHN) = severe pain lasting >90 d after episode; may last mos to y, more frequent w/ ↑ age and delay of antiviral Rx

Diagnosis

- Appearance of rash; DFA is most Se from scrape of newly unroofed vesicle. Tzanck does not distinguish HSV or VZV, cx insensitive for VZV (unlike HSV).

Treatment

- Rx if can initiate **w/in 72 h of skin lesions** in healthy Pt or at *any time* in immunosupp.
- Valacyclovir or famciclovir × 7–14 d, or until lesions fully crusted; acyclovir 10 mg/kg IV q8h if disseminated or high-risk Pt (medically ill, immunosupp., V1 zoster w/ ophthalmic s/s, etc.)
- Prevention: vaccine approved for Pts >50 y (↓ lifetime risk from 20% to 10%, also ↓ PHN)

BACTERIAL ENDOCARDITIS

Definition

- Infection of endothelium of heart (including but not limited to the valves)
- Acute (ABE): infxn of normal valves w/ virulent organism (eg, *S. aureus*, β -hemolytic strep, *Strep pneumo*)
- Subacute (SBE): more indolent infxn w/ less virulent organism (eg, *S. viridans*, *Enterococcus*); often abnl valves

Predisposing conditions

- Abnormal valve**
High risk: prior endocarditis, rheumatic heart disease, AoV disease (incl. bicuspid), complex cyanotic lesions, prosthesis (annual risk 0.3–1%)
Medium risk: MV disease (including MVP w/ MR or thickened leaflet), HCMP
- Risk of bacteremia:** IVDU, indwelling venous catheters, poor dentition, hemodialysis, DM, prosthetic material in heart (eg, pacemaker, ICD, graft)

Modified Duke Criteria

Major

- BCx** with common endocarditis pathogen (grown in 2 separate cultures)
- Coxiella* serology $\geq 1:800$
- Endocardial involvement**, w/ either: echocardiogram w/ vegetation, abscess, or prosthetic dehiscence **new valvular regurgitation**

Minor

- Predisposing condition (see above)
- Fever
- Vascular phenomena:** septic arterial or pulmonary emboli, mycotic aneurysms, ICH, Janeway lesions
- Immune phenomena:** \oplus RF, GN, Osler's nodes, Roth spots
- \oplus **BCx** not meeting major criteria

Definitive (ie, highly probable): 2 major or 1 major + 3 minor or 5 minor criteria

Possible: 1 major + 1 minor or 3 minor criteria

Se ~90%, Sp >95%, NPV $\geq 92\%$ (*CID* 2000;30:633). *Serologic or molecular tests for other known agents of Cx
 \ominus endocarditis (see below) not yet included as major criterion, but may help dx.

Microbiology of Endocarditis

Etiology	Native valve endocarditis (NVE)		Prosthetic valve endocarditis (PVE)	
	Non-IVDA	IVDU	Early (≤ 60 d post)	Late (> 60 d post)
<i>S. viridans</i> et al.	36%	13%	<5%	20%
<i>Enterococcus</i>	11%	5%	8%	13%
<i>S. aureus</i>	28%	68%	36%	20%
<i>S. epidermidis</i>	9%	<5%	17%	20%
GNR	<5%	<5%	6%	<5%
Other	<5%	<5%	10%	10%
Fungal ^a	1%	1%	9%	3%
Culture \ominus^b	11%	<5%	17%	12%

^a↑ risk w/ DM, indwelling lines, immunosupp. ^bCx \ominus = abiotrophic strep, HACEK (*Haemophilus para-influenzae* & *aphrophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella* and *Kingella*), *T. whipplei*, *Bartonella*, *Coxiella*, *Chlamydia*, *Legionella*, *Brucella* (*JAMA* 2007;297:1354; *Annals* 2007;147:829; *J Clin Microbiol* 2012;50:216)

Clinical manifestations (*Lancet* 2016;387:882)

- Persistent bacteremia:** fever (80–90%), rigors, night sweats, anorexia, wt loss, fatigue
- Valvular or perivalvular infection:** CHF, conduction abnormalities
- Septic emboli:** systemic emboli (eg, to periphery, CNS, kidneys, spleen, or joints; *JACC* 2013;62:1384), stroke, PE (if right-sided), mycotic aneurysm, MI (coronary artery embolism)
- Immune complex phenomena:** arthritis, glomerulonephritis, \oplus RF, ↑ ESR
- SBE:** can p/w fatigue, nonspecific sx in Pts w/o risk factors; ∴ need high index of suspicion

Physical exam

- HEENT:** **Roth spots** (retinal hemorrhage + pale center), **petechiae** (conjunctivae, palate)
- Cardiac:** **murmur** (85%), **new valve regurgitation** (40–85%) ± thrill (fenestrated valve or ruptured chordae), muffled sounds (PV). Frequent exams for Δ murmurs, s/s CHF.
- Abdomen:** tender splenomegaly; musculoskeletal: arthritis, vertebral tenderness
- Extremities** (typically seen in SBE, not ABE)
 - Janeway lesions** (septic emboli → nontender, hemorrhagic macules on palms or soles)
 - Osler's nodes** (immune complexes → tender nodules on pads of digits)
 proximal nail bed splinter hemorrhages (8–15%); petechiae (33%); clubbing

- Neuro:** Δ MS or focal deficits
- Devices:** erythema, tenderness or drainage at catheter site, PM/ICD pocket tenderness

Diagnostic studies (EHJ 2015;36:3075)

- Blood cultures** (before abx): at least 3 sets (aerobic & anaerobic bottles) from different sites, ideally spaced ≥ 1 h apart. ✓ BCx (at least 2 sets) after appropriate abx have been initiated to document clearance; repeat q24–48h until \ominus .
 - CBC w/ diff (\uparrow WBC common in ABE; anemia in 90% SBE), ESR, RF, BUN/Cr, U/A, & UCx
 - ECG** (on admission and at regular intervals) to assess for new conduction abnormalities
 - Echocardiogram:** obtain TTE if low clinical suspicion, expect good image quality; TEE if
 - (i) mod-to-high suspicion, (ii) high-risk Pt (prosthetic valve, prior IE, congenital heart dis),
 - (iii) TTE nondx, (iv) TTE \ominus but high-risk endocarditis, or (v) suspect progressive or invasive infection (eg. persistent bacteremia or fever, new conduction abnl, etc.)
- (Circ 2015;132:1435)

Method	Sensitivity		
	NVE	PVE	Abscess
Transthoracic (TTE)	50–65%	36–69%	28–36%
Transesophageal (TEE)	>90%	~90%	80–87%

(EHJ 1999;20:232; J Am Soc Echo 2003;16:67; Heart 2004;90:614)

- ^{18}F -FDG PET/CT may have utility in assessing PVE (JACC 2013;61:2374)
- Brain MRI may be useful to detect silent cerebral emboli (Circ 2009;120:585)
- Cx \ominus endocarditis:** may be due to abx prior to BCx. PCR, bacterial 16S ribosomal RNA, serologies may be helpful. Detailed hx: animal exposure, travel, unpasteurized dairy, etc. Seek ID eval (NEJM 2007;356:715; CID 2010;51:131).

Treatment (Circ 2015;132:1435; EHJ 2015;36:3075)

- Obtain culture data first**
 - ABE \rightarrow abx should start promptly after cx data obtained
 - SBE \rightarrow if hemodynamically stable, may defer abx until BCx properly obtained
- Suggested empiric therapy**
 - NVE:** vanco \pm nafcillin (or cefazolin)
 - PVE:** early (≤ 60 d): vanco + cefepime + gent; intermediate (60–365 d): vanco + gent; late (> 1 y): vanco + CTX + gent
- Adjust abx regimen & duration based on valve (NVE vs. PVE)**
 - if possible, de-escalate abx to organism-directed Rx guided by *in vitro* sensi's or local patterns of Rx-resist
 - add rifampin for PVE due to staph spp. (usually after BCx \ominus to \downarrow risk resistance develops)
 - combination therapy for *Enterococcus* (amp + gent or amp + CTX)
- Repeat BCx q24–48h until Pt defervesces and BCx \ominus ; usually 2–3 d
- Fever may persist even > 1 wk after appropriate abx. Consider metastatic infxn if > 1 wk.
- Systemic anticoagulation relatively contraindicated given risk of hemorrhage in cerebral embolic strokes; w/o stroke, can continue short-acting anticoag for pre-existing indication
- Monitor for complications of endocarditis (CHF, conduction block, new emboli, etc., which can occur even on abx) and of abx Rx (interstitial nephritis, ARF, neutropenia, etc.)
- Duration of Rx: usually **4–6 wk**. With NVE & sx < 3 mo \rightarrow 4 wk of abx; sx > 3 mo \rightarrow ≥ 6 wk. Uncomplicated right-sided NVE or PCN-S strep spp \rightarrow 2 wk may be comparable.
- Posthospitalization outPt IV abx monitoring; future endocarditis Ppx

Indications for surgery (EHJ 2015;36:3075)

- Severe valvular dysfunction \rightarrow refractory CHF:** emergent if refractory cardiogenic shock (ie, despite ICU-level Rx); urgent (w/in days) if persistent refractory heart failure; elective (w/in wks) if asx severe AI or MR
- Uncontrolled infxn** (urgent surgery w/in days): periannular abscess (10–40% NVE, 60–100% PVE), fistula, worsening conduction, PVE w/ dehiscence, \uparrow veg. size or persistent sepsis (eg, \oplus BCx after ~ 1 wk of appropriate IV abx and no drainable metastatic focus or other identifiable cause)
- Organism:** consider surgery for *S. aureus*, fungal or multiRx-resistant organisms
- Systemic embolism** (20–50%): risk 4.8/1000 Pt days in 1st wk, 1.7/1000 thereafter
 - urgent surgery if L-sided w/ > 10 mm veg & severe AI/MR (NEJM 2012;366:2466) or if recurrent emboli, embolism & > 10 mm veg, or > 15 mm veg despite approp. abx
 - cerebral emboli no longer considered contraindic to surgery unless hemorrhage (then ideally wait 1 mo) or severe stroke (Stroke 2006;37:2094)
- PVE:** esp. w/ valve dysfxn or dehiscence or *S. aureus* or GNR infection. Seek ID eval.

Prognosis

- NVE: non-IVDU *S. aureus* \rightarrow 30–45% mortality; IVDU *S. aureus* (often right-sided) \rightarrow 10–15% mortality; SBE \rightarrow 10–15% mortality
- PVE \rightarrow 23% mortality
- Aortic valve worse prognosis than mitral valve

Cardiac conditions*	Prosthetic valve; previous NVE; congenital heart disease (CHD) including unrepaired or incompletely repaired cyanotic CHD (palliative shunts or conduits), 1st 6 mo after completely repaired CHD using prosthetic material; cardiac transplant recipients w/ valvulopathy (Prophylaxis no longer rec. in acquired valvular dysfxn, bicuspid AoV, MVP with leaflet thickening or regurgitation, HCMP)
Procedures*	Dental: manipulation of gingival tissue or periapical region of teeth or perf oral mucosa (eg, extraction, periodontal, implant, root canal, cleaning) Respiratory: incision or biopsy of respiratory mucosa (no prophylaxis for GI or GU procedures)
Regimens	Oral: amoxicillin 2 g 30–60 min before Unable to take PO: amp 2 g IM/IV or cefazolin or Cftx 1 g IM/IV PCN-allergic: clinda 600 mg PO/IM/IV

*Pts should meet both indications (high-risk condition & high-risk procedure) to qualify for Ppx

BACTEREMIA (JAMA 2014;312:1330)

Etiologies

- 1° infxn due to direct inoculation of the blood, frequently assoc w/ intravascular catheters.
Catheter-related bloodstream infection = same org from peripheral cx and cath tip cx or cx drawn from catheter (CID 2009;49:1).
- 2° infxn due to infection in another site (eg, UTI, lung, biliary tree, skin) spreading to blood

Microbiology

- 1° infxn/indwelling catheters (ICHE 2008;29:996): coag-neg staph (incl S. epi and others) 34%, S. aureus 10%, enterococci 16%, Candida spp. 12%, Klebsiella spp. 5%
- 2° infxn: dependent on source

Risk factors for true bacteremia (JAMA 2012;308:502)

- Pt: fever, rigors, SIRS (96% sens.), IVDU, comorbidities, immunosupp, indwelling lines
- Organism**
 - more likely pathogenic: S. aureus, β-hemolytic strep, enterococci, GNR, S. pneumo, Neisseria
 - less likely pathogenic: coag-neg staph (~10%), diphtheroids, Propionibacterium (~0%)
- Time to growth:** <24 h → higher risk, >72 h → lower risk (except for slow-growing organisms such as HACEK group)
- Factors increasing the likelihood of endocarditis:** high-grade bacteremia w/o source, persisting after line removal or drainage of focal source, in hosts at risk for endocarditis or w/ organisms known to cause IE; emboli

Diagnosis

- Obtain BCx prior to abx if possible, ≥2 sets (2 bottles in each set, each w/ 10 cc blood)
- If S. aureus, obtain TEE (TTE only if nosocomial, no intracardiac device, no e/o IE, no HD)

Treatment

- 1° infxn: antibiotics based on Gram stain/culture results; tailor abx to sensitivities empiric therapy for GPC: vanco to cover coag-neg staph and MRSA while awaiting sensi
- S. aureus bacteremia: if uncomplicated (*all* of following: ⊖ echo, no prosthetic material, no signs of metastatic infxn, after starting abx defervesce w/in 2–3 d and BCx ⊖ w/in 2–4 d) then 2 wks of abx, o/w 4 wks min. (depends on site of infxn, see individual sections)

Short-Term Central Venous Catheter-Related Bloodstream Infections (CID 2009;49:1)

S. aureus	Risk of endocarditis in bacteremia: ~25% (JACC 1997;30:1072) D/c CVC, TEE to r/o endocarditis; if echo ⊖ and not immunosupp. and no intravasc prosthesis, Rx × 2 wk from first ⊖ BCx. If no echo obtained, Rx × 4–6 wk. Preferred abx: MSSA → nafcillin or cefazolin; MRSA → vancomycin
Coag-neg staphylococci	May consider keeping catheter. Catheter retention does not ↓ rate of bacteremia resolution, but a/w ↑ rate of recurrence (CID 2009;49:1187). If catheter left in place, Rx × 10–14 d and consider abx or ethanol lock If catheter d/c, Rx × 5–7 d
Enterococcus	D/c catheter & Rx × 7–14 d
GNR	Rx × 7–14 d. Abx based on sensitivities. D/c catheter if <i>Pseudomonas</i> .
Fungi	D/c catheter & Rx × 14 d from first ⊖ BCx

- 2° infxn: assess for primary source of infection and treat. Source control essential for cure and to prevent recurrence.
- Persistently ⊕ BCx:** d/c indwelling catheters, consider metastatic infxn, infected thrombosis or infected prosthetic material (joint, abscess, vascular graft, PPM, etc.)

TUBERCULOSIS

TB
6-15

Epidemiology

- U.S.: 10–15 million infected (10x ↑ risk if foreign-born or minority); worldwide: ~2 billion
- After resurgence in U.S. 1984–1992, rates have declined
- Multidrug resistant (**MDR**) TB: resistant to isoniazid (INH) and rifampin (RIF). Can occur as primary infxn if exposed in former Soviet Republics, China
- Extensively drug resistant (**XDR**) TB resistant to INH, RIF, FQ and injectables
- Pts more likely to develop TB disease** (NEJM 2011;364:1441)

High-prevalence populations (more likely to be exposed & infected): immigrant from high-prevalence area, homeless, IVDU or medically underserved, resident or worker in jail or long-term facility, HCW at facility w/ TB, close contact to Pt w/ active TB

High-risk populations (infected & likely to progress to active disease): HIV +, immunosupp. incl. biologics, uncontrolled DM & smoking, close contact w/ active TB Pt, underweight, CKD, organ Tx, IVU, EtOH, malnourished, cancer, gastrectomy

Microbiology & natural history

- Transmission of *Mycobacterium tuberculosis* via small-particle aerosols (droplet nuclei)
- 90% of infected normal hosts will never develop clinically evident disease
- Localized disease: healing & calcification or progressive 1° TB (at site of infection)
- Hematogenous spread: latent infection ± reactivation TB or progressive disseminated TB

Screening for latent infection

- Whom to screen:** high-prevalence and high-risk populations (HIV + Pts should have PPD testing as part of initial evaluation and annually thereafter)
- How to screen:** Mantoux tuberculin test (ie, purified protein derivative or PPD) inject 5-TU (0.1 mL) intermediate strength PPD *intradermally* → wheal; examine 48–72 h
- How to interpret a PPD:** determine max. diameter of *induration* by palpation

Size of reaction	Persons considered to have + test
>5 mm	HIV + or immunosupp (eg, prednisone 15 mg/d × >1 mo) Close contacts of Pt w/ active TB; CXR w/ apical fibrosis c/w TB
>10 mm	All other high-risk or high-prevalence populations Recent conversion (↑ in induration by >10 mm in last 2 y)
>15 mm	Everyone else
False -	Faulty application, anergy (including from active TB), acute TB (2–10 wk to convert), acute non-TB mycobacteria (NTM), malignancy
False +	Improper reading, cross-reaction with NTM, BCG vaccination (although usually <10 mm by adulthood)
Booster effect	↑ induration b/c immunologic boost by prior skin test in prev sensitized individual (by TB, NTM or BCG). Test - → + but not true conversion due to recent infxn. 2 nd test true baseline. Can be 1 y after initial test.

(NEJM 2002;347:1860)

- IFN-γ release assays (IGRA):** (Ag-stimulated IFN-γ release from Pt's T-cells): can use to screen when PPD could be used (MMWR 2010;59:1); ↑ Sp, esp. in BCG Rx'd Pts (Annals 2008;149:177). Does not distinguish active vs. latent or past infxn. Relies on host immune fxn; Se limited in immunosupp. (J Clin Epidemiol 2010;63:257; CID 2011;52:1031).

Clinical manifestations (Lancet 2016;387:1211)

- Primary TB pneumonia:** middle or lower lobe **consolidation**, ± effusion, ± cavitation
- TB pleurisy:** can occur w/ primary or reactivation. Due to breakdown of granuloma w/ spilling of contents into pleural cavity and local inflammation. **Pulmonary effusion** ± pericardial and peritoneal effusions (tuberculous polyserositis).
- Reactivation TB pulmonary disease:** apical infiltrate ± volume loss ± cavitation
- Miliary TB:** acute or insidious; due to hematogenous dissemination; usually in immunosupp, DM, EtOH, elderly or malnourished. **Constitutional sx** (fever, night sweats, weight loss) usually prominent. Pulm disease w/ millet seed-like lesions (2–4 mm) on CXR or chest CT (latter more Se) present in 60–80% of those w/ miliary TB.
- Extrapulmonary TB:** lymphadenitis, pericarditis, peritonitis, meningitis, nephritis ± sterile pyuria, osteomyelitis (vertebral = Pott's disease), hepatitis, splenitis, cutaneous, arthritis
- TB and HIV:** HIV + at ↑ risk infxn, progressive 1° infxn & reactivation. Risk of progression from infxn to disease >8–10%/y, higher risk with ↓ CD4. Reinfection (also w/ MDR) significant, esp. in hyperendemic areas.

Diagnostic studies for active TB (high index of suspicion is key!)

- AFB smear** (rapid dx) and **culture** (↑ Se & allows sensitivity testing) of sputum, BAL, pleura, etc.; avoid FQ if considering TB (can compromise dx yield)

- Gene Xpert PCR (rapid dx) can also detect INH resistance; validated on nonbloody sputum only. Sp 98% & Se 74% independent of HIV status (*AJRCCM* 2014;189:1426).
- PCR: 94–97% Se c/w smear; 40–77% Se c/w culture (*JAMA* 2009;301:1014)
- CXR: classically fibrocavitory apical disease in reactivation vs. middle & lower lobe consolidation in 1^o TB but distinction imperfect. HIV + assoc. w/ nonapical disease regardless of timing (*JAMA* 2005;293:2740).
- Adenosine deaminase testing: useful in extrapulmonary sites; best validated for ascites

Preventive therapy (prevent progression to active disease)

- Prophylaxis reduces incidence of active disease by 65–75%
- Treat Pts who are + based on guidelines (*NEJM* 2015;372:2127; *Eur Respir J* 2015;46:1563) or any exposed HIV + or immunocompromised Pt
- R/o active disease** in any Pt w/ suggestive s/s before starting INH. If HIV +, routinely ask if cough, fever or night sweats; if yes → ✓ sputum smear, CXR, CD4

Scenario	Prophylaxis Regimen
Likely INH sensitive	INH 300 mg PO qd + pyridoxine 25 mg PO qd × 6–9 mo or 12-wk observed combo Rx (INH + rifapentine) (<i>NEJM</i> 2011;365:2155)
HIV +	INH 300 mg PO qd + pyridoxine 25 mg PO qd × 9 mo
Contact case INH resistant	RIF × 4 mo
Contact case known or suspected to have MDR TB	No proven regimen: ? PZA + EMB, ? PZA + FQ

(INH, isoniazid; RIF, rifampin; PZA, pyrazinamide; EMB, ethambutol; FQ, fluoroquinolone)

- ✓ LFTs monthly (risk ↑ w/ age; *Chest* 2005;128:116): if 5x ULN or sx → stop TB meds & re-eval

Treatment of active tuberculosis (*NEJM* 2015;373:2149; *Lancet* 2016;387:1211)

- Isolate Pt per infection control if hospitalized, modified isolation per Dept of Health if outPt
- Use multiple drugs (see below) to which organism susceptible; consult ID before empiric Rx if possible MDR-TB (suspect if prior TB Rx, from or travel to area w/ ↑ rates of MDR, exposure to person w/ likely MDR-TB, poor Rx adherence) or if INH resistance in community ≥4% (includes most of U.S.), extrapulm. TB or HIV + (*NEJM* 2008;359:636)
- Screen for HIV in Pts starting TB Rx; if HIV +, consult ID re: timing of concurrent HIV Rx
- Promote adherence to Rx; directly observed Rx cost-effective if high risk for nonadherence
- Obtain monthly smears/cx on treatment until 2 consecutive are – for TB
- Monthly clinical evaluation to monitor for Rx response and adverse drug rxns
- “Paradoxical worsening” of sx can occur after starting Rx. More common w/ extrapulm. TB (eg, tuberculoma, LAN) likely due to hypersensitivity response to killing of bacilli. More frequent/severe w/ concurrent immune reconstitution (eg. HIV + Pts started on ARVs, Pts taken off immunosuppression). Must r/o Rx failure (repeat Cx, imaging, etc.).

Antituberculous Medications

Drug	Dose	Adverse effects*
Isoniazid (INH)	300 mg PO qd	Hepatitis, periph neuropathy (↓ risk by suppl. vit B ₆), drug-induced lupus
Rifampin (RIF)	600 mg PO qd	Orange tint of body fluids, GI upset, hepatitis, hypersensitivity, fever, drug interactions, avoid EtOH
Pyrazinamide (PZA)	25 mg/kg PO qd	Hepatitis, hyperuricemia, arthritis
Ethambutol (EMB)	15–25 mg/kg PO qd	Optic neuritis
Streptomycin (SM)	15 mg/kg IM qd	Ototoxicity, nephrotoxicity
Amikacin (AMK)	15 mg/kg IM qd	Ototoxicity, nephrotoxicity
Quinolone (moxifloxacin)	400 mg PO qd	GI upset, tendinopathy, ↑ QTc

*Risk of hepatitis ↑ w/ pre-existing liver disease. Consult ID if mod to severe liver disease, and consider holding/replacing PZA or INH.

Scenarios

Antituberculous Treatment Regimens*

Pulmonary TB ≥4% INH-resist. in community (includes most of U.S.)	INH + RIF + PZA + (EMB) until suspect. known If sensitive to INH & RIF → INH + RIF + PZA × 2 mo, then → INH + RIF × 4 mo If resistant, see next row
Drug-resistant TB (INH-R, RIF-R or MDR/XDR)	Consult ID specialist (<i>NEJM</i> 2008;359:636)
Extrapulmonary TB	Consult ID specialist
TB in HIV + patient	Consult ID specialist

*Individualize duration based on host, disease form, and rate of clinical/microbiologic improvement

Definition

- AIDS: HIV + CD4 <200/mm³ or AIDS-defining opportunistic infection (OI) or malignancy

Epidemiology

- ~1 million Americans living w/ HIV; ~36 million worldwide
- 13% in U.S. unaware of infxn, many dx w/ late disease. CDC rec testing all people for HIV.
- Routes: sexual (risk is 0.3% for male-to-male, 0.2% for male-to-female, 0.1% for female-to-male transmission), IVDU, transfusions, needlesticks (0.3%), vertical (15–40% w/o ARV)

Prophylaxis (JAMA 2014;312:390)

- Postexposure (PEP): risk infxn ~0.3%; Rx: 2 NRTIs + II × 4 wks
- Preexposure (PrEP): TDF/FTC qd or on-demand effective (44–86% ↓) & safe in high-risk, adherent populations w/o renal insufficiency (NEJM 2010;363:2587 & 2015;373:2237; Lancet 2016;387:53). Monitor renal fxn, STDs, preg, & HIV status.

Acute retroviral syndrome

- Occurs in ~40–90% of Pts ~2–6 wk after infxn; ± ELISA +, + viral load (2 wk after infxn); early ART may be beneficial (NEJM 2013;368:207 & 218)
- Mono-like syndrome (↑ mucocut. & neuro manifestations compared to EBV or CMV)

Diagnostic studies

- **ELISA** for HIV-1 Ab/Ag: + 1–12 wk after acute infxn; >99% Se; 1° screening test
- If +, Ab differentiation assay confirms and differentiates HIV-1 vs. -2 (MMWR 2013;62:489)
- **Rapid tests:** Ab tests; use saliva, plasma, blood or serum; 99% Se & 96–99% Sp (Annals 2008;149:153); PPV in low prev populations is low; needs confirmation
- **PCR (viral load):** detects HIV-1 RNA in plasma; assay range is 20–10 million copies/mL ~2% false +, but usually low # copies; in contrast, should be very high (>750 k) in 1° infxn
- **At least 1-time HIV screening recommended for all adults** (Annals 2013;159:51)
- **CD4 count:** not a dx test, b/c can be HIV + w/ normal CD4 or be HIV - w/ low CD4

Approach to newly diagnosed HIV + Pt (Lancet 2014;384:258)

- **Document HIV infection;** counseling re: treatment options, adherence, & disclosure
- **H&P (including focus on h/o OIs, STDs); review all current meds**
- **Lab evaluation:** CD4 count, PCR, HIV genotype, CBC w/ diff., Cr, lytes, LFTs, A1c, & fasting lipids; PPD or IGRA, syphilis & toxo screen & CMV IgG; HAV, HBV, & HCV serologies; Chlamydia & gonorrhea screen; baseline CXR; Pap smear/anal pap in ♀/♂

Common Antiretrovirals (ARVs)		Common Side Effects
NRTI	abacavir (ABC; Ziagen) emtricitabine (FTC; Emtriva) lamivudine (3TC; Epivir) tenofovir (TAF or TDF) zidovudine (AZT; Retrovir)	Class: GI intol, lipoatrophy, lactic acidosis ABC: hypersensitivity (3%), ✓ HLA-B*5701 AZT: BM suppression (esp. macrocytic anemia) TDF: renal toxicity TAF: minimal renal toxicity
NNRTI	efavirenz (EFV; Sustiva) etravirine (ETR; Intelence) nevirapine (NVP; Viramune) rilpivirine (RPV; Edurant)	Class: rash, hepatitis, mixed CYP450 inducer/inhib EFV: CNS effects (incl depression) NVP: rash and hypersensitivity [risk factors are female, CD4 >250, pregnancy (∴ avoid)]
PI	atazanavir (ATV; Reyataz) darunavir (DRV; Prezista) lopinavir/ritonavir (LPV/r; Kaletra) ritonavir (RTV; Norvir)	Class: GI intol; hepatotoxicity; inhibit CYP450 (caution w/ statins); T2DM; truncal obesity; hyperlipid (less w/ ATV); MI (NEJM 2007;356:1723) ATV: crystalluria → nephrolithiasis DRV: rash (10%); possible sulfa cross-reactivity
FI	enfuvirtide (T20; Fuzeon)	injection site reaction
EI	maraviroc (MVC; Selzentry)	dizziness, hepatotoxicity; ✓ CCR5 tropism assay
II	dolutegravir (DTG; Tivicay) elvitegravir (EVG; Vitekta) raltegravir (RAL; Isentress)	Class: diarrhea & other GI intol; ↑ CPK DTG + metformin requires glc monitoring
B	ritonavir (r); cobicistat (COBI)	drug interactions (inhibit CYP450)

NRTI, nucleoside/tide reverse transcriptase inhibitor; NNRTI, nonnucleoside RTI; PI, protease inhibitor; FI, fusion inhibitor; EI, entry inhibitor (CCR5 antagonist); II, integrase inhibitor; *booster to give w/ other ARVs; several multiclass combination pills exist

- **ARVs should be given in consultation w/ HIV specialist** (JAMA 2016;316:191)
- Counseling re: strict adherence to ARVs is essential; genotype prior to ART-initiation
- All HIV + Pts should be treated w/ ARVs (NEJM 2015;373:795; <http://aidsinfo.nih.gov>); especially those w/ AIDS-defining illness, preg, HIV-assoc. nephropathy, HCV/HBV co-infxn
- Rec regimens include: 2 NRTI (eg, TAF + FTC) + either II or boosted PI (eg, DRV/r)

- Initiation of ARVs may transiently worsen existing OIs for several wks due to immune reconstitution inflammatory syndrome (IRIS)

Approach to previously established HIV + Pt

- H&P** (mucocutaneous, neurocognitive, OIs, malignancies, STDs); meds
- Review ARVs** (past and current); if any must be interrupted, stop all to ↓ risk of resistance
- Failing regimen = unable to achieve undetectable viral load, ↑ viral load, ↓ CD4 count or clinical deterioration (with detectable viral load consider genotypic or phenotypic assay)

OI Prophylaxis (<https://aidsinfo.nih.gov/guidelines>)

OI	Indication	1° Prophylaxis
Tuberculosis	⊕ PPD (≥ 5 mm)/IGRA or high-risk exposure	INH + vit B ₆ × 9 mo
Pneumocystis jiroveci (PCP)	CD4 <200/mm ³ or CD4 <14% or thrush	TMP-SMX DS or SS qd or DS tiw or dapsone 100 mg qd or atovaquone 1500 mg qd or pentamidine 300 mg inh q4wk
Toxoplasmosis	CD4 <100/mm ³ and ⊕ Toxo IgG	TMP-SMX DS qd or dapsone 50 mg qd + pyrimethamine 50 mg qwk + leucovorin 25 qwk
MAC	CD4 <50/mm ³	azithro 1200 mg qwk or clarithro 500 mg bid

Stop 1° prophylaxis if CD4 > initiation threshold > 3–6 mo on ARVs

Stop 2° prophylaxis (maintenance therapy for prior OI; drugs and doses differ by OI) if clinical resolution or stabilization and CD4 thresholds have been exceeded × 3–6 mo

COMPLICATIONS OF HIV/AIDS

CD4 Count	Complications
<500	Constitutional sx; noninfectious disease (CVD, bone, oncologic) Mucocutaneous: Kaposi's sarcoma; seborrheic dermatitis; oral hairy leukoplakia; lymphoma; candidiasis; HSV; VZV Recurrent bacterial infections, TB (pulm and extrapulm); neurosyphilis
<200	PCP, Toxo, Bartonella, Crypto, Histo, Coccidio
<50–100	CMV, MAC, CNS lymphoma, PML, death (<50 is medical emergency) Invasive aspergillosis, bacillary angiomatosis (disseminated Bartonella)

Fever

- Etiologies (*Infect Dis Clin North Am* 2007;21:1013)
 - infxn (82–90%): MAC, TB, CMV, early PCP, Histo, Crypto, Coccidio, Toxo, endocarditis**
 - noninfectious: lymphoma, drug reaction.** Non 1° HIV itself rarely (<5%) cause of fever.
- Workup: guided by CD4 count, s/s, epi, & exposures
 - CBC, chem, LFTs, BCx, CXR, UA, mycobact. & fungal cx, ✓ meds, ? ✓ chest & abd CT
 - CD4 <100–200 → serum crypto Ag, LP, urinary Histo Ag, CMV PCR or antigenemia
 - pulmonary s/s → CXR; ABG; sputum for bacterial cx, PCP, AFB; bronchoscopy
 - diarrhea → stool cx, O&P, AFB; direct visualization with bx on colonoscopy
 - cytopenias → BM bx for path & cx of aspirate including for mycobacteria & fungi
 - abnormal LFTs → abd CT, liver bx for path & cx including for mycobacteria & fungi

Cutaneous

- Seborrheic dermatitis; eosinophilic folliculitis; **warts** (HPV); HSV & VZV; MRSA skin & soft tissue infxns; scabies; candidiasis; eczema; prurigo nodularis; psoriasis; drug eruptions
- Dermatophyte infx: prox subungual onychomycosis (at nail bed); pathognomonic for HIV
- Molluscum contagiosum** (poxvirus): 2–5 mm pearly papules w/ central umbilication
- Kaposi's sarcoma** (KSHV or HHV8): red-purple nonblanching nodular lesions
- Bacillary angiomatosis** (disseminated Bartonella): friable violaceous vascular papules

Ophthalmologic

- CMV retinitis** (CD4 usu <50); Rx: gan- or valganciclovir, ganciclovir implant or cidofovir
- HZV, VZV, syphilis (at any CD4 count) or Toxo: CD4 usually <100

Oral

- Aphthous ulcers; KS; thrush** (oral candidiasis): curd-like patches typically w/ burning or pain; **oral hairy leukoplakia:** painless proliferation of papillae w/ adherent white coating usually on lateral tongue, caused by EBV but not precancerous

Endocrine/metabolic

- Hypogonadism;** adrenal insufficiency (CMV, MAC, TB, HIV or med-related); wasting osteopenia/porosis (at all CD4 counts); fragility fractures
- Lipodystrophy:** central obesity, peripheral lipoatrophy, dyslipidemia, hyperglycemia

Cardiac & vascular (JACC 2013;61:511)

- Dilated CMP (10–20%); PHT; CAD); pericarditis/effusion
- Higher rates of VTE, stroke, worse outcomes after MI (JAIDS 2012;60:351; Circ 2013;127:1767)

Pulmonary

Radiographic Pattern	Common Causes
Normal	Early PCP
Diffuse interstitial infiltrates	PCP, TB, viral or disseminated fungal
Focal consolidation or masses	Bacterial or fungal, TB, KS
Cavitory lesions	TB, non-TB mycobacteria, aspergillus, other fungal, bacterial (incl MRSA, Nocardia, Rhodococcus)
Pleural effusion	TB, bacterial or fungal, KS, lymphoma

- Pneumocystis jiroveci (PCP) pneumonia (CD4 <200)** (NEJM 1990;323:1444)
 - constitutional sx, fever, night sweats, dyspnea on exertion, nonproductive cough
 - CXR w/ interstitial pattern, ↓ PaO₂, ↑ A-a ∇, ↑ LDH, + PCP sputum stain, + β-glucan
 - Rx if PaO₂ >70: **TMP-SMX** 15–20 mg of TMP/kg divided tid, avg dose = DS 2 tabs PO tid
 - Rx if PaO₂ <70 or A-a gradient >35: **prednisone** before abx (40 mg PO bid; ↓ after 5 d).
 - Alternative Rx if sulfa-allergy or renal insufficiency.

Gastrointestinal & hepatobiliary

- Esophagitis:** *Candida*, CMV, HSV, aphthous ulcers, pills; EGD if no thrush or no response to empiric antifungals
- Enterocolitis:** bacterial (esp. if acute: shigella, salmonella, *C. diff*); protozoal (esp. if chronic: Giardia, Entamoeba, etc.); viral (CMV, adeno); fungal (histo); MAC; AIDS enteropathy
- GI bleeding:** CMV, KS, lymphoma, histo; **proctitis:** HSV, CMV, LGV, *N. gonorrhoeae*
- Hepatitis:** HBV, HCV, CMV, MAC, TB, histo, drug-induced
- AIDS cholangiopathy:** often a/w CMV or *Cryptosporidium* or *Microsporidium* (at ↓ CD4)

Renal

- HIV-associated nephropathy** (collapsing FSGS); nephrotoxic drugs (incl TDF)

Hematologic/oncologic (Lancet 2007;370:59; CID 2007;45:103)

- Anemia:** ACD, BM infiltration by infxn or tumor, drug toxicity, hemolysis
- Leukopenia; thrombocytopenia** (bone marrow involvement, ITP); infection, ↑ globulin
- Non-Hodgkin lymphoma:** ↑ frequency with any CD4 count, but incidence ↑ with ↓ CD4
- CNS lymphoma:** CD4 count <50, EBV-associated
- Kaposi's sarcoma (HHV-8):** at any CD4 count, incidence ↑ as CD4 ↓, usu. MSM
Mucocut. (violaceous lesions); pulmonary (nodules, infiltrates, LAN); GI (bleed, obstruct.)
- Cervical/anal CA (HPV):** ↑ rates of liver (a/w HBV/HCV), gastric, & lung CA

Neurologic

- Meningitis:** Crypto (p/w HA, Δ MS, CN palsy ± meningeal s/s; dx w/ CSF; serum CrAg 90% Se), bact (inc. *Listeria*), viral (HSV, CMV, 1° HIV), TB, histo, Coccidia, lymphoma
- Neurosyphilis:** meningitis, cranial nerve palsies, dementia, otic or ophtho s/s
- Space-occupying lesions:** may present as HA, focal deficits or Δ MS. Workup: MRI, brain bx if suspect non-Toxo etiology (Toxo sero ⊥) or no response to 2 wk of empiric anti-Toxo Rx (if Toxo, 50% respond by d3, 91% by d14; NEJM 1993;329:995)

Etiology	Imaging appearance	Diagnostic studies
Toxoplasmosis	Enhancing lesions, typically in basal ganglia (can be multiple)	+ Toxo serology (Se ~85%)
CNS lymphoma	Enhancing ring lesion (single 60% of the time)	+ CSF PCR for EBV + SPECT or PET scan
Progressive multifocal leukoencephalopathy (PML)	Multiple nonenhancing lesions in white matter	+ CSF PCR for JC virus
Other: abscess, nocardiosis, crypto, TB, CMV, HIV	Variable	Biopsy

- AIDS dementia complex:** memory loss, gait disorder, spasticity (usually at CD4 ↓)
- Myelopathy:** infxn (CMV, HSV), **cord compression** (epidural abscess, lymphoma)
- Peripheral neuropathy:** meds, HIV, CMV, demyelinating

Disseminated Mycobacterium avium complex (DMAC)

- Fever, night sweats, wt loss, HSM, diarrhea, pancytopenia. Enteritis and mesenteric lymphadenitis if CD4 <150, bacillemia if <50. Rx: clarithromycin + ethambutol ± rifabutin.

Cytomegalovirus (CMV)

- Usually reactivation with ↓ CD4. Retinitis, esophagitis, colitis, hepatitis, neuropathies, encephalitis. Rx: ganciclovir, valganciclovir, foscarnet or cidofovir.

TICK-BORNE DISEASES

Distinguishing Features of Tick-Borne Illnesses

Disease	Rash	↓ WBC	Anemia	↓ Plts	↑ LFTs
Lyme	80%: erythema migrans	-	-	-	+
RMSF	90%: petechiae, palms/soles	-	+	+	+++
Borrelia miyamotoi	<10%	++	+	+++	+++
Ehrlichiosis (HME)	25%: maculopapular, petechiae	+++	++	++++	++++
Anaplasmosis (HGA)	<5%	+++	+	+++	++++
Babesia	-	+	++++ (lysis)	++++	+++

-: <15%, +: 15–25%, ++: 25–50%, +++: 50–75%, ++++: > 75%

LYME DISEASE

Microbiology

- **Spirochete** *B. burgdorferi* (consider coinfection w/ *Ehrlichia*, *Babesia*, *B. miyamotoi*)
- Transmitted by **ticks** (*Ixodes*, deer tick); infxn usually requires **tick attached >36–48 h**

Epidemiology

- Most common vector-borne illness in U.S.; peak incidence in summer (May–Aug)
- Majority of cases in MN, WI, New England, northern mid-Atlantic, northern CA
- Humans contact ticks usually in fields with low brush near wooded areas

Clinical Manifestations

Stage	Manifestations
Stage 1 (early localized) 3-30d after bite	Pathogenesis: local effects of spirochete. General: flu-like illness Derm (~80%): erythema migrans (EM) = erythematous patches w/ central clearing, often popliteal, axilla, or inguinal; 6–38 cm in size
Stage 2 (early disseminated) wks to mos after bite	Pathogenesis: spirochetemia and immune response General: fatigue, malaise, LAN, HA; fever uncommon Derm: multiple (1–100) annular lesions ≈ EM Rheum (~10%): migratory arthralgias (knee & hip) & myalgias Neurologic (~15%): cranial neuropathies (esp. CN VII), aseptic meningitis, mononeuritis multiplex (± pain), transverse myelitis Cardiac (~8%): conduction block , myopericarditis
Stage 3 (late persistent) mos to y after bite	Pathogenesis: immune response Derm: acrodermatitis chronica atrophicans , panniculitis Rheum (~60%): recurrent mono- or oligoarthritis of large joints (classically knee), synovitis Neurologic: subacute encephalomyelitis, polyneuropathy, dementia

(CID 2006;43:1089; Lancet 2012;379:461; NEJM 2014;370:1724)

Diagnostic studies

- **EM** present: confirmed in appropriate geographic setting; no need for testing (ie, clinical dx)
- **EM absent** (ie, stage 2 or 3 disease): 2-step testing
 - 1st step: ELISA screen (false + common, false - w/ early abx or <6 wk after tick bite)
 - 2nd step: if + ELISA, confirm with Western blot (↑ Sp)
- ✓ CSF if suspected neuro disease: + CSF Ab if $(\text{IgG}_{\text{CSF}}/\text{IgG}_{\text{serum}})/(\text{alb}_{\text{CSF}}/\text{alb}_{\text{serum}}) > 1$

Treatment (NEJM 2014;370:1724; JAMA 2016;315:1767 & 2461)

- Prophylaxis: tick avoidance, protective clothing, tick ✓ q24h, DEET
Chemoprophylaxis w/ doxycycline 200 mg PO × 1 only if all of the following:
 1. *Ixodes scapularis* tick attached ≥36 h
 2. Local Lyme carriage in ticks ≥20% (peak season in New England, mid-Atl, MN, WI)
 3. Abx can be given w/in ≤72 h of tick bite
 4. No contraindication to doxy (eg, preg, allergy, age <8 y)
 If criteria 1–4 met, NNT to prevent 1 case ~50; w/o doxy, risk of Lyme after tick bite 1–3%
Regardless of Ppx, monitor for fever, flu-like sx, rash (erythema migrans) × 30 d
- Antibiotics: if clin. manifestations and + serology in endemic area
 - Stage 1 or stage 2 w/o meningitis, arthritis, or carditis: **doxy** 100 mg PO bid × 2–3 wk
alternative (eg, preg, doxy allergy): amox 500 mg PO tid or cefuroxime 500 mg PO bid
 - Meningitis, arthritis, carditis: CTX 2 g IV qd × 2–4 wk;
alternative (eg, severe β-lactam allergy): doxy 100–200 mg PO bid × 2–4 wk
- Consider coinfection if severe/refractory sx, persistent fever, cytopenias

ROCKY MOUNTAIN SPOTTED FEVER (RMSF)

Microbiology & epidemiology

- Infection with *Rickettsia rickettsii* (Gram \ominus obligate intracellular bacterium)
- Transmitted by *Dermacentor variabilis*, *D. andersoni* (dog tick); peak in spring/early summer
- Occurs in mid-Atl, SE, Midwest, New Engl, NW, Canada, Mexico, Central & S. America
- Consider other rickettsial spp.: *R. akari* (Rickettsial pox), *R. conorii* (Mediterranean spotted fever), *R. africae* (African tick bite fever), *R. felis* (Flea rickettsiosis)

Clinical manifestations (typically w/in 1 wk of tick exposure)

- Nonspecific: fever, HA, Δ MS, myalgias, N/V, occasionally abdominal pain
- Rash** (2–5 d after onset) = centripetal: starts on ankles and wrists \rightarrow trunk, palms, & soles; progresses from macular to maculopapular to petechial
- Severe cases \rightarrow vasculitis, hypoperfusion/shock, end-organ damage; more likely in elderly
- Up to 75% mortality if untreated, 5–10% even w/ Rx (esp. if delayed) (NEJM 2005;353:551)

Diagnosis

- Usually a clinical dx; requires early clinical suspicion given risks of delayed Rx
- Acute illness dx by skin bx for rickettsiae (Se ~70%); 7–10 d after sx onset, serology \oplus

Treatment

- Doxycycline 100 mg PO bid (give empirically if clinical suspicion)

EHRlichiosis/ANAPLASMOSIS

Microbiology

- Gram \ominus obligate intracellular bacterium; **human monocytic ehrlichiosis** (*E. chaffeensis*, HME); **human granulocytic anaplasmosis** (*A. phagocytophilum*, HGA)
- Transmission: HME by *Amblyomma americanum*, *Dermacentor variabilis*; HGA by *Ixodes*

Epidemiology

- HGA cases typically in New Engl, mid-Atl, MN; HME in SE and south central US
- Peak incidence spring and early summer; can be transmitted by blood transfusion

Clinical manifestations (typically w/in 3 wk of tick exposure)

- Asx or nonspecific: fever, myalgias, malaise, HA, cough, dyspnea; onset often acute
- Laboratory: leukopenia, thrombocytopenia, \uparrow aminotransferases, LDH, A ϕ , renal insuff
- More severe disease can occur with bacterial superinfection in HGA

Diagnosis

- Acute: intraleukocytic morulae on peripheral blood smear (rare); **PCR**; later: serology

Treatment (JAMA 2016;315:1767)

- Start Rx based on clinical suspicion; definitive dx requires PCR (may not detect all spp.)
- Doxycycline 100 mg PO bid (often \times 10 d); should defervesce in \leq 48 h, else reconsider dx

BABESIOSIS

Microbiology & epidemiology

- Infxn w/ parasite *Babesia microti* (U.S.), transmitted by *Ixodes* ticks; also a/w transfusion
- Europe & U.S. (more commonly MN, WI, coastal areas & islands of MA, NY, NJ, RI, CT)
- Peak incidence June–August (MMWR 2012;61:505)

Clinical manifestations (typically 1–4 wk after tick exposure; <9 wk if transfusion)

- Range from asx to fevers, sweats, myalgias, & HA to severe hemolytic anemia, hemoglobinuria, & death (degree of parasitemia correlates roughly with severity)
- Risk factors for severe disease: asplenia, \downarrow cellular immunity, TNF inhib, \uparrow age, pregnancy

Diagnosis (NEJM 2012;366:2397)

- Clinical syndrome + **blood smear w/ intraerythrocytic parasites**
- Repeat smears (q12–24h) if sx persist despite negative initial smear
- PCR serum if smear \ominus and high clinical suspicion, serum IgG can help but some false \oplus

Treatment (JAMA 2016;315:1767)

- Atovaquone & azithro for mild/mod illness; clinda & quinine if severe (more toxic)
- Duration depends on host; immunosupp Pts often need longer Rx
- Exchange transfusion if parasitemia $>$ 10%, severe hemolysis or SIRS

TULAREMIA

Microbiology

- Infxn w/ *Francisella tularensis* via contact w/ animal tissue, aerosol, tick/insect bite

Clinical manifestations (typically w/in 2–10 d of exposure)

- Acute onset of fever, HA, nausea; ulcer w/ black eschar at site of entry; LAN; PNA

Diagnosis & treatment

- Hazardous and difficult to Cx, alert lab. Serology \oplus by wk 2. PCR by research lab.
- Streptomycin or gentamicin \times 7–14 d; empiric Rx may be needed given challenges in dx

FEVER SYNDROMES

Temperature $\geq 100.4^{\circ}\text{F}$ or $\geq 38^{\circ}\text{C}$

Diagnostic approach

- Thorough history including ROS, PMH/PSH, immunizations, including from childhood
- **Fever curve** (consider holding antipyretics); less likely to mount fever if: chronic renal or liver dis., extremes of age, protein calorie malnutrition, immunosupp., steroid use
- **Exposures:** travel, occupation or hobbies, animals and insects, sexual contacts, TB; consider age, geography, season and incubation time in relation to exposures
- **Physical exam:** complete exam w/ focus on mucous membranes & conjunctiva; cardiac murmurs; liver and spleen size; skin, genitals, lymph nodes, & joints; complete neuro exam incl cranial nerves and meningeal signs
- **If rash:** location, duration, progression/ Δ in appearance, was prodrome present

FEVER OF UNKNOWN ORIGIN (FUO)

Definition & etiologies

- **Fever** (as per above def) on >1 occasion during ≥ 3 wk & **no dx** despite 1 wk of evaluation
- More likely to be *unusual manifestation of common disease* than an uncommon disease
- In Pts with HIV: $>75\%$ causes are infectious, but *rarely due to HIV itself*
- **Frequent reassessment needed** to identify focal signs and progression of disease

Category	Etiologies of Classic FUO (Archives 2003;163:545; Medicine 2007;86:26)
Infection ~30%	Tuberculosis: disseminated or extrapulm disease can have normal CXR, PPD, sputum AFB; bx (lung, liver, bone marrow) for granulomas has 80–90% yield in miliary disease Abscess: dental, paraspinal, hepatic, splenic, subphrenic, pancreatic, perinephric, pelvic, prostatic abscess or prostatitis, appendicitis Endocarditis: consider HACEK orgs, Bartonella, Legionella, Coxiella Osteomyelitis, sinusitis, Lyme, typhoid, 1° CMV or EBV, malaria, Babesia
Connective tissue disease ~30%	Giant cell arteritis/PMR: headache, scalp pain, jaw claudication, visual disturbances, myalgias, arthralgias, ↑ ESR Adult-onset Still's: evanescent truncal rash, LAN, pharyngitis, ↑↑ ferritin PAN, ANCA \oplus , other vascul.; SLE, RA, psoriatic or reactive arthritis
Neoplasm ~20%	Lymphoma: LAN, HSM, ↓ Hct or plt, ↑ LDH; leukemia, myelodysplasia Renal cell carcinoma: microscopic hematuria, ↑ Hct HCC, pancreatic and colon cancers, sarcomas, mastocytosis Atrial myxomas: obstruction, embolism, constitutional symptoms
Misc ~20%	Drugs, factitious, DVT/PE, hematoma Thyroiditis or thyroid storm, adrenal insufficiency, pheochromocytoma Granulomatous hepatitis (many causes), sarcoidosis, Kikuchi's, Behcet's Familial Mediterranean fever (peritonitis, episodic fever, pleuritis; ↑ WBC & ESR during attacks); other defects in innate immunity

Workup

- Focus by H&P, incl: CBC w/ diff, lytes, BUN, Cr, LFTs, ESR, CRP, ANA, RF, cryoglobulinin, LDH, CK, SPEP, 3 sets BCx (off of abx), U/A, UCx, PPD or IGRA, HIV Ab \pm PCR, heterophile Ab (EBV serologies if \ominus), CMV antigen, Hep serologies if LFTs abnl
- Stop unnecessary meds (only 20% with a med cause have eos or rash), reassess 1–3 wk
- Imaging: CXR, chest & abd CT, consider tagged WBC, gallium scan, PET, TTE, LENI
- Consider temporal artery bx if ↑ ESR and age >60 , particularly if other s/s
- Consider BM aspirate & bx (esp. if signs of marrow infiltration) or liver bx (esp. if ↑ Aphi): even w/o localizing s/s, yield may be up to 24% (path and cx) (Archives 2009;169:2018)
- Pursue abnormalities raised by above w/u (eg, bx, MRI, etc., for dx, not screening)

Treatment

- Empiric abx *not indicated* (unless Pt neutropenic)
- Empiric glucocorticoids *not indicated* unless strong suspicion for specific rheumatologic dx
- Up to 30% of cases remain undiagnosed, most spontaneously defervesce (wks to mos)

FEVER AND RASH

Approach to diagnostic workup

- **Meningococcemia, endocarditis, RMSF, sepsis, toxic shock need urgent dx & Rx**
- Workup: CBC w/ diff, lytes, BUN/Cr, LFTs, LDH, CK, U/A, HIV Ab \pm PCR, BCx (off abx)
- To narrow Ddx: characterize time course of rash, progression & morphology

- Erythema multiforme:** symmetric "target" lesions often of palms, soles, & mucous memb
Infxn etiol: HSV 1/2, *Mycoplasma*, syphilis, tick-borne diseases, etc.
Non-infxn etiol: meds (eg, NSAIDs, sulfa), malignancy, autoimmune & rheum disease
- Erythema nodosum:** tender erythematous or violaceous nodules usually symmetric on LE
Infxn etiol: Strep, TB, EBV, *Bartonella*, HBV, psittacosis, fungal, *L. venereum*, etc.
Non-infxn etiol: sarcoidosis, IBD, Behcet's, other rheum, pregnancy/OCP use
- Pursue specific dx based on exposure hx & exam, including serologies, viral swab PCR, antigen tests and possibly skin biopsy ± exam of vesicular or bullae fluid if present
- Etiologies more broad in immunosupp. Pts, dx testing should be earlier and more extensive; higher risk of critical illness due to disseminated or rapidly progressive infxns

Variable	Possible Etiology
Summer/fall > other seasons	Enterovirus
Winter	Parvovirus, Meningococcemia
Spring/summer	Measles/rubella, Lyme, RMSF
Year-round	Adenovirus, <i>Mycoplasma</i>
Cat and dog exposure	<i>Bartonella</i> , <i>Pasteurella</i> , <i>Toxoplasma</i> , <i>Capnocytophaga</i>
Tick exposure	Lyme, RMSF, Ehrlichiosis, Anaplasmosis
Adult <30 y	Mononucleosis (EBV or CMV)
Inadequate immunization	Measles, Rubella, VZV, influenza
Sexually active	HIV, syphilis, disseminated gonococcal infection, HSV2

Consider noninfectious causes: allergy/DRESS, DVT, phlebitis, vasculitides, neutrophilic dermatoses, gout, connective tissues dis., malignancy, foreign body rxn

Treatment

- Empiric abx not indicated (unless Pt neutropenic or critically ill)

FEVER IN A RETURNED TRAVELER

Region or Exposure	Common Etiologies
Sub-Saharan Africa	Malaria >> dengue, rickettsial disease, enteric disease
Southeast Asia	Dengue > malaria, enteric disease (<i>S. typhi</i>), Chikungunya
Central & S. America	Enteric disease, malaria, dengue, Zika
Caribbean & Mexico	Dengue >> Chikungunya > malaria. Also consider Zika.
Middle East & S. Korea	Middle East Respiratory Syndrome
Freshwater swimming	Schistosomiasis, leptospirosis
Unpurified drinking water	Enteric disease (<i>E. coli</i> >> <i>S. typhi</i> , <i>Campylobacter</i> , hepatitis E > <i>Vibrio cholerae</i>), amebic liver abscess
Lacking immunizations	HAV/HBV, <i>S. typhi</i> , influenza, measles, rubella, yellow fever
Animal bite	Rabies
African "safari"	Rickettsial disease, African trypanosomiasis
Adult <30 years	Mononucleosis (EBV or CMV)

(NEJM 2002;347:505; CID 2007;44:1560; Curr Opin Infect Dis 2007;20:449)

- Pts visiting friends and relatives abroad are most likely to contract illness during travel
- Geography influences Ddx in returned travelers: <http://www.cdc.gov/travel/notices>
- Emerging pathogens: Influenza occurs year-round in the tropics. Chikungunya and dengue w/ ↑ areas of transmission, hemorrhagic fevers primarily in Central Africa.
- Consider domestic infxns, STIs, & non-infxn causes. Enteric parasites rarely cause fever.

Select clinical manifestations

- Ebola:** fever in traveler from area with active transmission of Ebola w/in 21 d: isolate & contact state health department (<http://www.cdc.gov/vhf/ebola>)
- Malaria:** nonspecific symptoms including diarrhea, myalgias, cough, altered mental status
- Dengue:** nonspecific symptoms including headache, severe myalgias, rash/petechiae
- Chikungunya:** nonspecific symptoms including joint pain, moderate myalgias, fever
- Typhoid** (Lancet 2015;385:1136): constipation, abd pain, possible rash, relative bradycardia
- Rickettsial disease:** headache, myalgias, lymphadenopathy, possible rash/eschar
- Zika:** fever, rash, arthralgia, H/A, conjunctivitis (<http://www.cdc.gov.zika>)

Workup

- Routine testing: CBC w/ diff, lyses, LFTs, BCx, UA, rapid malaria test
- Fever in a traveler from a malaria zone is malaria until proven otherwise; consider hospitalization and empiric Rx.** One ⊖ smear does not r/o malaria.
- Other tests based on s/s, labs, exposure, incubation period, geography and seasonality. O&P exam, CXR, blood smears for filaria/Babesiosis/Borrelia, serologies, STI & HIV, PPD or IGRA, bone marrow aspirate, bx of lymph nodes or skin lesions, CSF studies.

HYPOPITUITARY SYNDROMES

Panhypopituitarism (*Lancet* 2016;epub)

- Etiologies
 - Primary:** surgery, radiation (develops after avg 4–5 y), tumors (primary or metastatic), infection, infiltration (sarcoid, hemochromatosis), autoimmune, ischemia (including Sheehan's syndrome caused by pituitary infarction intrapartum), carotid aneurysms, cavernous sinus thrombosis, trauma, medications (eg, ipilimumab)
 - Secondary** (hypothalamic dysfunction or stalk interruption): tumors (including craniopharyngioma), infection, infiltration, radiation, surgery, trauma
- Clinical manifestations
 - Hormonal:** acute → weakness, easy fatigability, hypotension, polyuria and polydipsia; chronic → bradycardia, sexual dysfxn, loss of axillary & pubic hair, wt loss, amenorrhea
 - Mass effect:** headache, visual field Δs, cranial nerve palsies, galactorrhea
 - Apoplexy** (pituitary hemorrhage or infarction, usually w/ underlying pituitary adenoma): sudden headache, N/V, visual field Δs, cranial nerve palsies, meningismus, Δ MS, hypoglycemia, hypotension
- Diagnostic studies
 - Hormonal studies**
 - chronic: ↓ target gland hormone + ↓ or normal trophic pituitary hormone
 - acute: target gland hormonal studies may be *normal*
 - partial hypopituitarism is more common than panhypopituitarism*

Pituitary MRI

- Treatment
 - Replace deficient target gland hormones
 - Most important deficiencies to recognize and treat in inpatients are *adrenal insufficiency* and *hypothyroidism*; if both present, treat with glucocorticoids first, then replace thyroid hormone so as not to precipitate adrenal crisis

↓ ACTH

- Sx similar to 1° adrenal insufficiency (see "Adrenal Disorders") except:
 - no salt cravings or hypokalemia (b/c aldo preserved)
 - no hyperpigmentation (b/c ACTH/MSH is not ↑)

↓ TSH

- Sx of central hypothyroidism similar to 1° (see "Thyroid Disorders") except absence of goiter
- Dx with free T₄ in addition to TSH, as TSH may be low or *inappropriately normal*

↓ PRL

- Inability to lactate

↓ GH

- ↑ chronic risk for osteoporosis, fatigue, weight gain
- Dx with failure to ↑ GH w/ appropriate stimulus (eg, insulin tolerance test, glucagon stimulation)
- GH replacement in adults controversial (*Annals* 2003;35:419)

↓ FSH & LH

- Clinical manifestations: ↓ libido, impotence, oligomenorrhea or amenorrhea, infertility, ↓ muscle mass, osteoporosis
- Physical exam: ↓ testicular size; loss of axillary, pubic and body hair
- Dx with: ↓ a.m. testosterone or estradiol (also assess SHBG, esp. in obese) and ↓ or normal FSH/LH (all levels ↓ in acute illness, ∴ do not measure in hospitalized Pts)
- Treatment: testosterone or estrogen replacement vs. correction of the underlying cause

↓ ADH (hypothalamic or stalk disease): diabetes insipidus

- Typically from mass lesion extrinsic to sella; pituitary tumor does not typically present w/ DI
- Clinical manifestations: severe polyuria, *mild* hypernatremia (severe if ↓ access to H₂O)
- Diagnostic studies: see "Sodium and Water Homeostasis"

HYPERPITUITARY SYNDROMES

Pituitary tumors

- Pathophysiology: adenoma → excess of trophic hormone (if tumor fxnl, but 30–40% not) and potentially deficiencies in other trophic hormones due to compression; cosecretion of PRL and growth hormone in 10% of prolactinomas
- Clinical manifestations: syndromes due to oversecretion of hormones (see below)
 - ± mass effect: headache, visual Δs, diplopia, cranial neuropathies
- Workup: MRI, hormone levels, ± visual field testing
 - if <10 mm, no mass effect, no hormonal effects, can f/u q3–6mo

Hyperprolactinemia (NEJM 2010;362:1219 and JCEM 2011;96:273)

- Etiology
 - prolactinoma (50% of pituitary adenomas)
stalk compression due to nonprolactinoma → ↓ inhibitory dopamine → ↑ PRL (mild)
- Physiology: PRL induces lactation and inhibits GnRH → ↓ FSH & LH
- Clinical manifestations: **amenorrhea, galactorrhea, infertility**, ↓ libido, impotence
- Diagnostic studies
 - ↑ **PRL** (✓ fasting levels), but elevated in many situations, ∵ r/o pregnancy or exogenous estrogens, hypothyroidism, dopamine agonists (eg, psych meds, antiemetics), renal failure (↓ clearance), cirrhosis, stress, ↑ carb diet. Watch for hook effect: assay artifact yielding falsely low PRL if very high serum PRL levels; retest with sample dilution.
- MRI** to evaluate for tumor
- Treatment
 - If asx (no HA, galactorrhea, hypogonadal sx) & microadenoma (<**10 mm**), follow w/ MRI
 - If sx or macroadenoma (**≥10 mm**) options include:
 - medical** with dopamine agonist such as cabergoline (70–100% success rate) or bromocriptine (not as well tol); side effects include N/V, orthostasis, nasal congestion
 - surgical**: transphenoidal surgery (main indications: failed or cannot tolerate medical Rx, GH cosecretion or neurologic sx not improving); 10–20% recurrence rate
 - radiation**: if medical or surgical therapy have failed or are not tolerated

Acromegaly (↑ GH; 10% of adenomas; NEJM 2006;355:2558 & JCEM 2014;99:3933)

- Physiology: stimulates secretion of insulin-like growth factor 1 (IGF-1)
- Clinical manifestations: ↑ soft tissue, arthralgias, jaw enlargement, headache, carpal tunnel syndrome, macroglossia, hoarseness, sleep apnea, amenorrhea, impotence, diabetes mellitus, acanthosis/skin tags, ↑ sweating, HTN/CMP, colonic polyps
- Diagnostic studies: no utility in checking random GH levels because of pulsatile secretion
↑ **IGF-1** (somatomedin C); ± ↑ PRL; OGTT → GH not suppressed to <1 (<0.3 if newer assay) ng/mL; pituitary MRI to evaluate for tumor
- Treatment: **surgery**, octreotide (long- and short-acting preparations), dopamine agonists (if PRL co-secretion), pegvisomant (GH receptor antagonist), radiation
- Prognosis: w/o Rx 2–3x ↑ mortality, risk of pituitary insufficiency, colon cancer

Cushing's disease (↑ ACTH): 10–15% of adenomas; see "Adrenal Disorders"

Central hyperthyroidism (↑ TSH, ↑ α-subunit): extremely rare; see "Thyroid Disorders"

↑ **FSH & LH**: usually non-fxn, presents as *hypopituitarism* b/c of compression effects

Multiple Endocrine Neoplasia (MEN) Syndromes

Type	Main features
1 (<i>MENIN</i> inactiv.)	Parathyroid hyperplasia/adenomas → hypercalcemia (~100% penetrance) Pancreatic islet cell neoplasia (gastrin, VIP, insulin, glucagon) Pituitary adenomas (fxn or non-fxn)
2A (<i>RET</i> proto-oncogene)	Medullary thyroid carcinoma (MTC) Pheochromocytoma (~50%) Parathyroid hyperplasia → hypercalcemia (15–20%)
2B (<i>RET</i> proto-oncogene)	Medullary thyroid carcinoma (MTC) Pheochromocytoma (~50%) Mucosal and gastrointestinal neuromas

Autoimmune Polyglandular Syndromes (APS)

Type	Features
I (children)	Mucocutaneous candidiasis, hypoparathyroidism, adrenal insufficiency
II (adults)	Adrenal insufficiency, autoimmune thyroid disease, diabetes mellitus type 1

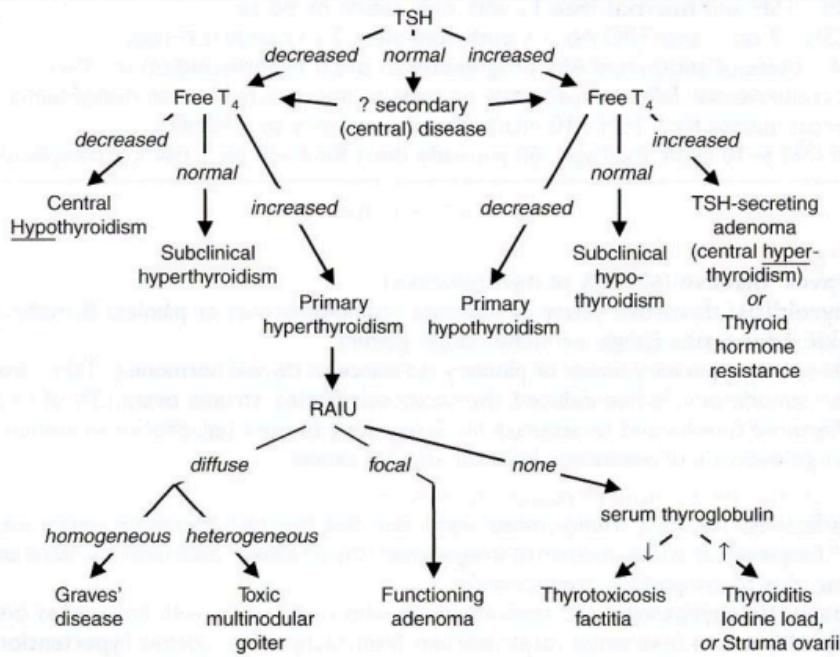
THYROID DISORDERS

Diagnostic Studies in Thyroid Disorders

Test	Comments
Thyroid-stimulating hormone (TSH)	Most sensitive test to detect 1° hypo- and hyperthyroidism May be inappropriately normal in central etiologies ↓d by dopamine, glucocorticoids, severe illness
Free T ₄ (FT ₄)	Unbound T ₄ , not influenced by TBG
Total T ₃ and T ₄	Total serum concentrations (∴ influenced by TBG)
Thyroxine-binding globulin (TBG)	↑ TBG (∴ ↑ T ₄): estrogen (OCP, pregnancy), hepatitis, opioids, hereditary ↓ TBG (∴ ↓ T ₄): androgens, glucocorticoids, nephritic syndrome, cirrhosis, acromegaly, antiepileptics, hereditary
Reverse T ₃	Inactive, ↑d in sick euthyroid syndrome
Thyroid antibodies	Antithyroid peroxidase (TPO) seen in Hashimoto's (high titer), painless thyroiditis and Graves' disease (low titer) Thyroid-stimulating Ig (TSI) and thyrotropin-binding inhibitory immunoglobulin (TBII) seen in Graves' disease
Thyroglobulin	↑d in goiter, hyperthyroidism and thyroiditis ↓d in factitious ingestion of thyroid hormone Tumor marker for thyroid cancer only after total thyroidectomy and radioiodine therapy
Radioactive iodine uptake (RAIU) scan	Useful to differentiate causes of hyperthyroidism ↑ uptake homogeneous = Graves' disease heterogeneous = multinodular goiter 1 focus of uptake w/ suppression of rest of gland = hot nodule no uptake = subacute painful (de Quervain's) or silent thyroiditis, exogenous thyroid hormone, recent iodine load, struma ovarii or antithyroid drugs

(Lancet 2001;357:619 & Thyroid 2003;13:19)

Figure 7-1 Approach to thyroid disorders



HYPOTHYROIDISM

Etiologies

- Primary (>90% of cases of hypothyroidism; ↓ free T₄, ↑ TSH)
 - Goitrous: **Hashimoto's thyroiditis** (after hyperthyroid phase of thyroiditis), iodine deficiency, lithium, amiodarone

- Nongoitrous: surgical destruction, s/p radioactive iodine or XRT, amiodarone
- Secondary (central): ↓ free T₄; TSH low, inappropriately nl, or slightly high (although functionally inactive due to abnormal glycosylation); due to hypothalamic or pituitary failure

Hashimoto's thyroiditis

- Autoimmune destruction with patchy lymphocytic infiltration
- Associated with other autoimmune disease and may be part of APS Type II
- ⊕ antithyroid peroxidase (anti-TPO) and antithyroglobulin (anti-Tg) Abs in >90%

Clinical manifestations (Annals 2009;151:ITC61)

- Early:** weakness, fatigue, arthralgias, myalgias, headache, depression, cold intolerance, weight gain, constipation, menorrhagia, dry skin, coarse brittle hair, brittle nails, carpal tunnel syndrome, delayed DTRs ("hung up" reflexes), diastolic HTN, hyperlipidemia
- Late:** slow speech, hoarseness, loss of outer third of eyebrows, **myxedema** (nonpitting skin thickening due to ↑ glycosaminoglycans), periorbital puffiness, bradycardia, pleural, pericardial, & peritoneal effusions, atherosclerosis
- Myxedema crisis:** hypothermia, hypotension, hypoventilation, Δ MS (including coma) hyponatremia, hypoglycemia; often precipitated by infection or major cardiopulmonary or neurologic illness (Med Clin North Am 2012;96:385)

Diagnostic studies

- ↓ FT₄; ↑ TSH in primary hypothyroidism; ⊕ antithyroid Ab (TPO) in Hashimoto's thyroiditis
- May see hyponatremia, hypoglycemia, anemia, ↑ LDL, ↓ HDL and ↑ CK
- Screening recommended for pregnant women

Treatment of overt hypothyroidism

- Levothyroxine (1.5–1.7 µg/kg/d), re ✓ TSH q5–6wk & titrate until euthyroid (can take mos)
- Lower starting dose (0.3–0.5 µg/kg/d) if at risk for ischemic heart disease or elderly
- ↑ dose typically needed if:
 - poor GI absorption: meds that ↓ absorption (iron, calcium, cholestyramine, sucralfate, PPI), celiac disease, IBD
 - meds that accelerate T₄ catabolism (eg, phenytoin, phenobarbital)
 - initiation of estrogen replacement; pregnancy (~30% ↑ by wk 8): TSH goals change by trimester: 1st = 0.1–2.5 mIU/L, 2nd = 0.2–3.0 mIU/L, 3rd = 0.3–3.0 mIU/L (Thyroid 2011;21:1081)
- Myxedema coma: load 5–8 µg/kg T₄ IV, then 50–100 µg IV qd; b/c peripheral conversion impaired, may also give 5–10 µg T₃ IV q8h if unstable w/ bradycardia and/or hypothermia (T₃ more arrhythmogenic); must give empiric adrenal replacement therapy first as ↓ adrenal reserves in myxedema coma

Subclinical hypothyroidism (Lancet 2012;379:1142)

- Mild ↑ TSH and **normal free T₄** with only subtle or no sx
- If TSH <7 or ⊖ anti-TPO Ab, ~½ euthyroid after 2 y (JCEM 2012;97:1962)
 - if ↑ titers of antithyroid Abs, progression to overt hypothyroidism is ~4%/y
- Rx controversial: follow expectantly or treat to improve mild sx or dyslipidemia
 - most initiate Rx if TSH >10 mU/L, goiter, pregnancy or infertility
 - if TSH 5–10 mU/L Rx if age ≤60 y (usually don't Rx if ≥60 b/c ↑ risk CV complications)

HYPERTHYROIDISM

Etiologies (Lancet 2016;epub)

- Graves' disease** (60–80% of thyrotoxicosis)
- Thyroiditis:** thyrotoxic phase of subacute (granulomatous) or painless (lymphocytic)
- Toxic adenomas** (single or multinodular goiter)
- TSH-secreting pituitary tumor or pituitary resistance to thyroid hormone (↑ TSH, ↑ free T₄)
- Misc: amiodarone, iodine-induced, thyrotoxicosis factitia, struma ovarii (3% of ovarian dermoid tumors and teratomas), hCG-secreting tumors (eg, choriocarcinoma), large deposits of metastatic follicular thyroid cancer

Clinical manifestations of hyperthyroidism

- Restlessness, sweating, tremor, moist warm skin, fine hair, tachycardia, AF, weight loss, ↑ frequency of stools, menstrual irregularities, hyperreflexia, osteoporosis, stare and lid lag (due to sympathetic overactivity)
- Apathetic thyrotoxicosis:** seen in elderly who can present with lethargy as only sx
- Thyroid storm** (extremely rare): delirium, fever, tachycardia, systolic hypertension but wide pulse pressure and ↓ MAP, GI symptoms; 20–50% mortality

Laboratory testing

- ↑ FT₄ and FT₃; ↓ TSH (except in TSH-secreting tumors)
- RAIU scan** is very useful study to differentiate causes (see table on page 7-3); cannot do if recent IV contrast or amio load b/c iodine blocks uptake, so ✓ autoantibodies instead
- Rarely need to ✓ for autoantibodies except in pregnancy (to assess risk of fetal Graves')
- May see hypercalciuria ± hypercalcemia, ↑ Aφ, anemia

Graves' disease (NEJM 2008;358:2594)

- ♀:♂ ratio is 5–10:1, most Pts between 40 and 60 y at dx
- ⊕ thyroid antibodies: TSI or TBII (⊕ in 80%), anti-TPO, antithyroglobulin; ANA
- Clinical manifestations in addition to those of hyperthyroidism (see above):
 - goiter:** diffuse, nontender, w/ thyroid bruit
 - ophthalmopathy (NEJM 2010;362:726):** seen in 50%; up to 90% if formally tested. Periorbital edema, lid retraction, proptosis, conjunctivitis, diplopia (EOM infiltration); associated w/ smoking. Stare and lid lag seen in any type of hyperthyroidism.
 - pretibial myxedema (3%):** infiltrative dermopathy

Thyroiditis (NEJM 2003;348:2646; Med Clin North Am 2012;96:223)

- Acute:** bacterial infection (very rare in U.S. except postsurgical), typically *Staph/Strep* spp.
- Subacute:** transient thyrotoxicosis → transient hypothyroidism → normal thyroid fxn
 - painful** (viral, granulomatous or de Quervain's): fever, ↑ ESR; Rx = NSAIDs, ASA, steroids
 - silent** (postpartum, autoimmune including Hashimoto's, or lymphocytic): painless, ⊕ TPO Abs; if postpartum, can recur with subsequent pregnancies
 - other:** meds (amiodarone, lithium, TKIs), palpation thyroiditis, post-radiation

Treatment (Thyroid 2011;21:593)

- β-blockers: control tachycardia (propranolol also ↓ T₄ → T₃ conversion)
- Graves' disease: either antithyroid drugs or radioactive iodine (JAMA 2015;314:2544)
 - methimazole:** 70% chance of recurrence after 1 y; side effects include pruritus, rash, arthralgia, fever, N/V and agranulocytosis in 0.5%. PTU: 2nd line (risk of hepatocellular necrosis; TID dosing; slower effect; JCEM 2007;92:2157). For both, need to ✓ LFTs, WBC, TSH at baseline and in follow-up.
 - radioactive iodine (RAI) (NEJM 2011;364:542):** typically done as outPt; preRx selected Pts w/ CV disease or elderly w/ antithyroid drugs to prevent ↑ thyrotoxicosis, stop 3 d before to allow RAI uptake; >75% of treated Pts become hypothyroid
 - surgery:** less commonly chosen for Graves', usually for Pts w/ obstructive goiter or ophthalmopathy
- Ophthalmopathy: can worsen after RAI; prophylax w/ prednisone in high-risk Pts; can be Rx'd w/ radiation and/or surgical decompression of orbits (NEJM 2009;360:994)
- Toxic adenoma or toxic multinodular goiter: RAI or surgery (methimazole preRx for surgery, in selected patients before RAI)
- Thyroid storm: β-blocker, PTU or methimazole, iopanoic acid or iodide (for Wolff-Chaikoff effect) >1 h after PTU, ± steroids (↓ T₄ → T₃)

Subclinical hyperthyroidism (Lancet 2012;379:1142)

- Mild ↓ TSH and **normal free T₄** with only subtle or no sx
- ~15% → overt hyperthyroidism in 2 y; ↑ risk of AF, CHD (Archives 2012;172:799), fracture (JAMA 2015;313:2055)
- Rx controversial: consider if TSH <0.1 mU/L and ↑ risk for CV disease or osteopenic

NONTHYROIDAL ILLNESS (SICK EUTHYROID SYNDROME)

(Thyroid 1997;7:125 and J Endocrinol 2010;205:1)

- TFT abnormalities in Pts w/ severe nonthyroidal illness (∴ in acute illness, ✓ TFTs only if ↑ concern for thyroid disease); may have acquired transient central hypothyroidism
- If thyroid dysfxn suspected in critically ill Pt, TSH alone not reliable; must measure total T₄, FT₄, & T₃
- Mild illness: ↓ T₄ → T₃ conversion, ↑ rT₃ ⇒ ↓ T₃; in severe illness: ↓ TBG & albumin, ↑↑ rT₃ ⇒ ↓↓ T₃, ↑ degradation of T₄, central ↓ TSH ⇒ ↓↓ T₃, ↓↓ T₄, ↓ FT₄, ↓ TSH
- Recovery phase: ↑ TSH followed by recovery of T₄ and then T₃
- Replacement thyroxine not helpful or recommended for critically ill Pts w/ ↓ T₃ and T₄ unless other s/s of hypothyroidism

AMIODARONE AND THYROID DISEASE**Overview (Annals 1997;126:63 & JCEM 2010;95:2529)**

- 6 mg iodine per 200-mg tablet; risk of thyroid dysfunction lower with lower doses
- ✓ TSH prior to therapy, at 4-mo intervals on amio, and for 1 y after if amio d/c'd

Hypothyroidism (occurs in ~10%; more common in iodine-replete areas)

- Pathophysiology
 - (1) Wolff-Chaikoff effect: iodine load ↓ I⁻ uptake, organification and release of T₄ & T₃
 - (2) inhibits T₄ → T₃ conversion
 - (3) ? direct/immune-mediated thyroid destruction

- Normal individuals: ↓ T₄; then escape Wolff-Chaikoff effect and have ↑ T₄, ↓ T₃, ↑ TSH; then TSH normalizes (after 1–3 mo)
- Susceptible individuals (eg, subclinical Hashimoto's, ∴ ✓ anti-TPO) do not escape effects
- Treatment: thyroxine to normalize TSH; may need larger than usual dose

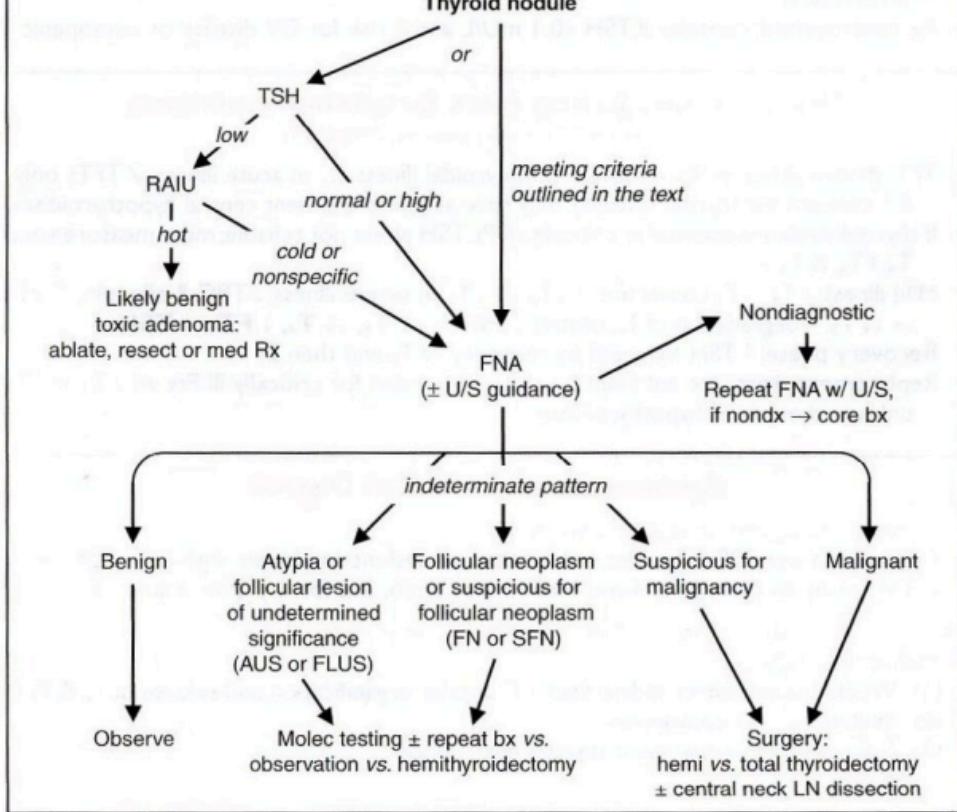
Hyperthyroidism (3% of Pts on amio; ~10–20% of Pts in iodine-deficient areas)

- Type 1 = underlying multinodular goiter or autonomous thyroid tissue
Jod-Basedow effect: iodine load → ↑ synthesis of T₄ and T₃ in autonomous tissue
- Type 2 = destructive thyroiditis
↑ release of preformed T₄ & T₃ → hyperthyroidism → hypothyroidism → recovery
- Doppler U/S: type 1 w/ ↑ thyroid blood flow; type 2 w/ ↓ flow
- Treatment: not absolutely necessary to d/c amio b/c amio ↓ T₄ → T₃ conversion
methimazole for type 1; steroids (eg, 40 mg prednisone qd) for type 2
often difficult to distinguish, so Rx for both typically initiated (JCEM 2001;86:3)
consider thyroidectomy in severely ill patient

THYROID NODULES (NEJM 2015;373:2347 & Thyroid 2016;26:1)

- Prevalence 5–10% (50–60% if screen with U/S), ♀ > ♂, ~7–15% malignant
- Features associated w/ ↑ risk of malig: age <20 or >70 y, ♂, h/o neck XRT, hard & immobile mass, cervical LAN, dysphonia
- Worrisome U/S findings: hypoechoic, solid, irregular borders, microcalcifications, height > width, >20 mm (JAMA IM 2013;173:1788)
- Features associated w/ benign dx: cystic nodules, "spongiform" sonographic pattern
- Screening U/S recommended for those with FHx of MEN2 or medullary thyroid cancer, personal h/o neck XRT, palpable nodules or multinodular goiter
- Any evidence of tracheal deviation or compression → consider ✓ PFTs & refer to surgery
- >10-mm nodule: FNA if hypoechoic solid or solid component of cystic; ↑ suspicion of malig if irregular margins, microcalcifications, rim Ca²⁺, height > width, or extrathyroidal extension
- >15-mm nodule: FNA if solid isoechoic, or partially cystic with mural solid component
- >20-mm nodule: FNA if spongiform/other benign solid pattern (no FNA if purely cystic)
- Molecular testing if indeterminate pattern on FNA (occurs in ~15–30%)
- Suppressive Rx w/ high-dose levothyroxine no longer recommended for benign nodules in iodine-sufficient regions
- Cancer very rare in axs nodules diagnosed as benign (JCEM 2014;99:510 & JAMA 2015;313:926)
- After complete surgical resection of thyroid cancer, RAI in medium- and high-risk Pts (Lancet 2013;381:1046 & 1058)

Figure 7-2 Approach to thyroid nodules (NEJM 2015;373:2347 & Thyroid 2016;26:1)



ADRENAL DISORDERS

CUSHING'S SYNDROME (HYPERCORTISOLISM)

Definitions (*Lancet* 2015;386:913)

- Cushing's syndrome = cortisol excess
- Cushing's disease = Cushing's syndrome 2° to pituitary ACTH hypersecretion

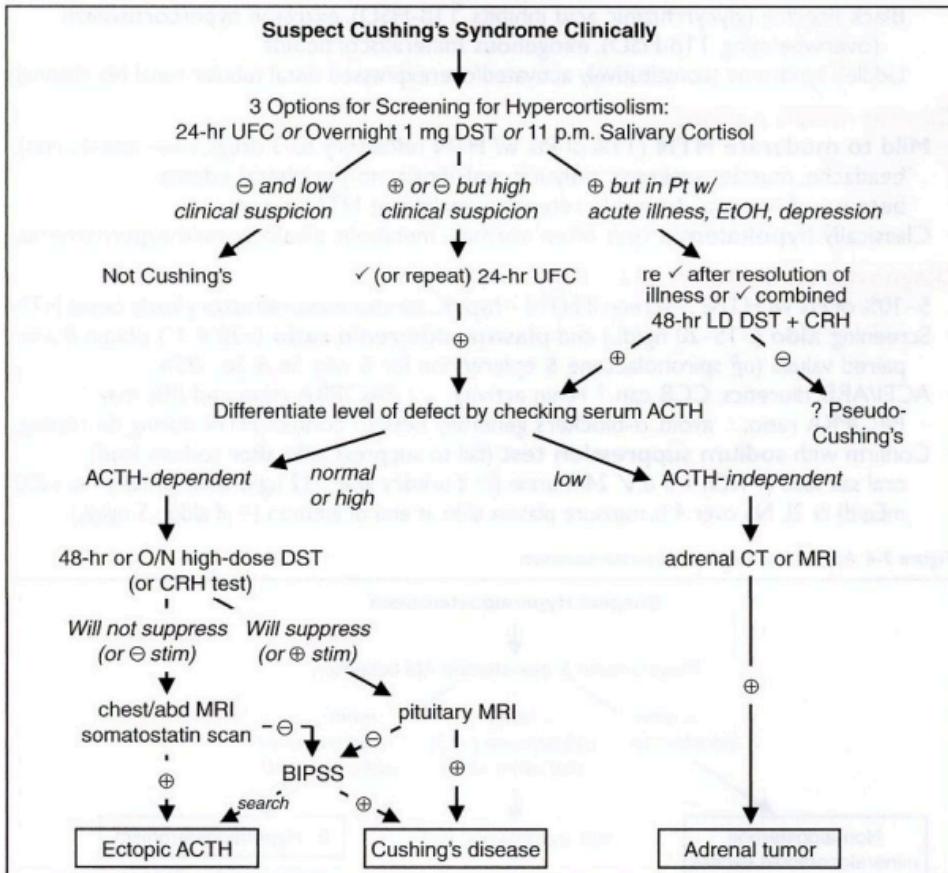
Etiologies of hypercortisolism

- Most commonly iatrogenic caused by exogenous glucocorticoids (though underreported)
- **Cushing's disease** (60–70%): ACTH-secreting pituitary adenoma (usually microadenoma) or hyperplasia
- **Adrenal tumor** (15–25%): adenoma or (rarely) carcinoma
- **Ectopic ACTH** (5–10%): SCLC, carcinoid, islet cell tumors, medullary thyroid cancer, pheo

Clinical manifestations (*Lancet* 2006;367:13)

- Nonspecific: glucose intolerance or DM, HTN, obesity, oligo- or amenorrhea, osteoporosis
- More specific: central obesity w/ extremity wasting, dorsocervical fat pads, spont. bruising
- Most specific: proximal myopathy, rounded facies, facial plethora, wide purple striae
- Other: depression, insomnia, psychosis, impaired cognition, hypokalemia, acne, hirsutism, hyperpigmentation (if ↑ ACTH), fungal skin infxns, nephrolithiasis, polyuria

Figure 7-3 Approach to suspected Cushing's syndrome (nb, very difficult to dx as an inPt) (*JCEM* 2008;93:1526)



CRH, corticotropin-releasing hormone; DST, dexamethasone suppression test; UFC, urinary free cortisol

Overnight 1 mg DST = give 1 mg at 11 p.m.; ✓ 8 a.m. serum cortisol (suppression if <1.8 µg/dL); <5% false ⊕ (primarily used to evaluate subclinical Cushing's in adrenal "incidentalomas")

11 p.m. salivary cortisol = abnl if level ↑; 24-h UFC = abnl if level ↑, >4X ULN virtually diagnostic

48-h LD DST + CRH = 0.5 mg q6h × 2 d, then IV CRH 2 h later; ✓ serum cortisol 15 min later (⊕ = >1.4 µg/dL)

48-h LD DST = 0.5 mg q6h × 2 d; ✓ 24-h UFC at base. & during last 24 h of dex (suppress if <10% of base)

48-h HD DST = 2 mg q6h × 2 d; ✓ 24-h UFC as per LD DST

O/N HD DST = 8 mg at 11 p.m.; ✓ 9 a.m. serum cortisol (suppression if <32% of baseline)

CRH test = 1 µg/kg IV; ✓ cortisol and ACTH (⊕ stim if >35% ↑ in ACTH or >20% ↑ in cortisol above baseline)

BIPSS, bilat. inferior petrosal sinus vein sampling; ✓ petrosal:peripheral ACTH ratio (⊕ = 2 basal, >3 after CRH)

Treatment of Cushing's syndrome (JCEM 2015;100:2807)

- Surgical resection of pituitary adenoma, adrenal tumor or ectopic ACTH-secreting tumor
- If transsphenoidal surgery (TSS) not successful → repeat TSS. Can do pituitary XRT, but XRT not effective immediately, ∴ initiate medical Rx w/ mitotane, ketoconazole, or metyrapone to ↓ cortisol, and/or mifepristone to block cortisol action at glucocorticoid receptor; or bilat surgical adrenalectomy if med Rx fails or is contraindicated.
- Glucocorticoid replacement therapy × 6–36 mo after TSS (lifelong glucocorticoid + mineralocorticoid replacement if medical or surgical adrenalectomy)

HYPERALDOSTERONISM**Etiologies**

- Primary** (adrenal disorders, renin-independent increase in aldosterone; JCEM 2015;100:1) adrenal hyperplasia (60–70%), adenoma (**Conn's syndrome**, 30–40%), carcinoma glucocorticoid-remediable aldosteronism (GRA; ACTH-dep. rearranged promoter)
- Secondary** (extra-adrenal disorders, ↑ aldosterone is renin-dependent)
 - Primary reninism: renin-secreting tumor (rare)
 - Secondary reninism: renovascular disease: RAS, malignant hypertension; edematous states w/ ↓ effective arterial volume: CHF, cirrhosis, nephrotic syndrome; hypovolemia, diuretics, T2D, Bartter's (defective Na/K/2Cl transporter = receiving loop diuretic), Gitelman's (defective renal Na/Cl transporter = receiving thiazide diuretic)
- Nonaldosterone mineralocorticoid excess** mimics hyperaldosteronism
 - 11 β -HSD defic. (→ lack of inactivation of cortisol, which binds to mineralocorticoid recept.)
 - Black licorice (glycyrrhetic acid inhibits 11 β -HSD), extreme hypercortisolism (overwhelming 11 β -HSD), exogenous mineralocorticoids
 - Liddle's syndrome (constitutively activated/overexpressed distal tubular renal Na channel)

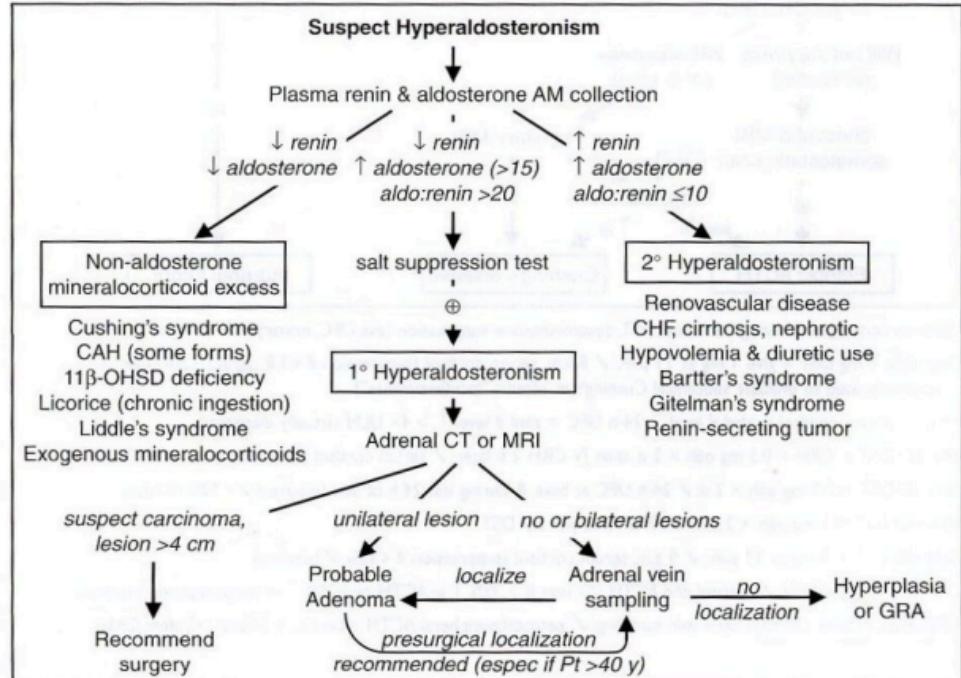
Clinical manifestations

- Mild to moderate HTN** (11% of Pts w/ HTN refractory to 3 drugs; Lancet 2008;371:1921), headache, muscle weakness, polyuria, polydipsia; no peripheral edema because of “escape” from Na retention; malignant HTN is rare
- Classically **hypokalemia** (but often normal), metabolic alkalosis, mild hypernatremia

Diagnostic studies (JCEM 2008;93:3266)

- 5–10% of Pts w/ HTN; ∴ screen if HTN + hypoK, adrenal mass, refractory/early onset HTN
- Screening: **aldo** (>15–20 ng/dL) and **plasma aldo:renin ratio** (>20 if 1°) obtain 8 a.m. paired values (off spironolactone & eplerenone for 6 wk); Se & Sp >85%
- ACEI/ARB, diuretics, CCB can ↑ renin activity → ↓ PAC/PRA ratio and βBs may ↑ PAC/PRA ratio; ∴ avoid. α-blockers generally best to control HTN during dx testing.
- Confirm with **sodium suppression test** (fail to suppress aldo after sodium load) oral salt load (+ KCl) × 3 d, ✓ 24-h urine (⊕ if urinary aldo >12 µg/d while urinary Na >200 mEq/d) or 2L NS over 4 h, measure plasma aldo at end of infusion (⊕ if aldo >5 ng/dL)

Figure 7-4 Approach to suspected hyperaldosteronism



Treatment (Surg Clin N Am 2014;94:643)

- Adenoma → adrenalectomy vs. medical Rx w/ spironolactone or eplerenone
- Hyperplasia → spironolactone or eplerenone; GRA → glucocorticoids ± spironolactone
- Carcinoma → adrenalectomy

ADRENAL INSUFFICIENCY

Etiologies

- **Primary** = adrenocortical disease = **Addison's disease**
 - autoimmune:** isolated or in assoc w/ APS (see table on page 7-2)
 - infection:** TB, CMV, histoplasmosis, paracoccidioidomycosis
 - vascular:** hemorrhage (usually in setting of sepsis), adrenal vein thrombosis, HIT, trauma
 - metastatic disease:** (90% of adrenals must be destroyed to cause insufficiency)
 - deposition diseases:** hemochromatosis, amyloidosis, sarcoidosis
 - drugs:** azole antifungals, etomidate (even after single dose), rifampin, anticonvulsants
- **Secondary** = pituitary failure of ACTH secretion (but aldosterone **intact** b/c RAA axis)
 - any cause of primary or secondary hypopituitarism (see "Pituitary Disorders")
 - glucocorticoid therapy (can occur after ≤ 2 wk of "suppressive doses"; dose effect variable; even <10 mg of prednisone daily chronically can be suppressive)
 - megestrol (a progestin with some glucocorticoid activity)

Clinical manifestations (Lancet 2014;383:2152)

- **Primary or secondary:** **weakness and fatigability** (99%), **anorexia** (99%), **orthostatic hypotension** (90%), nausea (86%), vomiting (75%), hyponatremia (88%)
- **Primary only** (extra s/s due to lack of aldosterone and ↑ ACTH): marked **orthostatic hypotension** (because volume-depleted), salt craving, **hyperpigmentation** (seen in creases, mucous membranes, pressure areas, nipples), **hyperkalemia**
- **Secondary only:** ± other manifestations of hypopituitarism (see "Pituitary Disorders")

Diagnostic studies (JCEM 2016;101:364)

- Early a.m. serum cortisol: <5 µg/dL virtually diagnostic; ≥ 18 µg/dL rules it out (except in severe septic shock—see below)
- Standard (250 µg) **cosyntropin stimulation test** (testing ability of ACTH → ↑ cortisol)
 - normal = 60-min (or 30-min) post-ACTH cortisol ≥ 18 µg/dL
 - abnormal in **primary** b/c adrenal gland diseased and unable to give adequate output
 - abnormal in **chronic secondary** b/c adrenals atrophied and unable to respond (very rarely, may be **normal** in **acute pituitary injury** b/c adrenals still able to respond → use early a.m. cortisol instead)
- Other tests (w/ guidance by endocrinologist): renin, aldosterone, insulin-induced hypoglycemia (measure serum cortisol response); metyrapone (blocks cortisol synthesis and therefore stimulates ACTH, measure plasma 11-deoxycortisol and urinary 17-hydroxycorticosteroid levels)
- Other lab abnormalities: hypoglycemia, eosinophilia, lymphocytosis, ± neutropenia
- ACTH: ↑ in 1°, ↓ or low-normal in 2°
- Imaging studies to consider
 - pituitary MRI to detect anatomical abnormalities
 - adrenal CT: small, noncalcified adrenals in autoimmune, enlarged in metastatic disease, hemorrhage, infection or deposition (although they may be normal-appearing)

Adrenal insufficiency & critical illness (NEJM 2003;348:727; JAMA 2009;301:2362)

- ↑ circulating cortisol despite ↓ ACTH due to ↓ clearance and possibly stimulation by cytokines; low cortisol binding proteins; ∴ dx of adrenal insufficiency problematic (NEJM 2013;368:1477)
- Nonetheless, reasonable to perform ACTH stim ASAP in hypotensive Pt suspected to have absolute adrenal insufficiency
- Reasonable to perform 250-µg ACTH stim and initiate glucocorticoid replacement if ↑ in cortisol <9 µg/dL or absolute cortisol level <10 µg/dL, but decision to Rx should be based on clinical assessment; unlikely to require Rx if spot or post-ACTH cortisol >18 µg/dL
- Initiate corticosteroids early: use hydrocortisone 50–100 mg IV q6–8h; prior to ACTH stim test, use dexamethasone 2–4 mg IV q6h + fludrocortisone 50 µg daily
- Rx of relative adrenal insufficiency controversial (see "Sepsis")

Treatment

- Acute insufficiency: volume resuscitation w/ normal saline + **hydrocortisone IV** as above
- **Chronic insufficiency**
 - prednisone –5 mg PO qam, or hydrocortisone: 15–25 mg PO qd ($\frac{2}{3}$ a.m., $\frac{1}{3}$ early p.m.)
 - fludrocortisone (not needed in 2° adrenal insufficiency): 0.05–0.1 mg PO qam
 - backup dexamethasone 4-mg IM prefilled syringe given to Pt for emergency situations

PHEOCHROMOCYTOMA & PARAGANGLIOMA

Clinical manifestations (five Ps) (*Lancet* 2005;366:665)

- **Pressure** (hypertension, paroxysmal in 50%, severe & resistant to Rx, occ orthostatic)
- **Pain** (headache, chest pain)
- **Palpitations** (tachycardia, tremor, wt loss, fever)
- **Perspiration** (profuse)
- **Pallor** (vasoconstrictive spell)
- "Rule of 10": 10% extra-adrenal (known as paraganglioma), 10% in children, 10% multiple or bilateral, 10% recur (\uparrow in paraganglioma), 10% malignant (\uparrow in paraganglioma), 10% familial, 10% incidentaloma
- Paroxysms can be triggered by meds (eg, β -blockers) abdominal manipulation
- Associated with MEN2A/2B, von Hippel Lindau, neurofibromatosis type 1, familial paraganglioma (mutations in succinate dehydrogenase gene B, C and D)

Diagnostic studies (*JCEM* 2014;99:1915)

- 24^h urinary fractionated metanephrenes: 85–97% Se, 69–95% Sp. Screening test of choice if low-risk (as false \oplus with severe illness, renal failure, OSA, labetalol due to assay interference, acetaminophen, TCAs, medications containing sympathomimetics).
- Plasma-free metanephrenes: 89–100% Se, 79–97% Sp (*JAMA* 2002;287:1427). Screening test of choice if high risk, but \uparrow rate of false \oplus in low-prevalence population. Draw blood in supine position after Pt supine for 30 min, estimated 2.8 \times \uparrow false \oplus if seated.
- Adrenal CT generally better than MRI; PET for known metastatic disease or to localize nonadrenal mass but usually easy to find; consider MIBG scintigraphy if CT/MRI \ominus
- Consider genetic testing if bilateral disease, young Pt, \oplus FHx, extra-adrenal

Treatment

- α -blockade first (usually phenoxybenzamine) \pm β -blockade (often propranolol) \rightarrow surgery
- Preoperative volume expansion is critical due to possible hypotension after tumor excision

ADRENAL INCIDENTALOMAS

Epidemiology

- 4% of Pts undergoing abdominal CT scan have incidentally discovered adrenal mass; prevalence \uparrow with age

Differential diagnosis

- **Nonfunctioning mass:** adenoma, cysts, abscesses, granuloma, hemorrhage, lipoma, myelolipoma, primary or metastatic malignancy
- **Functioning mass:** pheochromocytoma, adenoma (cortisol, aldosterone, sex hormones), nonclassical CAH, other endocrine tumor, carcinoma

Hormonal workup (*NEJM* 2007;356:601; *JCEM* 2010;95:4106)

- **Rule out subclinical Cushing's syndrome** in all Pts using 1 mg overnight DST (Sp 91%). Abnormal results require confirmatory testing.
- **Rule out hyperaldosteronism** if hypertensive w/ plasma aldo & renin (see above)
- **Rule out pheochromocytoma** in ALL Pts (b/c of morbidity unRx'd pheo) using 24-h urine fractionated metanephrenes or plasma free metanephrenes

Malignancy workup

- CT and MRI characteristics may suggest adenoma vs. carcinoma
Benign features: size <4 cm; smooth margins, homogenous and hypodense appearance; unenhanced CT <10 Hounsfield units or CT contrast-medium washout >50% at 10 min. Can follow such incidentalomas w/ periodic scans.
Suspicious features: size >6 cm or \uparrow size on repeat scan; irregular margins, heterogeneous, dense or vascular appearance; h/o malignancy or young age. Such incidentalomas warrant resection or repeat scan at short interval.
- Rule out metastatic cancer (and infection) as in Pts w/ h/o cancer, ~50% of adrenal incidentalomas are malignant

Follow-up

- If hormonal workup \ominus and appearance benign, yearly fxnl testing for 4 y w/ follow-up imaging at 6, 12, & 24 mos reasonable approach, but controversial

CALCIUM DISORDERS

Laboratory Findings in Calcium Disorders

Ca	PTH	Disease	PO ₄	25-(OH)D	1,25-(OH) ₂ D
↑	↑↑	Hyperparathyroidism (1° and 3°)	↓	↓ to nl	↑
	↑ or nl	Familial hypocalciuric hypercalcemia	↓	nl	nl
		Malignancy	var.	var.	var.
	↓	Vitamin D excess	↑	↑	var.
		Milk-alkali syndrome, thiazides	↓	nl	nl
↓		↑ Bone turnover	↑	var.	var.
	↑↑	Pseudohypoparathyroidism	↑	nl	↓
	↑	Vitamin D deficiency	↓	↓↓	nl / ↓
		Chronic renal failure (2° hyperpara)	↑	var.	↓
	var.	Acute calcium sequestration	var.	var.	var.
	↓	Hypoparathyroidism	↑	nl	↓

Pitfalls in measuring calcium

- Physiologically active Ca is free or ionized (ICa). Serum Ca reflects total calcium (bound + unbound) and ∴ influenced by albumin (main Ca-binding protein).
- Corrected Ca (mg/dL) = measured Ca (mg/dL) + {0.8 × [4 – albumin (g/dL)]}
- Alkalosis will cause more Ca to be bound to albumin (∴ total Ca may be normal but ↓ ICa)
- Best to measure **ionized Ca directly** (but accuracy is lab dependent)

HYPERCALCEMIA

Etiologies of Hypercalcemia

Category	Etiologies
Hyperparathyroidism (HPT) (NEJM 2011;365:2389)	1°: adenoma (85%), hyperplasia (15–20%; spont. vs. MEN1/2A), carcinoma (<1%), meds (Lithium → ↑ PTH) 3°: after long-standing 2° hyperparathyroidism (as in renal failure) → autonomous nodule develops, requires surgery
Familial hypocalciuric hypercalcemia (FHH)	Inact. mut. in Ca-sensing receptor (FHH1), Gα11 (FHH2), AP2S1 (FHH3) → ↑ Ca set point; ± mild ↑ PTH Acquired form due to autoAb vs. Ca-sensing receptor (rare) $FE_{Ca} [(24-h U_{Ca}/\text{serum Ca}) / (24-h U_{Cr}/\text{serum Cr})] < 0.01$
Malignancy (JCEM 2015;100:2024)	PTH-related peptide (PTHRP) → humoral ↑ Ca of malignancy (eg, squamous cell cancers, renal, breast, bladder) Cytokines → ↑ osteoclast activity (eg, hematologic malig) ↑ 1,25-(OH) ₂ D (eg, rare lymphomas) Local osteolysis (eg, breast cancer, myeloma)
Vitamin D excess	Granulomas (sarcoid, TB, histo, GPA) → ↑ 1-OHase → ↑ 1,25-(OH) ₂ D. Vitamin D intoxication.
↑ Bone turnover	Hyperthyroidism, immobilization + Paget's disease, vitamin A
Miscellaneous	Thiazides; Ca-based antacids or massive dairy consumption (milk-alkali syndrome); adrenal insufficiency

Among inPts w/ hypercalcemia: 45% have cancer, 25% 1° HPT, 10% CKD → 3° HPT

(JCEM 2005;90:6316; NEJM 2013;368:644)

Clinical manifestations ("bones, stones, abdominal groans and psychic moans")

- Hypercalcemic crisis** (usually when Ca >13–15): polyuria, dehydration, ΔMS
Ca toxic to renal tubules → blocks ADH activity, causes vasoconstriction and ↓ GFR → polyuria but Ca reabsorption → ↑ serum Ca → ↑ nephrotoxicity and CNS sx
- Osteopenia, fractures and osteitis fibrosa cystica (latter seen in severe hyperpara. only → ↑ osteoclast activity → cysts, fibrous nodules, salt & pepper appearance on X-ray)
- Nephrolithiasis, nephrocalcinosis, nephrogenic DI
- Abdominal pain, anorexia, nausea, vomiting, constipation, pancreatitis, PUD
- Fatigue, weakness, depression, confusion, coma, ↓ DTRs, short QT interval
- 1° HPT: 80% asx, 20% nephrolithiasis, osteoporosis, etc.

Diagnostic studies

- Hyperparathyroidism (HPT) and malignancy account for 90% of cases of ↑ Ca; HPT more likely if asx or chronic; malignancy (usually overt) more likely if acute or sx
- Ca, alb, ICa, PTH (may be inapprop. normal in 1° HPT & FHH; JAMA 2014;312:2680), PO₄; ↑ or high nl PTH: 24-h U_{Ca} > 200 mg → HPT; 24-h U_{Ca} < 100 mg & FE_{Ca} < 0.01 → FHH

↓ PTH: ✓ PTHrP, A₁, & search for malig (eg, CT, mammogram, SPEP/UPEP) and
✓ vit D: ↑ 25-(OH)D → meds; ↑ 1,25-(OH)₂D → granuloma (✓ CXR, ACE, r/o lymph)

Acute Treatment of Hypercalcemia

Treatment	Onset	Duration	Comments
Normal saline (4–6 L/d)	h	during Rx	Natriuresis → ↑ renal Ca excretion
± Furosemide	h	during Rx	Use cautiously, only if volume overloaded
Bisphosphonates	1–2 d	var.	Inhibit osteoclasts, useful in malignancy; caution in renal failure; risk of jaw osteonecrosis
Calcitonin	h	2–3 d	Quickly develop tachyphylaxis
Glucocorticoids	days	days	? Useful in some malig, granulomatous disorders & vitamin D intox.
Denosumab (JCEM 2014;99:3144)	days	months	Monoclonal Ab against RANKL; typically used in hyperCa of malignancy; not renally cleared
Hemodialysis	min	during Rx	If other measures ineffective or contraindicated

(BMJ 2015;350:h2723)

Treatment of asymptomatic 1° HPT (JCEM 2014 99:3561)

- Surgery if: age <50 y; serum Ca >1 mg/dL >ULN; CrCl <60 mL/min, DEXAT score <-2.5
- If surgery declined/deferred, can Rx with, cinacalcet (↓ Ca & PTH but may not ↑ BMD)
- If not yet candidate for surgery: ✓ serum Ca & Cr annually and BMD q1–2 y

Calcinification (calcific uremic arteriopathy)

- Calcinification of media of small- to med-sized blood vessels of dermis & SC fat
- Ischemia & skin necrosis. See "Chronic Kidney Disease" for further details.

HYPOCALCEMIA

Etiologies of Hypocalcemia

Category	Etiologies
Hypoparathyroidism (NEJM 2008;359:391)	Iatrogenic (s/p thyroidectomy, rarely after parathyroidectomy); sporadic; familial (APS1, activating Ca-sensing receptor mutations; see page 7-2); Wilson's, hemochromatosis; hypoMg (↓ secretion and effect); activating Ca-sensing receptor autoAb
Pseudo-hypoparathyroidism (JCEM 2011;96:3020)	Ia and Ib: PTH end-organ resistance (∴ ↑ serum PTH) Ia: + skeletal abnormalities, short stature, & retardation Pseudopseudohypoparathyroidism = Ia syndrome but n/ Ca & PTH
Vit D defic. or resist (NEJM 2011;364:248; JCEM 2012;97:1153)	Nutritional/sunlight deprivation; GI disease/fat malabs.; drugs (anticonvulsants, rifampin, ketoconazole, 5-FU/leucovorin); genetic (1α-hydroxylase, VDR mutations)
Chronic renal failure	↓ 1,25-(OH) ₂ D production, ↑ PO ₄ from ↓ clearance
Accelerated net bone formation	Postparathyroidectomy, Rx of severe vit D deficiency or Paget's disease (NEJM 2013;368:644), osteoblastic metastases
Calcium sequestration	Pancreatitis, citrate excess (after blood transfusions), acute ↑↑ PO ₄ (ARF, rhabdomyolysis, tumor lysis), bisphosphonates

Clinical manifestations

- Neuromuscular irritability:** perioral paresthesias, cramps, ⊕ **Trousseau's** (inflation of BP cuff ≥3 min → carpal spasm), ⊕ **Chvostek's** (tapping facial nerve → contraction of facial muscles), laryngospasm; irritability, depression, psychosis, ↑ ICP, seizures, ↑ QT
- Rickets and/or osteomalacia: chronic ↓ vit D → ↓ Ca, ↓ PO₄ → ↓ bone/cartilage mineralization, growth failure, bone pain, muscle weakness
- Renal osteodystrophy** (↓ vit D & ↑ PTH in renal failure): osteomalacia [↓ mineralization of bone due to ↓ Ca and 1,25-(OH)₂D] & osteitis fibrosa cystica (due to ↑ PTH)

Diagnostic studies

- Ca, alb, ICa, PTH, 25-(OH)D, 1,25-(OH)₂D (if renal failure or rickets), Cr, Mg, PO₄, A₁, U_{Ca}

Treatment (also treat concomitant vitamin D deficiency)

- Severely symptomatic: Ca gluconate (1–2 g IV over 20 min) + oral Ca + calcitriol (but takes hrs to work) ± Mg (50–100 mEq/d); 10% CaCl₂ in codes or via CVL
- Consider gtt or PO to follow as effect of IV bolus typically lasts only a few hours
- Chronic: oral Ca (1–3 g/d; Ca citrate better absorbed than Ca carbonate, esp. if achlorhydria or on PPI) and typically calcitriol (0.25–2 mcg/d), and replete vitamin D deficiency. Consider thiazide to ↓ urinary Ca or recombinant PTH 1–84.
- Chronic renal failure: phosphate binder(s), oral Ca, calcitriol or analogue

DIABETES MELLITUS

Definition (Diabetes Care 2016;39:S13)

- Either Hb_{A1c} ≥ 6.5, fasting glucose ≥ 126 mg/dL, or glucose 2 h after OGTT ≥ 200 mg/dL × 2 (for any test) or single random glucose ≥ 200 mg/dL w/ classic sx of hyperglycemia; all tests equally reasonable (nb, may be + on one test but not another); OGTT preferred during preg
- Blood glucose higher than normal, but not frank DM ("prediabetics," ~40% U.S. population)
Hb_{A1c} 5.7–6.4%, impaired fasting glucose (IFG) 100–125 mg/dL, or 2 h prandial glucose 140–199
Preventing progression to DM: diet & exercise (58% ↓), metformin (31% ↓; NEJM 2002;346:393), TZD (60% ↓; Lancet 2006;368:1096)

Categories

- Type 1** (Lancet 2014;383:69): islet cell destruction; absolute insulin deficiency; ketosis in absence of insulin; prevalence 0.4%; usual onset in childhood but can occur throughout adulthood; ↑ risk if + FHx; HLA associations; anti-GAD, anti-islet cell & anti-insulin autoAb
- Type 2** (Annals 2015;162:ITC1): insulin resistance + relative insulin ↓; prevalence 8%; onset generally later in life; no HLA assoc.; risk factors: age, + FHx, obesity, sedentary lifestyle
- Type 2 DM p/w DKA** ("ketosis-prone type 2 diabetes" or "Flatbush diabetes"): most often seen in nonwhite, ± anti-GAD Ab, eventually may not require insulin (Endo Rev 2008;29:292)
- Mature-Onset Diabetes of the Young (MODY)**: autosomal dom. forms of DM due to defects in insulin secretion genes; genetically and clinically heterogeneous (NEJM 2001;345:971)
- Secondary causes of diabetes:** exogenous glucocorticoids, glucagonoma (3 Ds = DM, DVT, diarrhea), pancreatic (pancreatitis, hemochromatosis, CF, resection), B endocrinopathies (Cushing's disease, acromegaly), gestational, drugs (protease inhibitors, atypical antipsychotics)

Clinical manifestations

- Polyuria, polydipsia, polyphagia with unexplained weight loss; can also be asymptomatic

Diabetes Treatment Options

Diet	Type 1: carb counting; Type 2: wt reduction diet + exercise
Metformin (biguanide) First-line pharmacotherapy for all T2D	↓ hepatic gluconeogenesis. ↓ Hb _{A1c} ~1.5%. Wt neutral, N/V & diarrhea, rare lactic acidosis Contraindic. in renal (eg, Cr >1.5) or liver failure
Sulfonylureas (SU)	↑ insulin secretion, ↓ Hb _{A1c} ~1.5%. Hypoglycemia, wt gain.
Thiazolidinediones (TZD) (PPAR γ agonists)	↑ insulin sens. in adipose & muscle. ↓ Hb _{A1c} ~1%. Wt gain, hepatotoxicity, fluid retention & CHF, bone fractures ? ↑ MI w/ rosiglitazone; not pioglitazone (BMJ 2011;342:d1309) Contraindic. in liver disease and NYHA III–IV, monitor LFTs
GLP-1 agonists	↑ glucose-depend insulin secretion, ↓ Hb _{A1c} ~0.5%. ↓ CV events (NEJM 2016;375:311). Wt loss, N/V & diarrhea (30–45%).
DPP-4 inhibitors	Block degrad. of GLP-1 & GIP → ↑ insulin. ↓ Hb _{A1c} ~0.5%. ? ↑ risk of CHF with some (NEJM 2013;369:1317 & 2015;373:232)
SGLT-2 inhibitors (block renal tubular glucose uptake)	↑ glucosuria. ↓ Hb _{A1c} ~0.6–1%. Wt loss, ↓ CV death & HF, slows progression of kidney disease (NEJM 2015;373:2117 & NEJM 2016;375:323). ↑ risk of normoglycemic DKA (Diabetes Care 2016;39:532), fungal GU infxn & UTIs, hypovolemia, ↑ LDL.
Glinides (nonsulfonylurea insulin secretagogues)	↑ insulin secretion, ↓ Hb _{A1c} ~1.5% Hypoglycemia (but less than w/ SU), wt gain
α -glucosidase inhibitors	↓ intestinal CHO absorption, ↓ Hb _{A1c} 0.5–0.8%. GI distress (gas).
Pramlintide	Delays gastric emptying & ↓ glucagon, ↓ Hb _{A1c} 0.5%. GI sx. To be used as adjunctive Rx w/ insulin in T1D or T2D
Insulin (Additional T1D options: insulin pump, pancreatic or islet cell transplant)	Hypoglycemia, wt gain. T1D: generally combine intermed./long-acting (NPH or glargin) & short-/rapid-acting (regular or lispro) insulin. T2D: consider if mono oral Rx not adequate (esp. if Hb _{A1c} high) and start if combo oral Rx not adequate.
Gastric bypass	Can cure DM & prevent complications (NEJM 2014;370:2002)

(Lancet 2014;383:1068; JAMA 2015;314:1052; Diabetes Care 2016;39:S52; Endocr Pract 2016;22:84)

Insulin Preparations (JAMA 2014;311:2315)

Preparation	Onset	Peak	Duration	Side effects/Comments
Lispro, aspart	5–15 min	60–90 min	2–4 h	Give immediately before meal
Regular	30–60 min	2–4 h	5–8 h	Give ~30 min before meal
NPH	1–2 h	4–8 h	12–18 h	Can cause protamine Ab prod
Glargine	2 h	No peak	20–24 h	Once daily (a.m. or p.m.)
Detemir	1–3 h	No peak	18–26 h	Once daily

• Retinopathy

- nonproliferative: "dot & blot" and retinal hemorrhages, cotton-wool/protein exudates
- proliferative: neovascularization, vitreous hemorrhage, retinal detachment, blindness
- treatment: photocoagulation, surgery, intravitreal bevacizumab injections

• Nephropathy: microalbuminuria → proteinuria ± nephrotic syndrome → renal failure

diffuse glomerular basement membrane thickening/nodular pattern (Kimmelstiel-Wilson)
usually accompanied by retinopathy; lack of retinopathy suggests another cause
treatment: strict BP control using ACE inhibitors or ARBs (Mayo Clin Proc 2011;86:444),
SGLT-2 inhib (NEJM 2016;375:323), low-protein diet, dialysis or transplant

• Neuropathy: peripheral: symmetric distal sensory loss, paresthesias, ± motor loss

autonomic: gastroparesis, constipation, neurogenic bladder, erectile dysfxn, orthostasis
mononeuropathy: sudden-onset peripheral or CN deficit (footdrop, CN III > VI > IV)

• Accelerated atherosclerosis: coronary, cerebral and peripheral arterial beds

• Infections: UTI, osteomyelitis of foot, candidiasis, mucormycosis, necrotizing external otitis

• Dermatologic: necrobiosis lipoidica diabetorum, lipodystrophy, acanthosis nigricans

Outpatient screening and treatment goals (Diabetes Care 2015;38:S49)

- ✓ HbA_{1C} q3–6mo, goal <7% for most Pts. Can use goal HbA_{1C} ≤ 7.5–8% if h/o severe hypoglycemia or other comorbidities. Microvascular & macrovascular complications ↓ by strict glycemic control in T1D (NEJM 2005;353:2643) & T2D (NEJM 2015;372:2197).
- Microalbuminuria screening yearly with spot microalbumin/Cr ratio, goal <30 mg/g
- BP** ≤ 140/90 (JAMA 2015;313:603); ≤ 130/80 in young or select high-risk; benefit of ACE-I
- Lipids:** statin initiation in all diabetics age 40–75 if LDL-C > 70 (see Lipids section)
- ASA** if age > 50 (♂) or 60 (♀) or other cardiac risk factors (Circ 2010;121:2694)
- Dilated retinal exam and comprehensive foot exam yearly

Management of hyperglycemia in inpatients (for ICU Pts: see "Sepsis")

- Identify reversible causes/exacerbators (dextrose IVF, glucocorticoids, postop, ↑ carb diet)
- Dx studies: BG fingersticks (fasting, qAC, qHS; or q6h if NPO), HbA_{1C}
- Treatment goals: avoid hypoglycemia, extreme hyperglycemia (> 180 mg/dL)
- Modification of outPt treatment regimen: In T1D, do not stop basal insulin (can → DKA). In T2D: stopping oral DM meds generally preferred to avoid hypoglycemia or med interaction (except if short stay, excellent outPt ctnl, no plan for IV contrast, nl diet)
- InPt insulin: can use outPt regimen as guide; if insulin naïve:
total daily insulin = wt (kg) ÷ 2, to start; adjust as needed
give ½ of total daily insulin as basal insulin in long-acting form to target fasting glucose
give other ½ as short-acting boluses (standing premeal & sliding scale corrective insulin)
- Discharge regimen: similar to admission regimen unless poor outPt ctnl or strong reason for Δ. Arrange early insulin and glucometer teaching, prompt outPt follow-up.

DIABETIC KETOACIDOSIS (DKA)

Precipitants (the I's)

- Insulin defic.** (ie, failure to take enough insulin); **Iatrogenesis** (glucocorticoids; SGLT2 inhibitors—can be w/o marked hyperglycemia; Diabetes Care 2016;39:532)
- Infection** (pneumonia, UTI) or **Inflammation** (pancreatitis, cholecystitis)
- Ischemia or Infarction** (myocardial, cerebral, gut); **Intoxication** (alcohol, drugs)

Pathophysiology (NEJM 2015;372:546)

- Occurs in **T1D** (and in ketosis-prone T2D); ↑ glucagon and ↓ insulin
- Hyperglycemia due to: ↑ gluconeogenesis, ↑ glycogenolysis, ↓ glucose uptake into cells
- Ketosis due to: insulin deficiency → mobilization and oxidation of fatty acids,
↑ substrate for ketogenesis, ↑ ketogenic state of the liver, ↓ ketone clearance

Clinical manifestations (Diabetes Care 2009;32:1335 & 2016;39:S99)

- Polyuria, polydipsia, & dehydration → ↑ HR, HoTN, dry mucous membranes, ↓ skin turgor
- N/V, abdominal pain (either due to intra-abdominal process or DKA), ileus
- Kussmaul's respirations (deep) to compensate for metabolic acidosis with odor of acetone
- Δ MS → somnolence, stupor, coma; mortality ~1% even at tertiary care centers

Diagnostic studies

- ↑ Anion gap metabolic acidosis: can later develop nonanion gap acidosis due to urinary loss of ketones (HCO₃⁻ equivalents) and fluid resuscitation with chloride
- Ketosis:** + urine and serum ketones (predominant ketone is β-OH-butyrate, but acetoacetate measured by assay; urine ketones may be + in fasting normal Pts)
- ↑ Serum glucose; ↑ BUN & Cr (dehydration ± artifact due to ketones interfering w/ some assays)
- Hyponatremia: corrected Na = measured Na + [2.4 × (measured glucose - 100)/100]
- ↓ or ↑ K (but even if serum K is elevated, usually total body K depleted); ↓ total body phosphorus
- Leukocytosis, ↑ amylase (even if no pancreatitis)

Typical DKA "Flow Sheet" Setup

VS	UOP	pH	HCO ₃	AG	Ketones	Glc	K	PO ₄	IVF	Insulin
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Note: Main ketone produced is β -OH-butyrate (β OHB), but ketone measured by nitroprusside is acetacetate (Ac-Ac). As DKA is treated, β OHB \rightarrow Ac-Ac, \therefore AG can decrease while measured ketones can increase.

Treatment of DKA (Diabetes Care 2009;32:1335)

Rule out possible precipitants	Infection, intra-abdominal process, MI, etc. (see above)
Aggressive hydration	NS 10–14 mL/kg/h, tailor to dehydration & CV status
Insulin	10 U IV push followed by 0.1 U/kg/h Continue insulin drip until AG normal If glc <250 and AG still high \rightarrow add dextrose to IVF and continue insulin to metabolize ketones AG normal \rightarrow SC insulin (overlap IV & SC 2–3 h)
Electrolyte repletion	K: add 20–40 mEq/L IVF if serum K <4.5 insulin promotes K entry into cells \rightarrow ↓ serum K careful K repletion in Pts with renal failure HCO ₃ : ? replete if pH <7 or if cardiac instability PO ₄ : replete if <1

HYPEROSMOLAR HYPERGLYCEMIC STATE

Definition, precipitants, pathophysiology (Diabetes Care 2003;26:S33)

- Extreme hyperglycemia (w/o ketoacidosis) + hyperosm. + Δ MS in T2D (typically elderly)
- Precip same as for DKA, but also include dehydration and renal failure
- Hyperglycemia \rightarrow osmotic diuresis \rightarrow vol depletion \rightarrow prerenal azotemia \rightarrow ↑ glc, etc.

Clinical manifestations & dx studies (Diabetes Care 2016;39:S99)

- Volume depletion and Δ MS
- ↑ serum glc (usually >600 mg/dL) and ↑ meas. serum osmolality (>320 mOsm/L)
effective Osm = $2 \times \text{Na}$ (mEq/L) + glc (mg/dL)/18
- No ketoacidosis; usually ↑ BUN & Cr; [Na] depends on hyperglycemia & dehydration

Treatment (r/o possible precipitants; ~15% mortality due to precipitating factors)

- Aggressive hydration:** initially NS, then $\frac{1}{2}$ NS, average fluid loss up to 8–10 L
- Insulin** (eg, 10 U IV followed by 0.05–0.1 U/kg/h)

HYPOGLYCEMIA

Clinical manifestations (glucose <~55 mg/dL)

- CNS:** headache, visual Δs, Δ MS, weakness, seizure, LOC (neuroglycopenic sx)
- Autonomic:** diaphoresis, palpitations, tremor (adrenergic sx)

Etiologies in diabetics

- Excess insulin, oral hypoglycemics, missed meals, renal failure (↓ insulin & SU clearance)
- β-blockers can mask adrenergic symptoms of hypoglycemia

Etiologies in nondiabetics

- ↑ **insulin:** exogenous insulin, sulfonylureas, insulinoma, anti-insulin antibodies
- ↓ **glucose production:** hypopituitarism, adrenal insufficiency, glucagon deficiency, hepatic failure, renal failure, CHF, alcoholism, sepsis, severe malnutrition
- ↑ **IGF-II:** non-islet tumor
- Postprandial, esp. postgastrectomy or gastric bypass: excessive response to glc load
- Low glc w/o sx can be normal

Evaluation in nondiabetics (JCEM 2009;94:709)

- If clinically ill: take measures to avoid recurrent hypoglycemia; ✓ BUN, Cr, LFTs, TFTs, prealbumin; IGF-I/IGF-II ratio when appropriate
- If otherwise healthy: 72-h fast w/ monitored blood glc; stop for neuroglycopenic sx
- At time of hypoglycemia: insulin, C peptide (↑ w/ insulinoma and sulfonylureas, ↓ w/ exogenous insulin), β-OH-butyrate, sulfonylurea levels
- At end of fast, give 1 mg glucagon IV and measure response of plasma glc before feeding

Treatment

- Glucose tablets, paste, fruit juice are first-line Rx for Pts who can take POs
- If IV access available, give 25–50 g of D₅₀ (50% dextrose)
- If no IV, can give glucagon 0.5–1 mg IM or SC (side effect: N/V)

LIPID DISORDERS

Measurements

- Lipoproteins = lipids (cholesteryl esters & triglycerides) + phospholipids + proteins include: chylomicrons, VLDL, IDL, LDL, HDL, Lp(a)
- Measure after 12-h fast; LDL typically calculated: $LDL-C = TC - HDL-C - (TG/5)$
underestim. if TG >400 or LDL-C <70 mg/dL; ∴ directly measure LDL-C
levels stable up to 24 h after ACS, then ↓ and may take 6 wk to return to nl
- PEx clues: tendon xanthomas (eg, Achilles), imply LDL >300 mg/dL; eruptive xanthomas on extensor surfaces imply TG >1000 mg/dL; xanthelasma (yellowish streaks on eyelids)
- Metabolic syndrome (≥3 of following): waist ≥40" (♂) or ≥35" (♀); TG ≥150; HDL <40 mg/dL (♂) or <50 mg/dL (♀); BP ≥130/85 mmHg; fasting glc ≥100 mg/dL (Circ 2009;120:1640)
- Lp(a) = LDL particle bound to apo(a) via apoB; genetic variants a/w MI (NEJM 2009;361:2518)

Dyslipidemias

- 1^o: familial hyperchol. (FH, 1:500): defective LDL receptor; ↑↑ chol, nl TG; ↑ CAD; familial hypertrig. (FHTG, 1:500): ↑ TG, ±↑ chol, ↓ HDL, pancreatitis; and many others
- 2^o: DM (↑ TG, ↓ HDL), hypothyroidism (↑ LDL, ↑ TG), nephrotic syndrome (↑ LDL, ↑ TG), liver failure (↓ LDL), alcohol (↑ TG, ↑ HDL), thiazides (↑ LDL, ↑ TG), protease inhib (↑ TG)

Drug Treatment

Drug	↓ LDL	↑ HDL	↓ TG	Side effects/comments
Statins	20–60%	5–10%	10–25%	↑ ALT in 0.5–3%; ✓ before starting and then prn Myalgias <10%, rhabdo <0.1%, dose-dependent ↑ risk of DM; screen if risk factors
Ezetimibe	15–20%	—	—	Well tolerated
Fibrates	5–15%	5–15%	35–50%	Myopathy risk ↑ w/ statin. ↑ Cr; ✓ renal fxn q6mo.
Niacin	10–25%	~30%	40%	Flushing (ASA preRx may ↓), ↑ glc & UA. No benefit if on statin w/ low LDL-C (NEJM 2014;371:203).
Resins	20%	3–5%	↑	Bloating, binds other meds
Ω-3 FA	5% ↑	3%	25–50%	Dyspepsia, diarrhea, skin Δs, bleeding; ? effective (JAMA 2012;308:1024), definitive trials underway
PCSK9i	40–65%	5–10%	15–25%	mAb inj SC q2w or q4w (JACC 2015;65:2638)

Treatment of LDL-C (Lancet 2014;384:607)

- Statins:** every 1 mmol (39 mg/dL) ↓ LDL-C → 22% ↓ major vascular events (CV death, MI, stroke, revasc) in individuals w/ & w/o CAD (Lancet 2010;376:1670)
- Ezetimibe:** ↓ major vascular events incl MI & stroke when added to statin post-ACS, w/ magnitude of benefit consistent w/ LDL-statin relationship (IMPROVE-IT, NEJM 2015;372:2387)
- PCSK9 inhibitors:** ~60% ↓ LDL on top of statin, as monoRx, and in FH (EHJ 2014;35:2249); prelim data w/ encouraging ↓ CV outcomes (NEJM 2015;372:1500), definitive trials ongoing

Treatment of other lipid fractions (Lancet 2014;384:618 & 626)

- HDL-C:** low levels a/w ↑ risk of MI, but no clinical yet benefit by raising
- Triglycerides:** reasonable to treat levels >500–1000 mg/dL w/ fibrates or Ω-3 FA to ↓ risk of pancreatitis; genetically mediated lower levels a/w ↓ risk of CAD (NEJM 2014;371:22); modest benefit of fibrates on CV outcomes (NEJM 2010;362:1563 & 2013;368:1800)
- Lp(a):** consider ↓ to <50 mg/dL w/ niacin in intermed- to high-risk Pts (EHJ 2010;31:2844)

2013 ACC/AHA Guideline & 2016 Expert Consensus Decision Pathway

Population	10-y CV risk	Statin Recommendation
Clinical ASCVD	n/a	High intensity (? moderate if age >75 y)
LDL-C ≥190 mg/dL	n/a	High intensity
DM, age 40–75 y	n/a	High intensity (? moderate if risk <7.5%)
Age 40–75 y (and none of the above)	≥7.5% 5–<7.5% <5%	High or moderate intensity Reasonable to offer moderate intensity Consider statin if additional risk factor

Consider EZE or PCSK9i if LDL-C ≥70 & h/o ACS, athero event while on statin, DM, or FH

Circ 2014;129(Suppl 2):S1 & JACC 2016;68:92. ASCVD incl h/o ACS, stable angina, art. revasc, stroke, TIA, PAD. 10-y CV Risk Score: <http://my.americanheart.org/cvriskcalculator>. Additional risk factors to consider: LDL-C ≥160 mg/dL, genetic hyperlipid., FHx premature ASCVD, hsCRP >2 mg/L, CAC score ≥300 or ≥75th %ile, ABI <0.9

Statin Doses & LDL-C Reduction (doubling of dose → 6% further ↓ LDL-C)

Intensity	↓ LDL-C	Rosuva	Atorva	Simva	Prava	Lova	Fluva	Pitava
High	≥50%	20–40	40–80	(80)				
Mod	30–50%	5–10	10–20	20–40	40–80	40	80	2–4
Low	<30%			10	10–20	20	20–40	1

Doses are in mg. Simva 80 mg has ↑ myopathy risk and should not be used unless dose already tolerated >12 mo.

APPROACH TO RHEUMATIC DISEASE

Approach to patient with joint pain

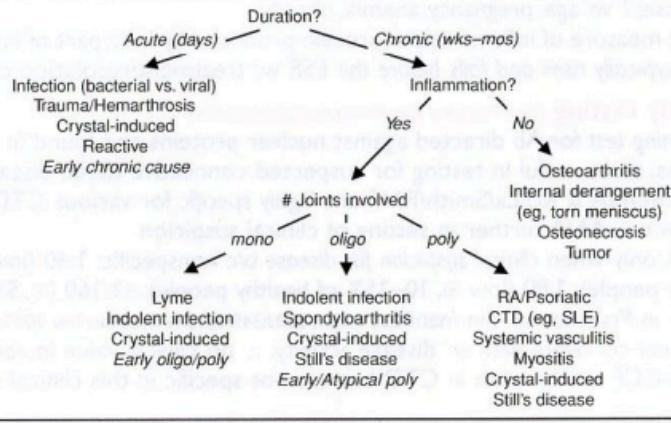
- Articular vs. periarticular** (bursitis, tendinitis) source of pain: typically active ROM more painful than passive ROM in periarticular process
- Inflammatory vs. noninflammatory** pain: features of inflammatory pain include swelling, warmth or redness in specific joint, prolonged morning stiffness (>30 min), improvement of pain/stiffness w/ motion/exercise
- Physical exam (see table): localize complaint and identify objective signs of inflammation
- The physical exam is only 50–70% sensitive for detecting inflammatory arthritis

Key Physical Exam Findings in Joint Pain

Physical exam	Articular (joint) disease			Periarticular/soft tissue	
	OA	Inflammatory arthritis ^a	Arthralgia	Bursitis or tendinitis	Myofascial
Swelling	varies	yes	no	yes	no
Erythema	no	varies	no	yes	no
Warmth	no	yes	no	yes	no
Tenderness	joint line	yes	varies	periarticular	yes
ROM ^b	limited	limited	full or limited	full, often limited by pain	full
Pain w/ active or passive	both	both	usually both	active > passive	usually both

^aMay initially present as arthralgia w/o overt arthritis. ^bRange of motion of joint or joint a/w bursa or tendon.

Figure 8-1 Approach to arthritis



Analysis of Joint Fluid

Test	Normal	Noninflamm	Inflammatory	Septic
Appearance	clear	clear, yellow	clear to opaque yellow-white	opaque
WBC/mm ³	<200	<2000	>2000	>2000 (usually >50k*)
Polys	<25%	<25%	≥50%	≥75%
Culture	⊖	⊖	⊖	⊕
Intracellular Crystals	⊖	⊖	⊕ in some (eg, gout)	⊖

*WBC count of aspirated fluid in septic bursitis often < WBC count in septic arthritis.

Radiologic features of major arthritides

- OA:** plain films: **osteophytes**, asym joint space narrowing (JSN), subchondral sclerosis & cysts. MRI may show early disease not seen on plain films; U/S ≈ MRI for structural damage.
- RA:** plain films: early = periarticular **osteopenia**; late = **erosions**, symmetric JSN. MRI & U/S able to detect early and subclinical disease; MRI ≈ U/S for erosions.
- Gout:** plain films: early = nonspec swelling; late = **tophus**, joint erosions w/ overhanging edges. U/S used for detection of microtophi (double contour sign); MRI ≈ U/S for erosions.
- Spondyloarthritis** (sacroiliac joint): plain films: pseudo-widening of joint space (early), sclerosis, erosions, **ankylosis**. MRI most Se for early Δ; U/S ≈ MRI to detect enthesitis.

Comparison of Major Arthritis

Feature	OA	RA	Gout/CPPD	Spondyloarthritis
Onset	gradual	gradual	acute	variable
Inflammation	⊖	⊕	⊕	⊕
Pathology	degeneration	pannus	microtophi	enthesisitis
# of joints	poly	poly	mono to poly	oligo or poly
Typical joint involvement	hips, knees, spine, 1st CMC DIP, PIP	MCP, PIP wrists, feet, ankles, knees	MTP feet, ankles, knees	sacroiliac spine large periph
Joints often spared	MCP, shoulder, elbow, wrist	L & T spine, DIPs	spine	any joint can be involved
Special articular findings	Bouchard's & Heberden's nodes	ulnar dev. swan neck boutonnière deformities	urate/CPPD crystals tophi	dactylitis enthesitis (eg, Achilles) bamboo spine syndesmophytes
Extra-articular features		SC nodules pulmonary sicca	olec. bursitis renal stones	psoriasis IBD uveitis
Lab data	normal	often ⊕ RF & anti-CCP	↑ UA (may be nl during flare)	± HLA-B27

INFLAMMATORY MARKER & AUTOANTIBODY TESTING

Inflammatory markers (Mod Rheumatol 2009;19:469)

- ESR:** indirect measure of inflammation (↑ RBC aggregation due to acute-phase proteins); slow to rise; ↑ w/ age, pregnancy, anemia, obesity
- CRP:** direct measure of inflammation (protein produced by liver, part of innate immune system); typically rises and falls before the ESR w/ treatment/resolution of process

Autoantibody testing (Best Pract Res Clin Rheumatol 2014;28:907)

- ANA: screening test for Ab directed against nuclear proteins and found in autoimmune conditions, most useful in testing for suspected connective tissue diseases
- Ab against dsDNA & Ro/La/Smith/RNP are highly specific for various CTD and can be used to w/u ⊕ ANA further in setting of clinical suspicion
- Order ANA only when clinical suspicion for disease b/c nonspecific: 1:40 (low ⊕, 25–30% of healthy people); 1:80 (low ⊕, 10–15% of healthy people); ≥1:160 (⊕, 5% of healthy). May be ⊕ in Pts prior to clin manifest (NEJM 2003;349:1526; Arthritis Res Ther 2011;13:1).
- ANA does not correlate well w/ disease activity, ∴ no clinical value in serial testing
- RF and anti-CCP can be seen in CTD but are not specific in this clinical setting

DDX & APPROACH TO COMMON INPATIENT RHEUM PRESENTATIONS

Presentation	Rheum Ddx	Rheum Lab Workup
Fever of unknown origin	GCA/PMR, adult-onset Still's, SLE, inflammatory arthritis, Takayasu's, PAN, ANCA ⊕ vasc, cryo, HSP	ESR, CRP, ANA, RF, ANCA, ± cryo
Pulmonary hypertension	Scleroderma (limited > diffuse), MCTD, SLE, PM/DM (less common)	ANA, Scl-70, centromere, RNA Pol III, RNP
Diff alveolar hemorrhage	ANCA ⊕ vasc, Goodpasture's, SLE, APS	ANCA, GBM, ANA, C3/C4
Interstitial lung disease	Scleroderma (diffuse > limited), sarcoid, RA, DM/PM, antisynthetase syndrome, Sjögren's, MCTD, SLE (esp. pleura), ANCA ⊕ vasc (esp. MPA)	ANA, Ro/La, RF/anti-CCP, ANCA, ± myositis panel
Pleuro-pericarditis	SLE, RA, MCTD, DM/PM, ANCA ⊕ vasc, Sjögren's, PAN	ANA, dsDNA, Sm, RNP, Ro/La, RF, anti-CCP, ANCA
Acute kidney injury	SLE (GN or nephrotic), ANCA ⊕ vasc (GN), scleroderma renal crisis (diffuse), Sjögren's (RTA/TIN), PAN (infarct), HSP, Goodpasture's (GN), cryo	ANA, Ro/La (RTA/TIN), dsDNA, C3/C4, RNA Pol III (SRC), Scl-70 (SRC), ANCA, GBM, cryos
Neuropathy	ANCA ⊕ vasc, SLE, RA, PAN, Sjögren's, cryo, sarcoid	ANA, Ro/La, ANCA, cryo RF/anti-CCP, HCV, HBV

RHEUMATOID ARTHRITIS (RA)

Definition & epidemiology (*Lancet* 2010;376:1094; *NEJM* 2011;365:2205; *Ann Rheum Dis* 2010;69:70)

- Chronic, symmetric, debilitating and destructive inflammatory polyarthritis characterized by proliferative synovial tissue (pannus) formation in affected joints
- Pathogenesis involves over-production of TNF, IL-1, and IL-6 (∴ used as drug targets)
- Risk stems from combination of genetic (~50% of risk), environmental influences (eg. smoking, silica dust), Pt factors (periodontal disease, Δs in gut microbiome)
- HLA-DRB1 haplotype a/w disease suscept., severity & response to Rx (*JAMA* 2015;313:1645)
- Prevalence = 1% adults; 5% of ♀ >70 y; ♀ to ♂ ratio = 3:1; peak incidence 50–75 y

Clinical manifestations (*Medicine* 2010;38:167)

- Usually insidious onset **pain, swelling** and impaired function of joints (typically PIPs, MCPs, wrists, knees, ankles, MTPs and cervical spine) with **morning stiffness** for ≥1 h
- Typically polyarticular (60% small joints, 30% large joints, 10% both), may be monoarticular (knee, shoulder, wrist) early in course; nb, rheumatoid joints can become infected
- Joint deformities: **ulnar deviation, swan neck** (MCP flexion, PIP hyperextension, DIP flexion), **boutonnière** (PIP flexion, DIP hyperextension), **cock-up deformities** (toes)
- C1–C2 instability** → myelopathy, ∴ C-spine flex/ext films prior to elective intubation
- Constitutional symptoms: low-grade fever, weight loss, malaise
- Extra-articular manifestations** (18–41% of Pts) can occur at any time; ↑ frequency in seropositive (+ RF or anti-CCP) and with active disease (*Autoimmun Rev* 2011;11:123)

Extra-Articular Manifestations (EAMs)

Skin	Rheumatoid nodules (20–30%, usually sero +): extensor surface, bursae; can be in lung, heart, sclera Raynaud's, pyoderma gangrenosum, cutan. vasculitis (ulcers, purpura, etc.)
Pulm	ILD, pleuritis, effusions (low glc), nodules, airway disease, PHT 20% of the time precedes joint manifestations
CV	Pericarditis (effusions in 1/3 of sero +), myocarditis, accelerated athero/MI, AF, coronary/systemic vasculitis. ↑ risk CV death (<i>Arth Rheum</i> 2015;67:2311).
Nervous	Mono/polyneuritis multiplex, CNS vasculitis, stroke, nerve entrapment
Ocular	Scleritis, episcleritis, keratoconjunctivitis sicca (2° Sjögren's)
Heme	Anemia of chronic disease Neutropenia Felty's syndrome (1%, typically long-standing RA): splenomegaly large granular lymphocyte leukemia: bone marrow infiltrated w/ lymphocytes ± myeloid hypoplasia NHL, amyloidosis
Renal	Glomerulonephritis (usually mesangial), nephrotic synd (2° amyloidosis) NSAIDs and MTX may also cause renal damage
Vasculitis	Small & medium vessels (usually ↑ RF titer, long-standing RA); pericarditis, ulcers, scleritis, & neuropathy most common (<i>Curr Opin Rheum</i> 2009;21:35)

Laboratory & radiologic studies (*Annals* 2007;146:797)

- RF** (IgM/IgA/IgG anti-IgG Ab) in ~70% of Pts; also seen in other rheumatic diseases (SLE, Sjögren's), infection (SBE, hepatitis, TB), types II & III cryo, 5% of healthy population
- Anti-CCP** (Ab to cyclic citrullinated peptide): in ~80% of Pts, similar Se (~70%), more Sp (>90%) than RF particularly for early RA (*Arth Rheum* 2009;61:1472); a/w increased joint damage and low remission rates
- ~20% are seronegative (RF and anti-CCP negative)
- ↑ ESR/CRP but nl in ~30%; + ANA in ~40%; ↑ globulin during periods of active disease
- Radiographs of hands and wrists: periarticular osteopenia, bone erosions, joint subluxation
- Increasing use of MSK U/S to diagnosis synovitis and erosive disease

ACR/EULAR classification criteria (*Arth Rheum* 2010;62:2569)

- Used in clinical research, but not in clinical practice
- Relevant for Pts with ≥1 joint with synovitis not better explained by another disease
- Likelihood of RA ↑ w/ higher # (espec. ≥4) of small joints involved, + (espec. high titer) RA or anti-CCP, ANA, ↑ ESR or CRP, and duration ≥6 wk

Management (*Ann Rheum Dis* 2014;73:516)

- Early dx and Rx (esp. DMARD) w/ frequent follow-up and escalation of Rx as needed to achieve **clinical remission** or low disease activity
- ↓ time to remission = ↑ length of sustained remission (*Arthritis Res Ther* 2010;12:R97)
- Sero-+ disease (eg, RF or anti-CCP) a/w aggressive joint disease & EAM
- At dx, start **both** rapid-acting agent (to acutely ↓ inflammation) and **Disease-Modifying Anti-Rheumatic Drug (DMARD)** (typically take 1–3 mo to have max effect)

- Rapid-acting drugs:
NSAIDs or COX-2 inhibitors (\uparrow CV, GI adverse events), consider starting with PPI; **glucocorticoids** [low-dose (<20 mg/d oral) or joint injection]; or
NSAIDs + glucocorticoids: \uparrow GI adverse events, minimize long-term concurrent use
- DMARDs**
MTX (1st line unless CKD, hepatitis, EtOH or lung disease), SAS or leflunomide; consider HCQ if seronegative and mild disease;
If inadequate response after 3 mo (despite DMARD dose escalation):
combination Rx w/ other DMARDs (eg, "triple therapy" w/ MTX, SAS and HCQ) or **biologic** (anti-TNF typically 1st line unless contraindication)
MTX/SAS/HCQ non-inferior to etanercept/MTX (NEJM 2013;369:307)
JAK inhibitor if fail biologics, although also promising data as initial DMARD (NEJM 2014;370:2377 & 2016;374:1243)
- Given \uparrow r/o early CV morbidity/mortality, try to \downarrow risk w/ lifestyle mgmt, lipid & DM screening

RA Therapeutics (Arth Rheum 2016;68:1)

Class	Drug	Side effects
Traditional DMARDs	Methotrexate (MTX) Leflunomide Sulfasalazine (SAS)	GI distress (esp. nausea), myelosuppression, ILD, hepatotoxicity ✓ G6PD prior to SAS Supplement MTX & SAS w/ folate
Biologic DMARDs (all anti-TNF have similar efficacy)	Anti-TNF: etanercept, infliximab, adalimumab, certolizumab, golimumab CTLA4-Ig: abatacept IL-6R Ab: tocilizumab (studied as mono-Rx w/o MTX) Anti-CD20: rituximab IL-1R Ab: anakinra	\uparrow risk bacterial/fungal/viral infxn (esp. TB, zoster, hepatitis, and w/ stdn or high-dose; Lancet 2015;386:258); \therefore ✓ for TB, Hep B/C prior to starting ? CHF & demyelinating CNS disease for anti-TNF Never use 2 biologics together
Other	Hydroxychloroquine (HCQ) JAK inhib: tofacitinib (TF), baricitinib Rarely: cyclosporine, azathioprine, gold	HCQ: retinopathy, rash JAK inhib: infxn, \uparrow Cr, \uparrow LFTs, HTN CsA: nephrotoxic, HTN, gum hyperplasia

(Lancet 2008;371:987; 2013;381:451,918, & 1541; NEJM 2012;367:495 & 508, & 369:307)

ADULT-ONSET STILL'S DISEASE & RELAPSING POLYCHONDROITIS

Adult-onset Still's disease (J Rheumatol 1992;19:424; Autoimmun Rev 2014;13:708)

- Rare autoinflammatory synd;** ♂ = ♀ w/ typical onset 16–35 y; sx evolve over wks to mos
- Dx if 5 criteria are present & ≥ 2 major; exclude infxn, malig, other rheumatic, drug rxn
major: fever $\geq 39^{\circ}\text{C}$ for ≥ 1 wk (usually daily or twice daily high-spiking fever); arthralgias/arthritis ≥ 2 wk; Still's rash (qv); \uparrow WBC w/ 80% PMN
minor: sore throat; LAN; HSM; \uparrow AST/ALT/LDH; negative ANA & RF
- Still's rash (>85%): nonpruritic macular or maculopapular salmon-colored rash; usually trunk or extremities; may be precipitated by trauma (Koebner phenomenon), warm water
- Plain films: soft tissue swelling (early) \rightarrow cartilage loss, erosions, carpal ankylosis (late)
- Treatment: NSAIDs; steroids; steroid-sparing (MTX, **anakinra**, anti-TNF, **tocilizumab**)
- Variable clinical course: 20% w/ long-term remission; 30% remit-relapse; ~50% chronic (esp. arthritis); \uparrow risk of macrophage activation syndrome (life-threatening)

Relapsing polychondritis (Rheum Dis Clin NA 2013;39:263)

- Inflammatory destruction of cartilaginous structures; onset usually age 40–60 y, ♂ = ♀
- Subacute onset of **red, painful** and **swollen cartilage**; ultimately atrophic & deformed
- Common clinical features: bilateral auricular chondritis; nonerosive inflammatory arthritis; nasal chondritis; ocular inflammation; laryngeal or tracheal chondritis; cochlear and/or vestibular dysfxn
- 40% of cases a/w immunologic disorder (eg, RA, SLE, vasc., Sjögren's), cancer or MDS
- Clinical diagnosis based on exam with multiple sites of cartilaginous inflammation
- Labs: \uparrow ESR & CRP, leukocytosis, eosinophilia, anemia of chronic inflammation
- Bx (not req for dx): proteoglycan depletion, perichondrial inflammation and replacement with granulation tissue and fibrosis; immunofluorescence with Ig and C3 deposits
- Screen for pulm (PFTs, CXR/CT, \pm bronch) and cardiac (ECG, TTE) involvement
- Therapy guided by disease activity and severity: **steroids** 1st line; NSAIDs, dapsone for sx control of arthralgias and mild disease; MTX, AZA, or biologics for steroid-sparing; cyclophosphamide for organ-threatening disease

CRYSTAL DEPOSITION ARTHRITIDES

Comparison of Gout and Pseudogout

	Gout (NEJM 2011;364:443)	Pseudogout (Rheum 2009;48:711)
Acute clinical	Sudden onset painful mono-articular arthritis (classically podagra [MTP of great toe]) or bursitis; freq. nocturnal Polyarticular in subseq flares Can mimic cellulitis (esp. in foot)	Mono- or asymmetric oligoarthritis (esp. knees, wrists and MCP joints); rare axial involvement (eg, crowned dens syndrome)
Chronic clinical	Solid crystal deposition (tophus) in joints (esp. toes, fingers, wrists, knees) & tissue (esp. olecranon bursa, pinna, Achilles)	"Pseudo-RA" w/ polyarticular arthritis w/ morning stiffness or "Pseudo-OA"
Assoc. conditions	Metabolic syndrome; CKD; CHF	3 H's: Hyperparathyroidism; Hypomagnesemia; Hemochromatosis
Crystal	Monosodium urate	Calcium pyrophosphate dihydrate
Polarized microscopy*	Needle-shaped, negatively birefringent	Rhomboid-shaped, weakly positively birefringent crystals
Radio-graphic findings	Erosions w/ overhanging edge (late); "double contour sign" on MSK US	Chondrocalcinosis: punctate, linear densities in articular cartilage, menisci, fibrocartilage of wrist, hands, symphysis pubis
Other	a/w uric acid stones; urate nephropathy	✓ Ca, Mg, Fe, ferritin, TIBC, UA, PTH in young or severe cases

*Crystals should be intracellular; Infection can coexist with acute attacks, ∴ always ✓ Gram stain & Cx

GOUT

Definition & epidemiology (Lancet 2010;375:318; Nat Rev Rheumatol 2015;11:649)

- Humans lack enzyme to metabolize urate (end-product of purine metabolism)
- Monosodium urate (MSU) crystal deposition in joints promotes inflammation
- ♂ > ♀ (9:1); peak incidence 5th decade; most common cause of inflammatory arthritis in ♂ over 30 y; rare in premenopausal ♀ (estrogens promote renal urate excretion)

Etiologies (Ann Rheum Dis 2012;71:1448)

- UA underexcretion (85–90%):** meds (eg, diuretics); idiopathic; ↓ renal function; obesity
- Uric acid (UA) overproduction (10–15%): ↑ meat, seafood, EtOH, psoriasis, idiopathic, myelo- and lymphoproliferative disease, chronic hemolytic anemia, cytotoxic drugs, rare inherited enzyme defic, genetic variants (Lancet 2008;372:1953)

Diagnosis

- ↑ UA is not diagnostic: 25% of measurements nl during flare; ± ↑ WBC & ESR
- Arthrocentesis is gold standard: negatively birefringent needles (see table above)
- 2015 ACR/EULAR Classification Criteria (Ann Rheum Dis 2015;74:1789) used 1° in research

Acute treatment (Arthritis Care Res 2012;64:1447; Am Fam Physician 2014;90:831)

- No superior option; start w/in 24 h of sx onset; continue until acute flare resolves; for severe cases, consider combination therapy; rest and ice; w/o treatment self-limited in 3–10 d

Acute Treatment for Gout

Drug	Initial dose	Comments
NSAIDs (nonselect or COX-2)	Full anti-inflammatory dose → tapering	Gastritis & GIB; avoid in CKD & CVD ≈ efficacy among NSAIDs never compared with colchicine
Colchicine (PO; IV no longer available in U.S.)	1.2 mg then 0.6 mg 1 h later → 0.6 mg bid	N/V, diarrhea (↑ w/ ↑ dose); ↓ dose in renal insufficiency (however, not nephrotoxic) a/w BM supp., myopathy, neuropathy
Corticosteroids (PO, IA, IV, IM) or Corticotropin	eg, prednisone ~0.5 mg/kg/d × 5–10 d ± taper	Rule out joint infection 1 st Comparable to NSAID as 1 st -line treatment (Annals 2016;164:464)
IL-1 inhibitors (Curr Opin Rheumatol 2015;27:156)	anakinra (100 mg SC qd × 3 d) canakinumab (150 mg SC × 1)	↑↑ cost; anakinra a/w injection site pain (Arthritis Res Ther 2007;9:R28); canakinumab approved in EU (Ann Rheum Dis 2012;71:1839; Arth Rheum 2010;62:3064)

Chronic treatment (*Lancet* 2011;377:165; *Am Fam Physician* 2014;90:831)

- Approach:** if ≥2 attacks/y, ≥1 tophus, joint erosions or urolithiasis → start urate lowering Rx & pharmacologic prophylaxis to ↓ risk of acute attacks
- Pharmacologic prophylaxis:** continue for at least 6 mos or longer if frequent attacks: low-dose **colchicine** (~50% ↓ risk of acute flare; *J Rheum* 2004;31:2429), **NSAIDs** (less evidence; *Ann Rheum Dis* 2006;65:1312), low-dose **steroids, IL-1 inhibitors** (see above)
- Urate-lowering Rx:** goal UA <6 mg/dL; do NOT discontinue during acute attack or acute kidney injury (unless allopurinol hypersensitivity syndrome)
- Lifestyle** Δs (*Rheum Dis Clin NA* 2014;40:581): ↓ intake of meat, EtOH & seafood, ↑ low-fat dairy products, wt loss, avoid dehydration

Urate-Lowering Therapy (Chronic Treatment for Gout)

Drug (route)	Mechanism	Comments
Allopurinol (PO)	Xanthine oxidase inhib	1st line; adjust starting dose in CKD; titrate ↑ q2–5wk a/w rash, hypersensitivity syndrome (see below), diarrhea, dyspepsia, BM suppression, hepatitis; monitor CBC & LFTs; <i>not nephrotoxic</i> max dose = 800 mg/d
Febuxostat (PO)	Nonpurine xanthine oxidase inhib	2nd line; use if allopurinol intolerant a/w LFT Δ, rash, arthralgias, nausea start 40 mg, max dose = 120 mg/d
Pegloticase (IV)	Recombinant uricase	For refractory tophaceous gout; infusion reactions (including anaphylaxis); Ab formation may limit use (<i>JAMA</i> 2011;306:711)
Probenecid (PO)	Uricosuric	Rarely used; risk of urolithiasis

- Allopurinol hypersensitivity syndrome:** 10–25% mortality; ↓ risk by starting w/ dose 100 mg/d if eGFR >40 or 50 mg/d if eGFR ≤40; titrate up by 100 mg/d (if eGFR >40) or 50 mg/d (if eGFR ≤40) q2–5wk until UA <6 mg/dL (dose can be >300 mg/d even in CKD)
- Associated with HLA-B5801**, esp. Han Chinese, Koreans, Thai; screen in these high-risk populations prior to initiating allopurinol (*Curr Opin Rheumatol* 2014;26:16)

CALCIUM PYROPHOSPHATE DIHYDRATE (CPPD) DEPOSITION DISEASE/PSEUDOGOUT

Definition

- Deposition of CPPD crystals w/in tendons, ligaments, articular capsules, synovium, cartilage; frequently asymptomatic

Etiologies (*Rheumatology* 2012;51:2070)

- Most cases **idiopathic**; consider further metabolic eval in young (<50 y) and florid forms
- Metabolic (3 H's): hemochromatosis; hyperparathyroidism; hypomagnesemia (esp. in Gitelman's or Bartter's syndromes)
- Joint trauma (incl. previous surgery); intra-articular hyaluronate can precipitate attacks
- Familial chondrocalcinosis (autosomal dominant disorder); early-onset, polyarticular dis.

Clinical manifestations (*Rheum Dis Clin NA* 2014;40:207)

- Chondrocalcinosis:** calcification of cartilage, resulting from CPPD deposition in articular cartilage, fibrocartilage or menisci
↑ incidence w/ age; 20% >60 y have knee chondrocalcinosis in autopsy studies
- Pseudogout:** acute CPPD crystal-induced mono- or asymmetric oligoarticular arthritis, *indistinguishable from gout except through synovial fluid exam for crystals*
location: **knees, wrists and MCP joints**
precipitants: surgery, trauma or severe illness
- Chronic forms: "Pseudo-RA" and pyrophosphate arthropathy (may involve axial skeleton, resembles OA)

Diagnostic studies

- Arthrocentesis is gold standard: **rhomboid-shaped, weakly positively birefringent crystals** (yellow perpendicular & blue parallel to axis on polarizer; see table above)

Radiographs: see table above

Treatment (*NEJM* 2016;374:2575)

- Asymptomatic chondrocalcinosis requires no treatment
- Acute therapy for pseudogout: no RCTs, extrapolated from practice in gout; ∴ same as for gout, though colchicine not as effective
- If associated metabolic disease, Rx of underlying disorder *may* improve arthritis sx
- Low-dose daily colchicine or NSAID may be effective for prophylaxis or chronic arthropathy

SERONEGATIVE SpondyloArthritis

Classification system (NEJM 2016;374:2563)

- 5 subtypes: ankylosing spondylitis (most common), reactive arthritis, psoriatic arthritis, IBD-associated arthritis and undifferentiated
- Can also distinguish axial-predominant from peripheral-predominant joint involvement
- All subtypes share common clinical manifestations: inflammatory spine disease, peripheral arthritis, enthesitis and extra-articular manifestations (primarily ocular and skin disease)

Epidemiology & pathogenesis (Nat Rev Rheumatol 2015;10:110)

- ↑ prevalence of HLA-B27; HLA-B27 accounts for ~30% of attributable genetic risk
- Environmental factors likely critical for disease, esp. reactive arthritis (eg, infection)
- Prevalence of 0.5–2% of population, worldwide

Spondyloarthritis (SpA) Epidemiology and Key Presentation Features		
Disease	Epidemiology	Other
Ankylosing spondylitis	♂:♀ = 3:1; onset in teens to mid-20s (rare after 40 y)	Progressive limitation of spine motion; "bamboo spine"
Psoriatic arthritis	♂ = ♀; peak incidence 45–54 y; seen in 20–30% of Pts w/ psoriasis (Ann Rheum Dis 2005;64:i14)	In 13–17%, arthritis precedes psoriasis by yrs. Does not correlate with psoriasis activity. A/w HIV.
Reactive arthritis	♂ >> ♀; 20–40 y; 10–30 d s/p post-GI or GU infxn* in genetically susceptible host	Previously "Reiter's syndrome": arthritis, urethritis and conjunctivitis. Most resolve w/in 12 mo.
IBD-associated	♂ = ♀; seen in 20% of IBD Pts; Crohn's > UC	Type I <5 joints: correlates w/ IBD Type II >5 joints or axial disease: does not correlate w/ IBD

*GU: Chlamydia, Ureaplasma urealyticum; GI: Shigella, Salmonella, Yersinia, Campylobacter, C. diff.

Major clinical manifestations (Lancet 2011;377:2127)

- **Inflammatory back pain:** SI joints (**sacroiliitis**), apophyseal joints of spine characterized by **IPAIN** (Insidious onset, Pain at night, Age of onset <40 y, Improves w/ exercise/hot water, No improvement w/ rest), a.m. stiffness, responsive to NSAIDs
- **Peripheral arthritis:** typically asymmetric, oligoarticular, large joints, lower > upper limb; however, can be symmetric & polyarticular (thus, mimic RA), esp. in psoriatic arthritis
- **Enthesitis:** inflammation at site of tendon/ligament insertion into bone, esp. Achilles, pre-patellar, elbow epicondyles, plantar fascia
- **Rigidity of spine:** bamboo spine by X-ray, ankylosis due to progressive growth of bony spurs which bridge intervertebral disc
- **Dactylitis** ("sausage digit"): inflammation of entire digit (joint + tenosynovial inflam)
- **Uveitis:** anterior uveitis most common extra-articular manifestation; p/w pain, red eye, blurry vision, photophobia, usually unilateral

	Distinguishing Features			
	Axial-predom	Peripheral-predominant		
Feature	Ankylosing spondylitis	Psoriatic	Reactive	IBD-assoc
Axial involv.	100%	20–40%	40–60%	5–20%
Sacroiliitis	Symmetric	Asymm	Asymm	Symmetric
Periph involv.	Less common (~50%)	Frequent	Frequent	Frequent
Periph distrib.	Lower > Upper	Upper > Lower (see below)	Lower > Upper	Lower > Upper
HLA-B27	80–90%	20%	50–80%	5–30%
Enthesitis	Frequent	Frequent	Frequent	Rare
Dactylitis	Uncommon	Common	Common	Uncommon
Ocular	Uveitis in 25–40%	Conjunctivitis, uveitis, episcleritis,	Conjunctivitis (noninfectious), uveitis, keratitis	Uveitis
Skin	None	Psoriasis; nail pitting and onycholysis	Circinate balanitis, keratoderma blennorrhagica	E. nodosum, pyoderma-gangrenosum
Imaging	Bamboo spine (symm syndes.)	"Pencil-in-cup" DIP deformity	Asymmetric syndesmophytes	Periph dis. rarely erosive
Other	↑ CAD; aortitis, AI, conduction defects	↑ CAD	Urethritis, AI, conduction defects	

Descriptions of skin manifestations

- Psoriasis:** erythematous plaques with sharply defined margins often w/ thick silvery scale
- Circinate balanitis:** shallow, painless ulcers of glans penis and urethral meatus
- Keratoderma blennorrhagica:** hyperkeratotic lesions on soles of feet, scrotum, palms, trunk, scalp
- Erythema nodosum:** red tender nodules due to panniculitis, typically on shins; Ddx incl. idiopathic, infxn, sarcoid, drugs, vasculitis, IBD, lymphoma
- Pyoderma gangrenosum:** neutrophilic dermatosis → painful ulcers w/ violaceous border; Ddx incl. idiopathic, IBD, RA, myelogenous leukemia

Psoriatic arthritis subtypes (*Lancet* 2011;377:2127)

- Monoarticular/oligoarticular** (eg, large joint, DIP joint, dactylitic digit): most common initial manifestation
- Polyarthritis** (small joints of the hands/feet, wrists, ankles, knees, elbows): indistinguishable from RA, but often asymmetric
- Arthritis mutilans:** severe destructive arthritis with bone resorption, esp. hands
- Axial disease:** unilateral/asymmetric sacroiliitis
- DIP-limited:** good correlation with nail pitting and onycholysis

Clinical assessment (*Nat Rev Rheumatol* 2012;8:253)**Axial disease assessment**

Nb: following not specific PEx findings but useful in monitoring disease during Rx
 Lumbar flexion deformity assessed by modified Schober's test (⊕ if <5 cm ↑ in distance between a point 5 cm below the lumbosacral jxn and another point 10 cm above, when going from standing to maximum forward flexion)

T-spine mobility (extension) and kyphosis severity measured by occiput-to-wall distance (although occiput-to-wall distance also increased in osteoporotic kyphosis)

- Seronegative:** notable for absence of rheumatoid factor or autoantibodies; ± ↑ESR/CRP
- HLA-B27:** nonspecific, as common in general population (6–8%); most useful when high clinical suspicion but nl imaging; ⊕ 90% of Pts w/ AS, but only 20–80% in other SpA
- Radiology**

MRI preferred for early detection of inflammation (sacroiliitis)

Plain films detect late structural changes (SI erosions/sclerosis)

calcification of spinal ligaments w/ bridging symm syndesmophytes ("bamboo spine")
 squaring and generalized demineralization of vertebral bodies ("shiny corners")

- Infectious evaluation for reactive arthritis** (⊖ studies do not r/o)
 - U/A, PCR of urine and/or genital swab for *Chlamydia*; urethritis usually due to *Chlamydia* infxn preceding arthritis, but also can see sterile urethritis post dysentery
 - ✓ stool Cx, *C. diff* toxin. Consider HIV in workup of reactive or psoriatic arthritis.

Treatment approach (*Ann Rheum Dis* 2012;71:319; *Arth Rheum* 2016;68:282)

- Untreated disease may lead to irreversible structural damage and associated ↓ function
- Early physiotherapy beneficial
- Tight control of inflammation improves joint outcomes in PsA (*Lancet* 2015;386:2489)
- NSAIDs:** 1st line; rapidly ↓ stiffness and pain; prolonged, continuous administration may modify disease course but associated w/ GI and CV toxicity (*Cochrane Database Syst Rev* 2015;17:CD010952); may exacerbate IBD
- Intra-articular corticosteroids** in mono- or oligoarthritis; limited role for systemic steroids, esp. for axial disease
- Conventional DMARDs** (eg, MTX, SAS, leflunomide): no efficacy for axial disease or enthesitis; may have role in peripheral arthritis, uveitis and extra-articular manifestations
- Anti-TNFs:** effective for both axial and peripheral manifestations; improves function (*Ann Rheum Dis* 2006;65:423) and may slow progression of structural changes (*Curr Rheumatol Rep* 2012;14:422); adalimumab or infliximab preferred if inflammatory eye disease
- Apremilast** (PO PDE-4 inhibitor): approved for use in PsA (*Ann Rheum Dis* 2014;73:1020); associated with GI side effects and significant wt loss
- Ustekinumab** (SC IL-12/23 inhibitor): approved for use in PsA (*Ann Rheum Dis* 2014;73:990)
- Secukinumab** (IL-17A inhibitor): improves signs & symptoms of PsA & ankylosing spondylitis (*NEJM* 2015;373:1329 & 2534; *Lancet* 2015;386:1137)
- Other:**

Abx in reactive arthritis if evidence of active infxn; consider prolonged abx for refractory *Chlamydia* ReA (*Arthritis Rheum* 2010;62:1298)

Involve ophthalmologist for any evidence of inflammatory eye disease (may benefit from steroid eye drops or intravitreal steroid injections).

Treat underlying IBD when appropriate

ETOLOGIES & DIAGNOSIS OF INFECTIOUS ARTHRITIS

Etiologies (Curr Rheumatol Rep 2013;15:332)

- **Bacterial** (nongonococcal): early diagnosis required
- **Gonococcal** (*N. gonorrhoea*): consider in sexually active young adults
- **Viral**: parvovirus, HCV, HBV, acute HIV; typically polyarticular, may mimic RA
- **Mycobacterial**: monoarticular or axial (Pott's disease)
- **Fungal**: *Candida* (esp. prosthetic joints), coccidiomycosis (valley fever), histoplasmosis
- **Other**: Lyme, *Mycoplasma*, *Salmonella* (2° to anti-TNF Rx), Brucellosis (unpast. dairy)

Diagnosis (JAMA 2007;297:1478)

- H&P w/ poor sensitivity and specificity for septic arthritis; ∴ **arthrocentesis** should be performed as soon as suspected and prior to starting antibiotics if possible
- Take care not to tap through an infected area, thus introducing infxn into joint space
- ✓ Synovial fluid cell count w/ differential, Gram stain, bacterial culture, crystals
WBC >50k w/ poly predom suspicious for bact. infxn; crystals do not r/o septic arthritis!

BACTERIAL (NONGONOCOCCAL) ARTHRITIS

Epidemiology & risk factors

- **Immunocompromised host**: DM, EtOH use, HIV, age >80, SLE, cancer, steroid use, etc.
- **Damaged joints**: RA, OA, gout, trauma, prior surgery/prosthetic, prior arthrocentesis (rare)
- **Bacterial seeding**: bacteremia secondary to IVDU, endocarditis or skin infection direct inoculation or spread from contiguous focus (eg, cellulitis, septic bursitis, osteo)

Clinical manifestations (JAMA 2007;297:1478; Lancet 2010;375:846)

- Acute onset **monoarticular arthritis** (>80%) w/ pain (Se 85%), swelling (Se 78%), warmth
- Location: **knee** (most common), hip, wrist, shoulder, ankle. In IVDU, tends to involve other areas inc. axial joints (eg, SI, symphysis pubis, sternoclavicular, manubrial joints).
- **Constit. sx**: fevers (Se 57%), rigors (Se 19%), sweats (Se 27%), malaise, myalgias, pain
- Infection can track from initial site to form fistulae, abscesses or osteomyelitis
- **Septic bursitis** must be differentiated from **septic intra-articular effusion**

Additional diagnostic studies (JAMA 2007;297:1478)

- Synovial fluid: **WBC usually >50k** (Se 62%, Sp 92%) but can be <10k, >**90% polys**; Gram stain + in ~75% of Staph, ~50% of GNR; Cx + in >90%. Synovial bx most sens.
- **Leukocytosis** (Se 90%, Sp 36%); **elevated ESR/CRP** (Se >90%)
- **Blood cultures** + in >50% of cases, ~80% when more than 1 joint involved
- Conventional radiographs should be obtained but usually normal until after ~2 wk of infection when bony erosions, joint space narrowing, osteomyelitis, periostitis can be seen
- **CT & MRI** useful esp. for suspected hip infection or epidural abscess

Treatment for native joints (Curr Rheumatol Rep 2013;15:332)

- Prompt empiric antibiotics guided by Gram stain after surgical drainage. If Gram stain -, empiric Rx w/ vancomycin; add anti-pseudomonal agent if elderly, immunosuppr.

Common microbes (by Gram stain)		Population	Initial antibiotic regimen (tailor based on Gram stain, cx, clinical course)
GPC	S. aureus (most common)	Normal joints Prosthetic joints Damaged joints	Vancomycin*
	S. epidermidis	Prosthetic joints Postprocedure	Vancomycin*
	Streptococci	Healthy adults Splenic dysfunction	PCN-G or ampicillin
GN	Diplococci: <i>N. gonorrhoea</i>	Sexually active young adults	Ceftriaxone or cefotaxime
	Rods: <i>E. coli</i> , <i>Pseudomonas</i> , <i>Serratia</i>	IVDU, GI infection immunosupp, trauma elderly	Cefepime or piperacillin/tazobactam + antipseudomonal aminoglycoside in IVDU

*Can later Δ to antistaphylococcal penicillin based on sensitivities

- **IV antibiotics** × ≥2 wk followed by oral antibiotics; varies by clinical course & microbiology
- Joint must be **drained**, often serially; arthroscopic drainage for larger joints and as initial treatment but may also be accomplished by arthrocentesis. Serial synovial fluid analyses should demonstrate ↓ in WBC and sterility.
- Prognosis: 10–50% mortality depending on virulence of organism, time to Rx, host

Prosthetic joint infections (Infect Dis Clin North Am 2012;26:29; CID 2013;56:e1)

- ↑ risk in first 2 y s/p procedure; rate generally low (0.5–2.4%); risk factors include obesity, RA, immunocompromised state, steroids, & superficial surgical site infxn
- Staphylococci (coag negative & *S. aureus*) in >50%; polymicrobial in 10–20%
- Early (<3 mo s/p surgery) or delayed (3–24 mo) onset typically acquired during implantation; early w/ virulent organisms (eg, MRSA) and delayed w/ less virulent organisms (eg, *P. acnes*, coag negative Staph) & more indolent presentation
- Late (>24 mo) onset typically related to secondary hematogenous seeding
- Diagnosis requires arthrocentesis by orthopedics; ESR & CRP (CRP Se 73–91%, Sp 81–86%; NEJM 2009; 361:787) can be helpful
- Treatment typically requires prolonged abx & 2-stage joint replacement (joint retention a/w ~40% failure rate; CID 2013;56:182) or life-long suppressive abx. ID and orthopedics consultation required.

DISSEMINATED GONOCOCCAL INFECTION (DGI)

Epidemiology (Infect Dis Clin North Am 2005;19:853)

- N. gonorrhoea*; most frequent type of infectious arthritis in sexually active young adults
- Normal host** as well as Pts w/ deficiencies of terminal components of complement
- ♀:♂ = 4:1; ↑ incidence during menses, pregnancy, & postpartum period, SLE; ↑ incidence in homosexual males; rare after age 40 y

Clinical manifestations

- Preceded by **mucosal infection** (eg, endocervix, urethra or pharynx) that is often axx
- Two distinct syndromes, although Pts can have both:
 - Joint localized:** purulent arthritis (40%), usually 1–2 joints (knees > wrists > ankles)
 - DGI:** triad of **polyarthralgias, tenosynovitis, skin lesions;** purulent arthritis rare acute onset of tenosynovitis (60%) in wrists, fingers, ankles, toes rash (>50%): gunmetal gray pustules with erythematous base on extremities & trunk
- Rare complications: Fitz-Hugh-Curtis syndrome (perihepatitis), pericarditis, meningitis, myocarditis, osteomyelitis from direct extension of joint-localized infection

Additional diagnostic studies

- Synovial fluid: **WBC >50k** (but can be <10k), **poly predominant** Gram stain ⊕ in ~25%; culture ⊕ in up to 50% if done w/ Thayer-Martin media
- Blood culture: more likely ⊕ in DGI; rarely in joint localized disease
- Gram stain and culture of skin lesions occasionally ⊕
- Cervical, urethral, pharyngeal, rectal PCR or cx on Thayer-Martin media; ✓ Chlamydia

Treatment

- Ceftriaxone or cefotaxime × 7 d w/ empiric doxycycline** for Chlamydia (fluoroquinolones no longer recommended due to resistance)
- Joint arthroscopy/lavage may be required if purulent arthritis; rarely >1 time

OLECRANON & PREPATELLAR BURSITIS

Epidemiology & risk factors (Infect Dis North Am 2005;19:991)

- >150 bursae in the body; 2 most commonly infected are **olecranon** and **prepatellar**
- Most commonly (esp. superficial bursae) due to direct trauma, percutaneous inoculation or contiguous spread from adjacent infection (eg, cellulitis)
- Other risk factors: recurrent noninfectious inflammation (eg, gout, RA, CPPD), diabetes
- S. aureus* (80%) most common, followed by streptococci

Diagnosis

- Physical exam: discrete bursal swelling, erythema, maximal tenderness at center of bursa with preserved joint range of motion
- Aspirate bursa if concern for infxn, ✓ cell count, Gram stain, bacterial cx, crystals
WBC >20k w/ poly predominance suspicious for bacterial infection, but lower counts common (crystals do *not* rule out septic bursitis!)
- Assess for adjacent joint effusion, which can also be septic
- Take care not to tap through infected skin, thus introducing infxn into bursa*

Initial therapy

- Prompt empiric coverage for staphylococci and streptococci: PO abx acceptable for mild presentation; **vancomycin** if ill-appearing; broaden spectrum based on risk factors
- Modify antibiotics based on Gram stain, culture results, & clinical course. Duration of tx is 1–4 wks. **Serial aspirations** every 1–3 d until sterile or no reaccumulation of fluid.
- Surgery if unable to drain bursa through aspiration, evidence of foreign body or necrosis, recurrent/refractory bursitis w/ concern for infxn of adjacent structures.

CONNECTIVE TISSUE DISEASES

Approx Prev of Autoantibodies in Rheumatic Diseases

Disease	ANA	dsDNA	Sm	Ro/ La	Scl- 70	RNA PIII	Centr	Jo-1	U1- RNP	RF
SLE	≥95	75	20	25	⊖	⊖	⊖	⊖	45	35
Sjögren's	≥95	rare	⊖	45	⊖	⊖	⊖	⊖	rare	>75
Diffuse SSc	>90	⊖	⊖	rare	40	20	rare	⊖	rare	30
Limited SSc	>90	⊖	⊖	rare	10	rare	60	⊖	rare	30
IM	75–95	⊖	⊖	⊖	rare	⊖	⊖	25	⊖	15
MCTD	≥95	⊖	⊖	rare	⊖	⊖	⊖	⊖	always	50
RA	40	⊖	⊖	⊖	⊖	⊖	⊖	⊖	⊖	70

Centr, centromere; IM, inflammatory myopathies; RF, rheumatoid factor; SSc, systemic sclerosis. (Primer on the Rheumatic Diseases, 12th ed., 2001; Lancet 2013;382:797).

- Auto-Ab testing directed by clinical findings, as auto-Ab do not define a particular CTD
- Overlap syndromes may be reflected by multiple autoantibodies

see "Systemic Lupus Erythematosus" and "Rheumatoid Arthritis" for those diseases

SYSTEMIC SCLEROSIS AND SCLERODERMA DISORDERS

Definition & epidemiology

- (Best Pract Res Clin Rheumatol 2010;24:857)
- Scleroderma refers to the presence of tight, thickened skin
 - Localized scleroderma: morphea (plaques of fibrotic skin), linear (fibrotic bands), "en coup de sabre" (linear scleroderma on one side of scalp and forehead ≈ saber scar)
 - Systemic sclerosis (SSc) = scleroderma + internal organ involvement
 - SSc w/ limited cutaneous disease: formerly CREST syndrome (see below)
 - SSc w/ diffuse cutaneous disease: often rapidly progressive disorder affecting skin
 - SSc sine scleroderma (visceral disease without skin involvement, rare)
 - Peak onset of SSc between ages 30–50; ♀ > ♂ (7:1); African American > white
 - 1–2/100,000 annual incidence of systemic disease in the U.S.
 - Pathogenesis: immune damage to endothelial cells and reactive O₂ species production → persistent oxidative stress → perivascular inflammation → fibroblast activation and fibrosis. Cytokines, growth factors, genetics, environmental factors and autoantibodies (against PDGF receptor, endothelial cells and fibroblasts) all contribute (NEJM 2009;360:1989).

ACR/EULAR SSc classification criteria

- (Ann Rheum Dis 2013;72:1747)
- Sufficient for dx: skin thickening of fingers of both hands extending proximal to MCPs
 - Other items considered in criteria: Raynaud's, SSc-related auto-Ab, PAH and/or ILD, abnormal nailfold capillaries, telangiectasia, fingertip lesions (ulcers, scars), skin thickening limited to fingers (not beyond MCPs)
 - Rule out other causes of thickened skin: diabetes (scleredema ≠ scleroderma), toxin, hypothyroidism, nephrogenic systemic fibrosis, eosinophilic fasciitis, amyloidosis, GVHD

Diagnostic studies & monitoring

- (Semin Arthritis Rheum 2005;35:35)
- Autoantibodies: >95% Pts w/ auto-Ab; generally mutually-exclusive
 - ⊕ anti-Scl-70 (antitopoisomerase 1): a/w diffuse SSc; ↑ risk pulm fibrosis
 - ⊕ anticentromere: a/w limited SSc; ↑ risk of severe digit ischemia and PHT
 - ⊕ anti-RNA-Pol III: a/w diffuse SSc; ↑ risk renal crisis; a/w cancer
 - ⊕ ANA (>90%), ⊕ RF (30%), ⊕ anti-U1-RNP a/w overlap syndrome
 - Other: anti-Th/To (a/w limited SSc), U3-RNP (a/w ILD), PM/ScI (polymyositis-SSc overlap)
 - CXCL4 levels reported to help diagnose disease and be correlated w/ degree of lung & skin fibrosis and disease progression but awaits validation (NEJM 2014;370:433)
 - At baseline: ✓ BUN/Cr & UA for proteinuria, PFTs (spirometry, lung volumes, DLCO), high-res chest CT (if diffuse disease), TTE (RVSP for PHT), RHC if ↑ RVSP or suspect PHT
 - Annual PFTs; TTE q1–2y
 - Skin bx not routine, but helpful to assess other possible causes for skin thickening
 - ↑ risk of malignancy compared to general population, therefore must be vigilant
 - Frequent (eg, daily) BP ✓ to monitor for HTN suggestive of scleroderma renal crisis

Clinical Manifestations of Systemic Sclerosis

Skin	Tightening and thickening of extremities, face, trunk (bx not req for dx) “Puffy” hands, carpal tunnel syndrome, sclerodactyly Nailfold capillary dilatation & dropout Immobile, pinched, “mouse-like” facies and “purse-string” mouth Calcinosis cutis (subcutaneous calcification), telangiectasias
Arteries	Raynaud's phenomenon (80%); digital or visceral ischemia
Renal	Scleroderma renal crisis (SRC) = accelerated development of HTN (relative increase in Pt BP as compared with baseline BP), MAHA urine sediment typically bland; path w/ “onion-skin” hypertrophy of capillaries; affects 5–10% of Pts, 66% w/in 1 st year (Rheum 2009;48:iii32) ↑ risk w/ >15 mg/d of prednisone (Arthritis Rheum 1998;41:1613) poor prognosis w/ 50% mortality
GI (>80% of Pts)	GERD and erosive esophagitis Esophageal dysmotility → dysphagia, odynophagia, aspiration Gastric dysmotility → early satiety and gastric outlet obstruction Small intestinal dysmotility → malabsorption, bact overgrowth, bloating
Musculoskel	Arthralgias/arthritis; myositis; joint contractures; tendon friction rubs
Cardiac	Myocardial fibrosis; pericardial effusion; conduction abnormalities
Pulmonary	Pulmonary fibrosis (typically develops w/in 4 y); pulmonary arterial hypertension (typically develops after many yrs). #1 cause of mortality
Endocrine	Amenorrhea and infertility common; thyroid fibrosis ± hypothyroidism

SSc Subgroup Comparison

	Limited	Diffuse
General		Fatigue, weight loss
Skin	Thickening on extremities distal to elbows/knees and face only	Thickening of distal and proximal ext, face and trunk
Pulmonary	PAH (rapidly progressive) > fibrosis	Fibrosis > PAH
GI	PBC	
Renal	SRC later in disease course	SRC earlier & more common
Cardiac		Restrictive cardiomyopathy
Other	CREST syndrome = Calcinosis, Raynaud's, Esophageal dysmotility, Sclerodactyly, Telangiectasias	Raynaud's
Antibodies	Centromere (10–40%)	ScI 70, RNA-Pol III (40%)
Prognosis	Survival >70% at 10 y	Survival 40–60% at 10 y

Treatment (Ann Rheum Dis 2009;68:620)

- Minimize steroid exposure to reduce risk of renal crisis
- Pulmonary fibrosis: **cyclophosphamide** (NEJM 2006;354:2655; Arth Rheum 2006;54:3692), MMF under investigation; improvement may be minimal (Rheum Dis Clin NA 2015;41:237)
PAH: pulmonary **vasodilators** (see “Pulm Hypertension”), early Rx a/w better outcomes
- Renal crisis: **ACEI** (not ARB) for Rx, not prophylaxis (Semin Arthritis Rheum 2015;44:687)
- GI: PPI and/or H2-blockers for GERD; antibiotics for malabsorption hypomotility: metoclopramide or erythromycin; nonoperative Rx of pseudo-obstruction
- Cardiac: NSAIDs or steroids for pericarditis
- Arthritis: acetaminophen, NSAIDs, hydroxychloroquine, MTX
- Myositis: MTX, AZA, steroids
- Skin: PUVA for morphea. For pruritus: emollients, topical or oral steroids (↓ dose). MTX or MMF effectiveness for skin fibrosis debated (Ann Rheum Dis 2011;70:1104).

INFLAMMATORY MYOPATHIES

Definition & epidemiology (JAMA 2013;305:183; NEJM 2015;372:1734)

- All lead to skeletal muscle inflammation & weakness, variable extramuscular involvement
- Polymyositis** (PM): idiopathic diffuse polymyopathy, onset typically 40s–50s; ♀ > ♂
- Dermatomyositis** (DM): similar to PM; also occurs in childhood, but differentiated from other myopathies by skin manifestations; malignancy a/w PM (10%) & DM (24%)
- Necrotizing autoimmune myositis** (NM): usually in adults; occurs after viral infections, statin exposure (+ anti-HMGCR)
- Inclusion body myositis** (IBM): onset after age 50; ♂ > ♀; often misdiagnosed as PM

Clinical manifestations (NEJM 2015;372:1734)

- Muscle weakness:** gradual (wks → mos) except in NM, progressive and painless

DM/PM/NM: proximal and symmetric; difficulty climbing stairs, arising from chairs, brushing hair; fine motor skills (eg, buttoning) lost late

IBM: may be asymmetric and distal

- Dermatologic:** may precede myositis by mos to yrs (uncommon for converse **erythematous rash** on sun-exposed skin: neck & shoulders (shawl sign), face, chest **heliotrope rash** (purplish discoloration) over upper eyelids ± periorbital edema **Gottron's papules** (in >80% & pathognomonic): violaceous often scaly areas symmetrically over dorsum of PIP and MCP joints, elbows, patellae, medial malleoli subungual erythema, "mechanic's hands" (skin cracks on digits), pruritus

DM sine myositis (amyopathic DM): dermatologic features w/o myositis, in 10–20%

- Polyarthralgias or polyarthritis: usually early; nonerosive; small joints > large joints
- Raynaud's (30%, DM and overlap CTD) w/ dilatation & dropout of nail bed capillaries
- Visceral involvement** (*J Rheumatol* 2009;36:2711)
 - pulmonary:** acute alveolitis; ILD; respiratory muscle weakness; aspiration
 - cardiac** (33%): often asx; conduction abnl; myo/pericarditis; HF uncommon; ↑ CK-MB/Tn
 - GI:** dysphagia, aspiration
- Antisynthetase syndrome** (PM > DM): fever, ILD, Raynaud's, mechanic's hands, arthritis
- DDx: drug-induced myopathy (statins, cocaine, steroids, colchicine); infxn (HIV, EBV, CMV); metabolic (hypothyroid, hypo-K, hypo-Ca); neuromuscular dis. (eg, myasthenia gravis); glycogen storage disease; mitochondrial cytopathy; muscular dystrophy

Diagnostic studies

- ↑ CK (rarely >100,000 U/L, can be ↑↑ in NM), aldolase, SGOT, LDH; ± ↑ ESR & CRP
- Autoantibodies: + ANA (>75%) (*Curr Rheumatol Rep* 2013;15:335)
 - + anti-Jo-1 (25%): most common specific Ab; a/w antisynthetase syndrome
 - + anti-Mi-2 (DM > PM 15–20%) is a/w disease that responds well to steroids
 - + anti-SRP is a/w NM, poor Rx response; + anti-HMGCR in NM a/w statin exposure
- Consider **EMG** (↑ spontaneous activity, ↓ amplitude, polyphasic potentials w/ contraction) or **MRI** (muscle edema, inflammation, atrophy) for evaluation; may guide biopsy
- Pathology and muscle biopsy:** all with interstitial mononuclear infiltrates, muscle fiber necrosis, degeneration & regeneration (required for definitive diagnosis)
 - PM: T cell-mediated muscle injury; endomysial inflam. surrounds non-necrotic fibers
 - DM: immune complex deposition in blood vessels with complement activation; perimysial, perivascular inflam (B & CD4 T cells), complement in vessels.
- NM: necrotic fibers w/ macrophages
- IBM: T cell-mediated muscle injury, vacuole formation; same as PM with eosinophilic inclusions and rimmed vacuoles (EM)

Treatment (PM & DM, no effective treatment for IBM) (*Autoimmun Rev* 2011;11:6)

- Steroids** (prednisone 1 mg/kg); MTX or AZA early if mod/severe or taper fails (2–3 mo)
- For resistant (30–40%) or severe disease: AZA/MTX combo, IVIg (DM ± PM), rituximab (*Arthritis Rheum* 2013;65:314), MMF, cyclophosphamide (esp. if ILD or vasculitis)
- IVIg w/ pulse steroids acutely for life-threatening esoph or resp muscle involvement
- ✓ for occult malignancy (esp. if DM); monitor respiratory muscle strength with spirometry
- NM: discontinue statin if taking; steroids + MTX or IVIG if needed (*Muscle Nerve* 2010;41:185)

Myositides, Myopathies and Myalgias

Disease	Weakness	Pain	↑ CK	↑ ESR	Biopsy
DM/PM/NM	+	-	+	±	as above
IBM	+	-	+	-	as above
Hypothyroidism	+	±	+	-	mild necrosis inflam, atrophy
Steroid-induced	+	-	-	-	atrophy
PMR	-	+	-	+	normal
Fibromyalgia (JAMA 2014;311:1547)	-	+	-	-	normal
		(tender points)			

SJÖGREN'S SYNDROME

Definition & epidemiology

- Chronic dysfxn of **exocrine glands** (eg, salivary/lacrimal) due to lymphoplasmacytic infiltration. Extraglandular manifestations common in primary form.
- Can be primary or secondary (a/w RA, scleroderma, SLE, PM, hypothyroidism, HIV)
- More prevalent in ♀ than ♂; typically presents between 40 & 60 y of age

Clinical manifestations

- Dry eyes** (keratoconjunctivitis sicca): ↓ tear production; burning, scratchy sensation

- Dry mouth** (xerostomia): difficulty speaking/swallowing; dental caries; xerotrachea; thrush

- **Parotid gland enlargement:** intermittent, painless, typically bilateral
- **Vaginal dryness and dyspareunia**
- **Recurrent nonallergic rhinitis/sinusitis** due to upper airway gland involvement
- **Extraglandular manifestations:** arthritis; interstitial nephritis (40%); type I RTA (20%); cutaneous vasculitis (25%); neuropathies (10%); PNS or CNS disease; ILD; PBC
- ↑ risk of lymphoproliferative disorders (~50x ↑ risk of lymphoma and WM in 1° Sjögren's)

Diagnostic studies

- Autoantibodies: + ANA (95%), + RF (75%)
Primary Sjögren's: + anti-Ro (anti-SS-A, 56%) and/or + anti-La (anti-SS-B, 30%)
- **Schirmer test:** filter paper in palpebral fissures to assess tear production
- **Rose-Bengal staining:** dye that reveals devitalized epithelium of cornea/conjunctiva
- **Ocular staining score:** substitute for Rose-Bengal staining to determine degree of keratoconjunctivitis sicca using fluorescein and lissamine green
- **Biopsy** (minor salivary, labial, lacrimal or parotid gland): lymphoplasmacytic infiltration

Classification criteria (2 of 3 have 93% Se & 95% Sp; Arthritis Care Res 2012;64:475)

1. + anti-Ro or anti-La or RF + ANA >1:320
2. Labial salivary gland bx w/ lymphocytic sialadenitis and score >1 focus/4 mm²
3. Keratoconjunctivitis sicca w/ ocular staining score ≥3

Treatment (Arth Rheum 2005;52:27 & 2007;57:310; Arth Res Ther 2013;15:R172)

- Ocular: artificial tears, cyclosporine eyedrops, autologous tears
- Oral: sugar-free gum, lemon drops, saliva substitute, hydration, pilocarpine, cevimeline
- Systemic: NSAIDs, steroids, DMARDs, rituximab (RCTs are needed)

MIXED CONNECTIVE TISSUE DISEASE (MCTD)

Definition (Best Pract Res Clin Rheumatol 2012;26:61)

- Features of **SLE**, **systemic sclerosis**, and/or **polymyositis** that appear gradually and often evolve to a dominant phenotype of SLE or systemic sclerosis
- Different from undifferentiated CTD (UCTD): fail to meet criteria for any CTD; 30% go on to develop CTD over 3–5 y (usually SLE)

Clinical & laboratory manifestations (variable clinical course)

- **Raynaud's phenomenon** typical presenting symptom (75–90%); see below
- Hand edema ("puffy hands"), sclerodactyly, RA-like **arthritis** w/o erosions, polyarthralgias
- Pulmonary involvement (85%) with **pulmonary hypertension**, fibrosis
- Pericarditis most frequent cardiovascular manifestation; GI: dysmotility (70%)
- Membranous & mesangial GN common (25%); low risk for renal HTN crisis or severe GN
- + ANA (>95%); + RF (50%); **anti-U1-RNP** in all but not specific (seen in ~50% SLE)

Treatment: As per specific rheumatic diseases detailed above

RAYNAUD'S PHENOMENON

Clinical manifestations (NEJM 2016;375:556)

- Episodic, reversible digital ischemia, triggered by cold temp, or stress, classically: **blanching** (white, ischemia) → **cyanosis** (blue, hypoxia) → **rubor** (red, reperfusion); color Δ usually well demarcated; affects fingers, toes, ears, nose.

Primary vs. Secondary Raynaud's Phenomenon

	Primary (80–90%)	Secondary (10–20%)
Vessel wall	Functionally abnl	Structurally abnl
Etiologies	Idiopathic, however can be exacerbated by comorbid conditions, including HTN, athero, CAD, DM	SSc, SLE, PM-DM, MCTD, Sjögren's, RA Arterial dis (athero, Buerger's); trauma Heme (cyro, Waldenström's, APLAS) Drugs (ergopeptides, estrogens, cocaine)
Epidem.	20–40 y; ♀ > ♂ (5:1)	>35 y
Clinical	Mild, symm. episodic attacks No PVD, tissue injury, or systemic sx	Tissue ischemia & injury (eg, digital ulcers); can be assoc w/ systemic sx
Auto Ab	⊖	Depends on above etiology, often +
Nailfold	Normal	Dropout and/or enlarged or distorted loops

Treatment (Curr Opin Rheumatol 2011;23:555; BMJ 2012;344:e289)

- All: avoid cold, maintain warmth of digits & body; avoid cigarettes, drugs, caffeine & trauma
- Mild-mod: **long-acting CCB**, topical nitrates, SSRI, ARB, α-blockers, ASA/clopidogrel
- Severe: PDE inhibitors, anti-ET-1 receptor (if ulcers esp. w/ PHT), digital sympathectomy
- Digit-threatening: IV prostaglandins, digital sympathectomy, ± anticoagulation
- Others: fish oil (1° RP only; Am J Med 1989;86:158), abx for infected ulceration

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Multisystem inflammatory autoimmune disease with a broad spectrum of clinical manifestations in association with antinuclear antibody (ANA) production

Epidemiology (Lancet 2014;384:1878)

- Prevalence 15–50/100,000; predominantly affects women 2nd to 4th decade
- ♀:♂ ratio = 8:1; African American:Caucasian ratio = 4:1
- Complex genetics; some HLA association; rarely C1q & C2 deficiency

Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria

Clinical Criteria	SLICC Classification Criteria	Other Clinical Features
Constit (84%)		Fever, malaise, anorexia, ↓ wt
Cutaneous/Oral/Ophthalmologic (81%)	<ol style="list-style-type: none"> 1. Acute or subacute cutaneous changes 2. Chronic cutaneous changes 3. Oral or nasal ulcers 4. Nonscarring alopecia 	Malar rash (spares nasolabial folds), discoid rash (papules w/ keratosis & plugging), bullous SLE, urticaria, TEN Photosens. (n/v, rash, fever) Vasculitis, panniculitis (lupus profundus) Raynaud's, nailfold cap Δs, Sicca syndrome Conjunctivitis, episcleritis
Musculoskeletal (85–95%)	<ol style="list-style-type: none"> 5. Joint disease: synovitis or tenderness & morning stiffness involving ≥2 joints 	Arthralgias and myalgias Avascular necrosis of bone
Cardiopulmonary (33%)	<ol style="list-style-type: none"> 6. Serositis: pleuritis (37%) or pleural effusion, pericarditis (29%) or pericardial effusion 	Pneumonitis, IPF, shrinking lung, PAH, DAH Myocarditis, CAD Libman-Sacks endocarditis
Renal (77%)	<ol style="list-style-type: none"> 7. Proteinuria (>0.5 g/dL) or RBC casts 	Nephrotic syndrome Lupus nephritis (qv)
Neurologic (54%)	<ol style="list-style-type: none"> 8. Seizures or psychosis w/o other cause 	Cognitive dysfxn, stroke, cranial or periph neuropathies, transverse myelitis, mononeuritis multiplex
GI (~30%)		Serositis (peritonitis, ascites) Vasculitis (bleeding, perf.) Hepatitis, pancreatitis
Hematologic	<ol style="list-style-type: none"> 9. Hemolytic anemia 10. Leukopenia (<4000/mm³) or lymphopenia (<1000/mm³) 11. Thrombocytopenia (<100,000/mm³) 	Anemia of chronic disease Antiphospholipid synd (VTE w/ ⊕ ACL Ab, lupus anticoag, and/or B2GPI Ab) Splenomegaly, LAN
Immunologic	<ol style="list-style-type: none"> 12. ⊕ ANA; 13. ⊕ anti-ds-DNA 14. ⊕ anti-Sm; 15. ⊕ APLA 16. ↓ Complement 17. ⊕ Direct Coombs' (w/o #9) 	↑ ESR/CRP, ⊕ anti-Ro/La, ⊕ anti-RNP, ⊕ RF, ⊕ anti-CCP

Expert opinion, not dx criteria for SLE: ≥4/17 SLICC criteria, including ≥1 clinical & ≥1 immunologic, or bx proven SLE nephritis w/ ⊕ ANA or anti-ds-DNA (Arth Rheum 2012;64:2677)

Autoantibodies in SLE (NEJM 2008;358:929)

Auto-Ab	Frequency (approx)	Clinical associations	Timeline
ANA	95–99% if active disease 90% if in remission Homogeneous or speckled	Any or all of broad spectrum of clinical manifestations Sensitive but not specific	May appear yrs before overt disease
Ro La	15–35% ⊕ anti-Ro may be seen w/ ⊖ or low titer ANA	Sjögren's/SLE overlap Neonatal lupus Photosens.; subacute cutan.	
ds-DNA	70%; ~95% Sp; titers may parallel dis. activity, esp. renal	Lupus nephritis Vasculitis	Appears mos before or at dx, but may become ⊕ after dx
Sm	30%; very specific for SLE	Lupus nephritis	
U1-RNP	40%	MCTD; Raynaud's Tend not to have nephritis	
Histone	90% in DLE; 60–80% in SLE	Mild arthritis and serositis	At diagnosis

Workup

- Autoantibodies: ANA, if + → ✓ anti-ds-DNA, anti-Sm, anti-Ro, anti-La, anti-U1-RNP
- Lyses, BUN, Cr, U/A, urine sed, spot microalb:Cr ratio or 24-h urine for CrCl and protein
- CBC, APLA (+ in 20–40%; ACL, B2GP1, lupus anticoagulant), total complement, C3 & C4
- If ↓ GFR, active sediment, hematuria or proteinuria (>0.5 g/dL) → renal bx to guide Rx

Treatment of SLE (Curr Rheumatol Rep 2011;13:308; Arthritis Care Res 2015;67:1237)

Drug	Indication	Adverse effects
Hydroxychloroquine (HCQ)	All Pts as ↓ flares (NEJM 1991;324:150); monoRx for arthritis, serositis, skin disease	Retinal damage (<1%) Stevens-Johnson; myopathy Not immunosuppressive
NSAIDs	Arthritis, myalgias, serositis	Gastritis, UGIB, renal failure
Immunosuppressive agents		
Corticosteroids	Low dose (10–15 mg) for arthritis, serositis; high-dose (1 mg/kg) ± pulse (1 g × 3 d) for major dis (eg, renal, CNS, heme)	Adrenal suppression, DM, cataracts, osteopenia, avascular necrosis of bone, myopathy
Mycophenolate (MMF)	Nephritis (induction/maint) Nonrenal refractory to HCQ	Cytopenias, ↑ LFTs, diarrhea, teratogen
Cyclophosphamide (CYC)	Nephritis CNS disease (induction, minimize exposure)	Cytopenias, infertility, teratogen, myeloproliferative disorders, hemorrhagic cystitis, bladder cancer
Azathioprine (AZA)	Nephritis (maintenance) Non-renal disease refractory to HCQ	Myelosuppression (✓TPMT), hepatotoxicity, teratogen lymphoproliferative disorders
Methotrexate (MTX)	Arthritis (preferred over MMF/AZA) Skin disease & serositis	Myelosuppression, hepatotoxicity, pneumonitis, alopecia, stomatitis, teratogen
Cyclosporine (CsA)	Renal disease	Hyperplastic gums, HTN hirsutism, CKD, anemia
Belimumab (NEJM 2013;368:1528)	Arthritis, serositis, skin disease (esp. if + ds-DNA or ↓ C3/C4)	B-cell depletion (< RTX, different mechanism)
Rituximab (RTX)	Refractory SLE, ITP, AIHA	Allergic rxn; serum sickness; PML

Lupus Nephritis (Arthritis Care Res 2012;64:797)

Class	Presentation	Treatment (all benefit from HCQ)
I: Min. mesangial	Normal U/A & creatinine	No specific treatment
II: Mesangial prolif	Micro hematuria/proteinuria	No specific treatment ± ACEI
III: Focal prolif	Hematuria/proteinuria, ± HTN, ↓ GFR, ± nephrotic	Induce: MMF or CYC + steroids Maintenance: ? MMF > AZA
IV: Diffuse prolif	Hematuria/proteinuria and HTN, ↓ GFR, ± nephrotic	
V: Membranous (Can coexist with class III or IV)	Proteinuria, nephrotic	ACEI If nephrotic range proteinuria induce w/ MMF + steroids Maint.: MMF superior to AZA
VI: Adv. sclerotic	ESRD	Renal replacement therapy

(Ann Rheum Dis 2010;69:2083; NEJM 2004;350:971 & 2005;353:2219 & 2011;365:1886)

Prognosis (Arth Rheum 2006;54:2550; Rheum [Oxford] 2016;55:252)

- 5-y survival rate >90%, 10-y survival rate >80%
- Leading causes of morbidity and mortality: **infection, renal failure, neurologic and cardiovascular events; thrombotic complications** (Medicine 2003;82:299)

Drug-induced lupus (DLE) (Drug Saf 2011;34:357; Curr Opin Rheumatol 2012;24:182)

- Many drugs: **procainamide, hydralazine, penicillamine, minocycline, INH, methyldopa, quinidine, chlorpromazine, diltiazem, anti-TNF** (esp. infliximab), interferons
- Idiosyncratic onset; generally mild disease with arthritis, serositis, skin disease
- ⊕ Anti-histone (95%) (may be ⊖ in anti-TNF); ⊖ anti-ds-DNA (often ⊕ in anti-TNF even w/o manifestations of DLE) & anti-Sm; normal complement levels
- Usually reversible w/in 4–6 wk after stopping medication

VASCULITIS

OVERVIEW

- Inflammation w/in blood vessel walls causing end-organ damage often a/w systemic sx; may be primary or secondary (eg, infection, malignancy) in etiology
- Classified by size of predominant vessel affected (*Arthritis Rheum* 2013;65:1); overlap of vessel size affected is common
- Clinical manifestations based on size of vessels involved; constitutional sx (low-grade fever, fatigue, weight loss, myalgias, anorexia) common to all

Distinguishing Characteristics of Vasculitis Subtypes

	Large vessel		Medium vessel	Small vessel	
	TAK	GCA	PAN	ANCA-assoc.	IC
Epidem	Young, ♀ > ♂	Elderly, ♀ > ♂	Middle-aged to older	Variable	Variable
Renal	Arteries	None	Microaneurysms	GN	GN
Pulm	Rare	None	Rare	Frequent	Cryo > HSP
Periph Neurop	No		Yes	Yes	Yes
GI	Uncommon		Yes	Yes	HSP > Cryo
Skin	Rare	None	Common	Common	Common
Granul.	Yes		No	Yes, except MPA	No
Other			Mesenteric aneurysms, testicular involv.	GPA: upper airway EGPA: asthma	HSP: IgA-dep Cryo: HCV

TAK, Takayasu's arteritis; GCA, giant cell arteritis; PAN, polyarteritis nodosa; ANCA-assoc. is GPA, EGPA, & MPA; IC, immune complex small vessel vasculitis (eg, HSP, cryoglobulinemia); GN, glomerulonephritis.

LARGE-VESSEL VASCULITIS

Takayasu's arteritis ("pulseless disease")

- Arteritis of aorta and its branches** → **stenosis/aneurysm** → claudication; onset <50 y
- Pattern of involvement: aorta and branches; most often **subclavian** and **innominate arteries** (>90%), as well as carotid, coronary, renal, pulmonary (~50%)
- Epidemiology: Most common in **Asia**; ♀:♂ ~9:1; age <50 y
- Clinical manifestations and physical findings (*Circ* 2015;132:1701)
 - Systemic inflamm with **fever, arthralgias, wt loss**
 - Vessel inflamm w/ pain & tenderness, ↓ & **unequal pulses/BPs in extremities, bruits**, limb claudication, renovascular HTN (>50%), neurogenic syncope; Ao aneurysm ± AI "Burnt out" or fibrotic period (eg, vascular stenosis)
- Dx studies: ↑ ESR (75%), CRP; **angiography** → occlusion, stenosis, irregularity and aneurysms; carotid U/S Doppler studies; PET-CT; MRA; **pathology** → focal panarteritis, cellular infiltrate with **granulomas** and giant cells (bx not required for dx)
- Treatment: **steroids** ± MTX or AZA; anti-TNF (2nd line, *Autoimmun Rev* 2012;11:678), ASA, surgical/endovascular revasc (*Circ* 2008;69:70)
- Monitoring: MRA or PET-CT (*Arth Rheum* 2012;64:866); ESR/CRP (*Ann Rheum Dis* 2009;68:318)

Giant cell arteritis (GCA) (*JAMA* 2016;315:2442)

- Granulomatous arteritis of aorta/branches** w/ predilection for **temporal artery**,
- Pattern of involvement: **extracranial branches of carotid artery**, esp. temporal artery (thus also called **temporal arteritis**); aorta and/or its branches in 10–80%
- 90% of Pts w/ GCA are >60 y, peak incidence at 70–80 y, extremely rare <50 y; ♀:♂ = 3:1
- Clinical manifestations (*NEJM* 2014;371:50)
 - constitutional sx: **fevers, fatigue, wt loss, PMR sx** (see below)
 - temporal artery (TA)** → **headache, tender TAs** and scalp; absent TA pulse
 - ophthalmic artery (20%) → optic neuritis, diplopia, amaurosis fugax, blindness
 - facial arteries → **jaw claudication**
- large vessel vasculitis → intermittent claudication of extremities; thoracic Ao aneurysm ~50% of Pts w/ GCA ultimately also diagnosed w/ PMR
- Dx studies: ↑ **ESR** (Se 84%, Sp 30%), ↑ CRP (Se 86%, Sp 30%), anemia (ESR related to fibrinogen & Ig in blood; Ddx for >100: malignancy esp. multiple myeloma, lymphoma; GCA or other vasculitis; ESRD; endocarditis, TB, osteomyelitis)
- temporal artery bx** whenever GCA suspected (Se ≤85%); 1–2 cm ± bilat to ↑ yield (3–7% discordance) (*Ann Rheum Dis* 2009;68:318) → **vasculitis & granulomas**
- if suspect aortitis or lg vessel involvement (BP Δ or bruits) → MRI/MRA or PET-CT

- **Polymyalgia rheumatica** (*Lancet* 2013;381:63; *JAMA* 2016;315:2442)
 - seen in 50% of GCA Pts; 15% of Pts w/ PMR develop GCA
 - age ≥ 50 y; ESR > 40 mm/h (and/or \uparrow CRP); **bilateral pain & morning stiffness** (> 30 min), involving 2 of 3 areas: neck or torso, shoulders or prox. arms, hips or prox. thighs; nighttime pain; \pm subdeltoid bursitis on U/S; exclude other causes of sx (eg, RA); nl CK
- Rx: **steroids** (do not await bx/path results to begin steroids, have at least 2 wk to bx)
 - GCA: 40–60 mg/d w/ slow taper; ASA daily; consider IV pulse if vision threatened. Adding tocilizumab to steroid may be beneficial (*Lancet* 2016;387:1921); await phase III results.
 - PMR: 12.5–25 mg/d; if clinical improvement, initiate slow taper. If no improvement, \uparrow dose. Consider MTX if at high risk for steroid side effects (*Ann Rheum Dis* 2015;74:1799).
- Follow clinical status & ESR/CRP (*Ann Rheum Dis* 2009;68:318); $\sim 1/3$ relapse over 2 y (*J Rheum* 2015;42:1213)

MEDIUM-VESSEL VASCULITIS

Polyarteritis nodosa ("classic" PAN) (*Arth Rheum* 2010;62:616)

- **Necrotizing nongranulomatous vasculitis of medium and small arteries** (w/ muscular media) w/o glomerulonephritis or capillary involvement (ie, DAH), not a/w ANCA
- Epidemiology: $\delta > \varphi$; average age of onset ~ 50 y; primary or **HBV-associated** ($\sim 10\%$)
- Clinical manifestations
 - constitutional sx (80%): wt loss, **fever**, fatigue
 - neuro (79%): **mononeuritis multiplex**, peripheral neuropathies, stroke
 - musculoskeletal (64%): **extremity pain**, myalgias, arthralgias, arthritis
 - renal (51%): **HTN**, hematuria, proteinuria, renal failure, *glomerulonephritis unusual*
 - GI (38%): **abd pain**, GLB/infarction, cholecystitis; GU (25%): ovarian or testicular pain
 - skin (50%): **livedo reticularis**, purpura, nodules, ulcers, Raynaud's
 - ophthalmic (9%): retinal vasculitis, retinal exudates, conjunctivitis, uveitis
 - cardiac (22%): coronary arteritis, cardiomyopathy, pericarditis
 - if lung involvement, suspect other vasculitis*
- Dx studies: \uparrow ESR/CRP, \ominus ANCA; \checkmark HBs Ag; \downarrow C3/C4 if HBV-associated
 - angiogram** (mesenteric or renal vessels) \rightarrow **microaneurysms** & focal vessel narrowing
 - CTA may be adequate to make dx, but conventional angiogram is most sensitive
 - biopsy** (sural nerve, skin or affected organ) \rightarrow vasculitis of small and medium vessel arteries with fibrinoid necrosis *without granulomas*
- Treatment: **steroids** \pm CYC (if severe or failure to induce remission); antivirals if a/w HBV

ANCA-ASSOCIATED SMALL-VESSEL VASCULITIS

Microvascular vasculitis (eg, capillaries, postcapillary venules, & arterioles)

Disease	Gran	Renal	Pulm	Asthma	ANCA Type ^a	ANCA \oplus
Granulomatosis with polyangiitis^b	\oplus	80%	90% (+ ENT)	—	anti-PR3 (c-ANCA)	90%
Microscopic polyangiitis	—	90%	50%	—	anti-MPO (p-ANCA)	70%
Eosinophilic granulomatosis with polyangiitis^b	\oplus	45%	70%	\oplus	anti-MPO (p-ANCA)	50%

^aPredominant ANCA type; either p- or c-ANCA can be seen in all three diseases (*NEJM* 2012;367:214).

^bGPA is formerly Wegener's granulomatosis and EGPA is formerly Churg-Strauss.

Differential diagnosis of ANCA (*Lancet* 2006;368:404)

- **anti-PR3 (c-ANCA):** granulomatosis w/ polyangiitis, eosinophilic granulomatosis and polyangiitis, microscopic polyangiitis (rarely)
- **anti-MPO (p-ANCA):** microscopic polyangiitis, eosinophilic granulomatosis and polyangiitis, granulomatosis w/ polyangiitis, drug-induced vasculitis, nonvasculitic rheumatic diseases
- **Atypical ANCA patterns:** drug-induced vasculitis, nonvasculitic rheumatic diseases, ulcerative colitis, primary sclerosing cholangitis, endocarditis, cystic fibrosis

Granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis)

- **Necrotizing granulomatous systemic vasculitis** frequently affecting nose, sinuses and/or upper respiratory tract in addition to kidneys, lungs, etc.
- Epidemiology: any age, but \uparrow incidence in young and middle-aged adults; $\delta = \varphi$
- Clinical manifestations
 - respiratory** (90%): *upper*: sinusitis, rhinitis, oral/nasal ulcers, saddle-nose deformity, otitis, hearing loss, subglottic stenosis; *lower*: pulmonary infiltrates, nodules, pulmonary hemorrhage, hemoptysis, pleurisy

renal (80%): RPGN (pauci-immune), RBC casts, dysmorphic RBCs, hematuria
 ocular (50%): episcleritis, scleritis, uveitis, orbital granulomas → proptosis, corneal ulcer
 neurologic: cranial and peripheral neuropathies, mononeuritis multiplex
 skin (50%): palpable purpura, livedo reticularis
 hematologic: ↑ incidence DVT/PE (20x) when disease active (*Ann Intern Med* 2005;142:620)

- Dx studies: **90% + ANCA** (80% PR3, 20% MPO), less Se in limited upper airway disease
 CXR or CT → nodules, infiltrates, cavities; sinus CT → sinusitis ± bone erosions
 ↑ BUN & Cr, proteinuria, hematuria; sediment w/ RBC casts, dysmorphic RBCs
 Biopsy → necrotizing granulomatous inflammation of arterioles, capillaries, veins

- Treatment: assess disease severity with BVAS/WG score (*Arth Rheum* 2001;44:912)
Mild disease (no end-organ dysfxn; BVAS 0-3): **MTX + steroids** (*Arth Rheum* 2012;64:3472)

Severe disease (end-organ damage incl. pulm hemorrhage, RPGN etc.; BVAS >3):

Induction: [RTX 375 mg/m²/wk × 4 wk or CYC 2 mg/kg/d × 3-6 mo or pulse 15 mg/kg q2-3wk] + **steroids** 1 g IV × 3 d → 1-2 mg/kg/d (*NEJM* 2005;352:351, 2010;363:211, & 2013;369:417; *Annals* 2009;150:670; *Ann Rheum Dis* 2015;74:1178)

If RPGN: ± plasma exchange to ? ↓ risk of ESRD (*Am J Kidney Dis* 2011;57:566)

Maintenance: RTX q6mo superior to AZA or watchful waiting (*Arth Rheum* 2012;64:3760; *NEJM* 2014;371:1771)

Relapse: mild → steroids ± MTX or AZA; severe → reinduce w/ steroids + RTX or CYC
 ↑ ANCA w/o clinical evidence of flare should not prompt Δ Rx (*Annals* 2007;147:611)

Microscopic polyangiitis (MPA) (*Rheum Dis Clin North Am* 2010;36:545)

- Similar to GPA, but w/o ENT/airway involvement & nongranulomatous
- Epidemiology: ♂ > ♀; avg onset 50-60 y
- Clinical manifestations: similar to GPA w/o upper respiratory involvement;
renal (80-100%): glomerulonephritis
pulmonary (25-50%): pulmonary capillary alveolitis, pulmonary fibrosis
 constitutional and neuro sx similar to GPA; skin lesions (eg, palpable purpura) in 30-60%
- Dx studies: **70% + ANCA** (almost all anti-MPO)
 biopsy → necrotizing, **nongranulomatous** inflammation of small vessels, pauci-immune (minimal deposition of complement or Ig; contrast w/ HSP, cryoglobulinemia, etc.)
 urine sediment and CXR findings similar to those seen in GPA
- Treatment: as for GPA; ↓ relapse rate compared to GPA

Eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg-Strauss)

- Similar to GPA w/ more frequent **cardiac involvement**, a/w asthma and **eosinophilia**
- Epidemiology: rare; can present at any age (typically 30-40 y); a/w HLA-DRB4
- Clinical manifestations (*Curr Rheumatol Rep* 2011;13:489)
 initial sx: **asthma**, sinusitis, allergic rhinitis (new asthma in adult raises suspicion)
 eosinophilic infiltrative disease: transient **pulm infiltrates**, gastroenteritis, or esophagitis
 systemic small-vessel vasculitis: **neuropathy** (mononeuritis multiplex), renal (glomerulonephritis), skin (palpable purpura, petechial, nodules)
cardiac: coronary arteritis, myocarditis, CHF, valvular insufficiency (*Medicine* 2009;88:236)
- Dx studies: 50% + ANCA (MPO > PR3), **eosinophilia** (5-10 k/μL, 80-100%),
 biopsy → microgranulomas, fibrinoid necrosis and thrombosis of small arteries and veins with eosinophilic infiltrates
- Treatment: high-dose **corticosteroids** + cyclophosphamide (if severe)

Renal-limited vasculitis

- Small vessel pauci-immune vasculitis causing RPGN w/o other organ involvement
- Dx studies: 80% + ANCA (MPO > PR3); biopsy with pauci-immune GN ± granulomas
- Treatment identical to that for GPA/MPA

IMMUNE COMPLEX (IC)-ASSOCIATED SMALL-VESSEL VASCULITIS

Henoch-Schönlein purpura (HSP)

- IgA-mediated vasculitis w/ predilection for **skin, GI tract and kidneys**
- Epidemiology: ♂ > ♀, children > adults, onset in winter > summer
- May develop after upper respiratory tract infection (esp. Strep) or drug exposure
- Clinical manifestations
palpable purpura on extensor surfaces (lower extremity first) & buttocks
polyarthralgias (nondeforming) esp. involving hips, knees, & ankles
colicky abdominal pain ± GIB or intussusception
 nephritis ranging from **microscopic hematuria** & proteinuria to ESRD
- Dx studies: **skin bx w/ immunofluorescence** → **leukocytoclastic vasculitis** w/ IgA and C3 deposition in vessel wall; renal bx → mesangial IgA deposition
- Treatment: often self-limiting over 4 wk; steroids ± DMARDs for renal or severe disease

Connective tissue disease-associated vasculitis

- Small vessel vasculitis a/w **RA, SLE or Sjögren's syndrome**
- Clinical manifestations
 - distal arteritis: digital ischemia, livedo reticularis, palpable purpura, cutaneous ulceration
 - visceral arteritis: pericarditis and mesenteric ischemia
 - peripheral neuropathy
- Dx studies: skin/sural nerve bx, angiography, EMG; ↓ C' in SLE; + RF or anti-CCP in RA
- Treatment: steroids, cyclophosphamide, MTX (other DMARDs)

Cutaneous leukocytoclastic angiitis

- Most common type of vasculitis; heterogeneous group of clinical syndromes due to **IC deposition** in capillaries, venules and arterioles; includes **hypersensitivity vasculitis**
- Etiologies
 - drugs: PCN, ASA, amphetamines, levamisole, thiazides, chemicals, immunizations
 - infections: Strep, Staph, endocarditis, TB, hepatitis
 - malignancy (paraneoplastic)
- Clinical manifestations: abrupt onset of **palpable purpura** and **transient arthralgias** after exposure to the offending agent; visceral involvement rare but can be severe
- Dx studies: ↑ ESR, ↓ complement levels, eosinophilia; ✓ U/A; **skin biopsy** → leukocytoclastic vasculitis w/o **IgA deposition** in skin (to distinguish from HSP); if etiology not clear, consider ANCA, cryoglobulins, hepatitis serologies, ANA, RF
- Treatment: withdrawal of offending agent ± rapid prednisone taper

Behcet's syndrome (Curr Rheum Opin 2010;12:429)

- **Systemic vasculitis** affecting all vessel sizes, a/w **oral and/or genital ulcers**
- Epidemiology: usually young adults (25–35 y); a/w HLA-B51 in areas of highest prevalence on the old Silk Road (Turkey, Middle East, and other Asian countries)
- Classification criteria (#1 + ≥2 others is 91% Se & 96% Sp; Lancet 1990;335:1078)
 1. recurrent **oral aphthous ulceration** (≥3x in 1 y, usually 1st manifestation)
 2. recurrent **genital ulceration** (labia in females, scrotum in males)
 3. **eye** lesions: uveitis, scleritis, retinal vasculitis, optic neuritis (may threaten vision)
 4. **skin** lesions: pustules, papules, folliculitis, erythema nodosum (scarring)
 5. + pathergy test (prick forearm w/ sterile needle → pustule) (not sensitive in Caucasians)
- Other clinical manifestations: most recur but are not chronic
 - arthritis: mild, ± symmetric, nondestructive, involving knees and ankles
 - neurologic: usually involvement of midbrain parenchyma; peripheral neuropathy rare
 - vascular: superficial or deep vein thrombosis (25%); arterial stenosis, occlusion and aneurysm can also occur; low incidence of thromboembolism
- Dx studies: ↑ ESR/CRP; ulcer swab to r/o HSV; ulcer bx nonspecific; ophtho eval if sx
- Treatment (Rheumatology 2007;46:736; Ann Rheum Dis 2008;67:1656 & 2009;68:1528)
 - mucocutaneous
 - mild: **topical steroids, colchicine** (esp. for erythema nodosum), dapsone, apremilast (PDE-4 inhib) for oral ulcers and ? genital ulcers (NEJM 2015;372:1510),
severe: oral steroids, steroid-sparing agents
 - arthritis: NSAIDs, colchicine, steroids, steroid-sparing agents
 - ocular: **topical and/or systemic steroids** ± steroid-sparing agents
 - steroid-sparing: AZA, anti-TNF, CYC (large vessel and CNS ds), CsA, MTX, IFN α -2A,
 - venous thrombosis: steroids and anticoagulation (careful if aneurysm present)

IgG4-RELATED DISEASE

Definition & etiology (NEJM 2012;366:539; Ann Rev Pathol 2014;9:315)

- Characterized by tumor-like inflammatory lesions that can affect nearly any organ
- Etiology unclear: ? autoimmune; unclear role of IgG4 Ab; Pt may have h/o atopy

Clinical manifestations (Lancet 2015;385:1460; Arth Rheum 2015;67:2466)

- Commonly pancreatitis, aortitis, cholangitis, sialadenitis, thyroiditis, orbital myositis ± pseudotumor, retroperitoneal fibrosis
- Multiple lesions may be present synchronously or metachronously

Diagnosis (Ann Rheum Dis 2015;74:1 & 14)

- **Biopsy** w/ specific histopathology & immunohistochemistry findings: lymphoplasmacytic infiltrate w/ significant IgG4+ plasma cell infiltrate, fibrosis, obliterative phlebitis
- ↑ serum IgG4 (Se 90%, Sp 60%); not specific seen in GPA, bronchiectasis (Ann Rheum Dis 2014;74:14)

Treatment (Arth Rheum 2015;67:1688)

- **Prednisone vs. rituximab** (Ann Rheum Dis 2015;74:1171)

CRYOGLOBULINEMIA

CRYO
8-21

Definition & types (Lancet 2012;379:348; Oncology 2013;37:1098)

- Proteins due to chronic immune stimulation and/or lymphoproliferation that precipitate on exposure to cold and redissolve on rewarming, characterized by their composition
- **Cryoglobulins** = proteins that precipitate from serum and plasma when cooled
- Distinguish from **cryofibrinogenemia** = proteins (eg, fibrin, fibrinogen) that precipitate only from plasma; found in autoimmune dis, malignancies, infxns; unclear clinical significance

Types of Cryoglobulinemia

Feature	Type I (monoclonal)	Type II (mixed)	Type III (mixed)
Frequency	10–15%	50–60%	25–30%
Cryoglobulin composition	monoclonal Ig (usually IgM or IgG)	monoclonal IgM w/ RF activity + polyclonal IgG	polyclonal IgG and IgM
Common etiologies	Plasma cell dyscrasias	Infection, malignancy, autoimmune syndromes	Autoimmune synd., infxn
Primary manifestations	Hyperviscosity ± thrombosis → ischemia	IC-mediated vasculitis, w/ multiorgan involvement. Can be asx.	

Etiologies

- Hematologic diseases
 - type I: multiple myeloma, MGUS, Waldenström's, chronic lymphocytic leukemia
 - type II: B-cell lymphomas, solid organ malignancies
- Infections (types II & III): viral (HCV [$>80\% \text{ RNA } \oplus$], HBV, HIV, HAV, EBV, CMV), bacterial (endocarditis, strep, etc.), fungal (coccidiomycosis, etc.), parasitic (malaria, amoebiasis)
- Autoimmune syndromes (type III > II): Sjögren's syndrome, SLE, RA, PAN
- Renal transplant recipients (Clin Nephrol 2008;69:239)
- Essential (idiopathic) in 10% of cases

Pathophysiology

- Type I: cryo precipitation in microcirculation → **hyperviscosity & vascular occlusion**
- Types II/III: defective/insufficient immune complex (IC) clearance → IC-mediated inflammation of blood vessels w/ complement activation → **vasculitis**

Clinical manifestations

- Most patients with circulating cryoglobulins are asx
- Type I: hyperviscosity (cold worsens sx) → H/A, visual disturbance, livedo, digital ischemia
- Type II/III: vasculitis (sx not affected by cold exposure)
 - "Meltzer's triad" (purpura, arthralgias, weakness) seen in 25–30% of Pts
 - General: **weakness**, low-grade fever
 - Dermatologic (54–80%): lower extremity **purpura**, livedo reticularis, leg ulcers
 - Joint (44–70%): symmetric, migratory **arthralgias** of small or medium joints
 - Renal (50%): **glomerulonephritis** (proteinuria, hematuria, ARF, HTN, edema)
 - Neurologic (17–60%): **peripheral neuropathy** (polyneuropathy > mononeuritis multiplex)
 - Hematologic: anemia, thrombocytopenia, ↑ risk of B-cell lymphoma
 - GI (5%): abdominal pain, hepatosplenomegaly, abnormal LFTs

Diagnostic studies

- ✓ Cryoglobulins; must keep blood warmed to 37°C at all times en route to lab; early cooling causes false \ominus cryoglobulin, loss of RF and $\downarrow\downarrow$ complement
- Cryocrit is quantification of cryoprotein, does not always correlate w/ disease activity
- False ↑ in WBC or plt on automated CBC, due to cryoprecipitation
- Type I: ✓ serum viscosity, symptomatic if ≥ 4.0 centipoise; complement levels normal
- Type II: ↓ **C4 levels**, variable C3 levels, ↑ ESR, \oplus rheumatoid factor (RF)
 - ✓ **HCV, HBV, & HIV serologies** in all Pts w/ mixed cryoglobulinemia
 - Bx of affected tissue: hyaline thrombi; vasculitis w/ mixed inflammatory infiltrates of small vessels; leukocytoclastic vasculitis in purpuric lesions

Treatment (Blood 2012;119:5996; Medicine 2013;92:61)

- **Treat underlying disorder:**
 - Lymphoproliferative disease: chemotherapy and/or radiation
 - HCV: antivirals ± immunosuppression for severe disease (NEJM 2013;369:1035)
 - Connective tissue-related disease: DMARD/steroids ± rituximab
- Type I: Plasma exchange if hyperviscosity; steroids, alkylating agents, rituximab, chemo
- Type II: NSAIDs for control of mild symptoms for Pts w/ normal renal function.
 - Rituximab or cyclophosphamide for major organ involvement. For mixed cryo, plasmapheresis or plasma exchange only in severe, life-threatening disease.

AMYLOIDOSIS

Deposition of misfolded and insoluble fibrous proteins in normal organs and tissues

Classification of Amyloidosis

Type	Precursor	Causative diseases	Main organs affected
AL (Primary) Most common ~2000 cases/y	Monoclonal Ig light chain	MM Light chain disease ($\lambda > \kappa$) MGUS, WM	Renal, cardiac, GI, neuro, cutaneous, hepatic, pulmonary
AA (Secondary)	Serum amyloid A (SAA)	Inflam: RA, IBD, FMF Chronic infxns: osteo, TB	Renal, GI, hepatic, neuro, cutaneous
Hereditary \uparrow incid Afr Am	Mutant TTR, etc.	Mutant proteins	Neurologic, cardiac
Senile	Normal TTR	Normal proteins; 2° aging	Cardiac, aorta, GI
Aβ_2M	β_2 -microglobulin	Dialysis-associated β_2 m (normally renally excreted)	Musculoskeletal
Localized	β -amyloid protein Peptide hormones	Localized production and processing	Neurologic Endocrine

TTR, transthyretin (prealbumin). Adapted from NEJM 1997;337:898; 2003;349:583; 2007;356:2361.

Clinical Manifestations of Amyloidosis (Lancet 2016;387:2641)

System	Manifestations	Amyloid
Renal	Proteinuria or nephrotic syndrome	AL, AA
Cardiac	CMP (either restrictive or dilated); orthostatic hypotension \downarrow QRS amplitude, conduction abnormalities, AF	AL, hereditary, senile
GI	Diarrhea, malabsorption, protein loss Ulceration, hemorrhage, obstruction Macroglossia \rightarrow dysphonia and dysphagia	all systemic
Neurologic	Peripheral neuropathy with painful paresthesias Autonomic neuro \rightarrow impotence, dysmotility, \downarrow BP Carpal tunnel syndrome	hereditary, AL, organ-specific, β_2 M
Cutaneous	Waxy, nonpruritic papules; periorbital ecchymoses “Pinch purpura” = skin bleeds with minimal trauma	AL
Hepatic & splenic	Hepatomegaly, usually without dysfunction Splenomegaly, usually without leukopenia or anemia	all systemic
Endocrine	Deposition with rare hormonal insufficiency	organ-specific
Musculoskel	Arthralgias and arthritis (especially shoulder)	AL, β_2 M
Pulmonary	Airway obstruction; pleural effusions	AL, AA
Hematologic	Factor X deficiency	AL

Diagnostic studies

- Biopsy (abdominal SC fat pad, rectal or affected tissue) \rightarrow apple-green birefringence on **Congo red stain**; fat pad bx Se 60–85%, Sp 90–100%
- If suspect AL \rightarrow ✓ SIEP & UIEP (\uparrow Se vs. SPEP & UPEP) & free light chains, \pm BM bx
- If suspect renal involvement ✓ U/A for proteinuria
- If suspect cardiac involvement ✓ ECG (\downarrow voltage, conduction abnl), TTE (biventricular thickening w/ granular sparkling appearance; \uparrow wall w/o \uparrow volt 75% Se, 95% Sp), MRI
- Genetic testing for hereditary forms

Treatment of Amyloidosis

AL	Limited involvement: high-dose melphalan \rightarrow auto HSCT (NEJM 2007;357:1083) Not HSCT candidate: [low-dose melphalan + dexamethasone] or [cyclophosphamide + bortezomib + dexamethasone] (Blood 2015;126:612) Relapsed: lenalidomide, thalidomide, or bortezomib (Blood 2010;116:1990 & 2014;124:2498)
AA	Rx underlying disease. Colchicine for FMF, esp. to prevent renal disease. Eprodisate promising for renal disease (NEJM 2007;356:2349) ? Biologics (anakinra, tocilizumab) for rheum associated disease (Arth Rheum 2003;48:2019; Clin Exp Rheumatol 2015;33:46)
ATTR	Liver Tx prevents further protein deposition (Muscle Nerve 2013;47:157) Small interfering RNA under study (NEJM 2013;369:819; JACC 2015;66:2451)

- Clearance of amyloid by Ab against serum amyloid P under study (NEJM 2015;373:1106)
- Cardiac involvement: diuretics; avoid dig, CCB, and vasodilators; ? ICD for 1° prevention
- Heart, kidney and liver Tx may be considered in those w/ advanced disease
- Median survival: 12–18 mos for AL (~6 if cardiac); 11 y for AA; variable for others

CHANGE IN MENTAL STATUS

Consciousness/Arousal (description of patient & timing is most helpful)

- Spectrum from awake/alert → drowsy → stupor → coma. Vague terms, thus most useful to simply describe response to increasing stimulation (eg, voice → noxious stimuli).
- Coma:** lack of response to external stimuli. Degree formalized in Glasgow Coma Scale. Caused by focal lesions in upper brainstem (eg, reticular activating system, thalamus) or diffuse dysfxn of cerebral hemispheres bilaterally. Mimics: locked-in synd., catatonia.
- Nb, quality of thought can be disturbed w/o affecting level of consciousness (eg, disorient.)
- Delirium/acute confusional state:** altered attention & awareness, develops over hrs to days, often fluctuating, accompanied by cognitive Δs (eg, disorientation, memory loss, perceptual Δs); sometimes w/ sleep-wake dysregulation, autonomic Δs, emotionality
- Dementia:** progressive cognitive impairment beyond baseline, develops over mos to yrs, often affecting memory, language, and executive function

Etiologies of Decreased Responsiveness

1° neurologic (usually with focal signs)	Systemic (esp. in elderly or prior CNS injury)
Vasc: ischemic stroke, ICH, ven. thromb	Cardiac: global ischemia, CHF, HTN enceph
Seizure: postictal, status, nonconvulsive	Pulmonary: ↓ PaO ₂ , ↑ PaCO ₂
Infxn: meningitis, encephalitis, abscess	GI: liver failure, ↑ NH ₃
Traumatic brain injury/concussion	Renal: uremia, dialysis, ↓ or ↑ Na
↑ intracranial pressure: mass, hydrocephalus, herniation	Endo: ↓ glc, DKA/HHNS, hypothyroid, Addisonian
Transient global amnesia	ID: pneumonia, UTI, sepsis
Autoimmune/paraneoplastic encephalitis	Hypothermia & hyperthermia
Neurodeg: late-stage (eg, Alzheimer's); or rapidly progressive (eg, CJD) dementia	Intoxication or withdrawal: EtOH, sedatives, opiates, carbon monoxide, anticholinergic
	Psychiatric: catatonia

Initial evaluation

- History** (witness & background crucial): tempo, premorbid sx (eg, focal neuro deficits, HA, infxn, pain, falls), medical conditions (eg, dementia, epilepsy, onc, cardiac, psych, infection/immune status), accompanied by head trauma, current meds (eg, sedatives, opioids, anticoag, anticonvulsants, immunosuppressants), drug/alcohol use
- General exam:** VS, nuchal rigidity (may be present in meningitis or SAH, do not test if possible trauma/cervical spine fx), breathing pattern (eg, Cheyne-Stokes), ecchymoses, rash, signs of head trauma (eg, Battle's, raccoon eyes, hemotympanum, CSF rhinorrhea), asterixis, liver disease stigmata, embolic phenomena/endocarditis, signs of drug use
- Neuro exam** (see below): perform off sedatives/paralytics if possible, look for deficits that suggest structural cause (eg, stroke, herniation syndrome), s/s of ↑ ICP (eg, HA, vomiting, papilledema, abducens nerve palsy, unilateral dilated pupil, ↑ BP/↓HR, fixed downgaze)

Neuro Exam in Patients with Decreased Responsiveness

Mental status	Arousal (behavioral response to ↑ intensity of stimulation, GCS)
Cranial nerves	Pupils: pinpoint → opiates, pontine lesion; midposition & fixed → midbrain lesion; fixed & dilated → severe anoxic enceph, hern., anti-cholin. Extraocular movements / vestibulo-ocular reflex tests: oculocephalic maneuver ("doll's eyes"): nl = eyes move opposite head movement (do not test if possible cervical spine trauma) vestibular (cold) caloric stimulation: in coma, nl = eyes move slowly to lavaged ear, then quickly away Corneal reflex, facial grimace to nasal tickle Gag & cough reflexes (with ET tube manipulation if necessary)
Motor	Tone, spont movements, flexor/extensor posturing of arms/legs, strength
Sensory	Response to painful stimuli: purposeful vs. reflexive/posturing
Reflexes	Deep tendon reflexes, Babinski, "triple" flexion (ankle, knee, & hip flexion to noxious stimulation → not suggestive of intact cortical function)

Glasgow Coma Scale (sum points from each of 3 categories to calculate score)

Eye opening	Best verbal response	Best motor response	Points
	Oriented	Follows commands	6
Spontaneous	Confused	Localizes pain	5
To voice	Inappropriate words	Withdraws from pain	4
To painful stimuli	Unintelligible sounds	Flexor posturing	3
None	None (intubated = 1T)	Extensor posturing	2
		None	1

Initial treatment

- Immobilization of C-spine if concern for cervical trauma
- Thiamine 100 mg IV → dextrose 50 g IVP (order to prevent exacerbation of Wernicke's)
- If opiates suspected: naloxone 0.01 mg/kg; supportive care important in nearly all tox cases
- If concern for ↑ ICP ± herniation: ↑ head of bed; osmotherapy w/ mannitol or hypertonic saline; ↑ ventilation; dexamethasone for tumor edema; c/s neurosurgery (? decompress)

Diagnostic studies (Continuum 2011;17:967)

- All patients: check CBC, electrolytes, BUN/Cr, tox screen, tox screen, U/A
- Based on clinical suspicion:
 - labs: NH₃, TSH, am cortisol, B₁₂, ABG, ESR, ANA, TPO, thyroglobulin, BCx
 - imaging: head CT, then MRI; radiographs to r/o C-spine fracture
 - lumbar puncture to r/o meningitis, SAH, or noninfectious inflammation (eg, autoimmune)
 - EEG to evaluate for nonconvulsive seizures, toxic/metabolic encephalopathy

Further treatment of delirium (Annals 2011;154:746)

- Treat underlying acute illness, eliminate precipitating factors, & provide supportive care
- Address sensory & cognitive impairments (frequent reorientation, etc.)
- Decrease/prevent infection/restraints if possible, remove lines/catheters if unnecessary
- Promote good sleep: reduce noise & nighttime interventions; sedative med if necessary
- Meds: consider antipsychotics; avoid benzos except for alcohol withdrawal or seizures

ANOXIC BRAIN INJURY (at risk if ≥5 min cerebral hypoxia)

Initial evaluation (Circulation 2010;57:68)

- Neuro exam: arousal/verbal, eyes & other cranial nerves, motor response to pain
- Imaging: CT usually not informative w/in first day after arrest, but should be done prior to initiating hypothermia if patient found down or has had head trauma

Temperature management (Circulation 2015;132:2448)

- Indications: comatose (eg, no meaningful response to verbal stimuli) <6 h following cardiac arrest (not isolated resp. arrest). Fully studied only in VT/VF, but consider after asystole or PEA arrest or 6–12 h after cardiac arrest.
- Exclusion: preg, CV instability despite pressors/assist devices, other cause of coma, persistent ↓ O₂
- Relative contraindications: major head trauma, coagulopathy/bleeding, major surgery <14 d, systemic infection/sepsis
- Target temp: 32–36°C × ≥24 h. Initial studies showing benefit targeted 32–34°C, but subsequent study showed ≈ outcomes for 36°C vs. 33°C (NEJM 2013;369:2197). Some still target 32–34°C and reserve 36°C for Pts w/ contraindic to more aggressive cooling.
- Method: can use cold saline infusions; ice packs to head, neck & torso; cooling blankets; cooling vest or endovascular catheter if available. Goal to achieve target temp <6 h (but no benefit to prehosp cooling; JAMA 2014;311:45). Start rewarming 24 h after cooling is initiated (rewarm ≤0.5°C per h).
- Complications
 - dysrhythmias (brady most common): if signif or hemodynamic instability, rewarm
 - coagulopathy (can receive lytics, GP IIb/IIIa inhibitors, etc.); ✓ PT and PTT.
 - infection: ✓ surveillance blood cultures during cooling
 - hyperglycemia during cooling, hypoglycemia w/ rewarming; stop insulin if glc <200 mg/dL
 - hypokalemia during cooling, hyperkalemia w/ rewarming; keep K 4–5 mEq/L

Ongoing evaluation

- Neuro exam: daily focus on coma exam. No exam finding is reliable <24 h or on sedation. Pt needs to be off sedation for an adequate time to evaluate (depends on doses used, duration of Rx, metabolic processes in the individual Pt).
- Labs: daily CBC, PT/PTT, electrolytes. Serum neuron-specific enolase (NSE) on days 1–3
- Imaging: noncontrast CT 24 h after arrest; if unrevealing, consider MRI around days 3–5
- EEG: consider in all to exclude seizures; greatest risk during rewarming
- Somatosensory evoked potentials (SSEP): helpful for prediction of poor outcome if cortical responses are absent bilaterally; perform 48 h after arrest (72 h if cooled)

Prognosis (Nat Rev Neuro 2014;10:190)

- For inPt arrest, ~20% survive, ~70% of Pts who survive have good long-term prognosis
- Prior to cooling era, uniformly poor prognosis could be predicted at 72 h only in Pts who have absent pupillary and corneal reflexes, and no motor response to pain; or with absent SSEPs at 48 h. With cooling, it is less clear if the prior measures are as reliable.
- Otherwise, prognosis requires multifactorial approach considering exam, age, comorbid diseases, ancillary data (NSE, EEG, SSEP; imaging is less reliable for poor outcome)
- When in doubt, err on giving more time (esp. if younger or induced hypothermia)

SEIZURES

SEIZURES

3-?

Definitions (Epilepsia 2014;55:475)

- Seizure:** transient neurologic symptoms due to excessive synchronous neuronal activity; may be provoked by a reversible factor lowering the seizure threshold, or *unprovoked*
- Epilepsy:** ≥2 unprovoked seizures occurring >24 h apart or 1 unprovoked seizure w/ ≥60% probability of further seizures over the next 10 yr (see below for prognostication)
- Generalized seizures** (involves brain diffusely)
 - Tonic-clonic (grand mal): tonic phase (10–20 sec) with contraction of muscles (causing expiratory moan, cyanosis, pooling of secretions, tongue biting) → clonic phase (~30 sec) with intermittent relaxing and tensing of muscles
 - Absence (petit mal): transient lapse of consciousness w/o loss of postural tone, usu pedi
 - Myoclonic (infantile spasms & juvenile myoclonic epilepsy): sudden, brief contraction
- Focal seizures** (involves discrete brain area, implies a structural lesion)
 - w/o impaired consciousness: focal motor/autonomic sx (formerly “simple partial seizure”)
 - or focal sensory/psychic symptoms (eg, aura)
 - w/ impaired consciousness: dyscognitive features (formerly “complex partial seizure”) evolving to bilateral, convulsive seizure (formerly “secondarily generalized seizure”)
- Status epilepticus:** continuous convulsive seizure ≥5 min or >2 seizures w/o resolution of postictal encephalopathy; *life-threatening*
- Nonconvulsive status epilepticus:** alteration of awareness (ranging from confusion to coma) w/o motor manifestations of seizure; dx with EEG.

Differential diagnosis

- Syncope** (Lancet Neurol 2006;5:171)

Feature	Seizure	Syncope
Aura	Unusual behavior/automatisms	Diaphoresis, nausea, tunnel vision
Convulsions	Variable duration	Usually <10 sec
Postictal state	Yes; can be ≥30 min	None or short
Other clues	Tongue biting, incontinence	Skin pallor, clamminess

- Nonepileptic seizure** (aka “psychogenic”): may see side-to-side head turning, asymmetric large-amplitude limb movements, diffuse shaking w/o LOC, crying/talking during event
- Other: metabolic disorders (eg, alcoholic blackouts, hypoglycemia), migraine, TIA, transient global amnesia, narcolepsy (cataplexy), nonepileptic myoclonus, tics, asterixis

Etiologies of seizures (vary strongly by age)

- Without focal lesion:** genetic predisposition to seizures or epilepsy syndrome; alcohol withdrawal, illicit drugs; meds (eg, β-lactams, bupropion, tramadol, MNZ, meperidine, CsA, antidepressants); electrolyte (hyponatremia) & other metabolic (eg, uremia, liver failure, hypoglycemia); autoimmune encephalitis, idiopathic (~60%)
- With focal lesion:** tumor, trauma, stroke, subdural hematomas, posterior reversible encephalopathy syndrome, mesial temporal sclerosis, focal cortical dysplasia

Clinical manifestations

- Aura** (sec to mins): premonition with paresthesias, focal motor contractions, abnormal smells/tastes, fear, depersonalization, déjà vu, autonomic changes, automatisms
- Ictal period** (sec to mins): tonic and/or clonic movements of head, eyes, trunk or extrem.
- Postictal period** (mins to h): slowly resolving period of confusion, disorientation, and lethargy. May be accompanied by focal neurologic deficits (Todd’s paralysis).

Clinical evaluation

- History key in differentiating seizure from other causes of transient loss of consciousness. Must talk to witnesses. Ask about prodrome, unusual behavior before spell, type & pattern of abnl movements incl. head turning & eye deviation (gaze preference usually away from seizure focus), loss of responsiveness.
- Recent events: illnesses/fevers, head trauma, sleep deprivation
- PMH: prior seizures or + FHx, prior meningitis/encephalitis, prior stroke or head trauma
- Medications (new or noncompliance), alcohol and illicit drug use
- General physical exam should include the skin, looking for neuroectodermal disorders (eg, neurofibromatosis, tuberous sclerosis) that are a/w seizures
- Neurologic exam should look for focal abnormalities → underlying structural abnormality

Diagnostic studies (Neurology 2007;69:1996)

- Lab: full lytes, BUN, Cr, glc, LFTs, tox screen, med levels (if on valproic acid, phenytoin; consider for other AEDs but may take days; levetiracetam level rarely useful unless? noncompliance)

- Routine EEG (~30 min): useful in workup of 1st-time unprovoked seizure, as may determine risk of seizure recurrence. Caveat: interictal EEG nl in 50% of Pts w/ epilepsy, and interictal epileptiform activity (spikes or sharp waves) may be seen in up to 2% of nl population; sleep deprivation and repeated studies ↑ dx yield of EEG.
- Long-term EEG monitoring (hrs to days): useful for differentiating epileptic from non-epileptic spells; video monitoring may help w/ nonepileptic seizures
- MRI to r/o structural abnormalities; ↑ Se w/ fine coronal imaging of frontal & temporal lobes
- LP (if no space-occupying lesion on imaging): if suspect meningitis (eg, fever, ↑ WBC, nuchal rigidity) or encephalitis and in all HIV + Pts

Treatment (Neurology 2015:84:1705; Lancet 2015:385:884)

- Treat any underlying precipitants, including CNS infections, intoxication, withdrawal, etc.
- Antiepileptic drug (AED) Rx usually reserved for Pts w/ ≥2 unprovoked seizures, single seizure w/ high risk of recurrence (see below), or underlying structural abnormality. Provoked seizures generally treated by addressing underlying cause; consider AED if status epilepticus on presentation, focal neuro exam, postictal Todd's paralysis.
- After 1st unprovoked sz, weigh risks of recurrence vs AED. ↑ risk of recurrence if abnl EEG, MRI, or nocturnal sz. If EEG & MRI nl → 65% sz-free at 5 y (Lancet Neurol 2006;5:317)
- Immediate treatment w/ AED after 1st unprovoked seizure ↓ risk of recurrence over 2 y, but does not Δ long-term prognosis
- If AED Rx indicated, choice dependent on type of seizure, side effects, cost, mechanism of elimination (if hepatic or renal insufficiency), teratogenesis and drug interactions
- Introduce gradually, monitor carefully
- May consider withdrawal if seizure-free (typically for at least 1 y) and normal EEG
- Individual state laws mandate seizure-free duration before being allowed to drive

Antiepileptic Drugs and Side Effects

Medication	Avg daily dose	Common side effects	
		Systemic	Neurologic (all: sedation)
Carbamazepine	400–1600 mg	Aplastic anemia, ↓ WBC, rash, hepatotoxicity, ↓ Na	Diplopia, confusion, ataxia
Ethosuximide	500–1500 mg	Rash, BM suppression	Behavioral Δs
Gabapentin	900–3600 mg	GI upset, wt gain	Nystagmus, ataxia
Lacosamide	200–400 mg	Prolonged PR interval	Dizziness, diplopia
Lamotrigine	100–300 mg	Rash (Stevens-Johnson)	Tremor, HA, blurred vision, insomnia
Levetiracetam	1000–3000 mg	GI upset (rare)	Emotional lability
Oxcarbazepine	600–2400 mg	Hyponatremia, rash	Diplopia, dizziness
Phenobarbital	50–200 mg	Rash	Cognitive slowing
Phenytoin	200–400 mg	Gum hyperplasia	Dizziness, ataxia
Topiramate	100–400 mg	↓ wt, hypohidrosis, kidney stones, glaucoma, met acid	Cognitive slowing
Valproic acid	500–2500 mg	Hepatotoxic, ↑ NH ₃ , ↑ wt, ↓ hair	Tremor
Zonisamide	200–600 mg	↓ wt, hypohidrosis, nephrolith	Cog slowing, fatigue

(NEJM 2008;359:166; Lancet Neurol 2011;10:446)

Status epilepticus (Neurocrit Care 2012;17:3)

- ABCs: vital signs, oral airway or endotracheal intubation. Place Pt in semiprone position to ↓ risk of aspiration. Obtain IV access. Give thiamine, dextrose, IV normal saline.
- STAT glc, metabolic panel, CBC, tox screen, lactate, AED levels, consider head CT, LP
- Start standing AED after loading dose.

Treatment of Status Epilepticus

Time (min)	Antiepileptic	Dosing regimen	Typical adult dose
<5	Lorazepam or Midazolam or Diazepam*	0.1 mg/kg IV 0.2 mg/kg IM 0.2 mg/kg PR	Successive 2–4 mg IV pushes Up to 10 mg IM
<10	Phenytoin or Fosphenytoin or Valproate or Levetiracetam	20 mg/kg 20 mg PE/kg 20–30 mg/kg 1000 mg	1.0–1.5 g IV over 20 min 1.0–1.5 g PE IV over 5–10 min 1.0–1.5 g IV over 5–10 min IV over 10–15 min
Subsequent steps mandate intubation, EEG monitoring and ICU admission			
<30–60	General anesthesia with continuous midazolam, pentobarbital, or propofol		

PE, phenytoin equivalents. *Consider PR diazepam if no IV access and IM midazolam is contraindicated.

ALCOHOL WITHDRAWAL

Pathophysiology

- Alcohol is a CNS depressant
- Chronic use → insensitivity to inhibitory neurotransmitter γ -aminobutyric acid (GABA)
- Abrupt alcohol cessation → CNS overactivity

Clinical manifestations

- Minor withdrawal sx (6–48 h after last drink): mild anxiety, tremulousness, HA
- Withdrawal seizures:** typically w/in 48 h after last drink; if unRx'd, $\frac{1}{3}$ → delirium tremens
- Alcoholic hallucinosis:** isolated hallucinations (typically visual) 12–48 h after last drink
- Delirium tremens (DT):** disorientation, agitation, hallucinations, ↑ HR & BP, fever, diaphoresis; begins 48–96 h after last drink, lasts 5–7 d
- Consider other dx: CNS infxn or bleed, sz, drug O/D, coingestions, acute liver failure, GIB

Clinical Institute Withdrawal Assessment scale for alcohol (CIWA-Ar)

- Assign points for each of the 10 criteria; each criteria is scored 0–7, except orientation, which is scored 0–4; add points to calculate score

CIWA-Ar Scale

Points	Anxiety	Agitation	Tremor	HA	Orientation
0	None	None	None	None	Oriented
1		Somewhat	Not visible, but felt at fingertips	Very mild	Cannot do serial additions
2				Mild	Disorient. by ≤ 2 d
3				Moderate	Disorient. by > 2 d
4	Guarded	Restless	Moderate w/ hands extended	Mod severe	Disoriented to person or place
5				Severe	n/a
6				Very severe	n/a
7	Panic	Pacing or thrashing	Severe	Extremely severe	n/a
Points	N/V	Sweats	Auditory halluc.	Visual halluc.	Tactile disturb
0	None	None	None	None	None
1		Moist palms	Very mild	Very mild photosens.	Very mild paresthesias
2			Mild	Mild photosens.	Mild paresth.
3			Moderate	Mod photosens.	Mod paresth.
4	Intermit. w/ dry heaves	Beads	Mod severe	Mod severe visual halluc.	Mod severe hallucinations
5			Severe	Severe	Severe
6			Very severe	Very severe	Very severe
7	Constant	Drenching	Cont.	Continuous	Continuous

SCORE: <8 none to minimal withdrawal; 8–15 mild; 16–20 moderate; >20 severe

HOME
9-5

Treatment (NEJM 2003;348:1786)

• Benzodiazepines (BDZ)

Drug: diazepam (long-acting w/ active metab; ↓ risk of recurrent withdrawal), lorazepam (short half-life), chlordiazepoxide, oxazepam (no active metab; good if cirrhosis)

Route: start IV, transition to PO

Dosing: typically start w/ diazepam 10–15 mg IV q10–15min (or lorazepam 2–4 mg IV q15–20min) until appropriate sedation achieved, then titrate to CIWA-Ar scale, evaluating q1h until score $<8 \times 8$ h, then q2h $\times 8$ h, and if stable, then q4h (JAMA 1994;272:519)

- If refractory to BDZ prn → BDZ gtt, phenobarb, dexmedetomidine, or propofol (& intubation)
- Avoid β B (mask sx)
- Mechanical restraints as needed until chemical sedation achieved
- Volume resuscitation as needed; thiamine then glucose to prevent Wernicke's encephalopathy (ataxia, ophthalmoplegia, short-term memory loss); replete K, Mg, PO₄
- Prophylaxis: if min sx or asx (ie, CIWA score <8) but prolonged heavy EtOH consumption or h/o withdrawal seizures or DTs → chlordiazepoxide 25–100 mg (based on severity of EtOH use) q6h \times 24 h, then 25–50 mg q6h \times 2 d

ISCHEMIC STROKE

Etiologies

- Embolic (~75%): artery → artery, cardioembolic, paradoxical, cryptogenic (AF found in ~12%)
- Thrombotic (~25%): large vessel (atherosclerosis) vs. small vessel ("lacunar," lipohyalinosis of small arteries, often related to HTN, hyperlipidemia, & DM)
- Other: dissection, vasculitis, vasospasm, prothrombotic states, hypoperfusion, genetic

Clinical Manifestations

- Timing: embolic → sudden onset; thrombotic → stuttering course

Stroke syndromes by vascular territory

Artery	Deficits
ICA → Ophth	Amaurosis fugax (transient monocular blindness)
ACA	Hemiplegia (leg > arm), abulia, urinary incontinence, primitive reflexes
MCA	Hemiplegia (face & arm > leg); hemianesthesia; homonymous hemianopia Aphasia if dom. hemisphere: sup. div. → expressive; inf. div → receptive Apraxia & neglect if nondom. hemisphere.
PCA	Macular-sparing homonymous hemianopia; alexia w/o agraphia Thalamic syndromes with contralateral hemisensory disturbance
Vertebral, PICA	Wallenberg syndrome = numbness of ipsilateral face and contralateral limbs, diplopia, dysarthria, ipsilateral Horner's, hiccups
Basilar	Pupillary Δs (midbrain=dilated, pons=pinpoint), long tract signs (quadriplegia, sensory loss), CN abnl, cerebellar dysfxn. Top of basilar → "locked in" synd.
Cerebellar	Vertigo, N/V, diplopia, dysarthria, nystagmus, ipsilateral limb ataxia
Lacunar (arterioles)	5 major syndromes: pure hemiplegia, pure hemianesthesia, ataxic hemiparesis, dysarthria + clumsy hand, mixed sensorimotor

Transient ischemic attack (TIA)

- Sudden deficit due to cerebral ischemia; **no stroke on imaging**; sx resolve <24 h (most <1 h)
- Ddx: seizure, migraine, hypoglycemia, amyloid spells, TGA, anxiety
- Risk of subsequent stroke ~2% by 1 wk (NEJM 2016;374:1533). Can stratify based on **ABCD²**:
 - Age ≥60 y (+1); BP ≥140/90 (+1); Clin features: unilat. weak. (+2), speech impair. w/o weakness (+1); Duration ≥60 (+2) or 10–59 min (+1); DM (+1)

Physical exam

- General: murmurs, carotid & subclavian bruits, peripheral emboli, endocarditis sequelae
- Neurologic exam, NIH stroke scale (http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf)

Acute workup

- Electrolytes, Cr (relevant for contrast); glc, CBC, coags (see exclusion criteria for lysis)
- Cardiac biomarkers, 12-lead ECG, tox screen
- **STAT CT** to r/o ICH prior to lysis (Se = MRI, faster, more widely available)
 - early signs: hyperdense artery, loss of gray-white differentiation, edema, insular ribbon
 - CT can be nl in 1st hrs after sx onset, not Se for small strokes & brainstem strokes
 - obtain CT-angio head & neck if endovascular intervention indicated

Acute treatment of ischemic stroke (JAMA 2015;313:1451 & 314:1832)

- **Thrombolysis (IV)**: tPA 0.9 mg/kg (max 90 mg), w/ 10% as bolus over 1 min, rest over 1 h consider if onset w/in 4.5 h, \ominus ICH, \ominus contraindic. (incl. current/prior ICH; head trauma or stroke w/in 3 mo; intracranial neoplasm, AVM or aneurysm; recent intracranial/intraspinal surgery; active internal bleeding; noncompressible arterial puncture; ↑ BP; multilobar infarct; plt <100k, INR >1.7, on Xa inhib, PTT >40, glc <50)
 - 0–3 h: 12% absolute ↑ in good neuro outcome (min/no disability), 5.8% absolute ↑ in ICH, trend toward 4% absolute ↓ mortality
 - 3–4.5 h: 7.4% absolute ↑ in good neuro outcome, 1.8% absolute ↑ in ICH, \ominus mortality benefit (nb, trial excluded patients with previous strokes + DM)
 - 0.6 mg/kg (tested 1° in Asians): ? slightly ↓ efficacy but 1/2 ICH rate (NEJM 2016;374:2313)
- BP: lower to <185/110 to consider lysis; if lyse keep <180/105 × 24 h (consider labetalol or nicardipine), o/w permissive HTN unless >220/120 or sx; if sx HoTN consider vasopressors
- Initiate ASA w/in 24–48 h; avoid anticoagulation w/in 24 h of lysis; see below for long-term Rx
- Cerebral edema → herniation: often occurs 1–5 d post large MCA or cerebellar strokes, ↑ risk in young. Temporize: elevate HOB >30°; mannitol ± 23% NaCl. Hemicraniectomy ↓ mortality (Lancet Neurol 2007;6:215). Neurosurgery consult in select MCA and all large cerebellar strokes.
- **Endovascular thrombectomy** (JACC Intv 2016;9:307): if anterior circulation prox cutoff (mostly MCA) and w/in ~6 h of sx onset, addition of thrombectomy to IV tPA ↑ odds of fxnal independence by 71%, w/ no Δ in ICH or mortality (NEJM 2015;372:11, 1009, 1019, 2285 & 2296; Lancet 2016;387:1723)

Workup to assess for etiology/modifiable risk factors

- Cardiac: Holter to assess for AF (found in ~12%; NEJM 2014;370:2467 & 2478;374:2065); echo to r/o thrombus/vegetation, w/ bubble study to r/o PFO/atrial septal aneurysm if suspect embolic
- Vessel imaging: carotid U/S and Doppler (if no vessel imaging obtained in acute eval)
- Labs: lipids, HbA1c, TSH, homocysteine, Lp(a), hypercoag w/u (if <65 y or cryptogenic stroke; ideally drawn before starting anticoag), ESR/CRP, blood cx if s/s systemic infection
- **MRI** helpful if dx of stroke unclear (esp. post circ) or to define stroke subtype, age, exact size DWI bright/ADC dark = earliest finding in acute ischemia (~w/in mins, up to days)
T2-FLAIR: hyperintense w/in hrs, persists for wks; PWI differentiates irreversibly infarcted core vs. viable penumbra; T1 fat-sat (neck vessels) if suspicious for dissection

Secondary stroke prevention (NEJM 2012;366:1914)

- **Antiplatelet therapy:** different agents likely have similar efficacy
ASA ↓ death & repeat stroke; equal to warfarin in nonembolic stroke (NEJM 2001;345:1444)
clopidogrel: marginally superior to ASA, slightly ↑ ICH (Lancet 1996;348:1329)
ticagrelor: trend toward 13% ↓ ischemic stroke vs. ASA (NEJM 2016;375:35)
clopidogrel + ASA (vs. ASA alone): × 90 d in minor strokes/TIA → 32% ↓ risk of stroke, no Δ ICH (NEJM 2013;369:11); extended Rx not more effective & ↑ ICH (Lancet 2004;364:331)
- **Anticoagulation (AC):** consider only if: AF (qv), cardiac/paradoxical emboli (except bacterial endocarditis); long segment extra-dural dissections; hypercoag state; bridge to CEA in sx carotid stenosis w/ongoing TIAs.
Hold off on AC in large strokes for ~2–4 wk given risk of hemorrhagic conversion.
- Long-term SBP target 120–139 mmHg (JAMA 2011;306:2137)
- Statin: ↓ recurrent stroke w/ atorvastatin 80 mg, LDL goal <70 (NEJM 2006;355:549)
- Fluoxetine: ? improved motor recovery after 3 mo (Lancet Neurol 2011;10:123)
- Pioglitazone: 24% ↓ risk of stroke in Pts w/ stroke/TIA + insulin resist. (NEJM 2016;374:1321)
- **Carotid revascularization** (NEJM 2013;369:1143)
CEA (if surgical morbidity & mortality ≤6%) indicated for:
sx stenosis 70–99% (benefit ↑ for males, >75 y, ≤2 wk from stroke) → 65% ↓ RR of repeat stroke, slight benefit for 50–69% stenosis (NEJM 1991;325:445; Lancet 2004;363:915)
axs stenosis 70–90%, <79 y: 50% ↓ RR of repeat stroke (Lancet 2004;363:1491 & 2010;376:1074)
stenting: c/w CEA, periprocedural risk of stroke ↑ (esp. in elderly) & MI ↓ (but many axs), subsequent rates of stroke similar (NEJM 2016;374:1011 & 1021; Lancet 2016;387:1305)

Patent foramen ovale (PFO; in ~27% of population) (NEJM 2005;353:2361)

- ↑ stroke risk: ≥4 mm separation, R→L shunting at rest, ↑ septal mobility, atrial septal aneurysm
- If PFO & stroke/TIA: no benefit of warfarin over ASA (Circ 2002;105:2625), but consider if at high risk for or has DVT/PE. No sig benefit shown for PFO closure so far; albeit studies small & w/ favorable trends (NEJM 2012;366:991; 2013;1083 & 1092).

INTRACRANIAL HEMORRHAGE (ICH)

Classification by location

- Hemorrhagic strokes: intraparenchymal hemorrhage (IPH) & subarachnoid hemorrhage (SAH)
- Other ICH: epidural hematoma (EDH) & subdural hematoma (SDH)

Etiologies

- AVM, aneurysm, cerebral venous sinus thrombosis → IPH or SAH
- HTN (basal ganglia, cerebellum, brainstem), cerebral amyloid (lobar), tumor (esp. w/ melanoma, renal cell CA, chorio-CA, thyroid CA) → IPH
- Trauma → all locations (nb, IPH or SAH caused by trauma technically not a stroke)

Clinical manifestations (Lancet Neurol 2005;4:662; BMJ 2010;341:c5204)

- ↓ consciousness, N/V, HA, progressive focal neurologic deficits
- SAH: thunderclap HA, onset w/ exertion; nuchal pain/rigidity; LOC. EDH: initial lucid interval.

Workup (Acad Emerg Med 2016;doi: 10.1111/acem.12984)

- STAT CT brain, angio (CT-A or conventional) if suspicious for vascular source
- ? LP for xanthochromia if no evid of ICH on CT (although ⊖ LR 0.01) & suspicious for SAH
- Coags (PT, PTT, INR)

Management

- Reverse coagulopathies (qv), goal INR <1.4. Plt goal >100k. No benefit to plt transfusion if on antiplt Rx (Lancet 2016;387:2605), but ? consider if expanding ICH; DDAVP if uremic.
- Strict BP control w/ art line, use nicardipine or labetalol gtt. SBP goal ~160 (NEJM 2013;368:2355 & ATACH-2, NEJM 2016;doi: 10.1056/NEJMoa1603460).
- SAH: endovasc coiling vs. surg clipping (depends on location, comorbid.; Lancet 2015;385:691) of aneurysm/AVM; nimodipine to ↓ risk of vasospasm (monitor w/ TCDs), seizure Ppx
- Surg evac: EDH; SDH if >1 cm or rapid ↑; IPH: no obvious benefit (Lancet 2013;382:397)
- Venous sinus thrombosis: start anticoagulation, manage ↑ ICP and seizures as needed

Feature	Upper motor neuron	Lower motor neuron	Neuromuscular junction	Myopathy
Distribution of weakness	UE Ext, LE Flex, hip abductors	Distal, segmental	Ocular, bulbar, proximal limb	Proximal, symmetric
Atrophy	None	Severe	None	Mild
Fasciculations	None	Common	None	None
Tone	↑	↓	Normal	Normal or ↓
Reflexes (DTRs)	↑	↓	Normal	Normal or ↓
Babinski	Present	Absent	Absent	Absent

PERIPHERAL NEUROPATHIES

Etiologies based on presentation

- **Mononeuropathy** (1 nerve): if acute → trauma; if chronic → entrapment, compression, DM, Lyme. Commonly seen: median n. (carpal tunnel synd.); ulnar n. (at elbow or wrist); common peroneal n. (at knee w/ habitual leg crossing); lat femoral cutan. n. (at inguinal lig.).
- **Mononeuropathy multiplex** (axonal loss of multiple, separate, noncontig. nerves): vasculitic synd. (eg, PAN, Churg–Strauss, Wegener's, cryo, SLE, RA, Sjögren's), DM, Lyme, leprosy, HIV, hereditary neuropathy w/ pressure palsies; sarcoid, lymphoma, leukemia
- **Polyneuropathy** (multiple symmetric nerves, generally length dependent). 50% idiopathic. W/ autonomic features: DM, EtOH, paraneoplastic, B₁₂ def, amyloid, chemo, 1° dysauto. Painful (small fiber neuropathies): DM, EtOH, amyloid, chemo, heavy metals, porphyria Demyelinating. Acute: acute inflam demyelinating polyneuropathy (AIDP) = Guillain-Barré Subacute: meds (taxanes), paraneoplastic Chronic: idiopathic, DM, CIDP, hypothyroidism, toxins, paraproteinemia, hereditary Axonal. Acute: acute motor axonal neuropathy (AMAN), porphyria, vasculitis, uremia Subacute: DM, meds (cisplatin, paclitaxel, vincristine, INH, ddi), EtOH, sepsis, paraneo. Chronic: DM, uremia, lead, arsenic, HIV, paraproteinemia, B₁₂ defic

Clinical manifestations

- Weakness, fasciculations, numbness, dysesthesias (burning/tingling), allodynia
- ± Autonomic dysfxn (orthostasis, bowel/bladder retention/incontinence, impotence)
- Depressed or absent DTRs (may be normal in small fiber neuropathy)

Diagnostic studies

- Distal symmetric polyneuropathy: CBC, lytes, BUN/Cr, Hb_{A1C}, B₁₂, TSH, ESR, SPEP + IF
- EMG & NCS (often no change in 1st 10–14 d or in small fiber neuropathy)
- Based on H&P: LFTs, ANA, anti-Ro/La, HIV, Cu, Lyme titers, RPR, UA, UPEP+IF, ACE, ANCA, genetic testing, heavy metal screen, LP (AIDP, CIDP), cryo, paraneoplastic panel
- Autonomic testing/skin bx (small fiber), nerve bx (mononeuropathy multiplex)
- MRI if possible radiculopathy or plexopathy (after EMG)

Pharmacologic treatment of neuropathic pain (*Lancet Neurol* 2015;14:162)

- Pregabalin, gabapentin, TCAs (nortriptyline, amitriptyline), SNRIs (duloxetine, venlafaxine)
- 2nd line: tramadol, topicals (lidocaine, capsaicin); 3rd line: opiates, botulinum toxin A

GUILLAIN-BARRÉ SYNDROME (GBS)

Definition & epidemiology (*Nat Rev Neurol* 2014;10:469)

- AIDP (60–80%); acute motor axonal neuropathy (AMAN; 7–30%; w/o sensory loss; a/w anti-GM1, GD1a Ab); Miller Fisher synd. (ophthalmoplegia & ataxia; a/w anti-GQ1b Ab).
- Incidence 1–2 per 100,000; most common acute/subacute paralysis
- Precipitants in 60%: viral illness (CMV, EBV, HIV), URI (*Mycoplasma*), gastroenteritis (*Campylobacter*), Lyme, immunizations (no proven risk w/ current), surgery

Clinical manifestations (*Lancet* 2016;388:717)

- Pain (55–90%), distal sensory dysesthesias & numbness often 1st sx, back pain common
- Progressive sym paralysis in legs and arms over hrs to days; plateau in 1–4 wk
- Hypoactive then absent reflexes. <10% w/ reflexes on presentation, but all develop hypo/areflexia during course. Minority of AMAN w/ preserved reflexes throughout.
- Resp failure requiring mech vent occurs in 25%; autonomic instability & arrhythmias in 60%

Diagnostic studies (results may be normal in first several days)

- LP: albuminocytologic dissociation = ↑ protein w/o pleocytosis (<10 WBCs) seen in up to 64% of Pts. ↑ protein in 1/2 in 1st wk, 3/4 by 3rd wk of sx. Unlikely to be GBS if WBC >50.
- EMG & NCS: ↓ nerve conduction velocity, conduction block; can be nl in 1st 2 wks
- FVC & NIF: to assess for risk of resp. failure (cannot rely on P_aO₂ or S_aO₂).

Treatment

- Plasma exchange or IVIg of equal efficacy (*Neurology* 2012;78:1009); steroids not beneficial
- Supportive care with monitoring in ICU setting if rapid progression or resp. failure
- Watch for autonomic dysfunction: labile BP, dysrhythmias (telemetry)
- Most recover near baseline in 1 y; 3–5% mortality. Residual deficits: pain, fatigue.

MYASTHENIA GRAVIS

Definition & epidemiology (*Lancet Neurology* 2015;14:1023)

- Autoimmune disorder with Ab against acetylcholine receptor (AChR, 80%), muscle specific kinase (MuSK, 4%), lipoprotein-related protein 4 (LRP4, 2%), or other NMJ proteins
- Prevalence: 1 in 7500; affects all ages, peak incidence 20s–30s (women), 60s–70s (men)
- 15% of AChR MG w/ thymoma; 30% of Pts w/ thymoma develop AChR MG

Clinical manifestations

- Fluctuating weakness w/ **fatigability** (worse w/ repetitive use, relieved by rest)
- Cranial muscles involved early → 60% present initially w/ ocular sx (ptosis, diplopia); 20% will only have ocular sx; 15% w/ bulbar (difficulty chewing, dysarthria, dysphagia). Often later progresses to generalized weakness.
- Limb weakness proximal > distal; DTRs preserved; minimal/no atrophy
- MuSK MG (F >> M): mostly cranial/bulbar, neck, and resp. weakness.
- LRP4 MG: mostly ocular and limb weakness. Resp failure rare.
- Exacerbations triggered by stressors such as URI, surgery, pregnancy or postpartum, meds (eg, aminoglycosides, macrolides, fluoroquinolones, procainamide, phenytoin, D-penicillamine). Prednisone can worsen sx acutely.
- Myasthenic crisis = exacerbation → need for respiratory assistance
- Cholinergic crisis = weakness due to **overtreatment** with anticholinesterase meds; may have excessive salivation, abdominal cramping and diarrhea; rare at normal doses

Diagnostic studies

- Bedside: ptosis at baseline or after >45 sec of sustained upgaze; improved ptosis with ice pack over eyes for 2–5 min, Se 77%, Sp 98%
- Neostigmine test: temporary ↑ strength; false + & – occur; premedicate w/ atropine
- EMG: ↓ response with repetitive nerve stimulation (vs. ↑ response in Lambert-Eaton)
- Anti-AChR Ab: Se 80%, 50% if ocular disease only; Sp >90%; muscle specific receptor tyrosine kinase (MuSK) Ab, AChR modulating Ab.
- CT or MRI of thorax to evaluate thymus (65% hyperplasia, 10% thymoma)

Treatment

- Thymectomy if thymoma; may lead to improvement in up to 85% Pts w/o thymoma
- Cholinesterase inhib (eg, pyridostigmine) most rapid acting (benefit in 30–60 min). Less effective for MuSK MG. Side effects: cholinergic stim (brady, diarrhea, drooling).
- Immunosuppression: prednisone (benefit in wks) + AZA (benefit in 6–15 mo). If no response: mycophenolate, rituximab, MTZ, CsA.
- Myasthenic crisis: treat precipitant; consider d/c cholinesterase inhib. if suspect cholinergic crisis. IVIg or plasmapheresis; if no response, high-dose glucocorticoids (in monitored setting as risk for initial worsening). ICU if rapid or severe (follow FVC, NIF).

MYOPATHIES

Etiologies

- Hereditary: Duchenne, Becker, limb-girdle, myotonic, metabolic, mitochondrial
- Endocrine: hypothyroidism, hyperparathyroidism, Cushing syndrome
- Toxic: statins, fibrates, glucocorticoids (incl. critical illness myopathy), zidovudine, alcohol, cocaine, antimalarials, colchicine, penicillamine
- Infectious: HIV, HTLV-1, trichinosis, toxoplasmosis
- Inflammatory (see "Rheumatology"): polymyositis, dermatomyositis, inclusion body myositis

Clinical manifestations

- Progressive or episodic weakness (not fatigue)
- Weakness most often symmetric, proximal > distal (stairs, rising from sitting, etc.)
- ± Myalgias (though not prominent or frequent), cramps, myotonia (impaired relaxation)
- May develop either pseudohypertrophy (dystrophies) or mild muscle atrophy
- Assoc. organ dysfxn: cardiac (arrhythmia, CHF), pulmonary (ILD), dysmorphic features

Diagnostic studies

- CK, aldolase, LDH, electrolytes, ALT/AST, PTH, TSH, ESR, HIV
- Autoantibodies (anti-Jo1, antisynthetase, anti-Mi-2, anti-SRP, ANA, RF)
- EMG/NCS: low-amp, polyphasic units w/ early recruitment, ± fibrillation potentials
- Muscle biopsy, molecular genetic testing (where indicated)

HEADACHE

Primary headache syndromes (International Headache Society Classification)

- **Tension-type:** bilateral, pressure-like pain of mild-mod intensity, not throbbing or aggravated by physical activity. A/w photophobia or phonophobia, not N/V. Freq a/w myofascial sensitivity in neck/head. Triggers: stress, sleep deprivation, dehydration, hunger. Rx: NSAIDs, acetaminophen (risk of med overuse HA) if episodic; TCAs if chronic.
- **Cluster HA** and other trigeminal autonomic cephalgias (TACs) (*Continuum* 2015;21:1041)
Characterized by unilateral rhinorrhea, red/tearing eye, miosis/ptosis, lid edema, sweating, pain is orbital or temporal, differentiated by timing
Cluster: ♂ > ♀, unilateral eye pain, restlessness, attacks 15 min–3 h, worsened by EtOH. Ppx: CCB (verapamil). Rx: high-flow O₂ via non-rebreather, sumatriptan IN/SC.
Paroxysmal hemicrania: similar to cluster; but ♀ > ♂, attacks 2–30 min. Rx: indomethacin.
Hemicrania continua: ♀ > ♂, ice pick-like pain lasting >3 mo. Rx: indomethacin.
Short-lasting unilateral neuralgiform HA (SUNA/SUNCT): ♂ > ♀, excruciating, stabbing, electrical pain, 5 sec–4 min, up to 200x/d. Rx: lamotrigine, gabapentin, topiramate.
- **Migraine:** see below

Secondary causes of headaches

- Traumatic: postconcussion, SAH, SDH, postcraniotomy
- ↑ ICP: mass (tumor, abscess, vascular malformations, ICH), hydrocephalus, idiopathic intracranial hypertension (pseudotumor cerebri), altitude associated cerebral edema
- ↓ ICP: post-LP headache, CSF leak/dural tear, overshunting
- Vascular causes: stroke (esp. posterior circ), dissection, vasculitis (incl. temporal arteritis), reversible cerebral vasoconstriction syndrome (RCVS), ICH, venous sinus thrombosis
- Meningeal irritation: meningitis, SAH
- Extracranial: sinusitis, TMJ syndrome, glaucoma
- Systemic causes: hypoxia, hypercapnia, dialysis HA, HTN, hypoglycemia, ↓ TSH
- Medication overuse (analgesics), withdrawal (caffeine, opioids, estrogen)

Clinical evaluation (JAMA 2006;296:1274 & 2013;310:1248)

- History: onset (sudden vs. gradual), quality, severity, location, duration, triggers, alleviating factors, positional component, hormonal triggers (menstruation), preceding trauma, associated sx (visual Δs, "floaters," N/V, photophobia, focal neurologic sx)
- Medications (analgesics), substance abuse (opioids, caffeine)
- General and neurologic exam (funduscopic exam, visual fields)
- **Warning signs (should prompt neuroimaging)**
explosive onset (vasc); "worst HA of my life" (SAH, RCVS); meningismus (SAH, infxn)
positional: lying > standing (↑ ICP); N/V (↑ ICP; migraines)
visual sx: diplopia, blurring, ↓ acuity (GCA, glaucoma, ↑ ICP); eye pain (glaucoma, trigeminal autonomic cephalgia)
abnl neuro exam (struct. lesion, poss. in migraine); ↓ consciousness (± fever): infxn, ICH
age >50 y; immunosuppression (CNS infections, PRES)
- LP if ? SAH (✓ for xanthochromia), idiopathic intracranial HTN (✓ opening press); image first!

MIGRAINE

Epidemiology: affects 15% of women and 6% of men; onset usually by 30 y

Definition & clinical manifestations

- **Migraine w/o aura** (most common): ≥5 attacks lasting 4–72 h and with both (a) N/V or photophobia & phonophobia, and (b) ≥2 of following: unilat., pulsating, mod-severe intensity, aggravated by routine activity
- **Migraine w/ aura:** ≥2 attacks w/: (a) aura defined as ≥1 fully reversible sx: visual Δs (flickering spots, visual loss), sensory sx (paresthesias, numbness), speech disturbance; and (b) unilateral progression of sx(s) over ≥5 but ≤60 min; and (c) HA w/in 60 min of aura
- Aura may occur w/o HA ("acephalic migraine"), must r/o TIA/stroke (typically rapid onset)
- If motor weakness, consider **sporadic hemiplegic migraine:** aura of fully reversible motor weakness lasting up to 24 hr, also w/visual and sensory aura + typical migraine HA
- Precipitants: stress, hunger, foods (cheese, chocolate) and food additives (MSG), fatigue, alcohol, menstruation, exercise

Treatment (Cephalgia 2015;35:271)

- Abortive Rx: 5-HT₁ agonists ("triptans") effective if given early in migraine attack, contraindicated if motor aura, CAD, prior stroke. Also consider acetaminophen, caffeine, NSAIDs, steroids; IV options include Mg, metoclopramide, prochlorperazine, valproate, dihydroergotamine (caution if CAD, recent triptan use). Avoid butalbital, opioids.
- Prophylaxis: valproic acid, topiramate, βB, TCAs, butterbur, NSAIDs, magnesium, riboflavin (Neurology 2012;78:1337 & 1346)

BACK AND SPINAL CORD DISEASE

Differential diagnosis of back pain

- Musculoskeletal:** involving spine (vertebra, facet joints), paraspinal muscles and ligaments, sacroiliac joint, or hip joint. Spondylolisthesis, vertebral fx, OA, inflam. spondyloarthritis (RA, ankylosing spondylitis, reactive, psoriatic), musculoligamentous "strain," myofascial pain syndrome, trochanteric bursitis.
- Spinal cord (myopathy)/nerve root (radiculopathy):**
Degenerative/traumatic: disc herniation, foraminal or lumbar stenosis, spondylolisthesis
Neoplastic: lung, breast, prostate, RCC, thyroid, colon, multiple myeloma, lymphoma
Infectious (also see ID section): osteomyelitis, epidural abscess, zoster, Lyme, CMV, HIV
- Referred pain from visceral disease:**
GI: PUD, cholelithiasis, pancreatitis, pancreatic cancer
GU: pyelonephritis, nephrolithiasis, uterine or ovarian cancer, salpingitis
Vascular: aortic dissection, leaking aortic aneurysm

Initial evaluation

- History:** location, radiation, trauma, wt loss, cancer hx, fever, immunocompromised, neurologic symptoms, saddle anesthesia, incontinence, urinary retention, IV drug use
- General physical exam:** local tenderness, ROM, signs of infection or malignancy; paraspinal tenderness or spasm in musculoskeletal strain
- Signs of radiculopathy** (sharp/lancinating pain radiating into limb):
Spurling sign (cervical radiculopathy): radicular pain w/ downward force to extended & ipsilaterally rotated head; 30% Se, 93% Sp
Straight leg raise (sciatica or lumbosacral radiculopathy): radicular pain at 30–70°; ipsilateral: 92% Se, 28% Sp; crossed (contralateral leg raised): 28% Se, 90% Sp
Patrick/FABER test (sacroiliac joint syndrome): severe pain on hip external rotation; 70% Se, 100% Sp
Neurogenic claudication in lumbar stenosis (see table on next page)
- Neurologic exam:** full motor (including sphincter tone), sensory (including perineal region) and reflexes including bulbocavernous, anal wink (S4), and cremasteric (L2)
- Red flags:** upper motor neuron signs (hyperreflexia, upgoing toes), cauda equina or conus medullaris syndromes (saddle anesthesia, bowel or bladder dysfunction, reduced rectal tone, loss of sacral reflexes).
- Laboratory** (depending on suspicion): CBC, ESR, Ca, PO₄, CSF
- Neuroimaging:** low yield if nonradiating pain, high false + rate (incidental spondylosis) depending on suspicion: X-rays, CT or CT myelography, MRI, bone scan
- EMG/NCS:** may be useful to distinguish root/plexopathies from peripheral neuropathies

SPINAL CORD COMPRESSION

Clinical manifestations

- Acute: flaccid paraparesis and absent reflexes ("spinal shock")
- Subacute–chronic: spastic paraparesis and hyperactive reflexes
- Posterior column dysfunction in legs (loss of vibratory sense or proprioception)
- Sensory loss below level of lesion
- ⊕ Babinski responses ± ankle clonus

Evaluation & treatment

- Empiric spine immobilization (collar, board) for all trauma patients
- STAT MRI (at and above clinical spinal level, with gadolinium) or CT myelogram
- Emergent neurosurgical and/or neurology consultation
- Urgent radiation therapy ± surgery for compression if due to metastatic disease
- High-dose steroids depending on cause:
Tumor: dexamethasone 16 mg/d IV (usually 4 mg q6h) with slow taper over wks
Trauma: methylprednisolone 30 mg/kg IV over 15 min then 5.4 mg/kg/h × 24 h (if started w/in 3 h of injury) or × 48 h (if started 3–8 h after injury) (Cochrane 2012:CD001046)

NERVE ROOT COMPRESSION

Clinical manifestations

- Radicular pain aggravated by activity (esp. bending, straining, coughing), relieved by lying
- Sciatica = radicular pain radiating from buttocks down lateral aspect of leg, often to knee or lateral calf ± numbness and paresthesias radiating to lateral foot. Caused by compression of nerve roots, plexus, or sciatic nerve.

Disc Herniation: Cervical and Lumbar Radiculopathy

Disc	Root	Pain/paresthesias	Sensory loss	Motor loss	Reflex loss
C4-C5	C5	Neck, shoulder, upper arm	Shoulder, lateral arm	Deltoid, biceps, infraspinatus	Biceps
C5-C6	C6	Neck, shoulder, lat. arm, radial forearm, thumb & index finger	Radial forearm, thumb & index finger	Biceps brachioradialis	Biceps, brachioradialis, supinator
C6-C7	C7	Neck, lat. arm, ring & index fingers	Index & middle fingers	Triceps, extensor carpi ulnaris	Triceps, supinator
C7-T1	C8	Ulnar forearm and hand	Ulnar half of ring finger, little finger	Intrinsic hand muscles, flexor dig profundus	Finger flexion
L3-L4	L4	Anterior thigh, inner shin	Anteromedial lower leg, inner foot	Quadriceps	Patella
L4-L5	L5	Lat. thigh & calf, dorsum of foot, great toe	Lat. calf & great toe	Foot dorsiflexion, invers. & evers., toe extension	Medial hamstring
L5-S1	S1	Back of thigh, lateral posterior calf, lat. foot	Lateral foot & toes, sole of foot	Gastrocnemius	Achilles

Nb, lumbar disc protrusion tends to compress the nerve root that exits 1 vertebral level below the protrusion.

Neurogenic vs. Vascular Claudication

Features	Neurogenic claudication	Vascular claudication
Cause	Lumbar spinal stenosis (with nerve root compression)	Peripheral artery disease (with limb ischemia)
Pain	Radicular back/buttock pain Radiating down legs	Cramping leg pain Mostly in calves; radiating up legs
Worse with	Walking & standing Hyperextension/lying prone	Walking Biking
Better with	Bending forward, sitting	Rest (standing or sitting)
Other sx	Numbness/paresthesias	Pale, cool extremity
Exam	± Focal weakness, ↓ reflexes ↓ Lumbar extension Preserved pulses	Diminished/absent pulses (dorsalis pedis/posterior tibialis) Pallor
Diagnostic studies	MRI lumbar spine CT myelogram (if no MRI) EMG/NCS	Arterial Doppler studies Ankle-brachial index (ABI) Arteriography
Treatment	PT (flexion exercise), NSAIDs, steroid injections (ESI) Surgery (if other Rx fails)	Modify vascular risk factors, exercise rehab, antiplatelet Rx, revascularization

Nb, diagnosis complicated by overlap between presentations & possibility of both diagnoses in the same patient. (NEJM 2007;356:1241 & 2008;358:818)

Treatment of nerve root compression (NEJM 2016;374:1763)

- Conservative: avoid bending/lifting; soft cervical collar (cervical radiculopathy); NSAIDs; muscle relaxants; Rx neuropathic pain (see "Peripheral Neuropathies"); physical therapy.
- Spinal epidural steroid injections (ESI): limited short-term relief of refractory radicular pain (Pain 2013;154:2249)
- Surgery: cord compression or cauda equina syndrome; progressive motor dysfunction; bowel/bladder dysfunction; failure to respond to conservative Rx after 3 mo (NEJM 2007;356:2245)

SURGICAL ISSUES

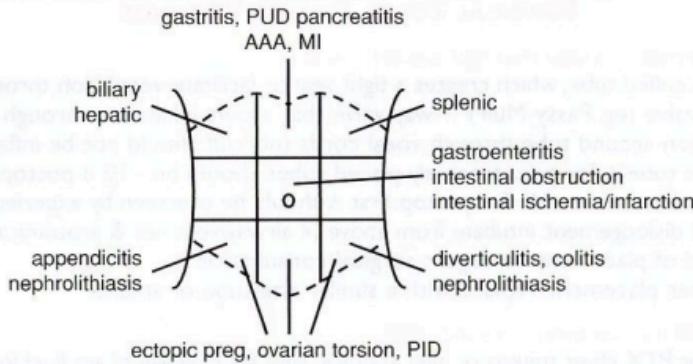
ABDOMINAL PAIN

Visceral Pain

Anatomic division	Viscera	Area to which pain referred
Foregut	Esophagus & duodenum	Epigastrium
Midgut	Jejunum to mid-transverse colon	Umbilicus
Hindgut	Mid-transverse colon to rectum	Hypogastrium

Pain due to pancreatitis and nephrolithiasis commonly radiates to the back

Figure 10-1 Etiologies of abdominal pain based on location



Initial evaluation

- History: onset of pain, location, exacerbating/relieving factors
- Assoc. sx: fevers/chills, N/V, Δ in bowel habits (diarrhea/constipation, stool diam. or color, hematochezia, melena), jaundice, Δ in urine color, Δ in wt, menstrual hx in women
- PMHx: previous incisions or abdominal surgeries; Ob/Gyn hx
- Exam: VS; general posture of Pt; comprehensive abdominal exam looking for signs of peritonitis, which include rebound tenderness and involuntary guarding, abdominal wall rigidity, pain w/ percussion/minimal palpation; presence of hernias; rectal/pelvic
- Labs: CBC, electrolytes, LFTs, amylase/lipase, pregnancy test
- Imaging: depends on suspected etiology, may include RUQ U/S for biliary/hepatic disease, KUB for intestinal obstruction, CT for pancreatitis or intestinal disease. Do not delay resuscitation or surgical consultation for ill Pt while waiting for imaging.

ACUTE ABDOMEN

Definition

- Acute onset abdominal pain that portends need for urgent surgery

Etiologies

- Perforated viscous → peritonitis (perforated ulcer, complicated diverticulitis, trauma)
- Intraperitoneal bleed
- Bowel obstruction (adhesions from previous surgeries, malignancies, hernias)
- Mimics: severe pancreatitis can resemble peritonitis; renal colic causes severe abdominal pain but not abdominal rigidity

Initial evaluation

- H&P as above
- Labs as above plus: PT/INR, PTT, type, & screen
- Imaging: KUB (upright) or if stable, CT abdomen/pelvis w/ IV contrast (IV/PO if suspect obstruction)

Initial management

- Immediate surgical consultation for suspected acute abdomen
- NPO, start IV fluids (NS or LR)
- Broad spectrum abx if perforation suspected

EXTREMITY EMERGENCIES

Acute limb ischemia (see "Peripheral Artery Disease" for details)

- Definition: sudden ↓ in perfusion causing threat to limb viability

- Evaluation: detailed vascular exam; CT angiography or arteriography
- Initial management: anticoag for embolism/thrombosis; immediate surgical consultation

Compartment syndrome (*Clin Orthop Relat Res* 2010;468:940)

- Definition: ↑ intracompartmental pressure w/ compressive closure of venules → ↑ hydrostatic force resulting in further increases in compartment pressure
- Etiologies: orthopedic (fracture), vascular (ischemia-reperfusion), iatrogenic (eg, vascular injury in anticoagulated Pt), soft tissue injury (eg, prolonged limb compression)
- Clinical manifestations: pain esp. on passive movement, swollen/tense compartment, paraesthesia, pallor, pulselessness, paralysis (late)
- Evaluation: surgical evaluation of compartment pressures; intracompartment pressure >30 or difference between diastolic & intracompartment pressure of >10–30 is diagnostic
- Treatment: fasciotomy

SURGICAL TUBES, DRAINS, WOUNDS

Tracheostomy (*Otolaryngol Head Neck Surg* 2013;148:6)

- Typically a cuffed tube, which creates a tight seal to facilitate ventilation throughout tube
- Speaking valve (eg, Passy-Muir): 1-way valve that allows inhalation through tube, but exhalation around tube through vocal cords (nb, cuff should not be inflated)
- 1st routine tube Δ for percutaneously placed tubes should be ~10 d postop; surgically placed tubes can be Δ'd >5 d postop; first Δ should be overseen by experienced person
- Accidental dislodgement: intubate from above (if airway/vent nec & anatomically possible) w/in 7 d of placement: emergent surgical consultation
>7 d after placement: replace with a similar size tube or smaller

Chest tubes (*Eur J Cardiothorac Surg* 2011;40:291)

- Inserted for PTX, chest trauma or after thoracic surg for drainage of air/ fluid from thoracic cavity. Range from small (8-10 Fr for spont PTX) to large (28-32 Fr after pulm resections)
- Connected to 3-chamber chest drainage system:
 - 1st: collection chamber for pleural fluid
 - 2nd: water seal chamber used to allow air to exit pleural space on exhalation and prevent air from entering on inhalation
 - 3rd: suction control chamber which regulates suction transmitted to pleural space
- Monitor for output and presence of air leak (indicated by bubbling in water seal chamber)
- Removal determined by overall daily outputs and presence of air leak
- If accidentally removed or dislodged, tube should be completely removed and an occlusive dressing (eg, 4 × 4 covered w/ Tegaderm or silk tape) should be placed rapidly over site. CXR STAT; new tube should be placed if persistent PTX.

Gastrostomy/jejunostomy tubes (*Paediatr Child Health* 2011;16:281)

- Placed for tube feedings, hydration and delivery of medications
- Securely anchor to skin to prevent inadvertent removal
- Should not be removed for ≥6–8 wk to allow establishment of mature gastrocutaneous tract
- Obstructed tubes can be cleared by flushing with agents such as carbonated water, meat tenderizer, & pancreatic enzymes. ↓ obstruction by flushing before & after meds and flushing q4–6h when receiving continuous feeds.
- Inadvertent removal: place Foley catheter of similar size or smaller into tract immediately to prevent stoma from closing. Tube then replaced and confirmed via fluoro study.

Suture/staple removal

- Should be done in consultation w/ surgical team; timing depends on location of wound
- Should not be removed if there is evidence of wound separation during removal!
- After removal, wound should be reapproximated w/ Steri-Strips

Decubitus ulcers (*J Wound Ostomy Continence Nurs* 2012;39:3)

- Sores in dependent areas exposed to repeated pressure (commonly sacrum, heels)
- Risk factors: immobility, poor nutritional status
- Stage I (non-blanchable erythema); Stage II (partial thickness); Stage III (full thickness skin loss); Stage IV (full thickness tissue loss)
- Treatment: offload area, air mattress, pillows and/or support boots
- Surgical consultation for debridement of ulcers with necrotic or infected tissue, may require plastic surgical reconstruction for advanced ulcers once clean
- Wound vac (negative pressure vacuum dressing) therapy may accelerate healing

MAXIMIZING A SURGICAL CONSULT

- For ill Pt, call surgical consult early, do not wait for labs & imaging results
- If potential surgical emergency, make Pt NPO, start IVF, ✓ coags, type, & screen
- Have appropriate-level MD who knows & has examined Pt call consult

VAGINAL BLEEDING

Abnormal bleeding from lower (vulva, vagina, cervix) or upper genital tract (uterus)

Etiologies

- Premenopausal
 - Not pregnant: menses, dysfunctional uterine bleeding (menorrhagia), leiomyoma, polyp, trauma, cervical dysplasia/cancer (rare), endometrial hyperplasia/cancer (rare)
 - Pregnant
 - 1st trimester: threatened abortion, spont. abortion (missed, incomplete or complete), ectopic pregnancy, molar pregnancy (partial or complete hydatidiform mole)
 - 2nd or 3rd trimester: preterm labor, placenta previa, placental abruption
- Postmenopausal: atrophy, polyp, leiomyoma, endometrial hyperplasia/cancer, cervical dysplasia/cancer

History & exam

- Age, menopausal status, gestational age if preg; volume & duration of current bleeding
- If premenopausal: menstrual hx including age of onset, interval between & duration of menses, any assoc. sx and LMP to assess timing of menstrual cycle
- Past Ob/Gyn hx (any structural abnl, STD, and contraception)
- Health maint. (Pap smear, HPV screening); domestic violence; anticoag or antiplt meds
- General physical & abdominal exam (incl. tenderness, masses)
- Pelvic exam: external (quantity of bleeding seen on vulva, any lesions, any trauma); also, w/ assistance from Ob/Gyn, speculum exam (quantity of bleeding; cervical os open or close and if open, dilation; any polyps), & bimanual exam (uterine size and tenderness, adnexal mass and tenderness)

Laboratory evaluation & imaging

- Urine (rapid test) & serum pregnancy test (beta-hCG); Hct/hemoglobin
- Pelvic U/S: visualize intrauterine preg to r/o ectopic; if preg, intrauterine not seen, & $\beta\text{HCG} >$ discrim. zone \rightarrow ? ectopic; if $\beta\text{HCG} <$ discrim. zone \rightarrow follow βHCG ; nl placental position to r/o placenta previa and likely severe abruption
- *Ectopic pregnancy is life-threatening dx, .. must rule out if Pt pregnant (JAMA 2013;309:1722)*

VAGINAL DISCHARGE

Fluid or mucus from vagina, cervix, or uterus

Etiologies

- Infectious: bacterial vaginosis, candida vulvovaginitis, trichomoniasis
- Noninfectious: physiologic (in preg or non-preg), rupture of membranes, foreign-body rxn

Initial evaluation

- Age, LMP, gestational age if preg. or menopausal status
- Discharge quantity, color, consistency, odor, assoc. sx (itchiness, redness, abd/pelvic pain)
- Past gyn hx incl STD and contraception usage (condoms \downarrow STD risk)
- Tampon or condom use as risk factors for retained foreign body
- Pelvic exam: external (quantity & quality of discharge on vulva, any lesions); speculum (discharge, appearance of cervix), bimanual (cervical motion tenderness)
- Laboratory: pH of discharge; microscopy (saline & KOH wet mounts); urine pregnancy test

Treatment

- Bacterial vaginosis: oral or vaginal metronidazole or clindamycin
- Candida vulvovaginitis: oral or topical antimycotic medications
- Trichomoniasis: oral metronidazole

ADNEXAL MASS IN NON-PREGNANT WOMAN

Mass arising from ovary, fallopian tube, or surrounding connective tissue

Etiologies

- Ovarian: functional (follicular and corpus luteum) or hemorrhagic cyst, endometriomas, ovarian torsion, tubo-ovarian abscess, benign & malignant ovarian tumors
- Fallopian tube: paratubal cyst, hydrosalpinx, ovarian torsion, tubo-ovarian abscess

Initial evaluation

- LMP/menopausal status; associated sx of abd/pelvic pain, FHx of gyn cancers
- Abd exam (distension, tenderness, masses); bimanual (uterine or adnexal masses)
- Preg test if premenopausal (if \oplus , then mass likely pregnancy); CA-125 if postmenopausal
- Pelvic U/S (even if mass 1st identified on CT, as U/S is best modality); U/S appearance of mass most important factor used to determine risk of malignancy

OPTHALMIC ISSUES

INITIAL EVALUATION

- Ocular symptom: onset (sudden or progressive) & duration of sx; unilateral vs. bilateral; pain; photophobia; discharge; Δ in near (eg, book) or far (eg, TV across room) vision
- Pre-existing ocular conditions, eye meds (incl any Δs), recent h/o ocular surgery, trauma
- Ocular exam: vision (✓ with Pt's correction [glasses/contacts]) w/ each eye; pupillary exam; EOM; confrontation visual fields (important if suspect CNS problem)
- Overall: VS, immunocomp., s/s of infxn, h/o malig, CNS issues, Δ in meds, CBC, coags

COMMON VISUAL SYMPTOMS

- **Fluctuation in vision (ie, blurry):** med-induced refractive error (eg, systemic steroids, chemoRx), hyperglycemia, dry eye (common). **Visual defect** may p/w "blurred vision." Bilateral: glaucoma (common), homonymous contral. CNS lesion; bitemporal: pituitary, toxic/nutritional. Unilateral: ipsilateral orbital, retinal, or optic nerve lesion.
- **Red eye:**
 - Bilateral: viral conjunct. (starts in 1 eye; also w/ lid swelling, discharge); chronic inflammation (dry eyes, rosacea, autoimmune disease)
 - Unilateral: subconj. hemorrhage, infxn, or inflam (eg, episcleritis, iritis, uveitis, scleritis); acute angle closure (qv). Scleritis & acute angle closure p/w severe pain, H/A, nausea.
- **Double vision (diplopia):** fixed double vision w/ ophthalmoplegia from orbital process or cranial nerve palsy (III, IV, VI). Transient "diplopia" due to fatigue or sedation.
- **Flashing lights/floater:** vitreous detach. (common, benign); retinal detach. (unilateral visual field defect; urgent ophthalmology consult); hemorrhage; intraocular lymphoma

ACUTE VISUAL CHANGES

Etiologies of Acute Vision Loss (italics indicates a/w pain)

	Unilateral	Bilateral
Transient (<24 h, often <1 h)	Ret. art. embolism, impending retinal artery or vein occlusion (amaurosis fugax), vasospasm, carotid disease	Ocular surface dis. (dry eye), bilat. carotid dis., TIA, migraine, high ICP (papilledema)
Prolonged (>24 h)	Retinal art/vein occl, retinal detach., retina/vitreous heme, retinitis, ant. optic neurop./corneal ulcer, GCA, acute angle closure glaucoma	Visual cortex stroke, post. ischemic neuropathy (profound hypotension during surgery), post. reversible enceph. synd., GCA

COMMON OCULAR CONDITIONS (FRONT TO BACK)

Orbit: **orbital cellulitis** (fever, proptosis, ↓ EOM; emergent abx & referral)

Lids: hordeolum or chalazion (stye); preseptal cellulitis; **ptosis** (age; Horner's; **CN III palsy**: EOM restricted in all directions except laterally [eye is "down & out"], a/w ptosis & mydriasis, seen w/ uncal herniation, aneurysm of post com art., GCA, HTN, DM); incomplete lid closure (**CN 7th palsy**)

Conjunctiva: conjunctivitis (**red eye**); subconj. hemorrhage (HTN, blood thinner); ocular surface disease (dry eyes); episcleritis/scleritis (deep vessels of sclera)

Cornea: contact lens related ulcer; herpetic keratitis/scarring/neurotropic ulcers (**CNV paresis**); pterygium; keratoconus; corneal dystrophy

Ant. chamber: iritis (inflam. cells); hyphema (blood, post trauma); hypopyon (inflam./infxn)

Pupil: Anisocoria (physiologic); Horner's, CN III

Lens: cataract (age, trauma, medication, radiation, congenital); post cataract surgery infxn

Vitreous/Retina/Macula: diabetic retinopathy; macular degen; retinal detachment; retinal ± vitreous hemorrhage; retinitis (infectious)

Optic nerve (CN II): ischemic neuropathy p/w acute unilat. visual loss, altitudinal field defect; a/w GCA; nonarteritic a/w HTN, hyperchol., DM, thrombophilia. Optic neuritis: often p/w unilat. central scotoma, pain w/ EOM, ↑ visual loss over days; a/w demyelinating disease (eg, MS), also seen w/ sarcoidosis & CTD. Optic neuropathy (glaucoma common).

OCULAR EMERGENCIES

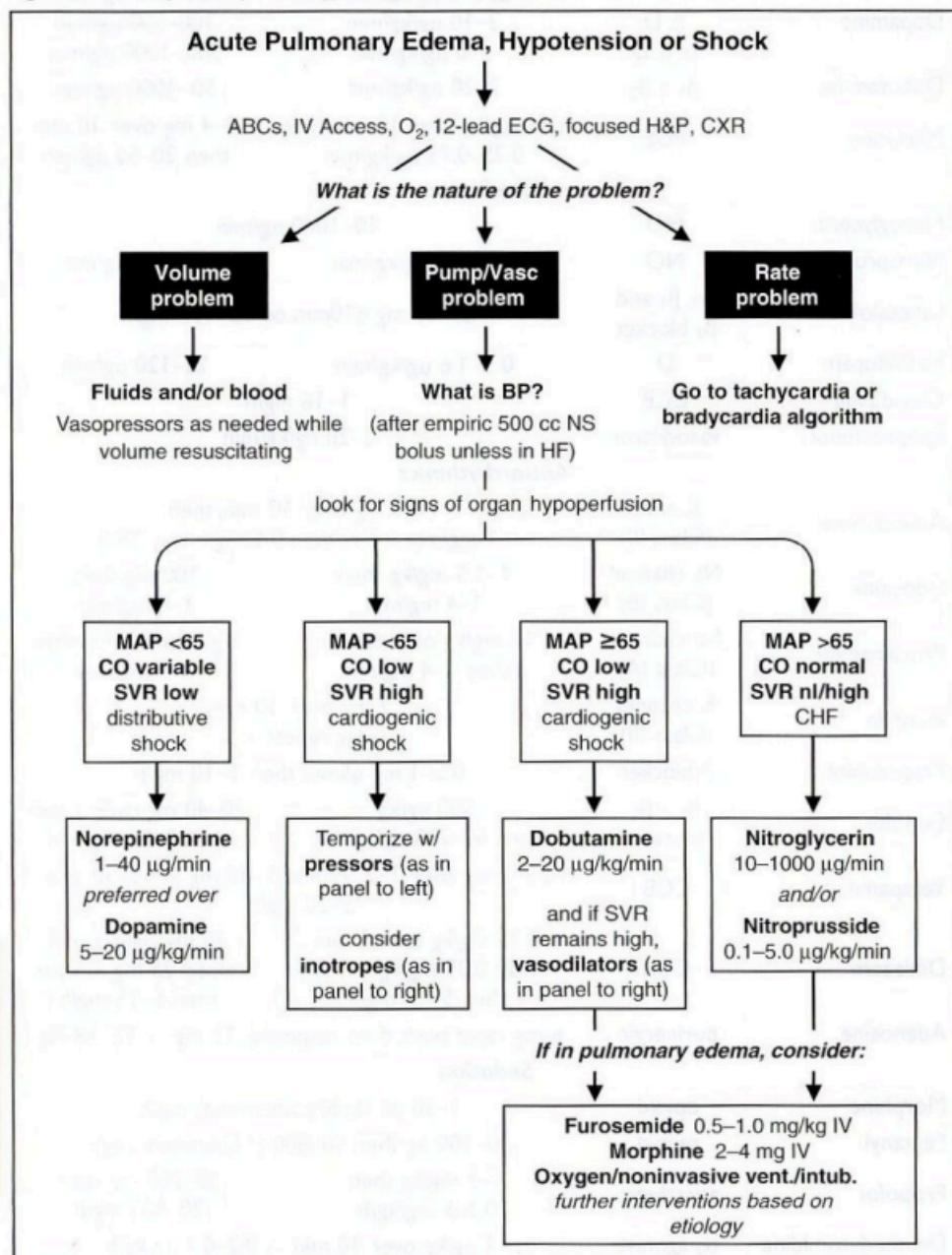
- **Chemical splash:** alkali worse than acid; immediate eye flush; pH 7.3–7.4 normal
- **Acute angle closure glaucoma:** fixed mid-dilated pupil, corneal edema, high intraocular pressure (typically >50; normal 8–21). Rx w/ topical drops; may require AC tap/laser.
- **Penetrating eye injury:** protect eye (no patching), IV antibiotics, NPO, surgical prep

ICU MEDICATIONS

Drug	Class	Dose	
		per kg	average
Pressors, Inotropes and Chronotropes			
Phenylephrine	α ₁	10–300 µg/min	
Norepinephrine	α ₁ > β ₁	1–40 µg/min	
Vasopressin	V ₁	0.01–0.1 U/min (usually <0.04)	
Epinephrine	α ₁ , α ₂ , β ₁ , β ₂	2–20 µg/min	
Isoproterenol	β ₁ , β ₂	0.1–10 µg/min	
Dopamine	D β, D α, β, D	0.5–2 µg/kg/min 2–10 µg/kg/min >10 µg/kg/min	50–200 µg/min 200–500 µg/min 500–1000 µg/min
Dobutamine	β ₁ > β ₂	2–20 µg/kg/min	50–1000 µg/min
Milrinone	PDE	± 50 µg/kg over 10 min then 0.25–0.75 µg/kg/min	3–4 mg over 10 min then 20–50 µg/min
Vasodilators			
Nitroglycerin	NO	10–1000 µg/min	
Nitroprusside	NO	0.25–10 µg/kg/min	10–800 µg/min
Labetalol	α ₁ , β ₁ and β ₂ blocker	20–80 mg q10min or 10–120 mg/h	
Fenoldopam	D	0.1–1.6 µg/kg/min	10–120 µg/min
Clevidipine	CCB	1–16 mg/h	
Epoprostenol	vasodilator	2–20 ng/kg/min	
Antiarrhythmics			
Amiodarone	K et al. (Class III)	150 mg over 10 min, then 1 mg/min × 6 h, then 0.5 mg/min × 18 h	
Lidocaine	Na channel (Class IB)	1–1.5 mg/kg then 1–4 mg/min	100 mg then 1–4 mg/min
Procainamide	Na channel (Class IA)	17 mg/kg over 60 min then 1–4 mg/min	1 g over 60 min then 1–4 mg/min
Ibutilide	K channel (Class III)	1 mg over 10 min, may repeat × 1	
Propranolol	β blocker	0.5–1 mg q5min then 1–10 mg/h	
Esmolol	β ₁ > β ₂ blocker	500 µg/kg then 50–200 µg/kg/min	20–40 mg over 1 min then 2–20 mg/min
Verapamil	CCB	2.5–5 mg over 1–2', repeat 5–10 mg in 15–30' prn 5–20 mg/h	
Diltiazem	CCB	0.25 mg/kg over 2 min reload 0.35 mg/kg × 1 prn then 5–15 mg/h	20 mg over 2 min reload 25 mg × 1 prn then 5–15 mg/h
Adenosine	purinergic	6 mg rapid push; if no response: 12 mg → 12–18 mg	
Sedation			
Morphine	opioid	1–30 (in theory, unlimited) mg/h	
Fentanyl	opioid	50–100 µg then 50–800 (? unlimited) µg/h	
Propofol	anesthetic	1–3 mg/kg then 0.3–5 mg/kg/h	50–200 mg then 20–400 mg/h
Dexmedetomidine	α ₂ agonist	1 µg/kg over 10 min → 0.2–0.7 µg/kg/h	
Diazepam	BDZ	1–5 mg q1–2h then q6h prn	
Midazolam	BDZ	0.5–2 mg q5min prn; 0.02–0.1 mg/kg/h or 1–10 mg/h	
Lorazepam	BDZ	0.01–0.1 mg/kg/h	
Naloxone	opioid antag.	0.4–2 mg q2–3min to total of 10 mg	
Flumazenil	BDZ antag.	0.2 mg over 30 sec then 0.3 mg over 30 sec prn may repeat 0.5 mg over 30 sec to total of 3 mg	

Drug	Class	per kg	Dose average
Miscellaneous			
Aminophylline	PDE	5.5 mg/kg over 20 min then 0.5–1 mg/kg/h	250–500 mg then 10–80 mg/h
Octreotide	somatostatin analog		50 µg then 50 µg/h
Glucagon	hormone	3–10 mg IV slowly over 3–5 min then 3–5 mg/h	
Mannitol	osmole		1.5–2 g/kg over 30–60 min repeat q6–12h to keep osm 310–320

Figure 11-1 ACLS pulmonary edema, hypotension or shock algorithm



ANTIBIOTICS

The following tables of spectra of activity for different antibiotics are generalizations.
Sensitivity data at your own institution should be used to guide therapy.

Penicillins

Generation	Properties	Spectrum
Natural (eg, penicillin)	Some GPC, GPR, GNC, most anaerobes (except <i>Bacteroides</i>)	Group A streptococci Enterococci, <i>Listeria</i> , <i>Pasteurella</i> <i>Actinomyces</i> , <i>Syphilis</i>
Anti-staph (eg, nafcillin)	Active vs. PCNase-producing Staph Little activity vs. Gram ⊖	Staphylococci (except MRSA) Streptococci
Amino (eg, ampicillin)	Penetrate porin channel of Gram ⊖ Not stable against PCNases	<i>E. coli</i> , <i>Proteus</i> , <i>H. influenzae</i> <i>Salmonella</i> , <i>Shigella</i> Enterococci, <i>Listeria</i>
Extended (eg, piperacillin)	Penetrate porin channel of Gram ⊖ More resistant to PCNases	Most GNR incl. <i>Enterobacter</i> , <i>Pseudomonas</i> , <i>Serratia</i>
Carbapenems (eg, imipenem)	Resistant to most β-lactamases	Most Gram ⊕ & ⊖, including anaerobes; not MRSA or VRE
Monobactams (aztreonam)	Active vs. Gram ⊖ but not Gram ⊕	Gram ⊖ bacterial infxn in Pt w/ PCN or Ceph allergy
β-lact. Inhib. (eg, sulbactam)	Inhibit plasma-mediated β-lactamases	Adds staph, <i>B. fragilis</i> & some GNR (<i>H. flu</i> , <i>M. cat</i> , some <i>Klebs</i>); intrinsic activity against <i>Acinetobacter</i> (sulbactam only)

Cephalosporins

Resistant to most β-lactamases. No activity vs. enterococci.

Gen.	Spectrum	Indications
1st (eg, cefazolin)	Most GPC (incl. staph & strep, not MRSA) Some GNR (incl. <i>E. coli</i> , <i>Proteus</i> , <i>Klebsiella</i>)	Used for surgical Ppx & skin infxns
2nd (eg, cefuroxime, cefotetan)	↓ activity vs. GPC, ↑ vs. GNR. 2 subgroups: Respiratory: <i>H. influenzae</i> & <i>M. catarrhalis</i> GI/GU: ↑ activity vs. <i>B. fragilis</i>	PNA/COPD flare Abdominal infxns
3rd (eg, ceftriaxone)	Broad activity vs. GNR & some anaerobes Ceftazidime active vs. <i>Pseudomonas</i>	PNA, sepsis, meningitis
4th (eg, cefepime)	↑ resistance to β-lactamases (incl. of staph and <i>Enterobacter</i>)	Similar to 3 rd gen. MonoRx for nonlocalizing febrile neutropenia
5th (eg, ceftaroline)	Only class of cephalosporin with MRSA activity. NOT active vs <i>Pseudomonas</i>	MRSA. Not 1 st line for MRSA bactemia.

Other Antibiotics

Antibiotic	Spectrum
Vancomycin	Gram ⊕ bacteria incl. MRSA, PCNase-producing pneumococci and enterococci (except VRE)
Linezolid	
Daptomycin	GPC incl. MRSA & VRE (check susceptibility for VRE)
Quinupristin/Dalfopristin	
Quinolones	Enteric GNR & atypicals. 3 rd & 4 th gen. ↑ activity vs. Gram ⊕.
Aminoglycosides	GNR. Synergy w/ cell-wall active abx (β-lactam, vanco) vs. GPC. ↓ activity in low pH (eg, abscess). No activity vs. anaerobes.
Macrolides	GPC, some respiratory Gram ⊖, atypicals
TMP/SMX	Some enteric GNR, PCP, <i>Nocardia</i> , <i>Toxoplasma</i> , most community-acquired MRSA
Clindamycin	Most Gram ⊕ (except enterococci) & anaerobes (incl. <i>B. fragilis</i>)
Metronidazole	Almost all anaerobic Gram ⊖, most anaerobic Gram ⊕
Doxycycline	<i>Rickettsia</i> , <i>Ehrlichia</i> , <i>Anaplasma</i> , <i>Chlamydia</i> , <i>Mycoplasma</i> , <i>Nocardia</i> , Lyme
Tigecycline	Many GPC incl. MRSA & VRE; some GNR incl. ESBL but not <i>Pseudomonas</i> or <i>Proteus</i> . Approved for abdominal or skin/soft tissue infections. Check susceptibility if organism isolated.

CARDIOLOGY

Hemodynamic parameters	Normal value
Mean arterial pressure (MAP) = $\frac{SBP + (DBP \times 2)}{3}$	70–100 mmHg
Heart rate (HR)	60–100 bpm
Right atrial pressure (RA)	≤ 6 mmHg
Right ventricular (RV)	systolic 15–30 mmHg diastolic 1–8 mmHg
Pulmonary artery (PA)	systolic 15–30 mmHg mean 9–18 mmHg diastolic 6–12 mmHg
Pulmonary capillary wedge pressure (PCWP)	≤ 12 mmHg
Cardiac output (CO)	4–8 L/min
Cardiac index (CI) = $\frac{CO}{BSA}$	2.6–4.2 L/min/m ²
Stroke volume (SV) = $\frac{CO}{HR}$	60–120 mL/contraction
Stroke volume index (SVI) = $\frac{CI}{HR}$	40–50 mL/contraction/m ²
Systemic vascular resistance (SVR) = $\frac{MAP - \text{mean RA}}{CO} \times 80$	800–1200 dynes × sec/cm ⁵
Pulmonary vascular resistance (PVR) = $\frac{\text{mean PA} - \text{mean PCWP}}{CO} \times 80$	120–250 dynes × sec/cm ⁵

"Rule of 6s" for PAC: RA ≤ 6 , RV $\leq 30/6$, PA $\leq 30/12$, WP ≤ 12 . Nb 1 mmHg = 1.36 cm water or blood.

Fick cardiac output

Oxygen consumption (L/min) = CO (L/min) \times arteriovenous (AV) oxygen difference
CO = oxygen consumption/AV oxygen difference

Oxygen consumption must be measured (can estimate w/ 125 mL/min/m², but inaccurate)

AV oxygen difference = Hb (g/dL) \times 10 (dL/L) \times 1.36 (mL O₂/g of Hb) \times (S_aO₂ – S_{ve}O₂)

S_aO₂ is measured in any arterial sample (usually 93–98%)

S_{ve}O₂ (mixed venous O₂) is measured in RA, RV or PA (assuming no shunt) (nl ~75%)

$$\therefore \text{Cardiac output (L/min)} = \frac{\text{Oxygen consumption}}{\text{Hb (g/dL)} \times 13.6 (\text{S}_a\text{O}_2 - \text{S}_v\text{O}_2)}$$

Shunts

$$Q_p = \frac{\text{Oxygen consumption}}{\text{Pulm. vein O}_2 \text{ sat} - \text{Pulm. artery O}_2 \text{ sat}} \quad (\text{if no R} \rightarrow \text{L shunt, PV O}_2 \text{ sat} \approx \text{S}_a\text{O}_2)$$

$$Q_s = \frac{\text{Oxygen consumption}}{\text{S}_a\text{O}_2 - \text{mixed venous O}_2 \text{ sat}} \quad (\text{MVO}_2 \text{ drawn proximal to potential L} \rightarrow \text{R shunt})$$

$$\frac{Q_p}{Q_s} = \frac{\text{S}_a\text{O}_2 - \text{MV O}_2 \text{ sat}}{\text{PV O}_2 \text{ sat} - \text{PA O}_2 \text{ sat}} \approx \frac{\text{S}_a\text{O}_2 - \text{MV O}_2 \text{ sat}}{\text{S}_a\text{O}_2 - \text{PA O}_2 \text{ sat}} \quad (\text{if only L} \rightarrow \text{R and no R} \rightarrow \text{L shunt})$$

Valve equations

Simplified Bernoulli: Pressure gradient (ΔP) = $4 \times v^2$ (where v = peak flow velocity)

Continuity (conservation of flow): Area₁ \times Velocity₁ = Area₂ \times Velocity₂ (where 1 & 2 different points)

$$\text{or AVA (unknown)} = A_{\text{LV outflow tract}} \times \left(\frac{V_{\text{LVOT}}}{V_{\text{AoV}}} \right) \quad (\text{all of which can be measured on echo})$$

$$\text{Gorlin equation: Valve area} = \frac{\text{CO}/(\text{DEP or SEP}) \times \text{HR}}{44.3 \times \text{constant} \times \sqrt{\Delta P}} \quad (\text{constant} = 1 \text{ for AS, } 0.85 \text{ for MS})$$

$$\text{Hakki equation: Valve area} = \frac{\text{CO}}{\sqrt{\Delta P}}$$

Chest Imaging (CXR & CT) Patterns

Pattern	Pathophysiology	Ddx
Consolidation	Radiopaque material in air space & interstitium patent airway → "air bronchograms"	Acute: water (pulm edema), pus (PNA), blood Chronic: neoplasm (BAC, lymphoma), aspiration, inflammatory (BOOP, eosinophilic PNA), PAP, granuloma (TB/fungal, alveolar sarcoid)
Ground glass (CT easier than CXR)	Interstitial thickening or partial filling of alveoli (but vessels visible)	Acute: pulm edema, infxn (PCP, viral, resolving bact. PNA) Chronic: ILD w/o fibrosis: acute hypersens., DIP/RB, PAP w/ fibrosis: IPF
Septal lines Kerley A & B	Radiopaque material in septae	Cardiogenic pulm edema , interstitial PNA viral, mycoplasma), lymphangitic tumor
Reticular	Lace-like net (ILD)	ILD (esp. IPF, CVD, bleomycin, asbestos)
Nodules	Tumor Granulomas Abscess	Cavitory: Primary or metastatic cancer, TB (react. or miliary), fungus, Wegener's, RA septic emboli, PNA Noncavitory: any of above + sarcoid, hypersens. pneum., HIV, Kaposi's sarcoma
Wedge opac.	Peripheral infarct	PE , cocaine, angioinv. aspergillus, Wegener's
Tree-in-bud (best on CT)	Inflammation of small airways	Bronchopneumonia , endobronchial TB/MAI, viral PNA, aspiration, ABPA, CF, asthma, BOOP
Hilar fullness	↑ LN or pulm arteries	Neoplasm (lung, mets, lymphoma) Infxn (AIDS); Granuloma (sarcoid/TB/fungal) Pulmonary hypertension
Upper lobe	n/a	TB , fungal, sarcoid, hypersens. pneum., CF, XRT
Lower lobe	n/a	Aspiration , bronchiect., IPF, RA, SLE, asbestos
Peripheral	n/a	BOOP, IPF & DIP, eos PNA, asbestos

CXR in heart failure

- ↑ cardiac silhouette (in systolic dysfxn, not in diastolic)
- Pulmonary venous hypertension: cephalization of vessels (vessels size > bronchi in upper lobes), peribronchial cuffing (fluid around bronchi seen on end → small circles), Kerley B lines (horizontal 1–2-cm lines at bases), ↑ vascular pedicle width, loss of sharp vascular margins, pleural effusions (~75% bilateral)
- Pulmonary edema: ranges from ground glass to consolidation; often dependent and central, sparing outer third ("bat wing" appearance)

Dead space = lung units that are ventilated but not perfused

Intrapulmonary shunt = lung units that are perfused but not ventilated

$$\text{Alveolar gas equation: } P_{\text{A}}O_2 = [F_1O_2 \times (760 - 47)] - \frac{P_{\text{a}}CO_2}{R} \quad (\text{where } R \approx 0.8)$$

$$P_{\text{A}}O_2 = 150 - \frac{P_{\text{a}}CO_2}{0.8} \quad (\text{on room air})$$

A-a gradient = $P_{\text{A}}O_2 - P_{\text{a}}O_2$ [normal A-a gradient ≈ 4 + (age/4)]

Minute ventilation (V_E) = tidal volume (V_T) × respiratory rate (RR)(nl 4–6 L/min)

Tidal volume (V_T) = alveolar space (V_A) + dead space (V_D)

$$\text{Fraction of tidal volume that is dead space} \left(\frac{V_D}{V_T} \right) = \frac{P_{\text{a}}CO_2 - P_{\text{expired}}CO_2}{P_{\text{a}}CO_2}$$

$$P_{\text{a}}CO_2 = k = \times \frac{\text{CO}_2 \text{ Production}}{\text{alveolar ventilation}} = k \times \frac{\dot{V}_{CO_2}}{RR \times V_T \times \left(1 - \frac{V_D}{V_T} \right)}$$

NEPHROLOGY

Anion gap (AG) = $\text{Na} - (\text{Cl} + \text{HCO}_3)$ (normal = $[\text{alb}] \times 2.5$; typically $12 \pm 2 \text{ mEq}$)

Delta-delta ($\Delta\Delta$) = $[\Delta \text{ AG} \text{ (ie, calc. AG - expected)} / \Delta \text{ HCO}_3 \text{ (ie, } 24 - \text{ measured HCO}_3)]$

Urine anion gap (UAG) = $(\text{U}_{\text{Na}} + \text{U}_{\text{K}}) - \text{U}_{\text{Cl}}$

$$\text{Calculated osmoles} = (2 \times \text{Na}) + \left(\frac{\text{glc}}{18} \right) + \left(\frac{\text{BUN}}{2.8} \right) + \left(\frac{\text{EtOH}}{4.6} \right)$$

Osmolar gap (OG) = measured osmoles – calculated osmoles (normal <10)

$$\text{Estimated creatinine clearance} = \frac{[140 - \text{age (yes)}] \times \text{wt (kg)}}{\text{serum Cr (mg/dL)} \times 72} \quad (\times 0.85 \text{ in women})$$

$$\text{Fractional excretion of Na (FE}_{\text{Na}}, \%) = \left[\frac{\frac{\text{U}_{\text{Na}}(\text{mEq/L})}{\text{P}_{\text{Na}}(\text{mEq/L})} \times 100\%}{\frac{\text{U}_{\text{Cr}}(\text{mg/mL})}{\text{P}_{\text{Cr}}(\text{mg/dL})} \times 100 \text{ (mL/dL)}} \right] = \frac{\text{U}_{\text{Na}}}{\text{P}_{\text{Na}}} \frac{\text{P}_{\text{Cr}}}{\text{U}_{\text{Cr}}}$$

Corrected Na in hyperglycemia

$$\text{estimate in all Pts: corrected Na} = \text{measured Na} + \left[2.4 \times \frac{(\text{measured glc} - 100)}{100} \right]$$

however, Δ in Na depends on glc (Am J Med 1999;106:399)

Δ is 1.6 mEq per each 100 mg/dL ↑ in glc ranging from 100–440

Δ is 4 mEq per each 100 mg/dL ↑ in glc beyond 440

Total body water (TBW) = $0.60 \times \text{IBW}$ ($\times 0.85$ if female and $\times 0.85$ if elderly)

$$\text{Free H}_2\text{O deficit} = \text{TBW} \times \left(\frac{[\text{Na}]_{\text{serum}} - 140}{140} \right) \approx \left(\frac{[\text{Na}]_{\text{serum}} - 140}{3} \right) \text{ (in 70-kg Pt)}$$

$$\text{Trans-tubular potassium gradient (TTKG)} = \frac{\text{U}_{\text{K}}}{\text{P}_{\text{K}}} \frac{\text{P}_{\text{Osm}}}{\text{U}_{\text{Osm}}}$$

HEMATOLOGY

Peripheral Smear Findings (also see Photo Inserts)

Feature	Abnormalities and diagnoses
Size	normocytic vs. microcytic vs. macrocytic → see below
Shape	anisocytosis → unequal RBC size; poikilocytosis → irregular RBC shape acanthocytes = spur cells (irregular sharp projections) → liver disease bite cells (removal of Heinz bodies by phagocytes) → G6PD deficiency echinocytes = burr cells (even, regular projections) → uremia, artifact pencil cell → long, thin, hypochromic - very common in adv. iron deficiency rouleaux → hyperglobulinemia (eg, multiple myeloma) schistocytes , helmet cells → MAHA (eg, DIC, TTP/HUS), mechanical valve spherocytes → HS, AIHA; sickle cells → sickle cell anemia stomatocyte → central pallor appears as curved slit → liver disease, EtOH target cells → liver disease, hemoglobinopathies, splenectomy tear drop cells = dacryocytes → myelofibrosis, myelophthisic anemia, megaloblastic anemia, thalassemia
Intra-RBC findings	basophilic stippling (ribosomes) → abnl Hb, sideroblastic, megaloblastic Heinz bodies (denatured Hb) → G6PD deficiency, thalassemia Howell-Jolly bodies (nuclear fragments) → splenectomy or functional asplenia (eg advanced sickle cell) nucleated RBCs → hemolysis, extramedullary hematopoiesis
WBC findings	blasts → leukemia, lymphoma; Auer rods → acute myelogenous leukemia hypersegmented (>5 lobes) PMNs: megaloblastic anemia (B_{12} /folate def.) pseudo-Pelger-Huët anomaly (bilobed nucleus, "pince-nez") → MDS toxic granules (coarse, dark blue) and Döhle bodies (blue patches of dilated endoplasmic reticulum) → (sepsis, severe inflammation)
Platelet	clumping → artifact, repeat plt count # → periph blood plt count ~10,000 plt for every 1 plt seen at hpf (100x) size → MPV (mean platelet volume) enlarged in ITP

Heparin for Thromboembolism

80 U/kg bolus

18 U/kg/h

PTT	Adjustment
<40	bolus 5000 U, ↑ rate 300 U/h
40–49	bolus 3000 U, ↑ rate 200 U/h
50–59	↑ rate 150 U/h
60–85	no Δ
86–95	↓ rate 100 U/h
96–120	hold 30 min, ↓ rate 100 U/h
>120	hold 60 min, ↓ rate 150 U/h

(Modified from Chest 2008;133:141S)

Heparin for ACS

60 U/kg bolus (max 4000 U)

12 U/kg/h (max 1000 U/h)

PTT	Adjustment
<40	bolus 3000 U, ↑ rate 100 U/h
40–49	↑ rate 100 U/h
50–75	no Δ
76–85	↓ rate 100 U/h
86–100	hold 30 min, ↓ rate 100 U/h
>100	hold 60 min, ↓ rate 200 U/h

(Modified from Circ 2007;116:e148 & Chest 2008;133:670)

- ✓ PTT q6h after every Δ ($t_{1/2}$ of heparin ~90 min) and then qd or bid once PTT is therapeutic
- ✓ CBC qd (to ensure Hct and plt counts are stable)

Warfarin Loading Nomogram

Day	INR				
	<1.5	1.5–1.9	2–2.5	2.6–3	>3
1–3	5 mg (7.5 mg if >80 kg)		2.5–5 mg	0–2.5 mg	0 mg
4–5	10 mg	5–10 mg		0–5 mg	0–2.5 mg
6	Dose based on requirements over preceding 5 d				

(Annals 1997;126:133; Archives 1999;159:46) or, go to www.warfarindosing.org

Warfarin-heparin overlap therapy

- Indications: when failure to anticoagulate carries ↑ risk of morbidity or mortality (eg, DVT/PE, intracardiac thrombus)
- Rationale: (1) Half-life of factor VII (3–6 h) is shorter than half-life of factor II (60–72 h); ∴ warfarin can elevate PT before achieving a true antithrombotic state
 (2) Protein C also has half-life less than that of factor II;
 ∴ theoretical concern of hypercoagulable state before antithrombotic state
- Method: (1) Therapeutic PTT is achieved using heparin
 (2) Warfarin therapy is initiated
 (3) Heparin continued until INR therapeutic for ≥2 d and ≥4–5 d of warfarin (roughly corresponds to ~2 half-lives of factor II or a reduction to ~25%)

Common Warfarin-Drug Interactions

Drugs that ↑ PT

Amiodarone

Antimicrobials: erythromycin, ? clarithro, ciprofloxacin, MNZ, sulfonamides

Antifungals: azoles

Acetaminophen, cimetidine, levothyroxine

Drugs that ↓ PT

Antimicrobials: rifampin

CNS: barbiturates, carbamazepine, phenytoin (initial transient ↑ PT)

Cholestyramine

OTHER

Ideal body weight (IBW) = [50 kg (men) or 45.5 kg (women)] + 2.3 kg/inch over 5 feet

$$\text{Body surface area (BSA, m}^2\text{)} = \sqrt{\frac{\text{height (cm)} \times \text{weight (kg)}}{3600}}$$

		Disease	
		present	absent
Test	⊕	a (true ⊕)	b (false ⊕)
	⊖	c (false ⊖)	d (true ⊖)

$$\text{Sensitivity} = \frac{\text{true positives}}{\text{all diseased}} = \frac{a}{a+c}$$

$$\text{Specificity} = \frac{\text{true negatives}}{\text{all healthy}} = \frac{d}{b+d}$$

$$\oplus \text{ Predictive value} = \frac{\text{true positives}}{\text{all positives}} = \frac{a}{a+b}$$

$$\ominus \text{ Predictive value} = \frac{\text{true negatives}}{\text{all negatives}} = \frac{d}{c+d}$$

ABBREVIATIONS

5'-NT	5'-nucleotidase	AVB	atrioventricular block
6-MP	6-mercaptopurine	AVNRT	AV nodal reentrant tachycardia
a/w	associated with	AVR	aortic valve replacement
AAA	abdominal aortic aneurysm	AVRT	AV reciprocating tachycardia
AAD	antiarrhythmic drug	AZA	azathioprine
Ab	antibody	Aϕ	alkaline phosphatase
ABE	acute bacterial endocarditis	 	
ABG	arterial blood gas	Bβ	beta-blocker
abnl	abnormal	b/c	because
ABPA	allergic bronchopulmonary aspergillosis	BAL	bronchoalveolar lavage
 		BBB	bundle branch block
abx	antibiotics	BCx	blood culture
AC	assist control	BD	bile duct
ACE	angiotensin-converting enzyme	BDZ	benzodiazepines
ACEI	ACE inhibitor	bili.	bilirubin
ACI	anemia of chronic inflammation	BiPAP	bilevel positive airway pressure
ACL	anticardiolipin antibody	BiV	biventricular
ACLS	advanced cardiac life support	BM	bone marrow
ACS	acute coronary syndrome	BMD	bowel movement
ACTH	adrenocorticotrophic hormone	BMI	bone mineral density
ACV	acyclovir	BMS	body mass index
ADA	adenosine deaminase	BNP	bare metal stent
ADH	antidiuretic hormone	BOOP	B-type natriuretic peptide
ADL	activities of daily living	 	bronchiolitis obliterans with organizing pneumonia
AF	atrial fibrillation	BP	blood pressure
AFB	acid-fast bacilli	BPH	benign prostatic hypertrophy
AFL	atrial flutter	BRBPR	bright red blood per rectum
AFP	α -fetoprotein	BS	breath sounds
ATFP	ascites fluid total protein	BT	bleeding time
AG	aminoglycoside anion gap	BUN	blood urea nitrogen
Ag	antigen	bx	biopsy
AGN	acute glomerulonephritis	BYCE	buffered charcoal yeast extract
AI	aortic insufficiency	 	
 	aromatase inhibitor	C'	complement
AIDS	acquired immunodeficit. synd.	c/s	consult
AIH	autoimmune hepatitis	c/w	compared with
AIHA	autoimmune hemolytic anemia	CABG	coronary artery bypass grafting
AIN	acute interstitial nephritis	CAD	coronary artery disease
AIP	acute interstitial pneumonia	CAH	congenital adrenal hyperplasia
AKI	acute kidney injury	CALLA	common ALL antigen
ALF	acute liver failure	CAPD	chronic ambulatory peritoneal dialysis
ALL	acute lymphoblastic leukemia	CBC	complete blood count
ALS	amyotrophic lateral sclerosis	CBD	common bile duct
ALT	alanine aminotransferase	CCB	calcium channel blocker
AMA	anti-mitochondrial antibody	CCl₄	carbon tetrachloride
AMI	anterior myocardial infarction	CCP	cyclic citrullinated peptide
AML	acute myelogenous leukemia	CCS	Canadian Cardiovascular Society
amy	amylase	CCY	cholecystectomy
ANA	antinuclear antibody	CD	Crohn's disease
ANCA	antineutrophilic cytoplasmic Ab	CEA	carcinoembryonic antigen
AoD	aortic dissection	 	carotid endarterectomy
AoV	aortic valve	ceph.	cephalosporin
APAP	acetyl-para-aminophenol	CF	cystic fibrosis
APC	activated protein C	Cftx	ceftriaxone
APL	acute promyelocytic leukemia	CFU	colony forming units
APLA	antiphospholipid Ab	CHB	complete heart block
APS	antiphospholipid Ab synd.	CHD	congenital heart disease
ARB	angiotensin receptor blocker	CHF	congestive heart failure
ARDS	acute resp distress synd.	CI	cardiac index
ARV	antiretroviral	CIAKI	contrast-induced AKI
ARVC	arrhythmogenic RV CMP	CIDP	chronic inflammatory demyelinating polyneuropathy
AS	aortic stenosis	 	Creutzfeldt-Jakob disease
ASA	aspirin	CJD	creatinine kinase
ASD	atrial septal defect	CK	chronic kidney disease
AST	aspartate aminotransferase	CKD	chronic lymphocytic leukemia
asx	asymptomatic	CLL	carpometacarpal (joint)
AT	atrial tachycardia	CMC	chronic myelogenous leukemia
ATII	angiotensin II	CML	
ATIII	antithrombin III		
ATN	acute tubular necrosis		
ATRA	all-trans-retinoic acid		
AV	atrioventricular		
AVA	aortic valve area		

CMM	chronic myelomonocytic leukemia	DRESS	drug reaction w/ eosinophilia & systemic symptoms
CMP	cardiomyopathy	DSE	dobutamine stress echo
CMV	cytomegalovirus	DST	dexamethasone suppression test
CN	cranial nerve	DTRs	deep tendon reflexes
CNI	calcineurin inhibitor	DU	duodenal ulcer
CO	carbon monoxide	DVT	deep vein thrombosis
COP	cardiac output	dx	diagnosis
COPD	cryptogenic organizing PNA	EAD	extreme axis deviation
COX	chronic obstructive pulm dis.	EAV	effective arterial volume
CP	cyclo-oxygenase	EBV	Epstein-Barr virus
CPAP	chest pain	ECG	electrocardiogram
CPP	continuous positive airway pressure	ECMO	extracorporeal membrane oxygenation
CPPD	cerebral perfusion pressure	ED	emergency department
Cr	calcium pyrophosphate dihydrate	EDP	end-diastolic pressure
CrAg	creatinine	EDV	end-diastolic volume
CRC	cryptococcal antigen	EEG	electroencephalogram
CrCl	colorectal cancer	EF	ejection fraction
CRP	creatinine clearance	EGD	esophagogastroduodenoscopy
CRT	C-reactive protein	EGFR	epidermal growth factor receptor
CsA	cardiac resynchronization therapy	EGPA	eosinophilic granulomatosis with polyangiitis
CSF	cyclosporine A	EI	entry inhibitor
CSM	cerebrospinal fluid	EIA	enzyme-linked immunoassay
CT	carotid sinus massage	ELISA	enzyme-linked immunosorbent assay
CTA	computed tomogram	EM	electron microscopy
CTD	CT angiogram	EMB	ethambutol
CV	connective tissue disease	ENT	ears, nose, & throat
CVA	cardiovascular	EOM	extraocular movement/muscles
CVD	cerebrovascular accident	EP	electrophysiology
CVID	cerebrovascular disease	Epo	erythropoietin
CVP	collagen vascular disease	EPS	electrophysiology study
CVVH	common variable immunodeficit	ERCP	endoscopic retrograde cholangiopancreatography
CW	central venous pressure	ERV	expiratory reserve volume
cx	continuous veno-venous hemofiltration	ESP	end-systolic pressure
CXR	chest wall	ESR	erythrocyte sedimentation rate
CYC	culture	ESRD	end-stage renal disease
CY	chest radiograph	ESV	end-systolic volume
day	cyclophosphamide	ET	endotracheal tube
d	day	EtOH	essential thrombocythemia
D	death	ETT	alcohol
ΔMS	change in mental status	EUS	endotracheal tube
DA	dopamine	EVAR	exercise tolerance test
DAD	diffuse alveolar damage	FDP	endoscopic ultrasound
DAH	diffuse alveolar hemorrhage	FEV₁	endovascular aneurysm repair
DAT	direct antiglobulin test	FFP	fibrin degradation product
DBP	diastolic blood pressure	FHx	forced expir. vol in 1 sec
d/c	discharge discontinue	FI	fresh frozen plasma
DCCV	direct current cardioversion	FMD	family history
DCIS	ductal carcinoma <i>in situ</i>	FMF	fusion inhibitor
DCMP	dilated cardiomyopathy	FNA	fibromuscular dysplasia
Ddx	differential diagnosis	FOB	familial Mediterranean fever
DES	drug-eluting stent	FOBT	fine-needle aspiration
DFA	direct fluorescent antigen detection	FQ	fecal occult blood
DI	diabetes insipidus	FRC	fecal occult blood testing
DIC	disseminated intravascular coagulation	FSGS	fluoroquinolone
diff.	differential	FSH	functional residual capacity
DIP	desquamative interstitial pneumonitis	FTI	focal segmental glomerulosclerosis
DKA	distal interphalangeal (joint)	FUO	follicle stimulating hormone
D_LCO	diabetic ketoacidosis	f/up	free thyroxine index
DLE	diffusion capacity of the lung	FVC	fever of unknown origin
DM	drug-induced lupus		follow-up
DMARD	dermatomyositis		forced vital capacity
DOE	diabetes mellitus		glc-6-phosphate dehydrogenase
DRE	disease-modifying anti-rheumatic drug		gallbladder
	dyspnea on exertion		glomerular basement membrane
	digital rectal exam		

GBS	Guillain-Barré syndrome	ICa	ionized calcium
GCA	giant cell arteritis	ICD	implantable cardiac defibrillator
GCS	Glasgow coma scale	ICH	intracranial hemorrhage
G-CSF	granulocyte colony stimulating factor	ICP	intracranial pressure
GE	gastroesophageal	ICU	intensive care unit
gen.	generation	IE	infective endocarditis
GERD	gastroesophageal reflux disease	IGF	insulin-like growth factor
GFR	glomerular filtration rate	IGRA	interferon- γ release assay
GGT	γ -glutamyl transpeptidase	II	integrase inhibitor
GH	growth hormone	IIP	idiopathic interstitial PNA
GIB	gastrointestinal bleed	ILD	interstitial lung disease
GIST	gastrointestinal stromal tumor	IMI	inferior myocardial infarction
glc	glucose	infxn	infection
GMCSF	granulocyte-macrophage colony-stimulating factor	inh	inhaled
GN	glomerulonephritis	INH	isoniazid
GNR	gram-negative rods	INR	international normalized ratio
GnRH	gonadotropin-releasing hormone	IPAA	ileal pouch-anal anastomosis
GPA	granulomatosis w/ polyangiitis	IPF	idiopathic pulmonary fibrosis
GPC	gram-positive cocci	ITP	idiopathic thrombocytopenic purpura
GPI	glycoprotein IIb/IIIa inhibitor	IVB	intravenous bolus
GRA	glucocorticoid-remediable aldosteronism	IVC	inferior vena cava
GU	gastric ulcer	IVDU	intravenous drug use(r)
GVHD	graft-versus-host disease	IVF	intravenous fluids
h	hour	IVIg	intravenous immunoglobulin
H2RA	H2-receptor antagonist	JVD	jugular venous distention
HA	headache	JVP	jugular venous pulse
HACA	human antichimeric antibody	KS	Kaposi's sarcoma
HAV	hepatitis A virus	KUB	kidney-ureter-bladder (radiography)
Hb	hemoglobin	LA	left atrium long-acting lupus anticoagulant
HBIG	hepatitis B immunoglobulin	LABA	long-acting β_2 -agonist
HBV	hepatitis B virus	LAD	left anterior descending coronary artery
HCC	hepatocellular carcinoma	LAE	left axis deviation
HCMP	hypertrophic cardiomyopathy	LAN	left atrial enlargement
Hct	hematocrit	LAP	lymphadenopathy
HCV	hepatitis C virus	LBBB	left atrial pressure
HCW	health care worker	LCA	leukocyte alkaline phosphatase
HD	hemodialysis	LCIS	left bundle branch block
HDL	high-density lipoprotein	LCx	left coronary artery
HDV	hepatitis D virus	LDH	lobular carcinoma <i>in situ</i>
HELLP	hemolysis, abnl LFTs, low plt	LDL	left circumflex cor. art.
HEV	hepatitis E virus	LE	lactate dehydrogenase
HF	heart failure	LES	low-density lipoprotein
HGPRT	hypoxanthine-guanine phosphoribosyl transferase	LFTs	lower extremity
HHS	hyperosmolar hyperglycemic state	LGIB	lower esophageal sphincter
HIT	heparin-induced thrombocytopenia	LH	liver function tests
HK	hypokinesis	LLQ	lower gastrointestinal bleed
HL	Hodgkin lymphoma	LM	luteinizing hormone
h/o	history of	LMWH	left lower quadrant
HOB	head of bed	LN	left main coronary artery
HoTN	hypotension	LOC	low-molecular-weight heparin
hpf	high-power field	LOS	lymph node
HPT	hyperparathyroidism	LP	loss of consciousness
HR	heart rate	lpf	length of stay
HRT	hormone replacement therapy	LQTS	lumbar puncture
HS	hereditary spherocytosis	LR	low-power field
HSCT	hematopoietic stem cell transplantation	LUSB	long QT syndrome
HSM	hepatosplenomegaly	LV	lactated Ringer's
HSP	Henoch-Schönlein purpura	LVAD	left upper sternal border
HSV	herpes simplex virus	LVEDP	left ventricle
HTN	hypertension	LVEDV	LV assist device
HUS	hemolytic uremic syndrome	LVH	LV end-diastolic pressure
hx	history	LVOT	LV end-diastolic volume
I&D	incision & drainage	LVSD	left ventricular hypertrophy
IABP	intra-aortic balloon pump	mAb	left ventricular outflow tract
IBD	inflammatory bowel disease	MAC	LV systolic dimension
IBS	irritable bowel syndrome		monoclonal antibody
IC	inspiratory capacity		mitral annular calcification
			<i>Mycobacterium avium</i> complex

MAHA	microangiopathic hemolytic anemia	NRTI	nucleoside reverse transcriptase inhibitor
MALT	mucosa-assoc. lymphoid tissue	NS	normal saline
MAO	monoamine oxidase	NSAID	nonsteroidal anti-inflam. drug
MAP	mean arterial pressure	NSCLC	non-small cell lung cancer
MAT	multifocal atrial tachycardia	NSF	nephrogenic systemic fibrosis
MCD	minimal change disease	NTG	nitroglycerin
MCP	metacarpal phalangeal (joint)	N/V	nausea and/or vomiting
MCS	mechanical circulatory support	NVE	native valve endocarditis
MCTD	mixed connective tissue dis.	NYHA	New York Heart Association
MCV	mean corpuscular volume		
MDI	metered dose inhaler	O/D	overdose
MDMA	3,4-methylenedioxymethamphetamine (Ecstasy)	o/w	otherwise
MDR	multidrug resistant	O&P	ova & parasites
MDS	myelodysplastic syndrome	OA	osteoarthritis
MEN	multiple endocrine neoplasia	OCP	oral contraceptive pill
MG	myasthenia gravis	OG	osmolal gap
MGUS	monoclonal gammopathy of uncertain significance	OGT	orogastric tube
MI	myocardial infarction	OGTT	oral glucose tolerance test
min	minute	OI	opportunistic infection
min.	minimal	OM	obtuse marginal cor. art.
MM	multiple myeloma	OSA	obstructive sleep apnea
MMEFR	max. mid-expir. flow rate	OTC	over-the-counter
MMF	mycophenolate mofetil		
MN	membranous nephropathy	p/w	present(s) with
MNZ	metronidazole	PA	pulmonary artery
mo	month	PAC	pulmonary artery catheter
mod.	moderate	PAD	peripheral artery disease
MODS	multiple organ dysfxn synd.	PAN	polyarteritis nodosa
MPA	microscopic polyangiitis	PASP	PA systolic pressure
MPGN	membranoproliferative	PAV	percutaneous aortic valvuloplasty
	glomerulonephritis	pb	problem
MPN	myeloproliferative neoplasm	PBC	primary biliary cholangitis
MR	magnetic resonance	PCI	percutaneous coronary intervention
	mitral regurgitation	PCN	penicillin
MRA	magnetic resonance angiography	PCP	<i>Pneumocystis jiroveci</i> pneumonia
MRCP	MR cholangiopancreatography	PCR	polymerase chain reaction
MRI	magnetic resonance imaging	PCT	porphyria cutanea tarda
MRSA	methicillin-resistant <i>S. aureus</i>	PCWP	pulmonary capillary wedge pressure
MS	mitral stenosis	PD	Parkinson's disease peritoneal dialysis
MSA	multisystem atrophy	PDA	patent ductus arteriosus
MTb	<i>Mycobacterium tuberculosis</i>	PE	posterior descending cor. art.
mTOR	mechanistic target of rapamycin	PEA	pulmonary embolism
MTP	metatarsal phalangeal (joint)	PEEP	pulseless electrical activity
MTX	methotrexate		positive end-expiratory pressure
MV	mitral valve	PEF	peak expiratory flow
MVA	mitral valve area	PET	positron emission tomography
MVP	mitral valve prolapse	PEx	physical examination
MVR	mitral valve replacement	PFO	patent foramen ovale
Mφ	macrophage	PFT	pulmonary function test
		PGA	polyglandular autoimmune syndrome
NAC	N-acetylcysteine	PHT	pulmonary hypertension
NAFLD	non-alcoholic fatty liver disease	PI	protease inhibitor
NASH	non-alcoholic steatohepatitis	PID	pelvic inflammatory disease
NG	nasogastric	PIF	prolactin inhibitory factor
NGT	nasogastric tube	PIP	peak inspiratory pressure
NHL	non-Hodgkin lymphoma		proximal interphalangeal (joint)
NIDCM	non-ischemic dilated CMP	PKD	polycystic kidney disease
NIF	negative inspiratory force	PM	polymyositis
NJ	nasogastric	PMF	primary myelofibrosis
nl	normal	PMHx	past medical history
NM	neuromuscular	PMI	point of maximal impulse
NMJ	neuromuscular junction	PML	progressive multifocal leukoencephalopathy
NNRTI	non-nucleoside reverse transcriptase inhibitor		polymorphonuclear leukocyte
NNT	number needed to treat	PMN	polymyalgia rheumatica
NO	nitric oxide	PMR	percutaneous mitral valvuloplasty
NPJT	nonparoxysmal junctional tachycardia	PMV	
NPO	nothing by mouth		
NPPV	noninvasive positive pressure ventilation		
NPV	negative predictive value		

PMT	polymorphic ventricular tachycardia	RDW	red cell distribution width
PNA	pneumonia	RE	reticuloendothelial
PND	paroxysmal nocturnal dyspnea	RF	rheumatoid factor risk factor
PNH	paroxysmal nocturnal hemoglobinuria	RHD	rheumatic heart disease
PNS	peripheral nervous system	RI	reticulocyte index
PO	oral intake	RIBA	recombinant immunoblot assay
POTS	postural orthostatic tachycardia syndrome	RMSF	Rocky Mountain spotted fever
PPD	purified protein derivative	ROS	review of systems
PPH	primary pulmonary HTN	RPGN	rapidly progressive
PPI	proton pump inhibitors	RR	glomerulonephritis
Pplat	plateau pressure	RRT	respiratory rate
PPM	permanent pacemaker	RT	renal replacement therapy
PPV	positive predictive value	RTA	radiation therapy
Ppx	prophylaxis	RTX	renal tubular acidosis
PR	PR segment on ECG	RUQ	rituximab
PRBCs	pulmonary regurgitation	RUSB	right upper quadrant
PRL	packed red blood cells	RV	right upper sternal border
PRPP	prolactin	RVAD	residual volume
PRWP	phosphoribosyl-I-pyrophosphate	RVH	right ventricle
PS	poor R wave progression	RVOT	RV assist device
PSA	pressure support	RVSP	right ventricular hypertrophy
PsA	pulmonic stenosis	Rx	RV outflow tract
PSC	prostate specific antigen	RYGB	RV systolic pressure
PSGN	<i>Pseudomonas aeruginosa</i>	SA	therapy
PSHx	primary sclerosing cholangitis	SAAAG	roux-en-Y gastric bypass
PSV	post streptococcal glomerulonephritis	SAH	sinoatrial
Pt	past surgical history	SAS	serum-ascites albumin gradient
PT	pressure support ventilation	SBE	subarachnoid hemorrhage
PTA	patient	SBO	sulfasalazine
PTH	prothrombin time	SBP	subacute bacterial endocarditis
PTH-rP	percutaneous transluminal angioplasty	SBT	small bowel obstruction
PTT	parathyroid hormone	SC	spontaneous bacterial peritonitis
PTU	PTH-related peptide	SCD	systolic blood pressure
PTX	partial thromboplastin time	SCID	spontaneous breathing trial
PUD	propylthiouracil	SCLC	subcutaneous
PUVA	pneumothorax	s/e	sudden cardiac death
PV	peptic ulcer disease	Se	severe combined immunodefici.
PVD	psoralen + ultraviolet A	sec	small-cell lung cancer
PVE	polycythemia vera	SERM	side effect
PVR	portal vein	sev.	sensitivity
PZA	peripheral vascular disease	SHBG	second
qac	prosthetic valve endocarditis	SIADH	selective estrogen receptor modulator
qhs	pulmonary vascular resistance	SIBO	severe
QoL	pyrazinamide	SIEP	steroid hormone binding
Qw	before every meal	SIMV	globulin
r/i	every bedtime	SIRS	synd. of inappropriate ADH
r/o	quality of life	SJS	small intestine bacterial overgrowth
RA	Q wave	SLE	serum immunoelectrophoresis
RAA	rule in	SMA	synchronized intermittent mandatory ventilation
RAD	rule out	SMV	systemic inflammatory response syndrome
RAE	refractory anemia	SMX	Stevens-Johnson syndrome
RAI	rheumatoid arthritis	SOS	systemic lupus erythematosus
RAIU	right atrium	s/p	superior mesenteric artery
RAS	renin-angiotensin-aldosterone	Sp	superior mesenteric vein
RAST	right axis deviation	SPEP	sulfamethoxazole
RBBB	right atrial enlargement	SR	sinusoidal obstructive synd.
RBC	radioactive iodine	s/s	status post
RBF	radioactive iodine uptake	SSCY	specificity
RBV	renal artery stenosis	SSRI	serum protein electrophoresis
RCA	radioallergosorbent test	SSS	sinus rhythm
RCMP	right bundle branch block	ST	signs and symptoms
RCT	red blood cell	STD	<i>Salmonella</i> , <i>Shigella</i> , <i>Campylobacter</i> , <i>Yersinia</i>
	renal blood flow		selective serotonin reuptake inhibitor
	ribavirin		sick sinus syndrome
	right coronary artery		sinus tachycardia
	restrictive cardiomyopathy		sexually transmitted disease
	randomized controlled trial		ST-segment depression

STE	ST-segment elevation	TWI	T-wave inversion
SV	stroke volume	Tx	transplant
SVC	superior vena cava	TZD	thiazolidinediones
SVR	systemic vascular resistance		
SVT	supraventricular tachycardia		
sx	symptom(s) or symptomatic		
T1D	type 1 diabetes mellitus	U/A	urinalysis
T2D	type 2 diabetes mellitus	UA	unstable angina uric acid
T₃RU	T ₃ resin uptake	UAG	urine anion gap
TA	thoracic aortic aneurysm	UC	ulcerative colitis
TB	tuberculosis	UCx	urine culture
TBG	thyroid binding globulin	UES	upper esophageal sphincter
TCA	tricyclic antidepressant	UFH	unfractionated heparin
TCD	transcranial Doppler	UGIB	upper gastrointestinal bleed
TCN	tetracycline	UIP	usual interstitial pneumonitis
Tdap	tetanus, diphtheria, pertussis	ULN	upper limit of normal
TdP	torsades de pointes	UOP	urine output
TdT	terminal deoxynucleotidyl transferase	UPEP	urine protein electrophoresis
 		UR	urgent revascularization
TEE	transesophageal echo	URI	upper resp. tract infxn
tfn	transfusion	U/S	ultrasound
TFTs	thyroid function tests	UTI	urinary tract infection
TG	triglycerides		
TGA	transposition of the great arteries		
 		V/Q	ventilation-perfusion
TIA	transient ischemic attack	VAD	ventricular assist device
TIBC	total iron binding capacity	VAP	ventilator-associated PNA
TINU	tubulointerstitial nephritis and uveitis	VATS	video-assisted thoracoscopic surgery
 		VBI	vertebrobasilar insufficiency
TIPS	transjugular intrahepatic portosystemic shunt	VC	vital capacity
 		VD	vessel disease
TKI	tyrosine kinase inhibitor	VDRL	venereal disease research
TLC	total lung capacity		laboratory (test for syphilis)
TMP	trimethoprim	VEGF	vascular endothelial growth factor
Tn	troponin	VF	ventricular fibrillation
TP	total protein	VLDL	very-low-density lipoproteins
TPMT	thiopurine methyltransferase	VOD	veno-occlusive disease
TPN	total parenteral nutrition	VS	vital signs
Tpo	thrombopoietin	VSD	ventricular septal defect
TPO	thyroid peroxidase	VT	tidal volume
TR	tricuspid regurgitation	VTE	ventricular tachycardia
TRALI	transfusion-related acute lung injury	vWD	venous thromboembolus
 		vWF	von Willebrand's disease
TRH	thyrotropin-releasing hormone	VZV	von Willebrand's factor
TRS	TIMI risk score		varicella zoster virus
TRUS	transrectal ultrasound		
TS	tricuspid stenosis	 w/	with
TSH	thyroid-stimulating hormone	WBC	white blood cell (count)
TSI	thyroid-stimulating immunoglobulin	WCT	wide-complex tachycardia
TSS	toxic shock syndrome	WHO	World Health Organization
 		wk	week
TTE	transsphenoidal surgery	WM	Waldenström's
TTKG	transthoracic echo		macroglobulinemia
TTP	transtubular potassium gradient	WMA	wall motion abnormality
 		w/o	without
TV	thrombotic thrombocytopenic purpura	WPW	Wolff-Parkinson-White syndrome
Tw	tricuspid valve		
TWF	T wave	 w/u	workup
 		XRT	radiation therapy

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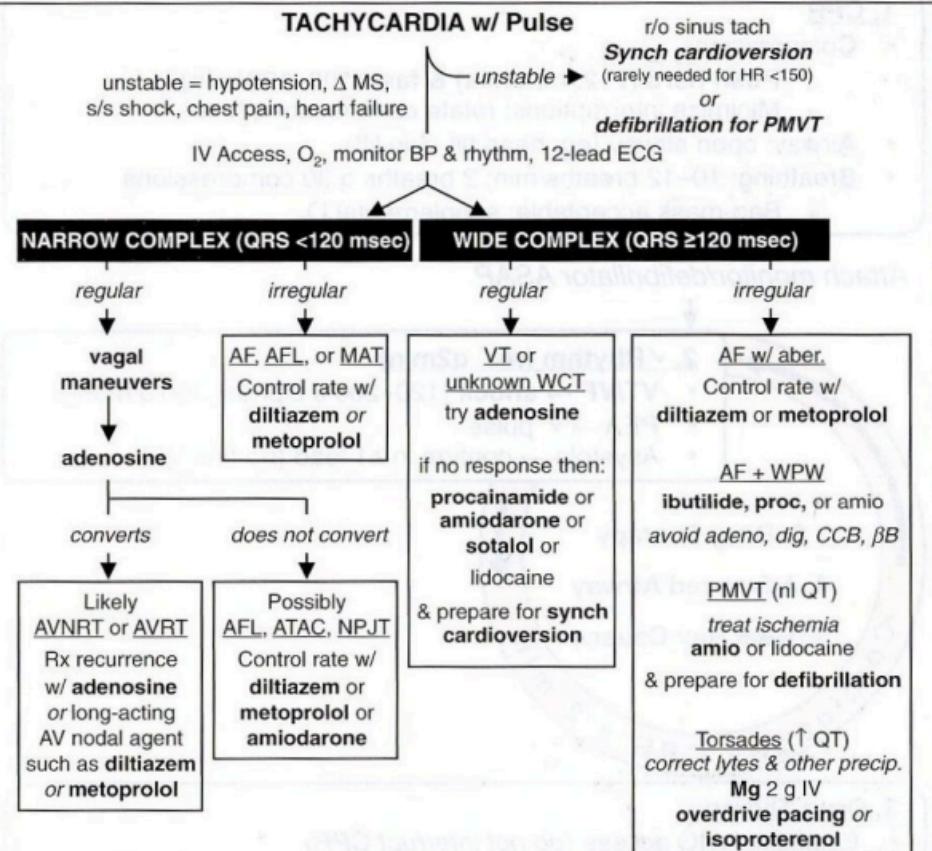
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ACLS ALGORITHMS

ACLS-1

Figure ACLS-1 ACLS Tachycardia Algorithm

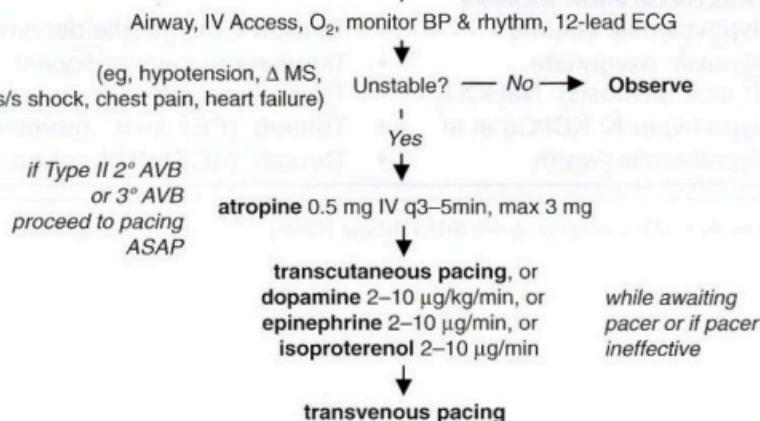


CARDIOVERSION	MEDICATIONS
<u>Ancillary equipment</u> O ₂ sat monitor suction, IV line intubation equipment	adenosine 6 mg rapid IVP then 20-cc NS bolus, 12 mg IVP q2min \times 2 if needed
<u>Premedicate</u> call anesthesia service midazolam 1–5 mg fentanyl 100–300 mcg	amiodarone 150 mg IV over 10 min
<u>Synch cardioversion</u> 50–200 J biphasic 100–200 J monophasic	diltiazem 15–20 mg IV over 2 min, 20–25 mg 15' later prn, 5–15 mg/h ibutilide 1 mg over 10 min, repeat \times 1 if needed lidocaine 1.0–1.5 mg/kg IVP, repeat in 5–10 min metoprolol 5 mg IV q5min \times 3 procainamide 17 mg/kg at 20–50 mg/min (avoid if EF ↓) sotalol 100 mg IV over 5 min verapamil 2.5–5 mg IV over 2 min, 5–10 mg 15–30 min later prn

(Adapted from ACLS 2015 Guidelines & Circ 2016;133:e506)

Figure ACLS-2 ACLS Bradycardia Algorithm

BRADYCARDIA w/ Pulse (HR <50 & inadequate for clinical condition)



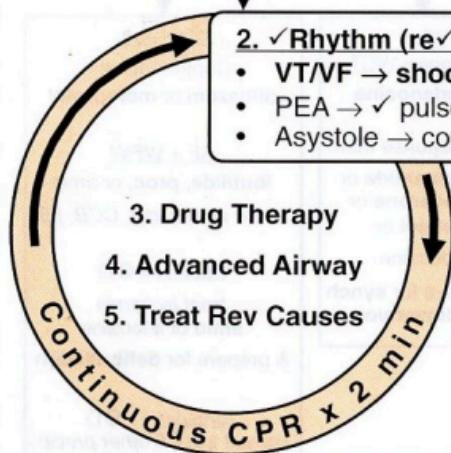
(Adapted from ACLS 2015 Guidelines)

PULSELESS ARREST

1. CPR

- Compressions
 - Push hard (2–2.4 inches) & fast (100–120/min)
 - Minimize interruptions; rotate compressor q2min
- Airway: open airway (eg, head tilt-chin lift)
- Breathing: 10–12 breaths/min; 2 breaths q 30 compressions
 - Bag-mask acceptable; supplemental O₂

Attach monitor/defibrillator ASAP



3. Drug Therapy

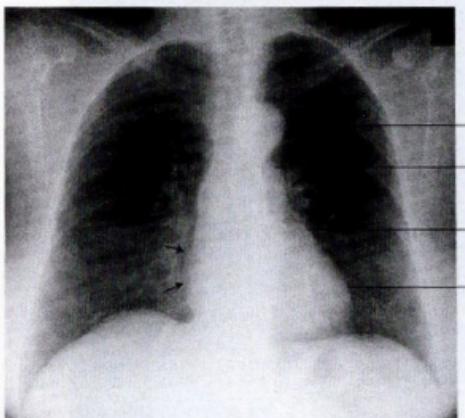
- Establish IV/IO access (*do not interrupt CPR*)
- **Epinephrine 1 mg IV q3–5min** (or 2 mg via ETT)
- **Amiodarone 300 mg IVB ± 150 mg IVB 3–5 min later**
 - ? lidocaine 1–1.5 mg/kg IVB (~100 mg) then 0.5–0.75 mg/kg (~50 mg) q5–10min, max 3 mg/kg
 - magnesium 1–2 g IV for TdP

4. Consider Advanced Airway

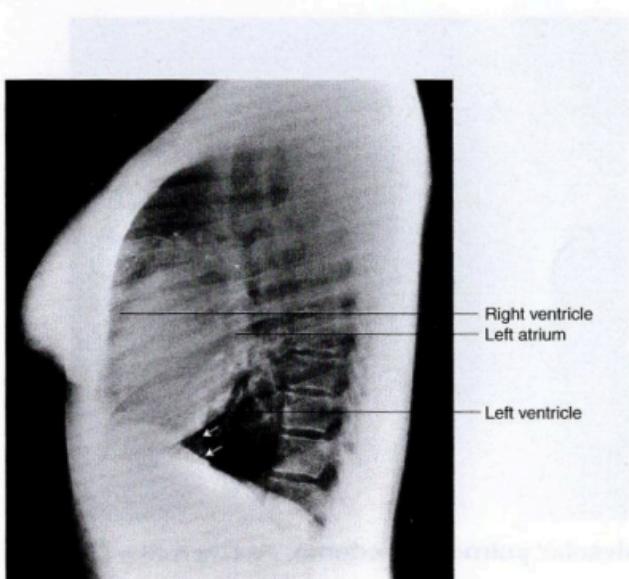
- Endotracheal intubation or supraglottic advanced airway
- Clinical assessment: bilat. chest expansion & breath sounds
- Device to ✓ tube placement
 - Continuous waveform capnography (~100% Se & Sp)
 - Colorimetric exhaled CO₂ detection (~ clinical assess.); false neg w/ ineffective CPR, PE, pulm edema, etc.
- 10 breaths/min w/ continuous compressions

5. Treat Reversible Causes

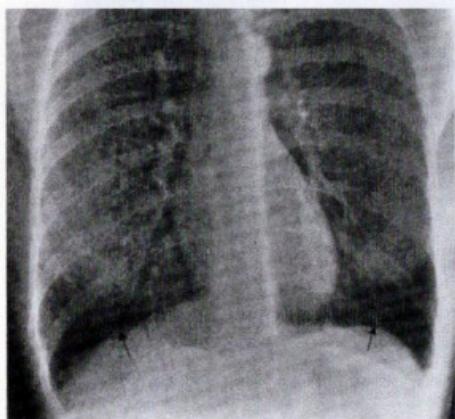
- Hypovolemia: volume
- Hypoxia: oxygenate
- H⁺ ions (acidosis): NaHCO₃
- Hypo/hyper K: KCl/Ca et al.
- Hypothermia: warm
- Tension PTX: needle decomp.
- Tamponade: pericardiocent.
- Toxins: med-specific
- Thromb. (PE): lysis, thrombect.
- Thromb. (ACS): PCI or lysis



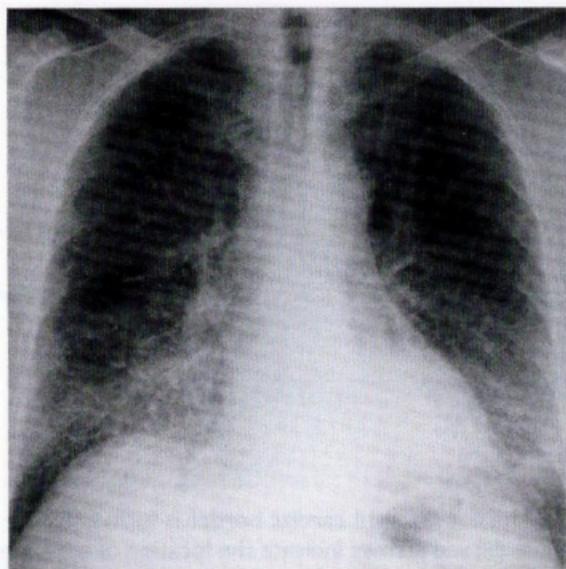
1 Normal PA CXR. The convex right cardiac border is formed by the right atrium (straight arrows), and the curved arrows indicate the location of the superior vena cava. The left cardiac and great vessels border what might be considered as 4 skiing moguls. From cephalad to caudad, the moguls are the aortic arch, the main and left pulmonary arteries, the left atrial appendage, and the left ventricle. (*Radiology* 101, 3rd ed, 2009.)



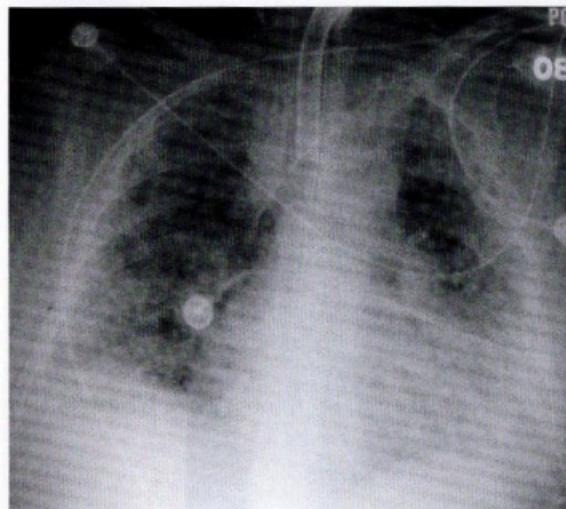
2 Normal lateral CXR. (*Radiology* 101, 3rd ed, 2009.)



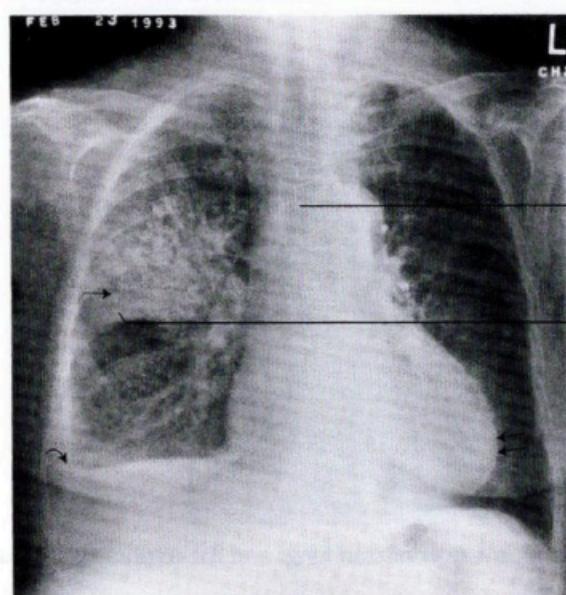
3 COPD: with hyperlucent, overinflated lungs and flat diaphragms. (*Radiology* 101, 3rd ed, 2009.)



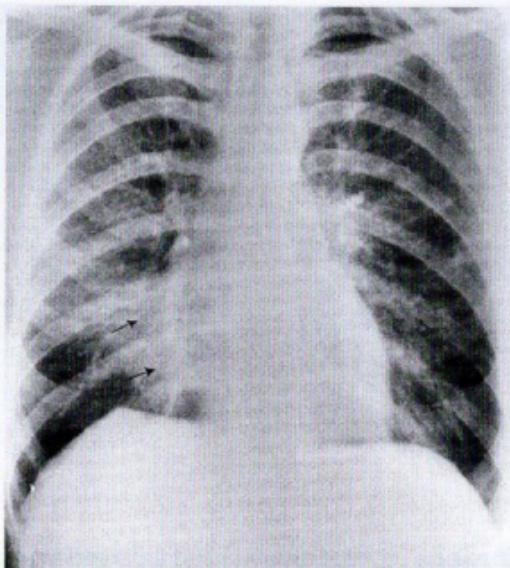
4 Interstitial pulmonary edema: with Kerley A, B, and C lines and cephalization of the vascular markings. (*Fund. Diag. Radiology* 3rd ed, 2006.)



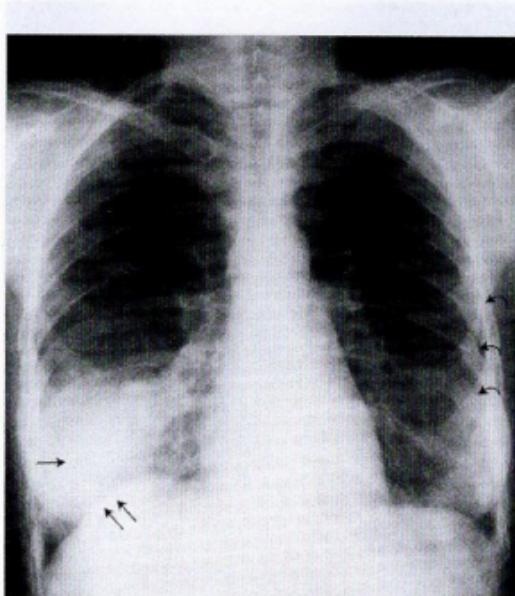
5 Alveolar pulmonary edema. (*Fund. Diag. Radiology* 3rd ed, 2006.)



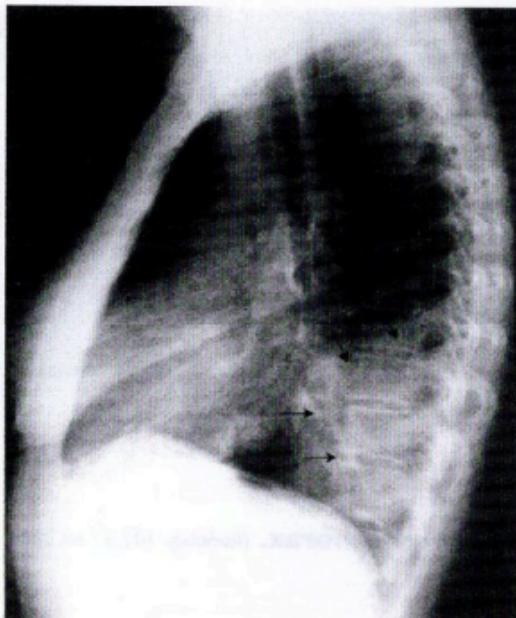
6 Right upper lobe pneumonia. (*Radiology* 101, 3rd ed, 2009.)



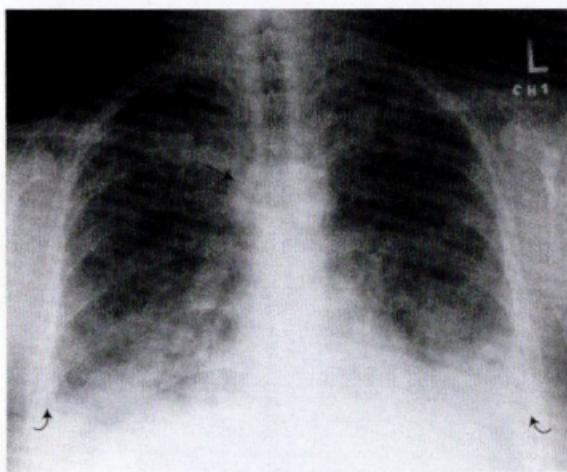
7 Right middle lobe pneumonia. (*Radiology 101*, 3rd ed, 2009.)



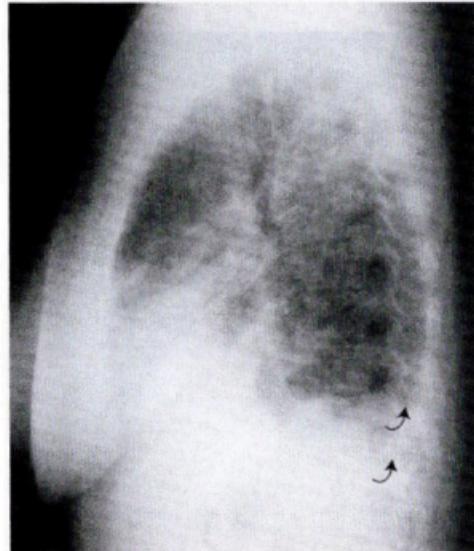
8 Right lower lobe pneumonia (PA). (*Radiology 101*, 3rd ed, 2009.)



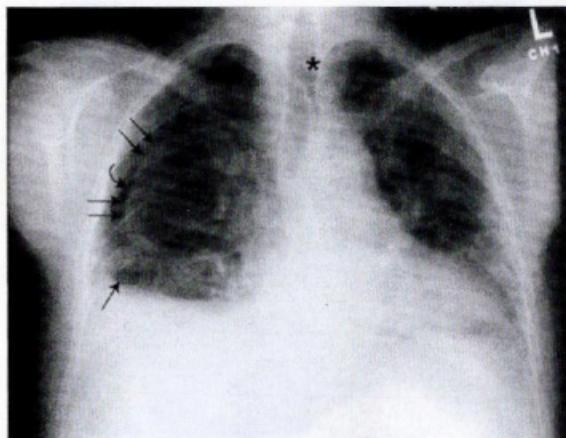
9 Right lower lobe pneumonia (lateral). (*Radiology 101*, 3rd ed, 2009.)



10 Bilateral pleural effusions (curved arrows) and enlarged azygous vein (straight arrow) (PA). (Radiology 101, 3rd ed, 2009.)



11 Bilateral pleural effusions (curved arrows) (lateral). (Radiology 101, 3rd ed, 2009.)

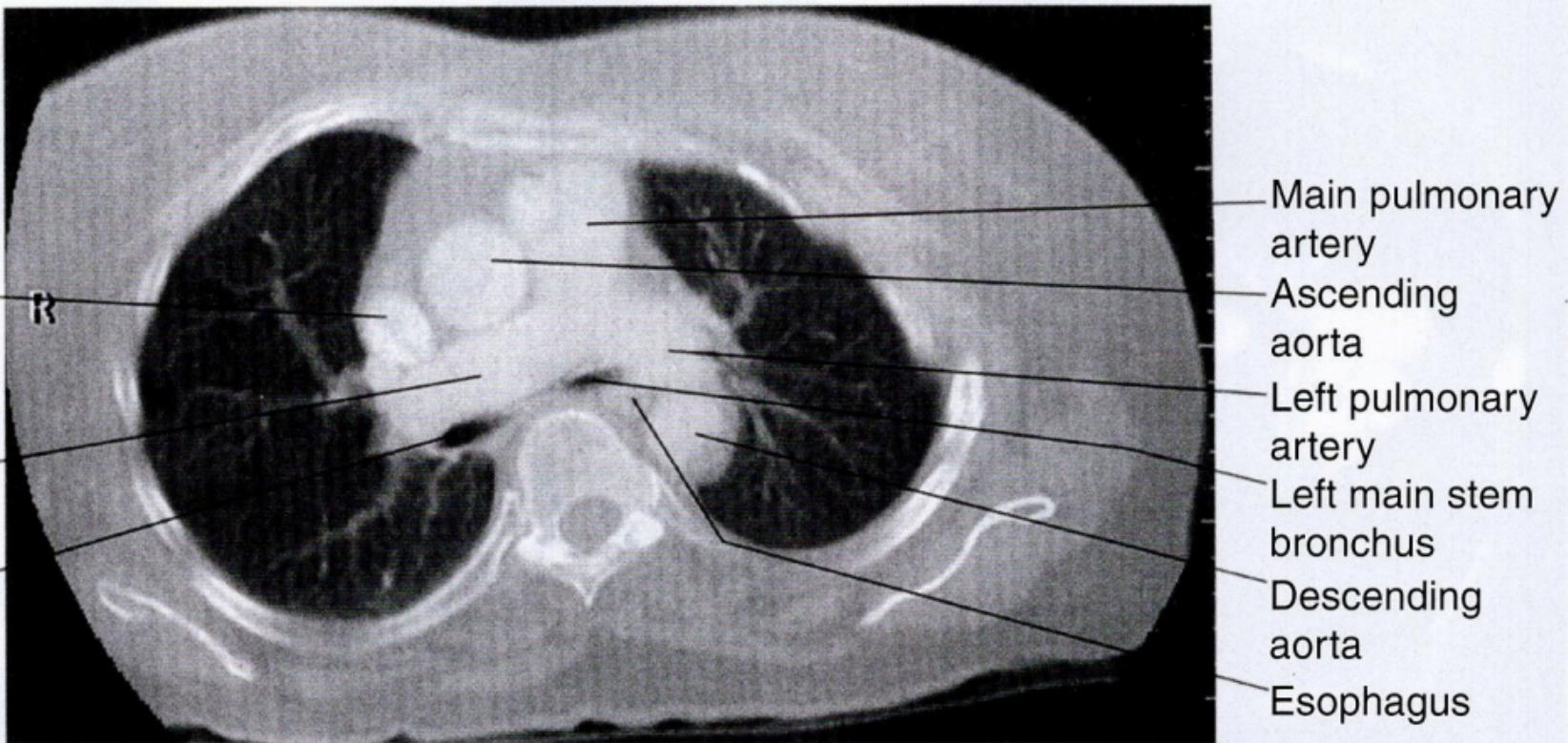


12 Pneumothorax. (Radiology 101, 3rd ed, 2009.)

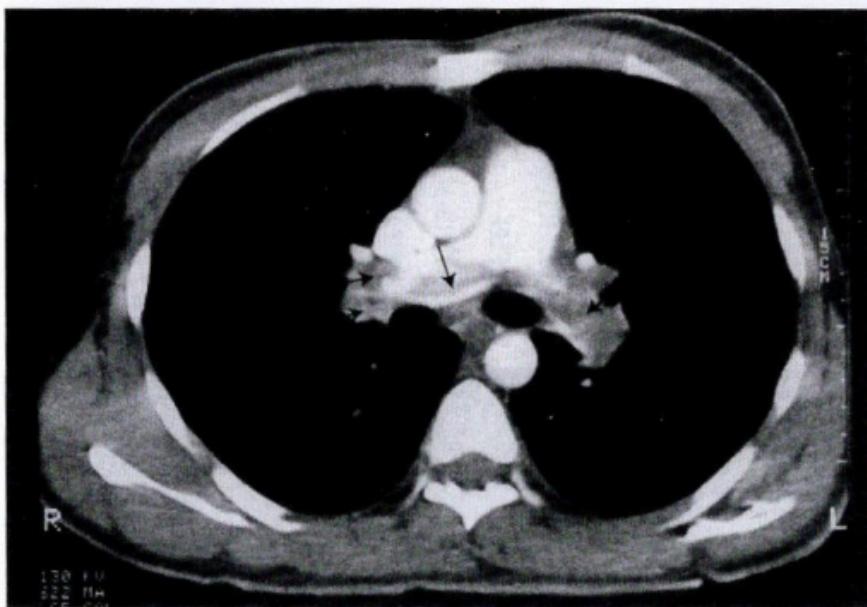
Superior vena
cava

Right pulmonary
artery

Right main
stem bronchus



13 Normal chest CT at level of pulmonary arteries (parenchymal windows).
(Radiology 101, 3rd ed, 2009.)



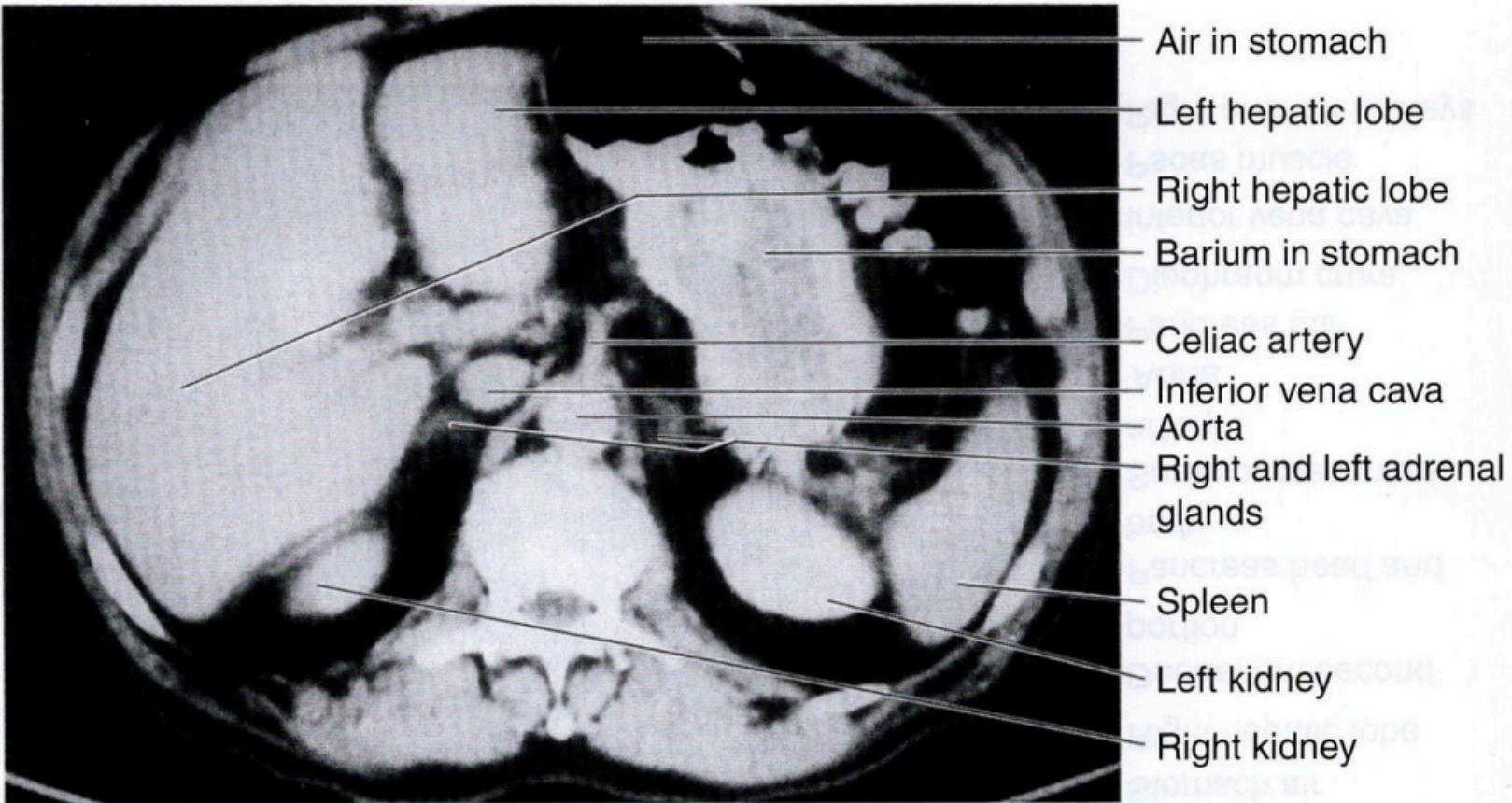
14 Bilateral PE (mediastinal windows). (Radiology 101, 3rd ed, 2009.)



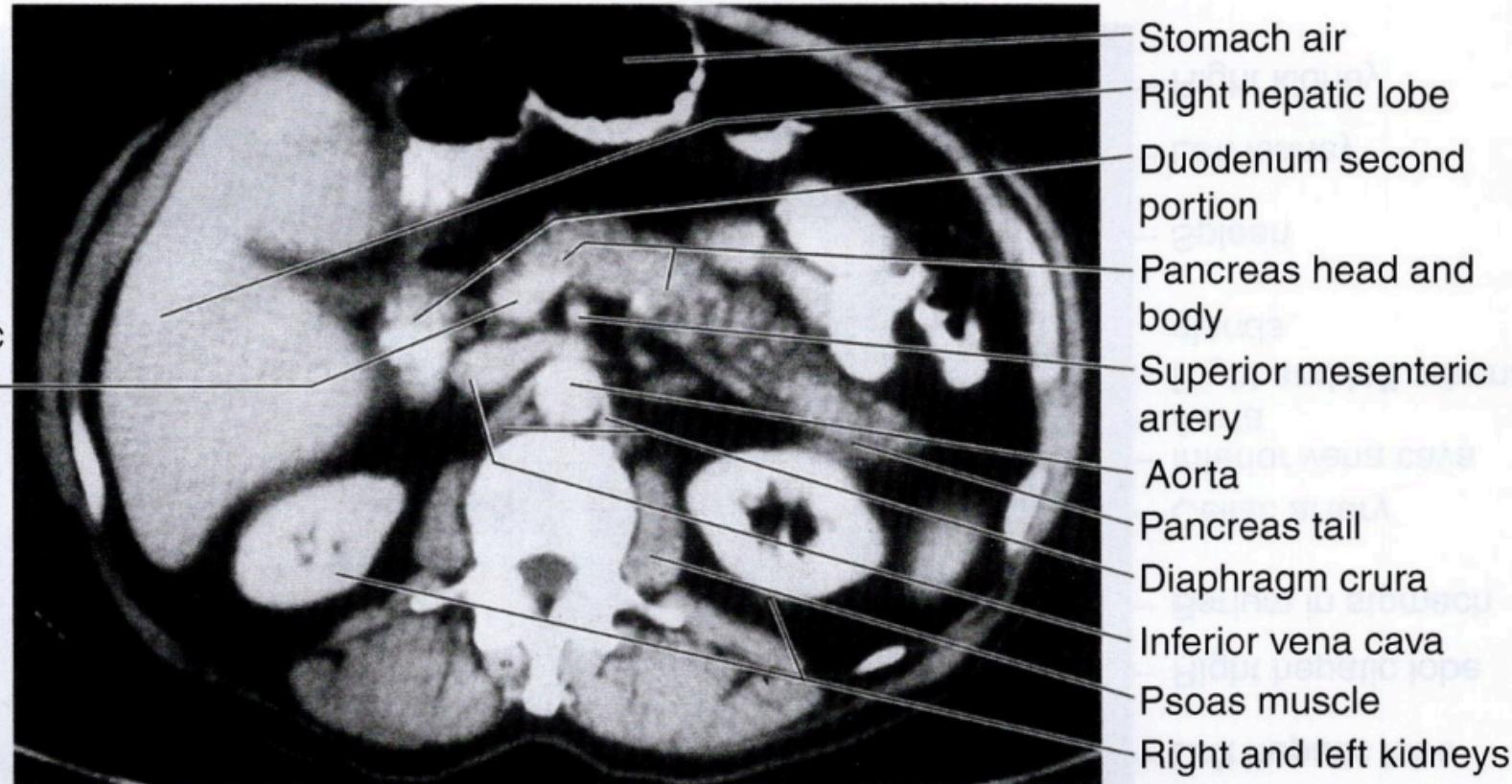
15 Sarcoidosis with perilymphatic nodules. (Fund. Diag. Radiology 3rd ed, 2006.)

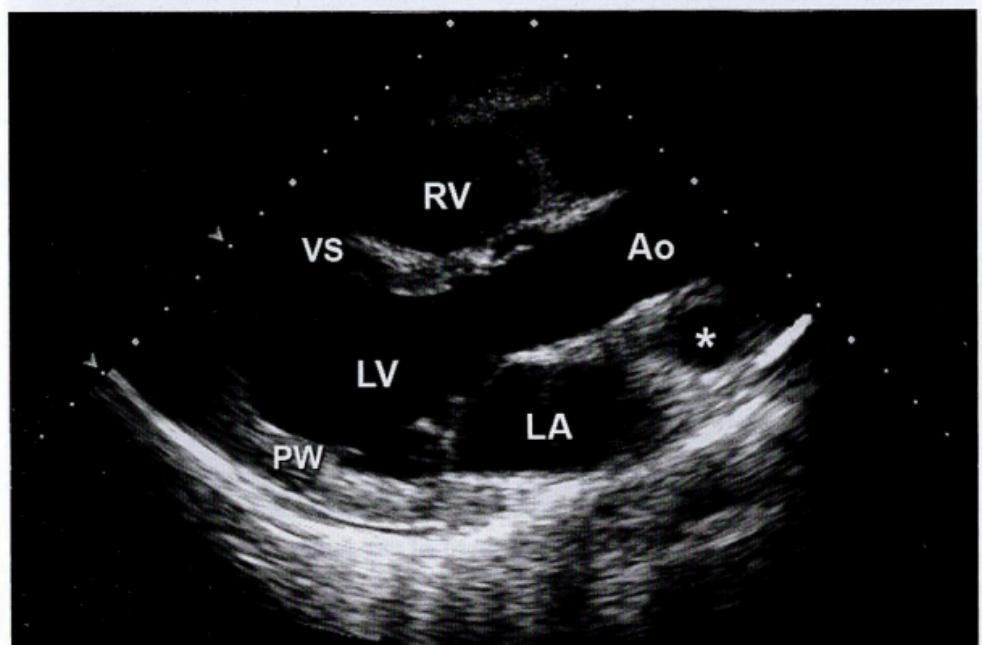
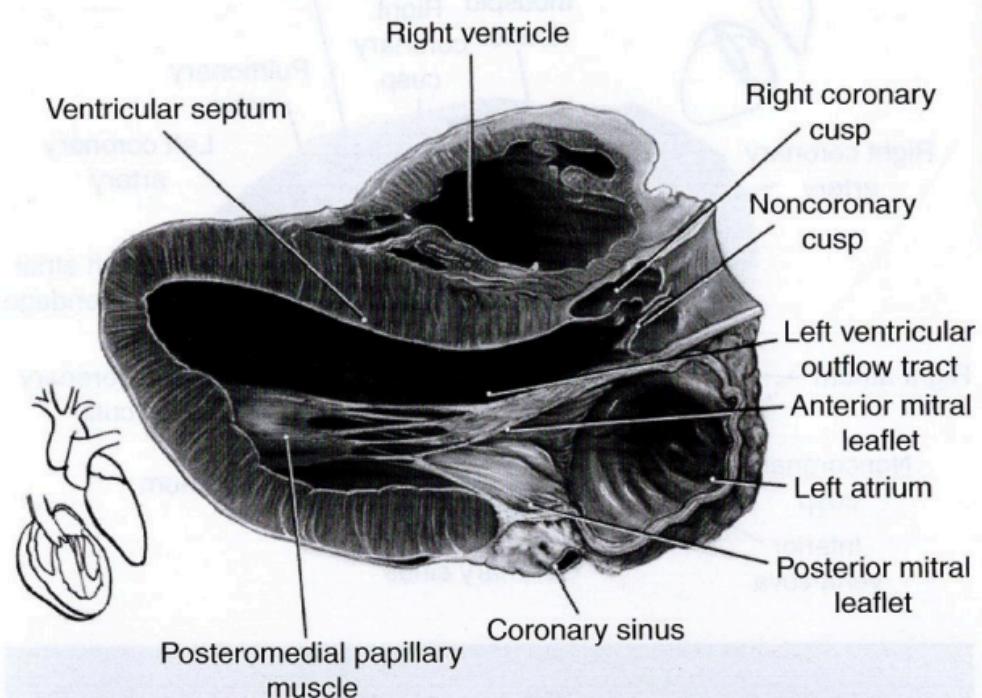


16 Idiopathic pulmonary fibrosis. (Fund. Diag. Radiology 3rd ed, 2006.)

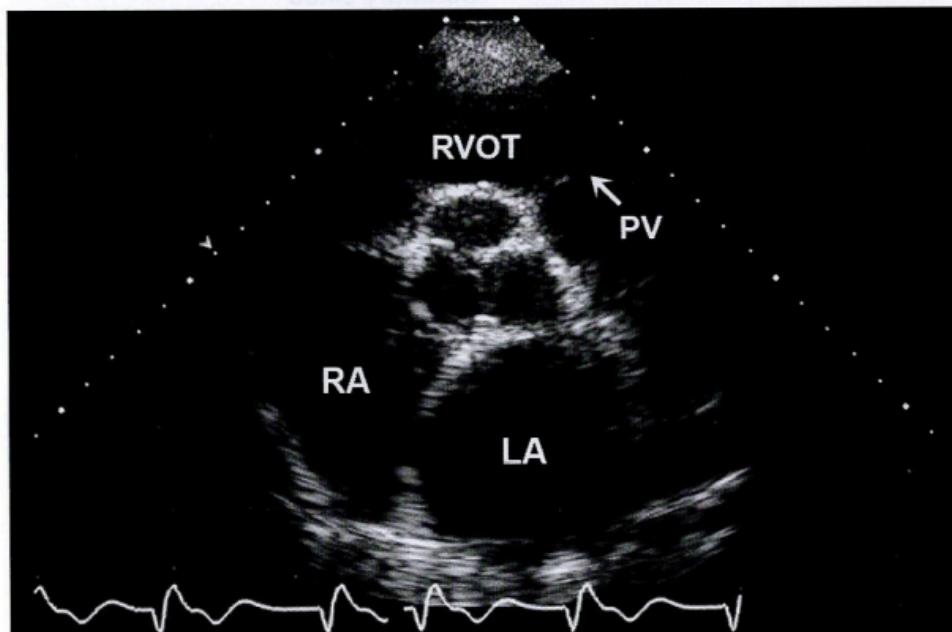
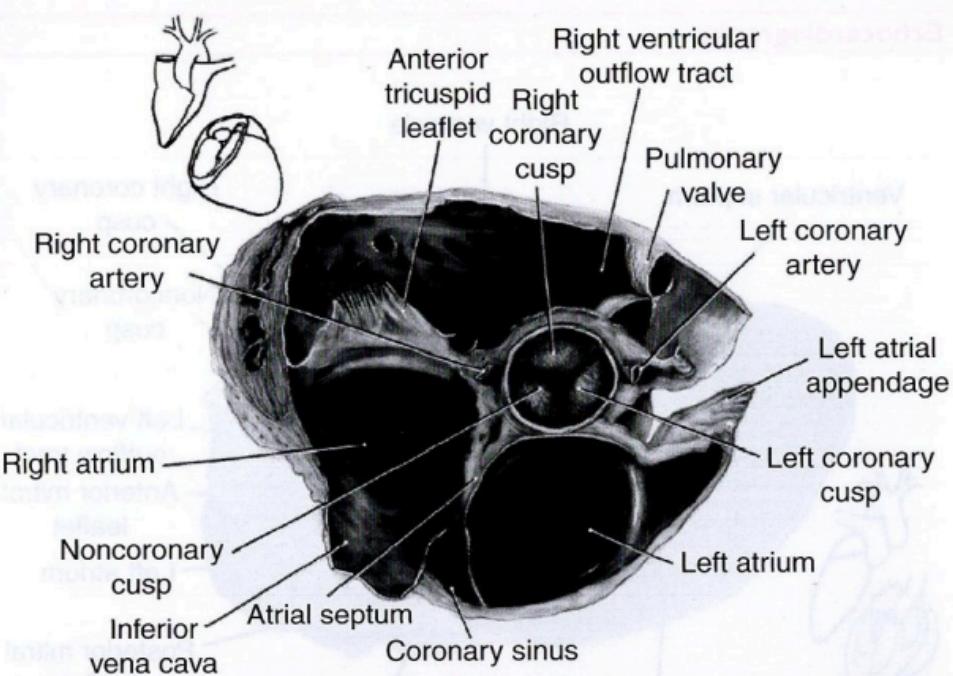


17 Normal abdomen CT at level of liver & spleen. (Radiology 101, 3rd ed, 2009.)

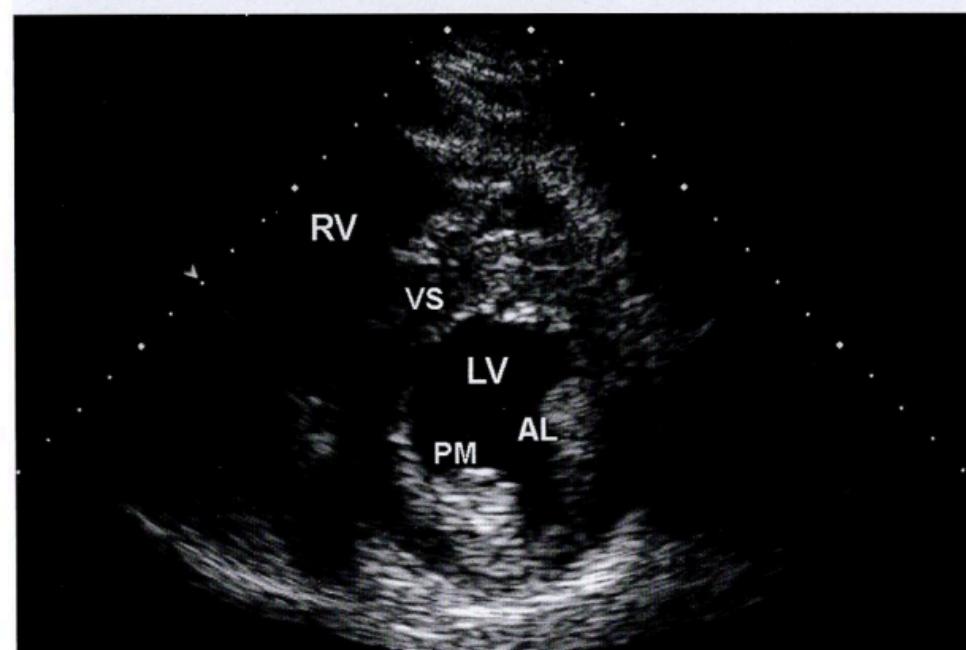
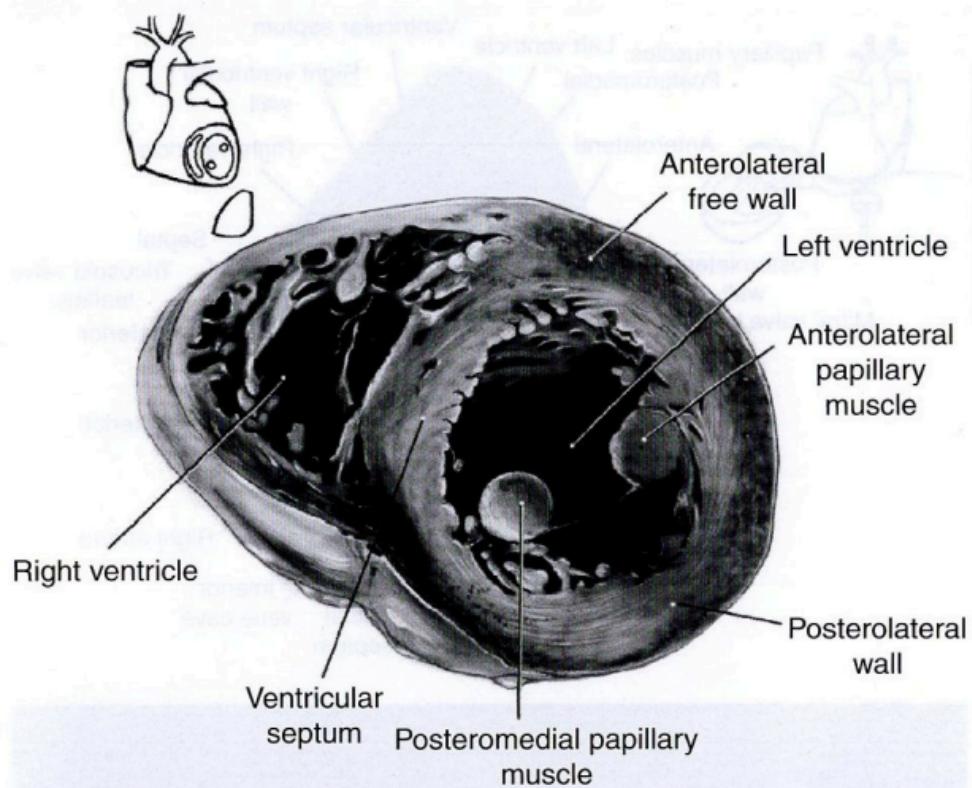
18 Normal abdomen CT at level of pancreas. (Radiology 101, 3rd ed, 2009.)



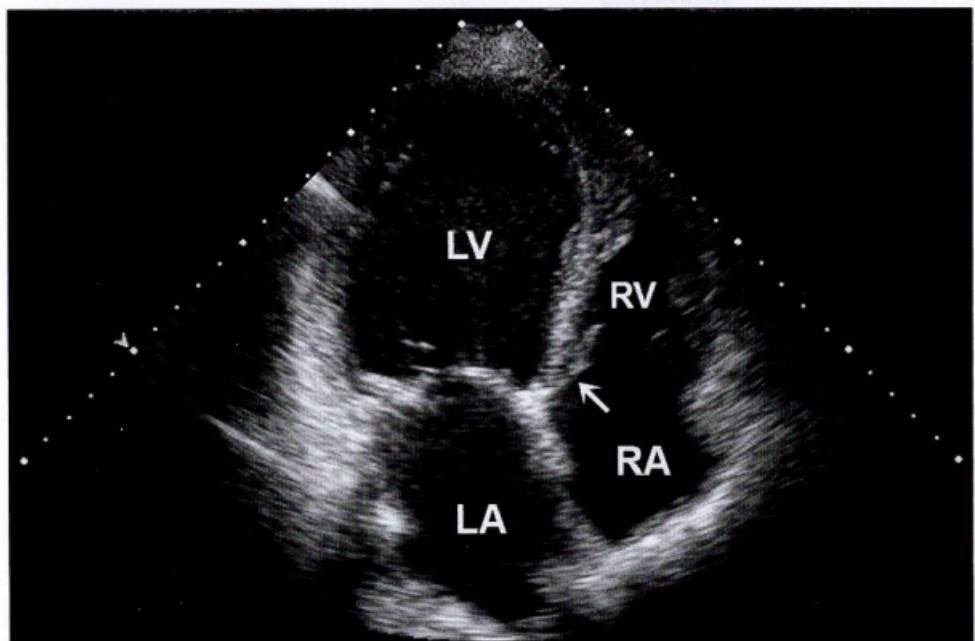
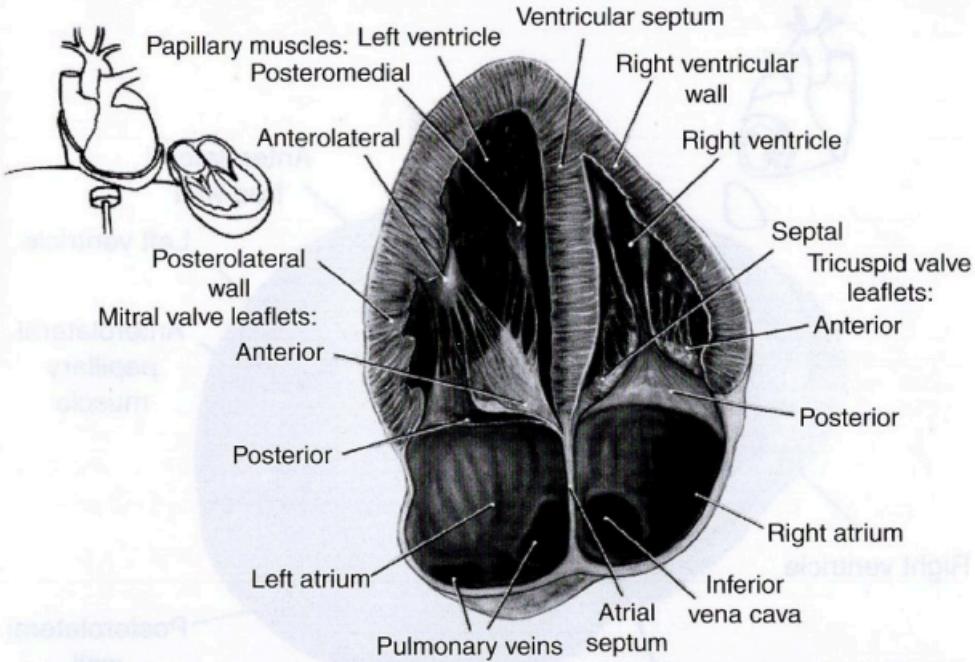
1 Parasternal long-axis view allows visualization of the right ventricle (RV), ventricular septum (VS), posterior wall (PW) aortic valve cusps, left ventricle (LV), mitral valve, left atrium (LA), and ascending thoracic aorta (Ao). *Pulmonary artery. (Top: From Mayo Clinic Proceedings. [Tajik AJ, Seward JB, Hagler DJ, et al. Two-dimensional real-time ultrasonic imaging of the heart and great vessels: Technique, image orientation, structure identification, and validation. Mayo Clinic Proceedings, 1978;53:271–303], with permission. Bottom: From Oh JK, Seward JB, Tajik AJ. *The Echo Manual*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2006. By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)



2 Parasternal short-axis view at the level of the aorta: LA, left atrium; PV, pulmonary valve; RA, right atrium; RVOT, right ventricular outflow tract. (Top: From Mayo Clinic Proceedings. [Tajik AJ, Seward JB, Hagler DJ, et al. Two-dimensional real-time ultrasonic imaging of the heart and great vessels: Technique, image orientation, structure identification, and validation. Mayo Clinic Proceedings, 1978;53:271–303], with permission. Bottom: From Oh JK, Seward JB, Tajik AJ. *The Echo Manual*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2006. By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)



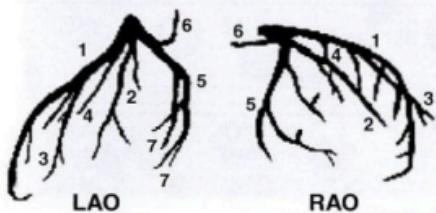
3 Parasternal short-axis view at the level of the papillary muscles: AL, anterolateral papillary muscle; PM, posteromedial papillary muscle; RV, right ventricle; VS, ventricular septum; LV, left ventricle. (Top: From Mayo Clinic Proceedings. [Tajik AJ, Seward JB, Hagler DJ, et al. Two-dimensional real-time ultrasonic imaging of the heart and great vessels: Technique, image orientation, structure identification, and validation. Mayo Clinic Proceedings, 1978;53:271–303], with permission. Bottom: From Oh JK, Seward JB, Tajik AJ. *The Echo Manual*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2006. By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)



4 Apical four-chamber view: Note that at some institutions the image is reversed so that the left side of the heart appears on the right side of the screen. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Top: From Mayo Clinic Proceedings. [Tajik AJ, Seward JB, Hagler DJ, et al. Two-dimensional real-time ultrasonic imaging of the heart and great vessels: Technique, image orientation, structure identification, and validation. Mayo Clinic Proceedings, 1978;53:271–303], with permission. Bottom: From Oh JK, Seward JB, Tajik AJ. *The Echo Manual*, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2006. By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

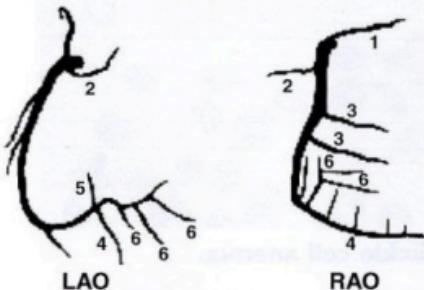
Coronary Angiography

LEFT CORONARY ARTERY



1. Left anterior descending artery (LAD)
2. Ramus medianus artery
3. Diagonal branches
4. Septal branches
5. Left circumflex artery (LCx)
6. Left atrial circumflex artery
7. Obtuse marginal branches

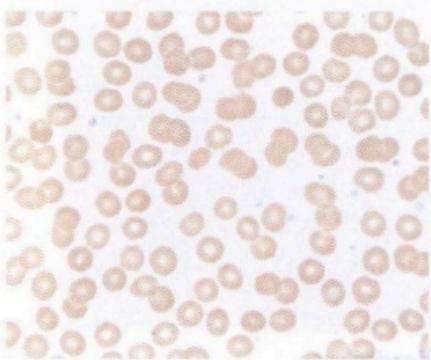
RIGHT CORONARY ARTERY



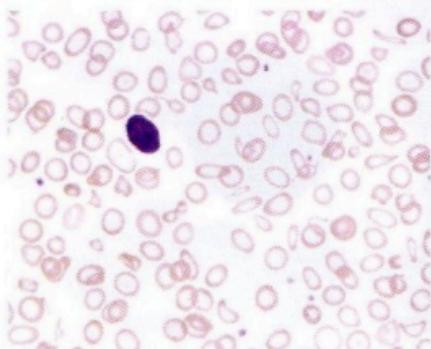
1. Conus artery
2. SA node artery
3. Acute marginal branches
4. Posterior descending artery (PDA)
5. AV node artery
6. Posterior left ventricular artery (PLV)

Coronary arteries. (From Grossman WG. *Cardiac Catheterization and Angiography*, 4th ed. Philadelphia: Lea & Febiger, 1991, with permission.)

Peripheral Blood Smears



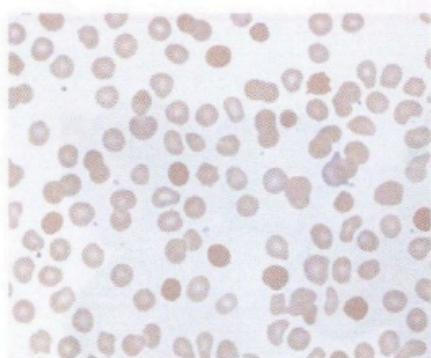
1 Normal smear.



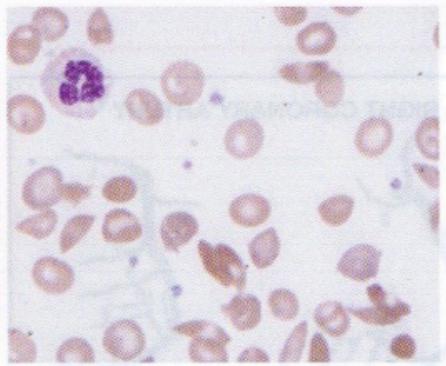
2 Hypochromic, microcytic anemia due to iron-deficiency.



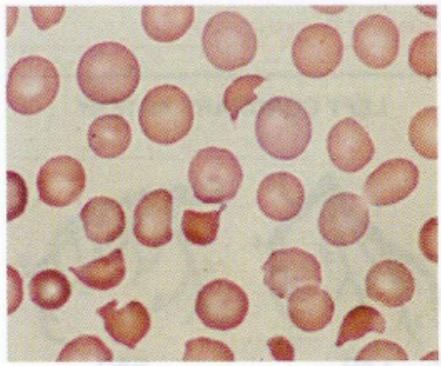
3 Macrocytic anemia due to pernicious anemia; note macro-ovalocytes and hypersegmented neutrophils.



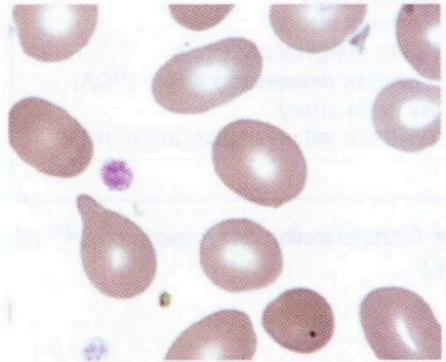
4 Spherocytes due to autoimmune hemolytic anemia.



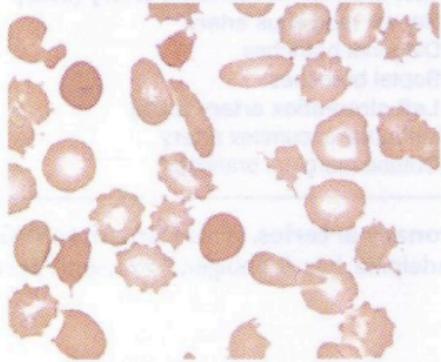
5 Sickle cell anemia.



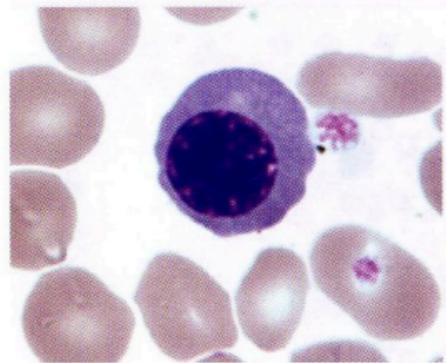
6 Schistocytes.



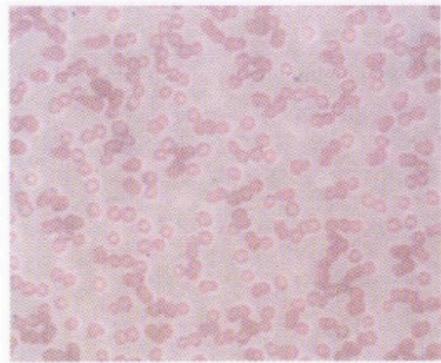
7 Teardrop shaped RBC (dacrocyte).



8 Acanthocytes.

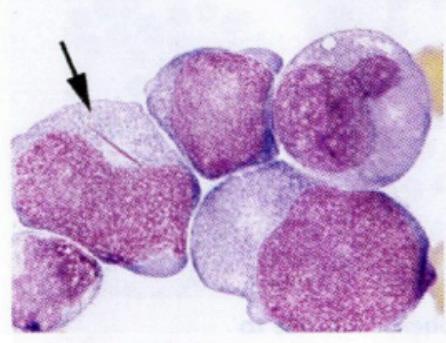


9 Nucleated RBC.

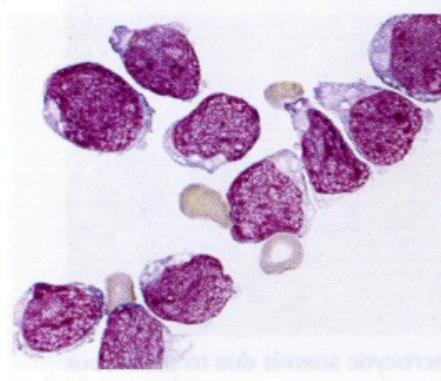


10 Rouleaux.

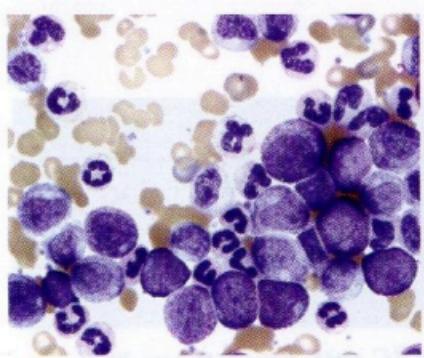
Leukemias



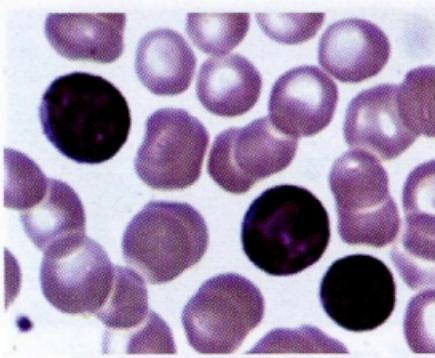
1 AML with Auer rod.



2 ALL.



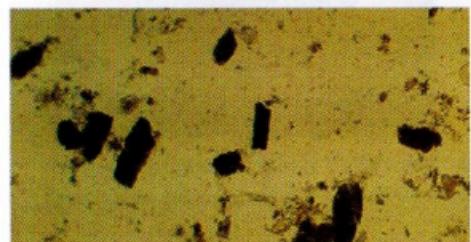
3 CML.



4 CLL.

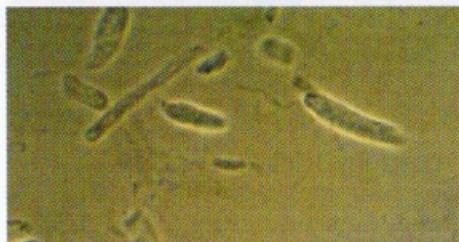
All photos excluding Leukemias Fig. 4: From Wintrobe's *Clin. Hematol.* 12th ed, 2009: Leukemias Fig. 4 From Devita, Hellman, and Rosenberg's *Cancer: Princip. & Prac. of Oncol.* 8th ed, 2008.

Urinalysis



1 "Muddy brown" or granular cast

(courtesy Nicholas Zwang, MD)



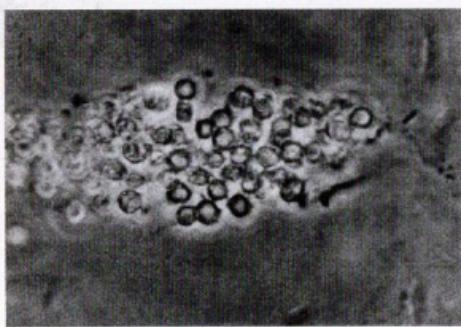
2 Hyaline cast (courtesy Nicholas Zwang, MD)



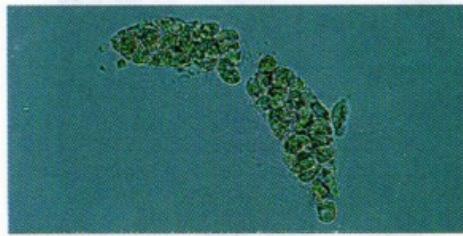
3 "Waxy broad" cast (courtesy Nicholas Zwang, MD)



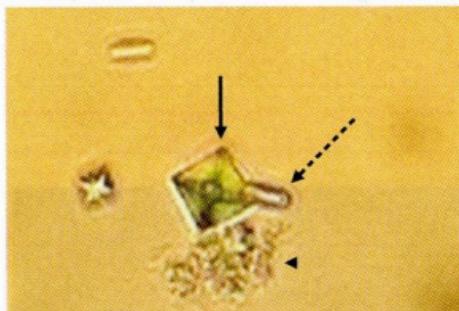
4 Renal tubular epithelial cell (courtesy Nicholas Zwang, MD)



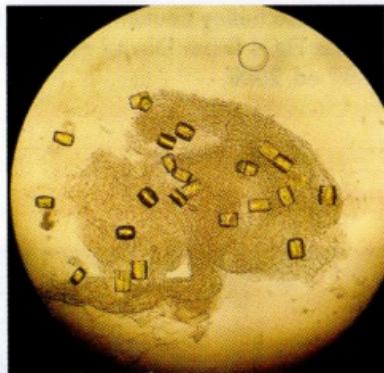
5 RBC cast. (*Dis. of Kidney & Urinary Tract*, 8th ed, 2006.)



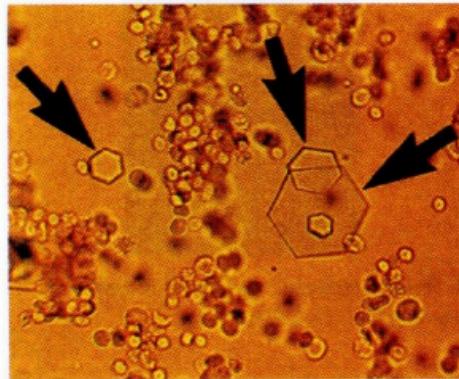
6 WBC cast. (*Clin. Lab. Medicine*, 2nd ed, 2002.)



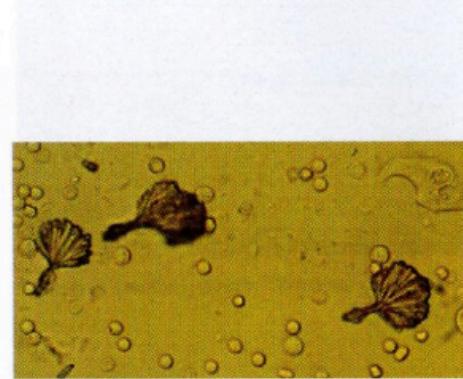
7 Calcium oxalate crystals (courtesy Mallika Mendum, MD). Calcium monohydrate (arrow), calcium dihydrate (dashed arrow), and amorphous calcium crystals (arrow-head)



8 "Struvite" magnesium ammonia phosphate crystals (courtesy Brett Carroll, MD)



9 Cystine crystals (*Clin. Lab. Medicine*, 1994.)



10 Sulfadiazine "shock of wheat" crystals (courtesy Nicholas Zwang, MD)