UCSD NEUROLOGY HOUSE STAFF HANDBOOK

3rd Edition, 2017-2018

Edited by Peter Ljubenkov, MD

Contributing Editors

UCSD Neurology Resident Physicians

Initial contributors:
Jaehoon Cho, MD
Walter Heine, MD, PhD
Austen Lefebvre, MD
David Jin Lee, MD, PhD
Peter Ljubenkov, MD
Karl Maki, MD
Konrad Schlick, MD
Amir Sabouri, MD, PhD
Ilana Spokoyny, MD
Michelle Van Noord, MD
Amanda Yu, DO, PhD

Revisions:
2016-17
Nathan Gaines, MD
2017-18
Nathan Gaines, MD, Jose Soria MD, Christine Tjandra MD, Michael Chen MD

UCSD Faculty

James Chen, MD
Fatta Nahab, MD
Leena Kansal, MD
Navaz Karanjia, MD
Chamindra Konersman, MD
Mark Kritchevsky, MD
Revere Kinkel, MD
Ross Mandeville, MD
Royya Modir, MD
David Piccioni, MD PhD
Michael S. Rafii, MD, PhD
Erik Viirre, MD, PhD

Disclaimer

Neurology is a rapidly evolving field. As research and clinical experience broaden our basic understanding of the nervous system, there are often new developments in diagnosis and treatment. The authors of this pocketbook have checked with sources believed to be reliable in their efforts to provide information that is complete and generally in accord with the standards accepted at the time of publication. However, in view of the possibility of human error or changes in practice guidelines, neither the authors nor the publisher nor any other party who has been involved in the preparation or publication of this work warrants that the information is in every respect accurate or complete, and they disclaim all responsibility for any errors or omissions or for the results obtained from use of this handbook. Residents are encouraged to confirm the information contained herein with other sources, including with supervising attendings. This handbook is meant to serve as a quick reference guide to help residents fully consider differential diagnosis, workup, and management of neurological illnesses.

TABLE OF CONTENTS

Paging & Page Forwarding Guide

Service Pager Numbers
Hillcrest 619-290-**2354**
Thornton 619-290-**2361**
VA 619-290-**7161**
NCCU 619-290-**6339**

Paging Directly From UCSD:

•Web paging: **webpaging.ucsd.edu**
•Numeric paging:
-call 137 + last 4 digits of pager
-Enter your call back number then press "#"

Paging From Outside UCSD:

•Test paging from cell: send text to 619-290-xxxx
•Web Paging: webpaging.ucsd.edu (AD\UCSD login)
(May need to access via internet explorer in cwp.ucsd.edu)
•Alpha Paging: -Dial 619-290-and the last four numbers.
-Enter your call back number then "#"

Paging from Rady's: click on the webpaging link from the intranet.
Paging Etiquette: Please include patient name, medical record number, room number, your name and contact information.

Pager Forwarding

•When covering the La Jolla hospitals you will forward the virtual call pager to you.
•At Hillcrest a physical call pager is handed off.

•How to Forward a Pager:

1. Dial the pager you wish to forward**:** 619-290-xxxx
2. At the prompt press 0.
3. Enter 1234 as the access code.
4. Press 1 then 6, then 6 again.
5. Enter the pager you are forwarding to as 290-xxxx and press "#".

Then reenter (number and # again)
The pager should now be forwarded, but always send a text page

•How to Cancel Forwarding on a Pager

1. Dial the pager you wish to stop forwarding:**:**619-290-xxxx
2. At the prompt press 0.
3. Enter 1234 as the access code.
4. Press 3.

The pager should no longer be forwarded

HINT: Make contacts in your cell phone for forwarding each of the La Jolla pagers, and to yourself. Use comas for each pause. You usually need 3 comas to synch with the initial prompt. This makes it much easier to transfer the pagers over at the start or finish of a busy call night.
Example to forward Thornton pager:
(619)290-2361,,,0 , 1234, 16, 6, 290-[your 4 digit pager]- #, 290-[your 4 digit pager]- #

Important Hillcrest Numbers

Calling from the outside: (619) 47**1**-####
(619) 54**3**-####

Stroke Code: x36111	Labs:
Brain Code Page: 2619 and 6339	Chem 36020
Neuro work room: 19670	Heme 32244
NCC phone: 650-798-4942	Micro 75766, 35940
	Serology 35797
Floors:	Cytology 35378
ED 32130 (front)	People and Places:
ED 31854 (back)	Pharmacy 35924
SICU(2) 37428	CM: see webpaging
5W 36080	Nutrition 33420
5E 33248	Transfer Center 13868
7W 19537	Angel (HC Clinic): 33259
7E 37505	Shivon (HC Clinic) 35443
733 19533	Spanish interpreter p3060
8W 36305	Anesthesia conscious sedation 36040
8E 36380	Anesthesia for intubation: p2622
MICU(9) 35962	Anesthesia scheduling 36363
10E 36300	Coumadin clinic 36303.
10E-Fax 619-543-7718	UCSD Main 619-543-6222
CCU(10W) 36592	Neurology Clinic 619-543-3500
11E 35280	Neurology Clinic fax: 619-543-6806
11W 36450	10 East work room 619-471-967x (x=0,1,2,3,4)
West Wing 36350	DELAY HOTLINE: 619-54-DELAY (33529)
Tests:	Angela Scoscia (Medical Director) x32699
Neuro CT read 32566	EPIC Help 77367.
Neuro MR read 32931, 32943	
MRI scan 37020, 37353	Codes/Combinations:
CT scan 36893	10E Neuro work room door: 351
Radiology to burn CD 32218	CCU (10W) 619*
EEG 35760	SICU 642*
Carotid US 32620	W Wing 7843
Echo 35715	BICU (5th) 543
Echo read 78183	SBH 6831
Contact re MRI for pts with pacemakers: cards EP	

NCC Contacts

- Navaz Karanjia: 650-906-9521
- Cynthia Gonzalez: 787-923-6287
- Brian Lemkuil: 909-534-7660; pager 619-290-9569
- AnushMinokadeh: 619-955-9109
- Jamie LaBuzetta: 949-285-5970
- Becky Dodd-Sullivan (NP): 619-322-8698
- **NCC cellphone**: 650-798-4942

Important Jacobs Numbers:
Calling from outside: (858) 657-####
(858) 249-####

Inter-facility communication:

UCSD to the VA: 15133-####
VA to UCSD: 68-#####

Stroke Code: x36111
Perlman/EXE clinic 78530
Thornton Operator 858-657-7000
ED 77660
Pharmacy 75891, 96181

Jacobs Floors:
2PACU 96225
3F 96340, 3G 96300, 3H 96330
4 96400
5H 96520, 5FG 96500
6 96600
8 95800
9F 95940, 9G 95910, 9H 95981
10 96155
Thornton Floors:
2W 76886, 2E 76295
3E 76340, 3W 76390
SC3A 78330, SC3B 78340
SC4A 78410, SC4B 78420

Labs:
Chem761595, Heme76164, Micro76959, Path76595
Flow cytometry 858-642-4774
Bone marrow read 858-822 6976

Antibiogram:
http://www.ucsdhealthcare.ucsd.edu/ic

Tests:
MRI tech 76674, 76671
CT tech 72296, 78129
Neuro read 72236, 96148
Heart Station 78909
Ultrasound 76663, 76662
Infusion Center 76301
IR72203
EEG 76080

Important VA Numbers (858) 552-8585	
Neuro workroom: 6124 **Floors:** ED 1570, 6141 Psych 2S: 9216 RN Stations: 3N: 3446, 3N-B: 7637, 3N-C: 7648 5E: 3295 DOU: 7979 ICU: 5400, 1985 VA Operator 858-552-8585 Call Room 3E: main ****, neuro 2282 **Lab**: 7707 **Tests:** Neuro MR read rm: 2850, after hours 619-543-7043. MR scanner 1663 or 7980 NeuroIR 6952 Rad 3226 Vasc Lab read MD 3289 Pharmacies: OP 1669, IP 2377, ICU/DOU 5344, ED 7866, Neuro pharm: 5991,p347-1910	People and Places: IT help 4767 EEG tech pager: 858-347-0344 Physical Therapy 7487, 3683 SW/Placement: 3N 7391, 5E 3329 Neuro clinic 3685 Anthony Harmon: (858) 642-3938 Medicine consult p7173 VA ICU resident: p9666 VA psych res p854 -230-2080 AOD 4344 Coumadin clinic: 1607 Door Codes/Combinations: ED: 6141 enter Call room 3E main (hold uncovered VA badge over panel) Neuro 3E call room: 2282 Psych door 9216 enter Neuro clinic doors 1284 Neuro EMG/Clean linens doo 3685 EEG: user: Neuro, password: neurology

Important Websites to Get You Started:

•**docs.google.com:** Ask your chief resident to invite you to have access to the necessary files. In the sheets section you will find

- **Neurology Resident Schedule [academic yr]**
- **Neurology Resident Call Schedule**

•groups.google.com: You will be invited to our google group. Once you accept, go to groups.google.com and under "My groups" you will see the "UCSD Neuro Residents" Group. Here you will find recent didactic PowerPoint slides, schedules, etc.

•calendar.google.com: go to googlec alendar and login. Under "Other Calendars", search "ucsdneurochief@gmail.com". It will add the calendar to your calendar list. Refer to this for list of didactics, etc. You may sync to mobile.

•Neurocriticalcare.ucsd.edu: This is Dr. Karanjia's site, an essential website that houses all official UCSD protocols and education materials for acute neurology care.

•Ishare.ucsd.edu: This is our file-sharing server where your daily patient sign out and monthly patient log can be accessed.
Click HC Neurology> "0 Hillcrest", "0 TH-VA service", and "0 stroke service"
Login: AD\UCSD username and password (same as your email/network access).
Adding a user and managing permissions (ask seniors to add you early on):

1. From the Settings tab select Document Library Settings
2. From Permissions and Management select Permissions for the Document Library
3. Select New to add a user. Enter their UCSD email address and select the level of permission allowed. Residents are the only ones with Full Control. Students are only allowed to have Contribute access.

Each resident has a folder. You can use this for storage and keep papers, reference files, etc. there if you want.

•Log Duty Hours and Procedures: https://www.new-innov.com/login.
Get log in info from Judy. Log your duty hours (weekly) and all procedures (LPs, botox injections, etc) you do ASAP. This documentation is needed for clinical procedure privileges at UCSD.

•5 Required Neurology Clinical Evaluations : (3 separate board certified neurologists)
Go to **ishare.ucsd.edu**> HC Neurology> 0.0 Residency Forms

>NEUROLOGY CLINICAL EVALUATION EXERCISE NEX v.2

Each resident must complete observed H&Ps in 5 categories to become board eligible. Be sure to get your pediatric, neuromuscular and NCC encounters on those rotations!!!

•**Registration for Board Exam:** http://www.abpn.com. Deadline February 16th of graduation year (late registration w/ $500 fee March 16th)

Remote Access (EPIC, CPRS) and VPN

• https://cwp.ucsd.edu
To access UCSD medical records (EPIC, UCSD & Impax) from home.
Your logon is your UCSD email/network username and password

•https://varcagwest.vpn.va.gov/vpn/index.html
Access to VA CPRS and Impax from home.
Email the ISO, currently Jesse.Christmas@va.govfor access.
Enter your VA username as: VHA22\VA username and your password.
Use MobilePASS if using mac or PIV card reader if PC.

•vpn.ucsd.edu: This allows access UCSD VPN services for library etc.
Your logon is your UCSD email/network username and password

Vacation

Sign out your inboxes while on vacation! Please ask a co resident nicely to cover for you while you are away. Then inform Shivon Carreno and Anthony Harmon so that they can inform the clinic staff of your time away.

To sign out the VA inbox: (notify staff as well)
Tools → Options → Notifications Tab →Surrogate Settings
To sign out the EPIC inbox:
In Basket → Out → New→ designate your covering resident

ACUTE ISCHEMIC STROKE

Edited by Peter Ljubenkov, MD Austin Lefevre, DO, and Royya Modir, MD

I. STROKE CODE

NOTE: Assessment is done as a pit stop protocol→ If patient stable, go straight to CT

NOTE: Always maintain communication with fellow/attending during code

1. Advance Directive: Determine if patient has an Advance Directive (ask patient & EMS (blue COAST form), look in EPIC for any ADs (DNR/ DNI/ POLST/ COAST)

2. Determine time of onset (last known normal), **Vitals** and **Fingerstick** in the field**.** Obtain brief and relevant history focusing on tPA exclusion criteria. Headache, seizures, LOC, nausea/vomiting raise concern for ICH.

3. NIHSS immediately while going to CT– detailed exam later (SEE APPENDIX)

4. CTH & likely CTA head/neck (Must discuss with stroke fellow)

-Order via **"CT Angiography Head and Neck -stroke code only"**

-Verify that Techs are doing non-Con CT and including "5 by 1" MIPs.

-If there is a large vessel occlusion and stroke team agrees, **call Endovascular Neurosurgery immediately**.

-Tell pharm. to mix tPA if likely tPA case & no ICH on CT.

→**Additional MRI/MRA Brain?:** optional at HC/TH, use in any case where MR will acutely change management.

-Do "**MR Safety**" DOCFLOWSHEET **before ordering MRI**

-Order via **"MRI Acute Stroke Code - Neurology Only"**

-Don't hold up tPA for MRI!

Radiology Guide in Acute Stroke:

Early signs of infarction on CT: (often negative if small or hyperacute)

• Look for blood on CT* (ICH, SDH, EDH)**

• Blurring of gray-white junction, particularly around insular ribbon and basal ganglia. Use stroke windowing (30/30) for better sensitivity

• Mild sulcal effacement

• Hyperdense vessel sign

• Subtle hypodensity

• Vessel cut-off on CTA

(Note: ask tech to process 5 by 1 MIPs on non-Con CT)

(see ASPECT Score)

MRI findings for ischemic stroke:

• DWI turns bright with ADC dark within 15 minutes (over 80% in 2 hrs)

• FLAIR hyperintensity in 6-12 hours or less

• May see vessel cutoff on MRA (overcalls occlusion)

• Check for any signs of bleed: bright early on FLAIR, quickly followed by dark blooming on GRE. Blooming artifact may also be thrombus.

• Check T1 Fat-sat neck if dissection is suspected.

(see radiology chapter for more discussion)

5. Initial labs/studies (initiated in ED-"Stroke code orders," on arrival but don't hold CT) CBC, INR/PT, PTT, CMP, Cardiac Markers (Troponin and CKMB), bHCG in females of childbearing potential, EKG, CXR, 2 Large bore IVs and weight or estimated weight

6. Determine if patient eligible for tPA and/or endovascular intervention
Stroke fellow and stroke attending will determine intervention.
Interventional neuro-radiology is made aware of all potential endovascular cases if LVO suspected or identified and stroke team agrees!

- **If time of onset is <3 or 3-4.5 hours** (special relative exclusion criteria): **potential IV tPA candidate**, and subsequent endovascular candidate
- **If time of onset > 6hours:** potential endovascular candidate Post-circ strokes consider intervention **up to 24 hours**

IV tPA EXCLUSION CRITERIA Per ACTIVASE Label:

- Current intracranial hemorrhage or subarachnoid hemorrhage
- Active internal bleeding
- Recent (within 3 months) intracranial or intraspinal surgery or serious head trauma
- Presence of intracranial conditions that may increase the risk of bleeding (e.g., some neoplasms, arteriovenous malformations, or aneurysms)
- Bleeding diathesis
- Current severe uncontrolled hypertension.

Additional Suggested AHA/ASA IV tPA Guidelines

Inclusion criteria

- Diagnosis of ischemic stroke causing measurable neurological deficit
- Onset of symptoms <3 hours before beginning treatment
- Aged ≥18 years

Exclusion criteria

- Significant head trauma or prior stroke in previous 3 months
- Symptoms suggest subarachnoid hemorrhage
- Arterial puncture at noncompressible site in previous 7 days
- History of previous intracranial hemorrhage
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Recent intracranial or intraspinal surgery
- Elevated blood pressure (systolic>185 mm Hg or diastolic >110 mm Hg)
- Active internal bleeding
- Acute bleeding diathesis, including but not limited to below
- Platelet count <100 000/mm³
- Heparin received within 48 hours, resulting in abnormally elevated aPTT greater than the upper limit of normal
- Current use of anticoagulant with INR >1.7 or PT >15 seconds
- Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)
- Blood glucose concentration <50 mg/dL (2.7 mmol/L)

CT demonstrates multilobar infarction (hypodensity cerebralhemisphere

Relative exclusion tPA criteria

Recent experience suggests that under some circumstances—with careful

consideration and weighting of risk to benefit—patients may receive fibrinolytic therapy despite 1 or more relative contraindications. Consider risk to benefit of IV rtPA administration carefully if any of these relative contraindications are present:
• Only minor or rapidly improving stroke symptoms (improving spontaneously)
• Pregnancy
• Seizure at onset with postictal residual neurological impairments
• Major surgery or serious trauma within previous 14 days
• Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
• Recent acute myocardial infarction (within previous 3 months)

Additional Relative Exclusion Criteria for 3-4.5 hour IV tPA Window

• Aged >80 years
• Severe stroke (NIHSS>25)
• Taking any oral anticoagulant regardless of INR
• History of **BOTH** diabetes and prior ischemic stroke

II. Initial Management of Acute Ischemic Stroke:

1. Blood Pressure Control:

• **IV tPA Eligible–target before tPA is <185/110, after is <180/105.** May use IV labetalol pushes (10-20 mg every 1-2 minutes), but get drip (nicardipine or enalapril) hung ASAP if active management needed

• **Not tPA Eligible:** permissive HTN **BP<220/120x24 hrs**
May use Labetalol, nicardipine, clevidipine or enalapril. (do not exceed 10-15% drop)

• **Hold home HTN meds after 48 hours of no worsening –** think before stopping CHF meds - may worsen hemodynamics. At times restart BB at half dose. (Note: There is a black box warning for stopping beta blockers in patients with ischemic heart disease, so you may consider continuation at a low dose)

2. IV Fluids:**NS Bolus (usual 1L) ASAP (unless contraindicated)** followed by continuous IV fluids. Use 0.9%NS NOT hypotonic solutions/dextrose

3. Bedside Swallow evaluation - MUST DOCUMENT BEFORE ANY PO INTAKE EVEN MEDS

4. **Start ASA/antiplatelet ASAP if no tPA, or 25 hours post tPA**
• **ASA 81 or 325mg** daily, start now (if not contraindicated)
• **Plavix 75mg:** "For patients with recent stroke or TIA (within 30 days) attributable to severe stenosis (70%-99%) of a major intracranial artery, the addition of clopidogrel 75 mg/d to aspirin for 90 days might be reasonable" (Class IIb; Level of Evidence B).
• **Aggrenox 200/25 BID:** not usually used
More efficacious than ASA alone but more expensive and often less compliance given headache and BID dosing.

III. Post Stroke Admission management

1. Additional Post stroke orders (most self populates in the order set)

- Neuro checks: Must use template in post tPA order set for post tPA patients, otherwise Q2 hours is max for IMU and Q4 hours for med/surg.
- Cardiac Monitoring
- Accuchecks QAC and QHS with ISS
- Cardiac Echo +bubble study
(TTE, if negative consider TEE if suspect cardioembolic).
- Vessel Imaging **(must include carotids prior to DC**): Carotid duplex, CTA Head/Neck, MRA Head/Neck, or Conventional Angiogram
- MRI Brain (+MRA if vessel imaging not done)

Additional Initial Management of Acute Ischemic Stroke

- Bedside swallow Eval (documented before first oral meds)
- PT/OT and Speech Therapy
- **Start statin if not already on statin and LDL over 100 or based on primary care guidelines**
- DVT prophylaxis, SCDs in all cases (tPA or otherwise). SQ Heparin in all cases not otherwise contraindicated (e.g. tPA)
- **Other Labs: Lipid panel (fasting), A1C**, CBC, BMP, coags, high sensitivity CRP, troponins, urinalysis, liver panel if not yet on statin.
- **Event monitor if suspecting occult Afib at D/C**

2. Admission Logistics:

- All UCSD stroke codes get a stroke note
-Smart text: **"STROKE RESUSCITATION NOTE 20151016"**
If stroke admission, cosigner is stroke attending.
If not stroke, staff with general chief/attending, cosigner is general attending.

- Acute Stroke **post-tPA** patients at UCSD
STAT HEAD CT WITH ANY NEURO CHANGES!
- **Hillcrest:** Discuss with NCCU team, usually transfer to Jacobs. Else MICU admission 24 hours with stroke consult
"IP NCC Neuro-ICU Orders for Acute Ischemic Stroke Post-TPA"
- **Jacobs/Thornton:** Direct NCCU admission for 24 hours
- **VA:** ICU under Pulmonary/CC at the VA

- Acute Stroke **non-tPA** patients:
- **UCSD:**
-Admit to tele/IMU or ICU using order sets:
"**IP NEU for Acute Ischemic Stroke (Non-ICU)"**
"IP NCC Neuro-ICU Orders for Acute Ischemic Stroke"
- **VA**

-Admit to Med-Telemetry or DOU
-If require ICU level care, admit to MICU with neuro consult

IV. Post Thrombolysis

A. Extension of ischemia: due to progressive thrombosis or failure of collaterals.
- •Consider endovascular recanalization
- •Collateral support (increase IVF, ?add pressors?)
- •Change in antithrombotics

B. Conversion to Hemorrhage: risk factors include older age, large infarct (>5 cm), severe hypertension, coagulopathy
- • STOP tPA infusion immediately or anticoagulation
- • Check CBC, INR, PTT, fibrinogen and consider cryoprecipitate and/or FFP + single donor platelets if needed
- • Refer to ICH Algorithm (See ICH Chapter)
- • Discuss with NCCU and/or Stroke team immediately

C. Edema: risk factor is large infarct, peaks at 3-5 days
- • Head CT to assess for edema, midline shift
- • HOB 30º & transfer to NCC for hyperosmotics
- • Consult neurosurgery for hemicraniectomy if indicated.

VI. Documentation Logistics: Document the applicable parts in your admit note and discharge summary at UCSD. Most of addressed in **Stroke Combined Doc Flowsheets**
•**"Stroke Combined Doc Flowsheet"**: Must be filled out for all Stroke codes at UCSD

•**TJC Portion of "Stroke Combined" DOCFlowsheet** must be included in all discharge summaries for patients admitted with stroke

•Use Stroke Discharge Note template at UCSD and document the following TJC measures at discharge via pulling in ".DFTJNEURO"
- NIHSS Score
- Bedside swallow examination
- tPA administration or not and why
- Fasting Lipid Profile
- A1C
- Vessel Imaging (at least of the carotids): CTA, MRA, Carotid Duplex or conventional angiogram
- Neuroimaging
- Rehabilitation Services (PT/OT/ST). If not ordered, explain why.
- Antiplatelet therapy initiated. If not ordered, explain why.
- Statin initiated. If not ordered, explain why.
- Smoking cessation counseling if indicated
- Stroke education

(**NOTE:** you can populate TJC info into to any note using .DFTJCNEURO smart phrase)

COMPREHENSIVE STROKE CERTIFICATION REQUIREMENTS
• Do this for every SAH, ICH, and ischemic stroke patient.
•Patient education in combined DOCFlowsheet **•COAST Advance Directive: Provide each stroke or TIA patient with a COAST AD form and instruct them to discuss with their stroke practitioner in clinic** **•Pink runsheets**: done by RN **•Post-tpa frequent vitals and neurochecks** must be done on every post-tPA patient.

•**Post-angio frequent vitals and neurovascular** checks most be done on every post-angio patient. When you have a pt post angio, use the "IP INT admission following neuro angiogram" or "IP INT Post-Procedure transfer neuro angiogram," or check off in any of the NCC ordersets the "Initial frequent monitoring orders for patients post-angiogram."

IV. Specialized Workups

A. Consideration for Cervical Carotid Artery Dissection:
• **Query trauma history / chiropractic manipulation**
• **Alpha-1 antitrypsin** (low level may indicate connective tissue disorder)
• FMD, connective tissue (Marfans, EDS), chiropractic manipulation, neck trauma

B. Suspected Occult Afib
Order Event Monitor at DC

C. Young patients (<55) get ANA & ESR and order the following

Hypercoagulable Workup:

- PT/INR, PTT (If abnormal do 1:1 mixing study)
- Fibrinogen
- Factor V Leiden Mutation analysis
- Activated Protein C Resistance (Factor V Leiden if abnormal)
- Protein C and S levels
- Factor VIII Level
- Antiphospholipid
  - -screen: dilute Russel viper venom (DRVVT)
  - -specific Ab: Anticardiolipin Ab, Beta2 Glycoprotein1 Ab
- Homocysteine
- Prothrombin gene mutation analysis (aka G20210A or factor 2 gene mutation)
- Antithrombin III
- MTHFR genetic analysis (especially if hx of spont. abortion/miscarriage)
- Alpha-galactosidase activity assay
  – if suspicious of metabolic disorder in adult causing stroke

Note: Studies that involve levels or function of factors in the clotting cascade will be abnormal/unreliable in acute period post thrombus. **Only Factor V Leiden, Prothrombin, MTHFR, antithrombin III gene tests will be accurate in acute phase**. Typically leave rest of workup for post-hospital follow up.

B. CNS Vasculitis workup:

•**MRI w/wo contrast and MRA**

•**Serum Labs:** (CBC, BMP, LFTs)
ESR/CRP
ANA, RF, P-ANCA, C-ANCA, C3, C4
SSA (anti-Ro), SSB (anti-La), and anti-RNP immune complex labs, quantitative immunoglobulin levels (IgG, IgM, IgA)
HIV, RPR
HSV 1 & 2 serologies
Hepatitis B and C panel
Cryoglobulins/ cryocrit
SPEP/UPEP

•**CSF Studies:** abnormal in 80-90% of cases, in contrast to RCVS
Cell count, protein, glucose
VDRL, HSV PCR, VZV PCR and IgG/IgM

•**Additional infectious labs to consider**
Bartonella, Mycobacterium, Cysticercosis, Treponema pallidum and Borrelia burgdorferi serology

•**Formal Angiogram/DCA:** classically "beading," usually in the small arteries, and usually several sites. (Note: Angiogram may look similar to RCVS/ Call-Fleming syndrome.)

•**Brain biopsy:** gold standard for diagnosis. This should be considered when suspicion remains high hand other studies are misleading or unclear.

V. Anticoagulation and Stroke

A. Heparin drip: Use this protocol for all inpatients with stroke who need heparin drip, whether the heparin is for stroke or something else (e.g., DVT, LV thrombus).

- **"IP Gen Therapeutic anticoagulation (access via order set)**
  - →"High Bleeding Risk Heparin Infusion (Goal PTT 55-85)"
  - →**"Acute stroke with any indication for anticoagulation"**
- When to bolus? (almost never, and with recs. by stroke attending/fellow)
  - Patients with stroke progression felt possibly due to clot propagation
  - Suspected unstable basilar artery severe stenosis/occlusion

B. LMW Heparin Dosing Protocol for Stroke Neurology

- DVT Prophylaxis Dose: Lovenox 30mg SQ BID or 40 mg SQ daily
- Stroke Prevention Dose: Lovenox 1mg/kg SQ BID

or Dalteparin 100-120 U/kg BID

C. Long Term Oral Anticoagulation

Risk Stratification of Non-Valvular A. fib				
Definition and Scores for $CHADS_2$ & CHA_2DS_2-VASc			**Stroke Risk Stratification with $CHADS_2$ &CHA_2DS_2-VASc**	
$CHADS_2$	**Score**		**$CHADS_2$**	**Unadjusted ischemic stroke rate (% per year)***
Congestive HF	1		0	0.6%
Hypertension	1		1	3.0%
Age ≥75 years	1		2	4.2%
Diabetes mellitus	1		3	7.1%
Stroke/TIA/TE	2		4	11.1%
Maximum score	6		5	12.5%
			6	13.0%
CHA_2DS_2-VASc	**Score**		**CHA_2DS_2-VASc**	**Score**
Congestive HF	1		0	0.2%
Hypertension	1		1	0.6%
Age ≥75 years	2		2	2.2%
Diabetes mellitus	1		3	3.2%
Stroke/TIA/TE	2		4	4.8%
Vascular disease (prior MI, PAD, or aortic plaque)	1		5	7.2%
Age 65 to 74 years	1		6	9.7%
Sex category (female)	1		7	11.2%
Maximum score	9		8	10.8%
			9	12.2%

Prescribing Warfarin/Anticoagulation For A.fib	
CHA_2DS_2-VASc score	**Recommendation**
0	ASA only
1	ASA or Anticoagulation
2 or more	Anticoagulation recommended

HOW DO OTHER ORAL ANTICOAGULANTS COMPARED TO WARFARIN?

Chart Courtesy of Dr. Konrad Schlick

This chart does not compare these medications to each other, it compares each drug to warfarin

	Dabigatran 150mg BID	Rivaroxaban	Apixiban
	% in drug group vs % in warfarin group per year		
All Stroke	1.53% vs 1.69%	2.1% vs 2.4%	1.27% 1.60%
Ischemic stroke	0.92 % vs 1.20%	1.34% vs 1.42%	0.97% vs 1.05%
ICH	0.20% vs 0.74%/yr	0.5% vs 0.7%/yr	0.33% vs 0.80%
Major GI Bleed	1.50% vs 1.02%/yr	3.2 vs 2.2%	0.76% vs 0.86%
Death	3.64% vs 4.13%/yr	4.5% vs 4.9%/yr	3.52% vs 3.94%

VI. Additional Score Calculators

ABCD2 Score

Risk assessment tool for stroke risk after TIA: designed to predict 2-day stroke risk, but also predicts 90 day stroke/cardiovascular outcomes. AHA recommends admission on of all TIA with an ABCD2 of at least 3, though most TIA's are admitted.

- **A**GE >60yrs (1 point)
- **B**LOOD PRESSURE (acutely) SBP>140 ***OR*** DBP>90 (1 point)
- **C**LINICAL:
  - Unilateral weakness +/- speech impairment (2 points), ***OR***
  - Speech impairment without unilateral weakness (1 point)
- **D**URATION of TIA:
  - >60min (2 points)
  - 10-59min (1 point)
- **D**M (1 point)

Total score 0-7 points

ABCD2 Score	Corresponding 2-day Stroke Risk
0-3	1%
4-5	4.1%
6-7	8.1%

ASPECT Score (Alberta Stroke Program Early Score)	
10-point quantitative score. Subtract 1 for each of the following	
-1	Caudate
-1	Putamen
-1	Internal Capsule
-1	Insular Cortex
-1	M1: anterior MCA cortex," corresponding to frontal operculum
-1	M2: MCA cortex lateral to insular ribbon" corresponding to anterior temporal lobe
-1	M3: posterior MCA cortex" corresponding to posterior temporal lobe
-1	M4: "anterior MCA territory immediately superior to M1"
-1	M5: lateral MCA territory immediately superior to M2
-1	M6: posterior MCA territory immediately superior to M3
Interpretation: •An ASPECTS score less than or equal to 7 predicts worse functional outcome at 3 months as well as symptomatic hemorrhage •ASPECTS score < 8 treated with thrombolysis did not have a good clinical outcome	

UCSD ICH EMERGENCY MANAGEMENT GUIDELINE

Adapted by from UCSD 6.20.14 ICH guidelines

	Follow the algorithm and contact NCCU immediately…
0 min	For suspected ICH (focal deficit with headache or deteriorating mental status): * Call stroke code, order stroke code CT and take labetalol/ hydralazine/ nicardipine to CT. *If rapidly deteriorating or comatose, page brain code (2619)& neurosurgery & anesthesia
0-10 min	**1. Airway:** Intubate IF GCS deteriorating or <8**. TELL WHOMEVER IS INTUBATING THAT SBP MUST STAY<150 DURING INTUBATION OTHERWISE PT MAY REBLEED.** Start propofol drip @ 20mcg/kg/h for sedation, if needed. **2. Normoventliate** (RR 14-18), place ETC02 monitor, target EtC02 30-35/PaCO2 35-40 **3. Position:** HOB@30°, neck straight; if herniating start UCSD Brain Code protocol, do not lay flat **4. Obtain stroke code CT.** DO NOT CANCEL CTA (it is needed if pt is getting emergent crani) **5. ONCE ICH SEEN ON CT, IMMEDIATELY LOWER BP IN CT SCANNER TO SBP <160.** **1st BP lowering agent should be given WITHIN 10 MIN of blood seen on CT, goal BP must be reached within 1 hr.** Start nicardipine drip 5-15 mg/h, use labetalol 10mg q15 min PRN or hydralazine 10mg q15 min PRN if nicardipine not available). **6. Emergent coagulopathy reversal: target INR </= 1.4 and platelets >100K within 1 HR, 1st dose WITHIN 30 MIN.** (See UCSD Reversal Protocol for ICH) 7. **Emergent ICP management**: IF HERNIATING CALL BRAIN CODE (see brain code guideline). If somnolent but not herniating, give 2% 250cc IV bolus (central line wide open/good PIV over 15 min) or mannitol 20% 1g/kg IVP (periph IV by RN) 8. **Neurosurgical management:** Request ICP monitor/EVD for GCS deteriorating or <8, IVH with hydrocephalus Consider immediate craniotomy for cerebellar hemorrhage w/ 4th ventricle effacement, lobar ICH <1 cm from surface with mass effect, or any ICH causing herniation or refractory ICP **9. CPP rx / contrast ppx:** Start NS 1L bolus and 100cc/h thereafter. Do not start pressors without consulting attending.
10 + min	Admit to NCC- order set "IP NCC Neuro-ICU orders for non-traumatic ICH If post coagulopathy reversal, continue labs q6h per UCSD Reversal Protocol for ICH Obtain another CT head non-con 6h after initial CT to ensure

	stability If intubated, turn down FiO2 immediately to 40% to target normal oxygenation (Pa02<150) If symptomatic hydrocephalus from IVH, consider intraventricular tPA

ICH score		
		Points given
Glasgow Coma Scale	score 13 to 15 score 5 to 12 score 3 to 4	**0** 1 2
ICH volume	<30 cm3 ≥30 cm3	**0** **1**
Intraventricular extension	Absent Present	**0** **1**
Infratentorial origin	No Yes	**0** **1**
Age	<80 years ≥80 years	**0** **1**
Calculation of Mortality based on ICH score		
ICH Score	Thirty-day mortality	
0	0%	
1	13%	
2	26%	
3	72%	
4	97%	
5	100%	
6	[100% -no study data]	

UCSD Reversal Protocol for Spontaneous Intracerebral Hemorrhage on Dabigatran, Rivaroxaban, or Apixaban

Adapted by from UCSD Guidelines by Navaz Karanjia, MD

•STAT labs: PT/INR, fibrinogen, platelets, CBC, PTT, TT, anti-Xa level, Type & Screen, troponin
•If crash craniotomy considered, type and cross 2U PRBC

↓↓↓ ↓↓↓

IF ON DABIGATRAN (direct thrombin inhibitor) and TT or PTT prolonged **Reversal agent: Idarucizumab**	**IF ON RIVAROXABAN or APIXABAN (factor Xa inhibitor) and PT/INR is prolonged or anti-Xa level elevated**

↓↓↓ ↓↓↓

•If ingestion within 2 hrs, give one dose activated charcoal orally
•Infuse 25 units/kg (+/- 10%) body weight* PCC (KCentra) over 5 minutes (Contraindications to Kcentra: thrombotic event within 6 wks (DVT, PE, trauma, ischemic stroke, ACS, mesenteric ischemia, etc); or HIT (can use Profilnine+FFP if HIT)
•Administer Vitamin K 10U PO or IV

↓↓↓

Stat labs at 15 min and q6 hours after completion of PCC infusion: PT/INR, TT, EKG, cardiac enzymes, fibrinogen, anti-Xa level. If TT or PT/INR is still prolonged AND patient still bleeding/extreme risk of hematoma expansion, consider repeating Kcentra or giving Factor 7, 20-40mcg/kg (1-3 mg) IV x1 & FIBA.

Dabigatran IS DIALYZABLE and reversible with idarucizumab: Emergent dialysis may be considered in certain circumstances (renal failure, overdose); ~ 65% removed by hemodialysis Dabigatran t ½ = 14 hrs (up to 34 hrs in severe renal impairment)	Rivaroxaban and Apixaban ARE NOT DIALYZABLE Rivaroxaban t 1/2 = 9 hrs (longer in renal impairment) Apixaban t ½ = 12 hrs (longer in renal impairment)

In obese patients, base dose on a maximum weight of ideal body weight + 20% ***

UCSD Reversal Protocol for Spontaneous Intracerebral Hemorrhage with INR > 1.4

Adapted by from UCSD Guidelines by Navaz Karanjia, MD

- STAT Labs: PT/INR, PTT, fibrinogen, platelets, CBC, Type and Screen, troponin
- If crash craniotomy considered, type and cross 2U PRBC

↓↓↓

•Give vitamin K 10mg PO (preferred) / IV stat and q24h thereafter for total of 3 doses

↓↓↓

INR 1.4 – 2.0	**INR > 2.0**
↓↓↓	↓↓↓
Can pt tolerate FFP (volume status)?	**Contraindication to Kcentra? (Major surgery or Thrombotic event within 6 wks** (DVT, PE, trauma, ischemic stroke, ACS, mesenteric ischemia, etc)**; or HIT (can use Profilnine+FFP if HIT)**
Yes ↓↓↓	No ⤫ Yes ↓↓↓ No contraindication
FFP PATHWAY **•Immediately give 2 units FFP** **•Repeat coags upon completion of infusion** **•If INR still >1.4, 2 more units FFP** **•If still >1.4, consider PCC and consult hematology**	**Kcentra(PCC) Pathway** **•INR 2 - <4: infuse 25 units/kg* Kcentra over 5 min, not to exceed 2ml/min, max dose 2500 U** **•INR 4-6: infuse 35 units/kg* Kcentra over 10 min, not to exceed 2ml/min, max dose 3500 U** **•INR >6: infuse 50 units/kg Kcentra over 15 min, not to exceed 2 ml/min, max dose 5000 U** **•Repeat INR 15 min post infusion. If INR not at target, repeat q15 min x2 until INR at target.** **•If INR not at target in 45 min, consider Factor 7,** 20-40 mcg/kg (1-3mg) IV x 1
↓↓↓	↓↓↓

Check PT/INR, PTT, EKG and cardiac enzymes, and fibrinogen q6 hrs after completion of PCC infusion. If INR>1.4, give vitamin K 10mg, consider FFP

In obese patients, base dose on a maximum weight of ideal body weight + 20% ***

UCSD GUIDELINES FOR MANAGEMENT OF ANEURYSMAL SUBARACHNOID HEMORRHAGE

Navaz Karanjia, Alex Khalessi, Andrew Nguyen, Bob Carter, Thomas Hemmen, 8.5.12

Grading Subarachnoid Hemorrhage		
Hunt and Hess Scale		
	Clinical Picture	Percent Survival
1	Asymptomatic or minimal headache and slight neck stiffness	70%
2	Moderate to severe headache; neck stiffness; no neurologic deficit except cranial nerve palsy	60%
3	Drowsy; minimal neurologic deficit	50%
4	Stuporous; moderate to severe hemiparesis; possibly early decerebrate rigidity and vegetative disturbances	20%
5	Comatose, showing signs of severe neurological impairment	10%
Fisher Grade		
I	Not Evident	~ 10% will spasm
II	Under 1mm thick	
III	Over 1mm thick	~ 30% will spasm
IV	Diffuse, or IVH, or parenchymal extension	

A. Initial SAH Management

1. Immediate Assessment

a. ***Airway:*** —Prophylactic Intubation for initial diagnostic angiogram not recommended. Intubation recommended for any of these: -GCS < 8
-Deteriorating GCS
-Hunt & Hess 4 & 5

b. ***ICP/hydrocephalus assessment***.
Consider ICP monitor/EVD for any of these:
-GCS <8
-Deteriorating GCS
-IVH with casted 3rd or 4th ventricle
-Symptomatic hydrocephalus

c. ***Intraparenchymal clot removal assessment***. Consider surgical intraparenchymal clot evacuation for patients with superficial hematomas, or clots causing mass effect.

d. ***Emergent BP reduction***
-**target SBP<140** with nicardipine drip if no increased ICP
-**target SBP<160** and **CPP>60** with nicardipine drip if increased ICP

e. ***Emergent Coagulopathy Reversal***

-Immediately reverse coagulopathy to INR </= 1.3

- INR 1.3-2.0, give FFP 2-4 u and vitamin K 10mg PO/IV
- INR>2, give PCC 25u/kg, FFP 2u, and vitamin K 10mg PO/IV
- INR>4, give PCC 40u/kg, FFP 2u, and vitamin K 10mg PO/IV
- Consider Factor VIIa (20-80 mcg/kg) in coumadin-associated coagulopathy ONLY if PCC is unavailable, INR>1.3, and emergent surgical procedure is planned

-Immediately correct platelets w/ transfusion if:

i. patient is on antiplatelet therapy WITH positive platelet inhibition test

ii. platelets<100,000

f. ***Management of mildly elevated ICP <20***

i. optimize analgesia/sedation, ensure normocarbia

ii. 3% saline 250cc bolus intermittently, with continuous 3% infusion 25- 150cc/h; check Na q4-6h to target Na goal 5 points over baseline, (usual starting target 145-155)

iii. mannitol 1gm/kg bolus, may repeat as needed q6h. Check osms and serum osmolal gap q6; stop if osms>340 or osmolal gap >55 mosm/kg

g. ***Management of clinical herniation or ICP emergency*** *(>20 x 3 min):*

-Initiate UCSD Neurocritical Care Brain Code protocol.

h. ***Vascular Access***

-**Arterial line** if labile BP requiring gtt.

-**Central line** subclavian line UNLESS patient has increased ICP; then use femoral line. NO IJs

i. *Volume status*

-Rehydrate w/ NS or hypertonic saline to euvolemia

-Place noninvasive cardiac output monitor

2. Admission orders

a. **Admit to: NCCU**. First Call: **Neurosurgery AND Neurocritical Care**. Immediately notify both neurosurgery and neurocritical care attendings of patient.

b. Diagnosis: subarachnoid hemorrhage

c. Condition: Fair or Critical

d. Vitals goals:

-**MAP > 65 and SBP < 140**
when **no concern** for elevated ICP

-**MAP goal >70 and SBP <160** when **concerned** for elevated ICP w/ NO EVD/ICP monitor.

-If patient has EVD/ICP monitor,
ICP goal<20; CPP goal>60

-HR, RR, 02 sat as per routine goals

e. Ventilator orders:

-**AC/CMV TV 500, PEEP 5, Fi02 40%, RR 12-16** to target

normocarbia—do NOT hyperventilate.
-ETC02 monitoring, goal 30-40
(correlate with ABG to target PaC02 35-45)
f. Activity order: Strict bedrest. Aneurysm precautions.
g. Nursing:

-Neurochecks q1h; notify MD for ANY change on exam.
-HOB 30 degrees, head midline, excessive pressure from ETT tape, suction only as needed using short acting sedative prior to suctioning.
-**Normothermia protocol (temp <38.0)**
-Foley, strict I/O
-SCD and TED
-**Vitals q1h INCLUDING TEMP and CVP q4h**
-NGT in select patients (well-sedated, not going to cough)

h. Diet: NPO
i. IV fluids: **NS at 1.5 ml/kg/h**
DO NOT give 1/2NS or fluids containing dextrose.
-Notify HO if UOP >250cc/h for >4h
j. IV Drips:

- Nicardipine drip 5-15 mg/h PRN use of IVP antihypertensive >1 time
- Fentanyl drip 25-150 mcg/hr, titrate to pain score 0 and RASS 0
- Propofol drip 20-60 mcg/kg/min PRN agitation, titrate to RASS 0
- Dexmedetomidine 0.2-1.4 mcg/kg/h PRN agitation, titrate to RASS 0
-Vasopressors: initiate ONLY if profoundly hypotensive and resistant to fluids (risk of rerupture). Norepinephrine > phenylephrine > dopamine as vasopressor of choice. If myocardial stun, consider dobutamine

k. Medications:
- **Levetiracetam** 1000mg IV q12h first dose now
- **Nimodipine** 60mg PO/NG q4h (if hypotensive, 30mg q2h)
- **PPI/H2 blocker**
- **Appropriate home meds**
- **Mucomyst** 600mg PO BID x 2 days if renal insuf.
- **Ondansetron** 8mg IV q8h PRN nausea/vomiting
- **Tylenol** 650mg PO/NG/PR PRN fever/pain
- **Fentanyl** 12.5-25mg IV q1h PRN pain (after Tylenol)
- **Labetalol** 5-10mg IV q30min PRN SBP>140
- **Hydralazine** 5-20mg IV q30min PRN SBP>140 if labetalol does not work or is contraindicated (bradycardia, heart block).
- **Electrolyte replacements**: Mg, K, Ca, Phos
- **Insulin sliding scale**, goal FSBG 140-180
- **NO SC Heparin until 24hrs from aneurysm securement**

l. Labs/studies:
-Admission CBC, CMP, PT/INR/PTT, cardiac enzymes q8hx3, UTox. EKG, CXR, TTE, CTH noncon if pt has not already had one. Conventional angiogram or CTA within 24h.
-Ongoing: Na/K q8h in H&H 4-5, q12h in H&H 1-3 (may increase to q4 if evidence of salt wasting/SIADH). CBC, BMP, INR QDay. CXR daily.
m. Code Status: document code status, medical decision maker

B. Ongoing management

1. *Workup*
- a. Conventional angio/CTA for aneurysm
- b. Repeat CTA/conventional angio in 1-2 weeks if angio negative and high suspicion for aneurysm.
- c. Consider other studies as appropriate if angio negative (MRI brain/C-spine, etc)

2. *Aneurysm repair* (surgical clipping/endovascular coiling)

3. *Mechanical ventilation*: see above.

4. *EVD management*:
- a. routine CSF surveillance sampling not indicated unless concern for ongoing CNS infection/ meningitis (fevers, neurological deterioration)
- b. strongly consider aggressive CSF diversion after aneurysm securement unless contraindicated

5. *Indications for noninvasive cardiac output monitor or Swan-Ganz monitoring* (noninvasive preferred): [Goals = CI>4.5 in patients with healthy cardiac status, >3 in patients with myocardial stun or CHF]:
- a. Any evidence of hemodynamic instability, myocardial dysfunction, or renal dysfunction caused by suspected ischemia
- b. Failure of volume/HTN therapy for vasospasm necessitating inotrope trial.
- c. Vasospasm in setting of significantly stunned myocardium (SM).
- d. Vasospasm in setting of patient with history of mod to severe CHF (EF </= 40%)

6. *Vitals goals*: relax SBP goal to <180 after aneurysm is secured and postop state allows; otherwise see above.

7. *Antiepileptics*: continue until aneurysm secured (levetiracetam preferred). After aneurysm secured, d/c antiepileptic UNLESS high risk for seizure. Seizure risk factors: post-craniotomy, associated SDH or cortical ICH, unclear etiology of SAH (possible traumatic), H&H grade 4-5, clinical/EEG evidence of sz.

8. *Nimodipine*: continue 60 mg po q4h x 21 days; alter regimen

to 30 po q2h if SBP<140 or neurological instability due to lowered BP, hold if SBP<120 or instability due to lower BP

9. *DVT prophylaxis*: 24h AFTER aneurysm is secure, initiate Heparin SQ 5000 q8h or Lovenox 40 qd; in patients <60kg heparin 5000 q12h. Hold 12h prior to and 24h after EVD insertion/removal, shunt, craniotomy, or any other surgical procedure. Check anti Xa level to ensure therapeutic.

10. *I/O goal when NOT in vasospasm*: target 0 to +500 ml/day by strict I/O with IVF (NS or hypertonic saline), always running at least 1.5 cc/kg. Goals:

a. CVP 5-8mmHg

b. PiCCO stroke volume variation (SVV) <10% or global end diastolic index (GEDI) >700 mL/m2

c. PA catheter wedge pressure 8-12mmHg, CI>3

11. *Lab goals when NOT in vasospasm*:

a. Hemoglobin: Hgb> 9-10 suggested especially in H&H grade 4-5 SAH. In lower grade SAH or patients presumed to be out of the time window for vasospasm, assess risk of transfusion vs benefit.

b. Na: NormoNa unless high ICP/mass effect

c. Mg: Goal higher end of normal 2-2.5 mg/dL.

d. Phenytoin: If phenytoin used, check daily total (goal 10-20) and free levels (goal 1.0-2.0).

e. INR: </= 1.3

f. Platelets: >100,000 prior to aneurysm securement/surgery; >50,000 thereafter

g. Glycemic control: maintain glucose 140-180 mg/dL w/ sliding scale insulin. insulin drip if glc > 200 mg/dL for two consecutive checks.

12. *Temperature control*: AGGRESSIVELY maintain normothermia (core temp <38.0) using Tylenol, cooling blankets, ice packs. Control shivering per normothermia protocol. If failure to achieve temp goal within 2 hrs initiate Arctic Sun protocol

13. *Multimodality monitoring*

a. TCD: Daily TCD surveillance for vasospasm from admission to day 14

b. Continuous EEG

i. in H&H grade 4-5 and patients with neurologic deterioration not otherwise explained, strongly consider 24-48h continuous EEG monitoring to rule out nonconvulsive status epilepticus.

14. *Physical therapy*: mobilize pt as soon as possible

15. *Occupational therapy*: splinting/orthotics

16. *Speech therapy*: dysphagia screening, using the Bedside Swallow Screen, to be completed prior to anything by mouth. Obtain ST consult for formal swallow evaluation as needed.

17. *Nutrition*: obtain nutrition consult

18. ***Tracheostomy*****:** early, if indicated
19. ***PEG*****:** consult as needed
20. ***Dispo*****:** social work consult for family/dispo
21. ***Stroke education*****:** prior to discharge.

C. Vasospasm management: for clinical (decreased mental status or focal deficit), angiographic, CTA/P, or TCD (MCA velocity > 120 / BA>80 with LI > 3; OR MCA velocity> 150 or BA > 100 irrespective of LI) evidence of vasospasm

1. If TCD/angiographic/CTA/P evidence of vasospasm with NO clinical symptoms (in patients whose neurologic exam is reliable and normal), ensure euvolemia has been achieved (I/O even to +500 mL, CVP: 5-8 mmHg, Swan Ganz PCWP 8-12mmHg, CI > 3). Do NOT prophylactically over-volume resuscitate or hypertensive.

2. If TCD/angiographic/CTA/P evidence of vasospasm with/without symptoms, transfuse to Hgb> 10.

3. If clinical symptoms of vasospasm, consider immediate angiography and start trial of NS/hypertonic crystalloid boluses with monitoring of neurological response (avoid if pt has CHF). Consider albumin if concern for extravascular volume overload. If volume status and neurological exam respond, maintain hemodynamic/volume goals correlated with improvement. May increase volume status up to CVP goal 8-12 mmHg, PCWP 12-16 mmHg; stop at lowest volume status that improves exam.

4. If clinical symptoms of vasospasm with no response to volume resuscitation, avoid further volume over-resuscitation, and move to hypertensive therapy. Consider immediate angio.

5. Hypertensive therapy:

a. First ensure baseline MAP and CPP goals have been achieved (MAP > 65 and CPP > 60). baseline EKG/trop

b. If TTE demonstrates normal systolic function, escalate MAP goal by 10mmHg every 30 minutes with goal titrated to reversal of neurological deficits, to max of 220/110. Phenylephrine >levophed> dopamine as vasopressor of choice for MAP goals.

c. In setting of myocardial stun, consider using dobutamine before using pressors mentioned above, and titrate to cardiac index >3 (CO/CI monitoring must be in place).

d. Check EKG and TnI daily, more frequently if patient at risk for cardiac event.

6. If clinical symptoms of vasospasm persist with no response to volume/hypertensive therapy, consider:
a. increasing cardiac index to supra-normal (>4.5) with dobutamine with CO/CI monitoring in place. b. formal angiogram with neurointerventional strategies (angioplasty, IA nicardipine, etc).

D. Management of Hyponatremia or Declining Sodium

1. DDX: Cerebral salt wasting (more common, suspect when UOP exceeds fluid input or significant UOP >250/h) vs SIADH (UOP normal and pt euvolemic). Send urine Na, Cr, Osm and serum osm.

2. If CSW:

-Bolus pt w/ IVF to target euvolemia, then increase IVF to 150cc/h and replace ongoing volume loss with NS/hypertonic saline using cc/cc replacement to euvolemia

-Consider albumin boluses (25g q6h PRN) if crystalloids insufficient

-Salt tabs 1-2g q6h PO

-Consider adding florinef 0.2 mg bid

3. If SIADH, hypertonic saline preferred rather than fluid restriction bc of increased risk of vasospasm with hypovolemia in SAH patients

4. Do not increase sodium more than 8-10 meq/24h in chronically hyponatremic patients; rapid correction of Na in acutely hyponatremic patients is safe.

ICP MANAGEMENT/ HERNIATION

Edited by: Karl Maki, MD and Peter Ljubenkov, June 2014
Sources: [1] Plum and Posner's' Diagnosis of Stupor and Coma, 4th ed
[2] UCSD status epilepticus protocol by Dr. Navaz Karanjia

Normal ICP: typically 5-10 mmHg.
(note this is not the same as lumbar OP)
ICP > 20 mmHg: can result in harm, due to herniation or global brain ischemia.

Broad DDX: Mass lesions (tumor, bleed, abscess), VP shunt malfunction, fulminate liver failure, anoxic brain injury, head trauma, dural sinus thrombosis, meningitis, etc

Evaluation
A. Symptoms: headache, lethargy, nausea, vomiting, visual sxs.
B. Physical exam: obtundation, abnormal posturing, parinaud's sign (vertical gaze palsy), loss of venous pulsations on fundoscopic exam, papilledema (later sign), blown pupil, gaze palsies (CN6 most sensitive to increased ICP, and beware that bilateral CN6 palsy may mean globally increased ICP and not bilateral pontine lesions), focal neurological deficits, Cushing's Triad (bradycardia, hypertension, irregular respirations).
C. **STAT Head CT** to rule out tumor, hemorrhage, abscess, meningitis, acute hydrocephalus, evidence of trauma or anoxia (MRI is better for some of these things, such as meningitis). Look for midline shift, hydrocephalus, loss of basal cisterns, effacement of sulci.
D. **If there is concern for herniation or impending herniation, call a BRAIN CODE immediately (**WEBPAGE "BRAIN, CODE" or pharmacy code pager: Hillcrest 2619; Thornton 0518) **– treatment should begin on the way to the CT scanner (see UCSD Brain Code Protocol).**

Herniation Syndromes
A. Uncal: temporal lobe mass causes medial temporal lobe to herniate under tentorium cerebelli. Clinically causes ipsilateral 3rd nerve palsy + contralateral hemiplegia/posturing (Kernohan's notch phenomenon).
B. Central Transtentorial: diffuse cerebral edema causes downward displacement of diencephalon. Clinically causes coma + b/l small pupils -> decorticate -> decerebrate posturing + rostral to caudal loss of brainstem reflexes.
C. Sub-Falcine: frontal/parietal mass causes cingulate gyrus to herniate under the falx. Clinically causes coma + contralateral weakness -> posturing and possible ACA stroke.
D. Tonsillar: cerebellar tonsils herniate into brainstem. Clinically causes cerebellar signs/symptoms + medullary dysfunction (e.g. hiccups) -> coma + bilateral posturing.

Stages of Central Herniation [1]					
	Consciousness	Respiration	Pupils	Eye Move-ments	Motor
Early Dien-cephalic	Drowsy/ obtunded, But arousable	Sigh/ yawn (or Cheyne-Stokes)	Small, reactiv e	VOR /doll's eye intact	Purposeful to pain
Late Dien-cephalic	Barely arousable, Stuporous	Cheyne-Stokes	Small, reactiv e	VOR /doll's eye intact	Decorticat e to pain (flexor)
Mid-brain	Unarousable, coma	Central hypervent. Or eupnic	Mid-positio n unreact ive	MLF dysfunctio n or no calorics	Decerebrat e to pain (extensor)
Ponto-Medul-lary	Unarousable, coma	Apneustic, Cluster, Or ataxic	Mid-positio n, unreact ive	Loss of calorics	Decerebrat e or flaccid
Stages of Uncal Herniation [1]					
Early CN III Stage	Drowsy, Obtunded	Normal eupnea	Dilated , Sluggis h pupil	VOR /doll's eye intact	Hemi-paresis or purposeful
Late CN III Stage	Deep stupor or Coma	Cheyne-Stokes	Fixed dilated pupil	3rd nerve palsy	Hemi-paresis or Decorticat e

	UCSD BRAIN CODE PROTOCOL [2]
0 min	• WEBPAGE "BRAIN, CODE" to pharmacy code pager (Hillcrest 2619; Thornton 0518) which pages code pharmacist and NCC resident; code pharmacist will bring brain code box w/ 23.4% saline, mannitol, neosticks (boxes are in Hillcrest SICU/Main Pharmacy, and TICU/CVCICU). • PAGE NEUROSURGERY
0-5 min	• **Surgical lesion?** (mass, big stroke/ICH, hydro) Consider stat crani/EVD/adjust EVD. • **ABC***: intubate, Sa02>94, cardiac monitor, send stat CBC, BMP, coags •**Position**: HOB at 45°, neck straight. -DO NOT LAY FLAT OR PLACE IJ LINE; if central line needed place femoral central line in reverse Trendelenburg. • **Mild hyperventilation** (RR 14-18), place ETC02 monitor, target EtC02 25-30/PaCO2 30-35 • **Osmotx: MANNITOL (20%,1g/kg)** IVP, periph IV by RN -**AND SALT 23.4% saline** (30cc IVP, by MD w/ direct or phone supervision by attending/fellow) over 3min -**OR 3% saline 250cc** IV bolus (central line wide open or good PIV over 15 min) **• CPP rx:** start NS 1L bolus and 100cc/h thereafter. Keep CPP 60-110 or MAP>80 with phenylephrine IVP [100-200mcg (1-2 cc) of neostick at a time, by MD ONLY]/drip or levophed drip. -Only lower BP (nicardipine/labetalol) if bleed, impaired autoreg, or CPP>110 • **Agitation/pain tx if indicated** (fentanyl 25-100mcg IVP, propofol 25-50mg IVP) • **If tumor/abscess:** dexamethasone 10mg IVP stat
	↓↓↓ ICP/EXAM NOT NORMALIZED?
5-10 Min	• Repeat 23.4% IVP or 3% saline 250cc IV bolus • **Stat Head CT if etiology of herniation unknown**. •Consider decompressive craniectomy
	↓↓↓ ICP/EXAM NOT NORMALIZED?
10-15 Min	• Propofol 100mg IVP (may ⇓BP), repeat x 1 in 2 minutes if no effect. If effective, start propofol drip & place SEDLINE; titrate to burst suppression. •Consider decompressive craniectomy
	↓↓↓ ICP/EXAM NOT NORMALIZED?
15-20 min	• Moderate hypothermia (32-34°C) w/ Arctic Sun •Or Pentobarbital 10mg/kg IV bolus over 30min. If ineffective, start pentobarb drip 3mg/kg/h x 3h then 1mg/kg/h & place SEDLINE; titrate to burst suppression. •Consider decompressive craniectomy
	↓↓↓ Post Treatment
• Start 3% NS @10-30cc/h, check Na q6h, goal Na 5-10 meq/L over initial Na • Immediately change vent to target normocarbia (PaC02 35-40), turn down FiO2 immediately to 40% to target normooxia (Pa02< 150) •Ensure normothermia (<37.5C) if pt. not made hypothermic already •MD must document administration of mannitol, 23.4%	

COMA EXAM & PROGNOSIS

Edited by Austin Lefevre, DO and Peter Ljubenkov, MD, March 2015

Sources: [1] AAN prediction of outcomes in comatose survivors after cardiopulmonary resuscitation
[2] Levy et al. Predicting outcome from hypoxic-ischemic coma. JAMA 1985;253(10)1420.

AAN Guidelines for prognosis in Hypoxic-Ischemic Coma [1]	
NOTE: Examine off sedation, normal temperature, without metabolic/toxic derangements	
Are ALL brainstem reflexes absent?	If yes: perform brain death testing (exam + calorics x 2 docs, apnea testing, cerebral flow study if available, etc)
Day 1: myoclonus status on EEG ?	If yes: Poor outcome (false positive 0% (0-8.8)
Day 1-3: Serum NSE> 33 ug/L post CPR?	If yes: Poor outcome (false positive 0% (0-3) **<u>However</u>**, not usually sufficiently standardized in most labs
Day 3: absent pupil or corneal reflex; extensor or absent motor response?	If yes: Poor outcome (false positive 0% (0-3)
Day 1-2: SSEP absent N20 response?	If yes: Poor outcome (false positive 0.7%) However: SSEP usually not available in timely manner at UCSD
In the answer to <u>ALL</u> of these questions is "no", then indeterminate outcome	

<u>Levy Criteria:</u> Predicting Prognosis in Hypoxic-Ischemic Coma [2]	
- NOT validated if patient was cooled - The most important examination is 72 hours post event. **-Before Exam:** Reverse metabolic/toxic derangements. No sedating medications. Normal temperature (Remember the liver may have been injured too and metabolism of meds may be slow)	
Pts with poor prognosis for meaningful functional recovery per Levy et al	
Initial	Pupils: no response – consider effect of resuscitation meds
1 day	Motor: no better than flexor and Spontaneous eye movements: neither orienting or roving conjugate
3 days	Motor response: no better than flexor
1 wk	Motor response: not obeying commands and Spontaneous eye movements: neither orienting nor roving conjugate at initial exam
2 wks	Oculocephalic response: abnormal and Eyes not spontaneous on day 3 and not improved by at least 2 grades (none→other→roving disconjugate→roving conjugate→orienting)
Pts with good prognosis for meaningful functional recovery per Levy et al	
Initia	Pupils: PERRL and

l	Motor: flexor or extensor and Spontaneous eye movements: roving-conjugate or orienting
1 day	Motor response: withdrawal or better and Spontaneous eye movements: improved at least 2 grades (none→other→roving disconjugate→ roving conjugate→orienting)
3 days	Motor response: withdrawal or better and Spontaneous eye movements: normal
1 wk	Motor response: obeying commands
2 wk	Oculocephalic response: normal

Levy Criteria: Exam at Admission, directly after event (500 patients)						
Any 2 reactive: Pupil, Corneals, VOR?			Number Patients	Best 1 year recovery		
No ↓ ↓ ↓	Yes↓			NO Recovery/ (vegetative)	Severe Disability	Good recovery/ Moderate disability
↓ ↓	Moans?	Yes →	56	46%	13%	41%
↓	No↓					
↓ ↓	Motor: With- drawl?	Yes →	106	58%	19%	23%
↓	No↓					
↓ ↓ ↓ ↓	Motor Extension or Flexion?	Yes →	135	69%	14%	17%
	No→→→→→→→→		83	80%	8%	12%
→→→→→→→→→→→→			120	97%	2%	1%

Levy Criteria: Exam at 1day/24 hours (387 patients)						
Any 3 reactive: -Pupil, Corneals, oculovestibular, or motor?			Number Patients	Best 1 year recovery		
No ↓ ↓ ↓	Yes↓			NO Recovery/ (vegetative)	Severe Disability	Good recovery/ Moderate disability
↓ ↓ ↓ ↓	Verbal -at least inapprop. Words?	Yes →	24	0%	33%	67%
↓	No↓					
↓ ↓ ↓	Motor: at least Withdrawal?	Yes →	136	42%	21%	37%
↓	No↓					
↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓	Any 1 norm? -occulovest. -occuloceph -spont. eye movement -motor flex/ex	Yes →	104	76%	13%	11%
	No→→→→→→→→		36	84%	11%	4%
→→→→→→→→→→→→			87	98%	0%	2%

Levy Criteria: Exam at 3 days/ 72 hours: 261 patient (MOST IMPORTANT DAY)						
Both reactive: -corneal, motor			Number Patients	Best 1 year recovery		
No ↓ ↓ ↓	Yes↓			NO Recovery/ (vegetative)	Severe Disability	Good recovery/ Moderate disability
↓ ↓ ↓ ↓	Verbal -at least inapprop. Words?	Yes →	68	0%	26%	74%
↓	No↓					
↓	Motor: at least With-drawal?	Yes →	75	40%	27%	33%
	No→→→→→→→→		62	76%	16%	8%
→ →→→→→→→→→→→			56	96%	4%	0%

Levy Criteria: Evaluation at 7 days/1week: 179 patients						
Eye opening at least to pain			Number Patients	Best 1 year recovery		
No ↓ ↓ ↓ ↓ ↓	Yes↓			NO Recovery/ (vegetative)	Severe Disability	Good recovery/ Moderate disability
	Motor: At least localizing?	Yes →	99	1%	24%	75%
	No→→→→		54	63%	28%	10%
→ →→→→→→→→			26	92%	8%	0%

BRAIN DEATH PROTOCOL

Edited by: Karl Maki, MD, June 2014

I. General:

• Irreversible loss of all brain functions from established, sufficient cause.
• Brain dead = legally dead (Federal Uniform Determination of Death Act)

II. Additional Prerequisites:

• Absence of potentially anesthetizing amounts of CNS depressants or neuromuscular blocking agents.
• Core temperature > 32.2 C (90F).
• MAP > 55 mmHg.
• Absence of metabolic or other medical conditions that may confound the clinical assessment (acid base disturbances, electrolytic abnormalities, severe hypoxia etc...)

III. Clinical Determination:

• Lack of behavioral or reflex responses that originate from nervous system structures above the spinal cord in response to pain applied to any part of the body.
• Two brain death assessments with 6 hours interval are recommended. At UCSD, one exam must be done by an attending neurologist or neurosurgeon.
• No brainstem reflexes:
    • Pupils must be fixed and unreactive to light.
    • Corneal reflexes must be absent.
    • No response to caloric vestibular stimulation. (30 cc of ice cold water in each ear canal)
    • Pharyngeal and tracheal reflexes must be absent.

IV. Apnea:

a. Apnea Test Prerequisites:

• Core temperature > 36.5 C (97F).
• SBP> 90 mmHg.
• Euvolemia (positive fluid balance in prior 6 hours if possible).
• Eucapnia (prior to testing PaCO2 35-45 mmHg).
• Normoxemia (pre-oxygenation with 100% O2 for 10 minutes to a PaO2 of >200 mmHg is recommended).

b. Apnea Test:

• Set ventilator rate to 0.
• positive if respiratory movements are absent after 10 min.
• must be a rise in arterial PaCO2 to > than 60 mmHg or alternatively a 20 mmHg rise in PaCO2 over the pretest baseline.
• abort test if pt becomes profoundly hypoxic or hemodynamically unstable.

VI. Confirmatory Testing:

• not mandatory but could be helpful when important components of the brain death examination cannot be assessed (e.g., extensive facial injury) OR where the apnea test unsafe. Consider EEG recording at a voltage of 2 uV that should show electrical silence over 30 minutes
• SPECT, angiography, etc are other options

MANAGEMENT OF STATUS EPILEPTICUS

Adapted by Austin Lefevre, DO and Peter Ljubenkov, MD, from UCSD status epilepticus protocol by Dr. Navaz Karanjia

Sources: Jan Claassen and Lawrence J. Hirsch. "Status Epilepticus," in Decision Making in Neurocritical Care, Jennifer Frontera, Ed. NY: Thieme, 2009. Pp 63-75.
Brophy GM et al, Guideline for the Evaluation and Management of Status Epilepticus. Neurocritical Care, April 2012
Chen JW, Wasterlain CG. Status epilepticus: pathophysiology and management in adults. Lancet Neurol 2006;5(3): 246-256
Ziai, W and Kaplan, P. Seizures and Status Epilepticus in the Intensive Care Unit. SeminNeurol 2008;28:668–681
Claassen J, Mayer SA, Kowalski RG, Emerson RG, Hirsch LJ. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology 2004;62:1743-1748

Definition of Status Epilepticus

5 min or more of continuous clinical and/or electrographic seizure activity or recurrent seizure activity without returning to baseline between seizures.

- As a seizure goes on beyond 5 minutes receptors in the brain alter their threshold for excitation. This can make seizures difficult to stop. Early intervention is key.
- Most Common causes: Discontinuation of AEDS, stroke, alcohol withdrawal, metabolic origin
- Greatest Risk > age 60

Non-convulsive status epilepticus: Electrographic seizures, no obvious convulsions. Subtle signs: Gaze deviation, twitching, staring

Refractory Status Epilepticus: Seizures that won't stop after first (benzo) and second line (1 AED) agent

Management: Treating status is an emergency!

- Mortality 34.8% > 1 hour vs 3.7% < 1 hour seizing
- Priorities: Protect Airway (intubate if needed). Stop Seizure

- Pre-Hospital intervention: Rectal diazepam, IV Benzos, IM Versed

- Associated with shorter duration 32min vs 60min, and less likelihood of recurrence in ED 58% vs 85%

- Quick Assessment: Still having seizures? Be aware of subtle GCSE with continuous rhythmic subtle motor phenomena.

FOLLOW NCCU STATUS ALGORITHM and CONTACT NCCU

UCSD STATUS EPILEPTICUS GUIDELINE

for generalized OR complex partial status, either continuous or without return to baseline mental status in between seizures

0-3 min	**Diagnose:** FSBG, CBC, CMP, coags, AED levels, troponin, ABG, utox, salicylates, EtOH level. Stat non-con head CT or MRI after pt stops seizing. **ABC**: cardiac monitor (cycle BP q2min), ensure IV access, intubate if 02 sat low >3min
	ONGOING SEIZURE?
3-10 min	**Lorazepam 2-4mg IVP STAT. Repeat q5 min until seizures stop (max total 0.1mg/kg)** - If no IV access, give midazolam 10mg IM/intranasal/buccal. -If midazolam unavailable, give Diastat 20mg PR (diazepam 20mg IV can be given PR if Diastat unavailable) - Thiamine 100mg IV and 50mL of D50 IV if low/unknown FSBG -Page anesthesia to prep for possible intubation **AND** **Load 1 AED STAT (send pharmacist/RN/tech to pharmacy to obtain immediately):** Fosphenytoin 20mg/kg IV @150mg/min(max 2g, MUST be on cardiac monitor)**.** **OR** Valproate 20mg/kg IV over 10 min(do NOT use in surgical or bleeding patients due to risk of platelet dysfxn). **OR** If pt is taking Keppra/phenobarbital/topamax at home, or if PHT/VPA are contraindicated, load IV Keppra (50mg/kg IV (up to 4g) at 100mg/min), IV Phenobarbital 20mg/kg IV at 50-100mg/min), or NG/PO Topamax (200-400mg) Note: Keppra is NOT FDA approved for treatment of status epilepticus and is less effective than PHT/VPA, so should not be used unless PHT/VPA contraindicated)
	ONGOING SEIZURE? See below

10-20 min	-I**ntubation and burst suppressant if generalized status, or vitals unstable. If complex partial status and vitals stable, consider not intubating until minute 20.** **-After intubation, start burst suppressant, and STAT cEEG / SEDLINE[1]*** **-Midazolam load***: 0.2mg/kg IVP bolus; repeat 0.1-0.2mg/kg boluses q5min until sz stop, up to max total loading dose 2mg/kg. Start IV midazolam drip at 5 mg/h, may increase to max of 50 mg/h. Decrease dose in renal failure. May ⇓BP. **OR** **Propofol load***: 1mg/kg IVP bolus; repeat 1-2mg/kg boluses q3-5min until sz stop, up to max total load 10mg/kg. Start IV propofol drip at 20mcg/kg/min, may increase to 200 mcg/kg/min. Check lactate/triglycerides/CK q8h. May ⇓BP. **OR** **Phenobarbital load***: 20mg/kg IV load at 50-100 mg/min
	ONGOING SEIZURE?
20-60 min	**Intubate and load burst suppressant (Midazolam OR Propofol OR Phenobarbital)** **If burst suppressant already started, bolus/titrate up q5 minutes; maximize dose** **Load additional AED:** If already loaded with fosphenytoin, give additional fosphenytoin 10mg/kg IV at 150mg/min. If already loaded with valproate, give additional valproate 10mg/kg IV over 5 min. If seizures continue, load 20mg/kg IV with whichever you have not already given. -If unable to use either PHT/VPA, load Keppra 2g over 20 min or Lacosamide 400mg IV
	ONGOING SEIZURE?
>60 min	**Add another burst suppressant** (propofol or midazolam or phenobarbital) **Consider ketamine:**load 2mg/kg.Start drip @10 mcg/kg/min, increase up to 50 mcg/kg/min **Consider pentobarbital***: load 5mg/kg at 50mg/min; repeat 5 mg/kg boluses until sz stop. Start drip at 1mg/kg/h, may increase up to 10mg/kg/h. **Consider additional AED's**: Keppra IV, Lacosamide IV, Topamax (200-400mgPO)
	ONGOING SEIZURE?
>days	Consider adding: lidocaine drip, ketogenic diet, moderate hypothermia, epilepsy surgery

1

ADDITIONAL POINTS TO CONSIDER:

Avoid fever, hypoxia, hypotension these exacerbate sz, increase mortality

Treat quickly and precisely per protocol: 74% of pts stop seizing if protocol is followed exactly; only 29% will stop if protocol is not exactly followed (Aranda, 2010)

If pt stops clinically seizing but mental status is not improving within 20 minutes, or has not returned to baseline mental status within 1hr, **obtain cEEG** (up to 50% of patients with generalized status epilepticus have nonconvulsive seizures after clinical seizure stop).

Status epilepticus kills: mortality is 17-26%, disability in survivors 40%

Continuous EEG, stat EEG's, and sedlines:

•**Continuous EEG:** NCC MUST be consulted. To order cEEG, look under "neurophysiology orderables" in EPIC, order "Prolonged EEG" and state "cEEG." EEG techs are available 8am-5pm to place leads, and are on call until 8pm from home. If you order a continuous EEG, page the tech immediately to inform them you want a cEEG. When a cEEG is placed, an NCC team member MUST review the EEG at least every 3 hours to ensure no seizures go unnoticed. Ensure the RN is writing down medication changes or relevant events on the paper that accompanies the EEG machine. **To Review**: login is "guest" and password "guest1."

•**Stat EEG:** Place the neurophysiology consult for a stat EEG and page the EEG tech on call ASAP.

•**Sedlines:** May be used when cEEG is unavailable. Go to the OR equipment room and ask for a sedline and some leads, or page the "anesthesia monitoring" tech in web-paging (there from 8am-10pm). The sedline shows 4 frontal raw EEG leads; it does not record. May be ok for pts who have global pathology that is unlikely to be intermittent (ie, post cardiac arrest patients, or patients we are keeping in burst suppression with meds).

EPILEPSY MANAGEMENT

Edited by Peter Ljubenkov, MD, and reviewed by Leena Kansal, MD

Sources: -Emilio Perucca. Clinically relevant drug interactions with antiepileptic drugs. Br J Clin Pharm. 2006 Mar; 61(3): 246–255
-Up-to-date

Essential things to ask about in any epilepsy evaluation
****Document like this to make it easier for the next person****

- **Onset age/date**
- **Semiology**: trigger, aura, laterality, motor features, GTC, incontinence, tongue biting, postictal period etc.
  Last over 5 Min?
- **Etiology**
- **Frequency/last:** (separate out of auras and full episodes)
- **Risk factors:** Birth history, childhood seizures/myoclonus, history of head trauma, history of CNS infection, FHx
- **Current AED's**: doses and side effects + sequence they were added to regimen
- **Failed AED's:** doses tried and reasons they failed including **Allergies and side effects.**
- **Previous EEG findings**
- **Previous MRI findings**
- **Driving?**: must be reported if LOC in the last 6 months
- **Refractory epilepsy referral**? (Surgical resection, vagal nerve stimulator, neuro-pace)
- **Women of childbearing potential**: document birth control?

Good Reasons to consider starting AED prophylaxis

• 2 or more unexplained/unprovoked seizures, or any ongoing risk of seizures (e.g. CNS pathology/procedures/etc)
•1 unprovoked seizure AND an abnormal EEG with epileptiform discharges
•Symptomatic seizure secondary to brain tumor, ICH, a lesion in a particularly epileptogenic location, or a medical condition that can't be adequately reversed.
•May also consider AEDs for first time seizure when seizure control is highly desirable and/or necessary for safety.

AED Drug Interactions
AED to AED interaction basics
Major Enzyme-inducing AEDs (↓↓↓ other AED levels) carbamazepine, phenytoin, phenobarbital, primidone
Major Enzyme-inhibiting AEDS -Valproate (↑ Lamotrigine and phenobarbital especially)
AED to Birth Control Interactions
These AEDS induce metab. of estrogen and progesterone (↓ efficacy) Carbamazepine, Felbamate, Oxcarbazepine, Lamotrigine, Phenobarbital, Phenytoin, Primidone, Topiramate
Lamotrigine: metabolism increased up to 50% by some estrogen containing pills and by pregnancy

Quick Guide AEDs

AED Titration Guide

Drug Name	Brand Name	Start dose (mg)	Increment (mg)	Maint dose (total daily)	Dosing schedule
Carbamazepine (CBZ)	Tegretol	200 BID	200/day qwk	800-1600	TID-QID
Clobazam	Onfi	5 BID	5/day qwk	30-80	BID
Diazepam	Valium	2 QD	Variable	10-30	PRN
Ethosuxamide	Zarontin	500 QD	250/day q4-7d	1500	QD-BID
Felbamate (FBM)	Felbatol	1200	600-1200 q1-2wk	2400-3600	TID
Gabapentin (GBP)	Neurontin	300 TID	300/dose q3-7d	1200-3600	TID
Lamotrigine (LMT)	Lamictal	Dosing schedule below	12.5-25 q2wk	400 alone 100 w/VPA 600 w/inducer	BID
Lacosamide (LCS)	Vimpat	100mg	100mg qwk	200-400	BID
Leviteracetam (LVT)	Keppra	500 BID	500/day qwk	2000-4000	BID
Oxcarbazepine (OXC)	Trileptal	300 BID	300/dose qwk	900-2400	BID
Phenobarbital (PHB)	Generic	30-60	30 q1-2wk	60-120	QD-BID
Phenytoin (PHT)	Dilantin	300 QD	30-100 based on level	200-600	QD
Pregabalin (PGB)	Lyrica	50 TID	50/dose q3-7d	150-600	TID
Primidone	Mysoline	100 QHS	50-100/day q3d	500-2000	TID
Rufinamide (RUF)	Banzel	400-800	400-800 q2d	3200	BID
Tiagabine TGB)	Gabatril	4	4-8 qwk	32-56	BID
Topiramate (TPM)	Topamax	25 BID	25 BID qwk	200-400	BID
Valproic acid (VPA)	Depakote	250	250 q3-7d	750-3000	TID-QID for DR BID for ER
Vigabitrin (GVG)	Sabril	500 BID	500/day qwk	2000	BID
Zonisamide (ZNS)	Zonegran	100 QD	100 q2wk	200-400	BID

Lamotrigine Starting Schedule
25 mg qd x 2wks
25 mg bid x 2wks
50 mg qAM (two 25 mg tabs)/ 50 mg qPM (two 25 mg tabs) x 2 wks
100 mg qAM (one 100 mg tab)/ 50mg qPM (two 25 mg tabs) x 1 wk
100 mg bid, continue until follow-up appointment

Can increase by 50-100mg daily q10d therafter
* note, pt must d/c med and present to ED if development of sig rash

AED Side Effects and Key Points

Drug	Monitoring	Common/Important Side Effects
VPA	LFTs/CBC at baseline, 2/3/6 mo, then yearly	Chronic: weight gain, hair loss, amenorrhea Idiosyncratic: liver failure, pancreatic failure, thrombocytopenia, hyperammonemia (without liver failure) Teratogenic Protein binding saturates at levels >75 then widely variably free levels
PHT	LFTs/CBC at baseline, 1mo, qyr	Chronic: gingival hyperplasia (prevent w/1mg folate daily), coarse features, cerebellar ataxia, atrophy, neuropathy (very long use), hypothyroid Idiosyncratic: SJS, lupus like reaction, hepatitis, blood dyscrasia Zero order kinetics and enzyme inducer
CBZ	Baseline LFTs/CBC/chem7 CBC 1, 2, 4 mo LFTs qyr	Chronic: hyponatremia, weight gain/edema, behavior changes Idiosyncratic: SJS, hepatotoxicity, agranulocytosis, aplastic anemia (1:50-200k) Autoinduction, inducer Check HLA-B*1502 in Asians
LMT	-	Chronic: HA, insomnia, incoordination, tic Idiosyncratic: increased myoclonic Sz, 10% incidence of rash (minimized by slow titration), rare SJS
LVT	-	Chronic: psychosis, agitation, depression – supplement with B6
TPM	Baseline Cr maint HCO3	Chronic: high risk cognitive effects: word-finding, memory loss Weight loss, paresthesias (self-limited), kidney stones Idiosyncratic: liver failure, oligohydrosis, angle closure glaucoma (rare)
OXC	Na	Chronic: hyponatremia, insomnia, headache Idiosyncratic: SJS, TEN
GBP/ PGB	-	Chronic: weight gain, peripheral edema, behavior change, myoclonus
FBM	Frequent LFT/CBC	Chronic: anorexia, weight loss, insomnia Idiosyncratic: aplastic anemia (1:5k-10k), liver failure, SJS Inducer and inhibitor
ZNS	-	Chronic: decreased appetite, word finding, paresthesia, weight loss, kidney stone, apathy Idiosyncratic: rash, sulfa hypersensitivity
TGB	-	Chronic: abnormal thinking, tremor, nervousness Idiosyncratic: non-convulsive spike-wave stupor
RUF	-	Chronic: incoordination, ataxia, shortened QT (dose related) Idiosyncratic: rash, DRESS
GVG	Baseline visual acuity/VF then q3mo	Chronic: weight gain, neuropathy, depression Idiosyncratic: permanent VF loss, psychosis
LCS	Baseline EKG, repeat at steady state if cardiac disease	Chronic: HA, tremor, ataxia, depression PR prolongation

HYPERKINETIC MOVEMENT DISORDERS

Edited By Peter Ljubenkov, MD, Karl Maki, MD, and Fatta Nahab, MD

Sources: - Continuum. 2013 Oct; 19(5 Movement Disorders): 1383–1396
- Albanese, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord 2013; 28:863
- www.uptodate.com

Describe it: At rest, with posture or with movement. Body part(s) affected (focal, segmental, lateralized, generalized). Amplitude and Frequency (e.g. constant, intermittent). Conditions that bring it out (e.g. rest, posture, intention). Triggers (e.g. stress, anxiety, movement [kinesigenic]) Suppression (e.g. volitional, with sensory trick, with weighting limb) Associated findings. Tests (e.g. Archimedes spiral, penpoint hovering, handwriting)

FUNCTIONAL/PSYCHOGENIC MOVEMENTS

NOTE: Always keep an open mind - people may embellish organic issues. Most are failing to identify their own actions, not malingering.

Consider in patients with the following historical clues:

Abrupt onset
Static course
Spontaneous remission
Spreading to multiple sites
Paroxysmal symptoms (note: this is not impossible for an organic issue)
Secondary gain
Risk factors for conversion disorder
Mild physical trauma before onset
Multiple somatizations/undiagnosed conditions
Previous exposure to a disease model (may have sick family member)
Variable phenomenology and severity over time

Clinical findings suggesting a functional/psychogenic movement disorder:

• **Inconsistency**:
-Increase with attention, decrease with distraction
-Entrainment of frequency of repetitive movements
-Variability of phenomenology (changes direction, frequency, muscles involved, etc.)
-Selective disability or functional disability out of proportion to exam findings.

• **Incongruency**:
-Mixed movement disorders
-Atypical stimulus sensitivity/triggers
-Paroxysmal attacks

• **False weakness** (giveaway, effort dependent, Hoover's sign, etc.)
• **False sensory changes**
• **Deliberate slowness**
• **Suggestibility**

Workup: It's important to not miss organic causes, but this is not a diagnosis of exclusion. This is a clinical diagnosis confirmed via the presence of the above features.

Approach/goal the diagnosis debriefing:

• Voice that the movements are not deliberate, subconsciously generated.
• Not a psychiatric disease (e.g., "You are not crazy").
• Provide validation that movements are real and preventing normal function (hence the term "functional movement disorder")
• Cultivate acceptance of the diagnosis to avoid future doctor-shopping.
• Cultivate a sense of partnership with the neurologist.
• Introduce the importance of multidisciplinary treatment strategies including: exercise, psych referral for comorbid anxiety/depression/etc, CBT, psychotherapy, mindfulness training, PT, OT, acupuncture, etc.
• Plan follow up visits to assess progress and provide patient with goals and timelines. PCP/other docs can focus on other problems if you follow for this.

TREMORS– Rhythmic, oscillatory alternating agonist/antagonist contraction

Resting Tremors

• **Parkinson's Disease:** PD may have an associated 3-5 Hz, coarse, low-high amplitude, resting tremor. May appear as **pill-rolling** in hands, **cogwheeling** in limbs, leg tremor and chin tremor. Worsened with distraction, stress, and fatigue; reduced with action. May have a postural component with about 6-8 second latency (re-emergent tremor)
(Treatment: see treatment of Parkinson's disease)
• Other causes: Parkinson's plus (MSA-P), vascular parkinsonism, SCA2&3, rubral
•Drug induced: Dopamine receptor blockers/neuroleptics, metoclopramide

Postural Tremors:

(Occur with holding arms outstretched in a fixed position)
• **Enhanced physiologic tremor:** 8-13 Hz, low amplitude; brought out by posture, stress, sympathetic stimulation, caffeine, etc. Present in everyone to some degree.
• **Essential tremor:** 8-12 Hz, low to high amplitude – *postural* (and kinetic) tremor, reduced by rest, typically affecting upper extremities. Vocal and head tremor are common. Worse with stress/fatigue and improved with alcohol. Possible family Hx.

Workup: TSH & med check (DAT scan only if PD is being considered), stop tremorogenic meds: valproate, lithium, amiodarone/calcium blockers
Treatment: (**NOT EtOH**- will worsen in long run)
• **Propranolol SR:** Start 60mg QAM
(usually need 80-120 mg/day)

- **Primidone:** Start 12.5-25 mg QHS. Titrate carefully by 25mg over weeks. max usually 250mg qday (BID or QHS)
- **Gabapentin:** Start 300mg daily (max 3,600 mg/day)
- **Topiramate:** Start 25mg daily, increase by 25-50mg/wk, max ~400mg/day (BID)
- **Botox:** Particularly if there is a component of head tremor

• **Dystonic Tremor:** May be in one part of body (e.g. cervical dystonia), jerky, position specific, and sometimes task specific.
- Treatment: Botox (especially if cervical, see dystonia management page 65)

• **Drugs/toxins:** Beta-agonists (albuterol), AEDs (especially Depakote), thyroxine, lithium, TCAs, caffeine, nicotine, cocaine, amphetamines, cyclosporine A, mercury
• **Other causes:** Hyperthyroidism, neuropathy, fragile X tremor-ataxia syndrome, rubral tremor

Kinetic Tremors: Worse with movement (also in some postural tremors)
• **Intention tremor:** Only at end point. Seen in a variety of **cerebellar dysfunction** (stroke, MS, phenytoin, alcoholism, etc.)
• **Rubral tremor/Holmes tremor:** Coarse tremor present at rest, worse with posture, the worst (larger amplitude) with movement. Usually due to an ipsilateral brainstem lesion (classically red nucleus, but may be midbrain tegmentum, posterior thalamus, and superior cerebellar peduncle)
• **Wilson's disease:** May look similar to rubral with bat wing component (↑ / arms in front and flexed at elbows)

Body Part Specific Tremors
• **Orthostatic tremor:** 13-16 Hz fine leg tremor upon standing, leading to instability. May be auscultated with stethoscope over the gastrocnemius. Typically responsive to clonazepam/diazepam, difficult to treat.
• **Palatal tremor:** (AKA palatal myoclonus) -Often associated with audible clicking. Etiologies: idiopathic, lesions of the Guillain-Mollaret triangle, adult onset Alexander's disease.

DYSTONIAS: Sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both
- Typically patterned, twisting, and may be tremulous/jerky
- Often initiated/worsened by voluntary action and associated with overflow muscle activation
-May be improved with a "sensory trick" or walking backwards (for leg/foot dystonias)

Causes of Acquired Dystonia (consider before obscure genetic causes)
• **Psychogenic:** Often distractible, suggestible, with changing pattern
• **Cerebrovascular abnormalities** (unusual): Stroke, ICH, AVM
• **Brain Injury:** Cerebral palsy, head trauma, surgery, electrocution
• **Infection**: Encephalitis lethargica, HIV, PML, syphilis, tuberculosis, viral encephalitis

• **Neoplastic:** Brain tumor, paraneoplastic syndromes
• **Toxic:** 3-NPA, carbon disulfide, cobalt, cyanide, disulfiram, MeOH
• **Drugs:** L-dopa/dopamine agonists, dopamine receptor blocking drugs (antipsychotics, compazine, reglan), anticonvulsants, calcium blockers

NOTE: for drug induced causes, stop agent and treat with:
Benadryl 25-50mg IV

Isolated Dystonias (just dystonia +/- tremor, not parkinsonism, chorea, etc.)

• **Early Onset Isolated Dystonia** (DYT1, 2, &6)

•**DYT1:**"Early-onset generalized torsional dystonia"
(TOR1 A) mediated (variable penetrance).
Usually Ashkenazi Jews.
Mean onset: Age 14. starts leg or arm → debilitating/generalized in ~5 yrs

• **Adult Onset**

(Note, genetic causes are rare; they are DYT 4,6,7,13,17,21,23,24 &25)

• Focal: Only one body region is affected (but ~30% spread). Common varieties include:

• **Blepharospasm:** Increased blinking and spasms of involuntary eye closure. Often abolished w/ sensory tricks
• **Oromandibular Dystonia (OMD):** Dystonia of the jaw (opening, closing, or deviation) or tongue
•**Tardive dystonia:** Typically characterized by retrocollis after prolonged use of dopamine receptor blocking agents (Generally also have tardive oromandibular dyskinesias. May also have an OMD component)
• **Cervical dystonia:** May be torticollis (twisted), anterocollis (forward), retrocollis (backward).
-Considered dystonia but also some shoulder too
• **Laryngeal dystonia/spasmodic dysphonia**
• **Task specific dystonias:** Writer's dystonia/cramp also typist's, golfer's, musician's dystonias, etc.

• Segmental: Two or more contiguous body regions
•**Cranial dystonia (Meige's syndrome)**
Blepharospasm + OMD (usually women >60yrs)

• Multifocal: Two non-contiguous or more (contiguous or not) body regions are involved.

• Generalized: Trunk + least two other sites, leg involvement is distinguished from those w/o leg involvement.
-Rare in adult onset; consider acquired etiologies.

• Hemidystonia: Multiple regions restricted to one body side due to acquired brain lesions in the contralateral hemisphere.

Combined Dystonias = Dystonia + Parkinsonism, myoclonus, etc. (may be persistent (DYT 3,5,11,12,15,16) or paroxysmal (DYT 8,10, 18,19,20)

• **Dystonias with Parkinsonism**:
• **Segawa Syndrome:** "Dopa-responsive dystonia"

(DYT5a & 14).Childhood onset (usually foot first).
- Excellent L-dopa response
- More stained & lower dose than juvenile PD
• **Wilson's disease**
• **Parkinson's disease** 2/2 by Parkin, PINK, DJ-1
• Brain-iron accumulation disease (**PKAN, neuroferritinopathy**, etc.)
• X-linked dystonia-parkinsonism/Lubag dystonia
-Mostly Filipino men
• Rapid-onset dystonia-parkinsonism (DYT12/ATP1A3)
-Rare, with subacute severe onset
• Myoclonus dystonia: DYT 11 (SGCE mediated) - alcohol responsive
• Paroxysmal dyskinesia with dystonia (rare, mistaken for psychogenic)
• **Paroxysmal kinesigenic choreoathetosis:** Choreoathetosis and dystonia triggered by voluntary movement (typically a sudden movement).
•**Paroxysmal nonkinesigenic dyskinesia**(PNKD): Dystonia and/or choreoathetosis with triggers that are not movement (alcohol, coffee, tea, fatigue, stress, etc.).
• **Paroxysmal exertion-induced dyskinesia** (DYT 9/18): (SLC2A1) autosomal dominant (low penetrance), dystonia after prolonged exertion (≥15 minutes).

Workup for Dystonia
• Typically a clinical diagnosis alone; isolated dystonias rarely need workup. • May consider in acquired, suspected hereditary, or atypical dystonias.
Imaging: MRI brain w/wo contrast (or at least a CT head) (basal ganglia calcifications, neoplasms, strokes, infections, etc.)
Labs: CBC, BMP, LFTs, ESR, ANA, HIV, RPR. Ceruloplasmin and 24-hour urine copper (urine kept refrigerated) if Wilson's disease suspected.
Levodopa trial: 25/100 TID, if focal or generalized dystonia of unknown etiology. - May confirm a "Dopa-Responsive Dystonia."
Genetic testing: Rarely needed; talk to movement specialist first. - TOR1A gene testing + appropriate genetic counseling in early-onset dystonia, or those with late-onset who have an affected relative with early-onset dystonia.

Treatment of Dystonias

• Treat underlying cause or remove offending toxin/drug.

• **Dopa-responsive dystonias:** Sinemet, start 25/100 QD and titrate to TID.

• **Focal Dystonias:** Local Botox injection is considered first line.

• **Focal and Generalized Dystonias:**

• **Trihexyphenidyl:** Start 1 mg BID. May titrate 2 mg Q 3-7 days. Full benefit delayed weeks-months. Max dose based on tolerability.
Anticholinergic side effects (worsens confusion in dementia).

•**Tetrabenazine:** Start 12.5 mg.
May titrate 12.5 mg Q week (BID).
SE: sedation, parkinsonism, depression, akathisia, nervousness, insomnia.

• **Clonazepam:** Start 0.5 QHS. May titrate by 0.5 Q week.
Watch for sedation, depression, confusion and dependence.

• **Baclofen**: 40-180 mg daily
(beware sedation, withdrawal seizures).
May give intrathecal if dose limited by side effects.

• Refractory Severe Dystonia: DBS in globus pallidus interna(GPi)

CHOREA-ATHETOSIS

• **Chorea:** (Greek for dance.) Fast, jerky, irregular, non-sustained, involuntary movements that flow from one muscle group to another. Discrete or confluent.

• **Parakinesia:** Incorporation of an involuntary movement into a pseudo-voluntary movement (e.g. crossing legs, gesturing)

• **Motor impersistence:** often associated with chorea (esp. Huntington's), cannot maintain an action with chorea. Can't keep tongue protruded >5 seconds or grip (milkmaid's grip).

• **Athetosis**: (Greek for changeable.) Slow, continuous, purposeless movements. Slower and affects distal musculature compared to chorea. Can form pattern (e.g. extension-pronation vs. flexion-supination of arm).

• **Ballism:** Uncontrolled, wild flinging of a limb; large-amplitude chorea, e.g. damage to subthalamic nucleus, b/l seen in nonketotic hyperosmolar coma. - Interestingly, responds to Haldol.

• **Dyskinesias:** Choreiform movements in response to dopaminergic medications.

Differential Diagnosis for Chorea Based on Clinic Features		
Age of onset	Childhood:	Sydenham's, cerebral palsy
	Young adulthood:	Autosomal dom. genetic, ataxia telangiectasia, specific protein deficiencies
	Adulthood	Huntington's, paraneoplastic, most other chorea
Time course	Acute:	Stroke
	Subacute & Chronic:	Metabolic, Wilson's
	Chronic:	Neurodegenerative disease
	Paroxysmal:	Episodic dyskinesia (SLC2A1)
Drug induced	Direct med effect:	L-dopa, antipsychotics, metoclopramide, prochlorperazine, estrogens
	Delayed:	Tardive dyskinesia
Additional medical conditions	Metabolic disease:	↓↑glucose, PTH, thyroid, Na, Mg, or Ca
	Pregnancy:	Choreagravidum
	Hemolytic anemia:	Neuroacanthocytosis
	Liver disease:	Wilson's, Mcleod syndrome
	Neoplasm:	Paraneoplastic syndromes
Family history	Genetic Diseases: **Huntington's***, Huntington's-like disease (HDL 1 & 2), DRPLA (more common in Japanese), SCA (1,2,3, 17), neuroacanthocytosis, Friedreich's ataxia, ataxia telangiectasia (numerous other diseases- see continuum article Oct	

	2013 for more)
Seizures	Neuroacanthocytosis (& young onset Huntington's and DRPLA)
Psych features Impaired cog.	Subcortical lesions, neurodegenerative disorders (e.g. Huntington's), Wilson's disease, CJD
Parkinsonism	Wilson's, Huntington's, HDL (1), Lubag, SCA (2,3,17), some forms of neuroacanthocytosis, Fahr disease
Dystonia	The majority of genetic causes
Neuropathy/ ↓DTRs	Friedreich's ataxia, SCA (1,2,3), ataxia with oculomotor apraxia
Unilateral/focal	Structural lesions (basal ganglia), occasionally metabolic issues
Paroxysmal	See discussion of paroxysmal dyskinesia with dystonia

First Tier Chorea Workup:	
Study	Condition Considered
MRI Brain w/wo contrast	Structural lesions, iron deposition (PKAN, neuroferritinopathy), Calcium (Fahr- CT actually better), Panda sign (Wilson's), patterns of atrophy
BMP +Ca, Mg	↓↑glucose, ↓↑Na, ↓↑Mg, ↓↑Ca
TSH, PTH	↓↑PTH, ↓↑thyroid
CBC w/peripheral smear	Neuroacanthocytosis (Chorea-acanthocytosis, HDL2, Mcleod, PKAN)
LFTs	**Wilson's (**and Chorea-acanthocytosis, Mcleod Acquired hepatocerebral degeneration)
Second Tier Workup: **Guided by CLINICAL SUSPICION, not shotgun approach**	
Uric acid	Lesch-Nyhan
Pregnancy test	Chorea gravidarum
CPK	Chorea-acanthocytosis, Mcleod
Ceruloplasmin (↓)	Wilson's disease, aceruloplasminemia
Check Kaiser Fleischer rings 24 hour urine copper (↓)	Wilson's disease
Ferritin (↓)	Neuroferritinopathy
ESR, ANA, SSA/SSB,	Autoimmune
Anti-DNA, lupus anticoag.	SLE
Antiphospholipid Ab	Antiphospholipid syndrome
Antistreptolysin O, Anti-DNase B titers	Sydenham chorea
HIV testing	HIV and related CNS infections/ malignancies
Anti-gliadin antibodies	Celiac disease causing ataxia
Paraneoplastic panel	Anti-NMDA receptor, CRMP/CV2, Hu, Yo
Alpha-fetoprotein (↑)	Ataxia-telangiectasia, ataxia with oculomotor apraxia
Cholesterol (↑)	Ataxia with oculomotor apraxia
CSF lactate/pyruvate (↑)	Mitochondrial and other energy metabolism diseases
CSF 14-3-3, total tau, RT-QuIC	CJD (see RPD chapter, page 89-90)
Urine/serum organic and amino acids	Organic/aminoacidopathies
EEG	CJD, neuroacanthocytosis (& young onset Huntington's and DRPLA)

Treatment of Chorea

- Stop or limit any offending drugs.
- Treating primary underlying cause is the main intervention.
- **Tetrabenazine**:
  - Start 12.5 mg. May titrate 12.5 mg Q week.
  - Stop 75 to 150 mg daily.
  - SE: Sedation, parkinsonism, depression, akathisia, nervousness, insomnia.
- Atypical antipsychotics are sometimes useful in treatment of hyperkinetic movement, but they can also cause hyperkinetic movements.

TARDIVE DYSKINESIA

- Grimacing, tongue movements, lip smacking, lip puckering, pursing of the lips, excessive eye blinking.
- Occasionally involuntary movements of the limbs, torso, and fingers included.
- **Occurs as consequence of prolonged use of dopamine receptor blocking agents.**

ADDITIONAL HYPERKINETIC MOVEMENT DISORDERS

- **Myoclonus:** Very fast, shock-like jerks. Usually general cortical secondary to general medical process dysfunction (just about anything that causes encephalopathy).
  - Hiccups and hypnic jerks are a common form in normal people.
  - **Known medical causes:** ↑Na, ↑Ca, ↑Thyroid, ↑Mg, ↑↓glucose, ↑NH_3, metabolic alkalosis, uremia, post-hypoxic (Lance-Adams).
  - **Iatrogenic Causes:** Valproate, lamotrigine, meperidine/opioids, amantadine, L-dopa, serotonin syndrome.
  - Sometimes epileptic, rarely essential (idiopathic or genetic).
  - Consider CJD, encephalitis, paraneoplastic, neurodegenerative in pts with cognitive/behavioral decline
  - **Clonazepam:** First line treatment after resolving cause

- **Asterixis**: "negative myoclonus". Transient loss of tone (may be observed as a hand flap) corresponding to an electrodecremental response on EEG. Classically seen in metabolic encephalopathy (hyperammonemia, uremia, azotemia) but not terribly specific numerous causes of general cortical dysfunction/ encephalopathy.
- **Tics**– Stereotyped, suppressible but irresistible action preceded by a premonitory urge. Suppression results in discomfort, decreased attention, and often an overflow of increased tics shortly afterwards. Worse with psychosocial stress. Often comorbid ADHD, OCD, and anxiety.
  - Simple vocal (e.g. sniff, grunt)
  - Simple motor (e.g. eye blink)
  - Complex motor (e.g. reaching up and touching nose)
  - Complex vocal (e.g. utterances, coprolalia is rare)

May be part of **Tourette Syndrome (TS):**

- Onset <21 years (18yrs for DSM 5)
- ≥1 vocal tic & multiple motor tics at some point in illness.
- May be multiple times a day, nearly daily, or intermittently throughout a period of more than one year.
- Anatomical location, number, frequency, type, complexity, or severity of tics must change over time.
- Must not be explained by other condition/med effect.
- Must be witnessed by a reliable examiner.

Treatment of TS:

- Clonidine, guanfacine
- **Typical Antipsychotics**:

Haldol (0.5-10mg/day) works best, but better tolerance for **Pimozide** (0.5-6mg/day) & **Fluphenazine** (0.5-20/day)

- Atypical Antipsychotics
- Benzodiazepines
- Tetrabenazine

• **Stereotypy**– Stereotyped, but without ultimately irresistible nature. Seen in patients with schizophrenia, developmental delay, autism. May also be seen in otherwise normal children.

• OTHER:

• **Akathisia:** (Greek for unable to sit) Inner feeling of restlessness causing inability to sit still, leading to variety of shifting movements that are somewhat voluntary. Tardive form may accompany dyskinesias.

• **Myokymia**: Spontaneous localized quivering of a few muscle bundles, often in the eye lid. Frequently happens in normal individuals with too much stress, caffeine, etc.

.

HYPOKINETIC MOVEMENT DISORDERS

Edited by Peter Ljubenkov, MD and Karl Maki, MD

Sources: - Continuum.2013 Oct; 19(5 Movement Disorders): 1383–1396
- www.uptodate.com
-Lectures by Doctors Litvan, Song, and Nahab

Parkinson's Disease:

• (Typically) intra-neuronal α-synuclein aggregates (Lewy bodies) in brainstem. Eventual loss of dopamine output from substantia nigra (SN) to the basal ganglia.

Preclinical Features: Depression/mood change, constipation, anosmia, REM sleep behavior disorder (RBD), orthostasis.

Clinical Features (TRAP)**:** Usually ~60yrs w/ slow asymmetric progression

- **Tremor:** Resting tremor of arms/hands, legs, chin, NOT head (think ET, see tremor chapter), not in all patients.
- **Rigidity:** Uniformed resistance to movement. Direction/velocity independent. Worse w/ contralateral movement.
- **Akinesia:**

More correctly **bradykinesia**, the cardinal feature of PD.

Paucity of movement, ↓ amplitude/speed of finger tap, hand opening, RAM, foot stomp, toe tap.

•Only truly "akinesia" at end stage

- **Postural instability:** Only late in disease.

- Will develop stooped posture, shuffling steps, en bloc turning and eventually retropulsion (>2 steps) first, before falls

Review of Systems (M.S.C.A.D.) during initial assessment and clinic follow up

- **Motor:** Falls/near falls, freezing episodes, dysphagia/choking
- **Sleep:** Quality/amount, restedness, fatigue, daytime somnolence, sleep attacks, nocturia, vivid dreams
- **Cognitive:** Hallucinations/illusions, compulsive behaviors (esp. on dopamine agonists!)
- **Autonomic:** Orthostatasis/lightheadedness, constipation, frequency/urgency, sialorrhea, sexual dysfunction
- **Depression:** Depression screen, apathy, abulia, anxiety

Diagnosis of Parkinson's Disease:

• Typically, a **clinical diagnosis** made via observation of 2 cardinal features (TRAP) including bradykinesia.
• **Review med list:** Dopamine blocking agents/neuroleptics, Valproate.
• **L-dopa trial response:** PD should be dopa-responsive to some degree, some Parkinson-plus syndromes (PSP, MSA-P) have negligible response.
•MRI brain: r/o vascular or other etiologies
• **DAT Scan:** Informative of level of dopamine connectivity in basal ganglia. Insurance will only approve to distinguish "PD vs. essential tremor."
•**Genetic Testing:** Almost never needed (Parkin, PINK, DJ-1, SNCA mutations, etc.) Use for early onset, rapid cases +/- family HX in which genetic counseling is relevant

What to expect after diagnosis

• **Life expectancy** approaches normal lifespan.
• **"Honeymoon stage":** May last the first 5-15 years.
Great response to meds with manageable side effects
• **Motor Complication phase:** May start in 5-10 years.
More one/off, gait dysfunction, freezing, falls, etc.
• **Non-Motor Complication phase: Last 5-10 years of treatment**
Increasing issues with cognitive decline, hallucinations, depression, constipation, sialorrhea, etc.
• **Clinical variants have different outcomes**
-**Tremor predominant:** Bad tremor, but slow progression to gait disability.
-**Postural instability/gait predominant (PIGD):** May have little to no tremor, but more rapid gait progression, falls, and cognitive impairment.

Parkinson Plus Syndromes		
Red flags:	• Early falls (PSP, MSA) • Rapid • Symmetric • Lack tremor • Axial>Limb (PSP, MSA) • Early onset (under 40)	• Poor L-dopa response • Early dementia (DLB) • Early psychosis/hallucinations • Early/severe orthostatic hypotension • Early dysarthria/dysphagia (MSA)

• **Dementia with Lewy Bodies (DLB)**
Likely on a spectrum with PD but with diffuse sub-cortical Lewy bodies (α-synuclein) **4 Core Features:**
1. Visual hallucinations
2. "Fluctuations" in alertness & attention
3. Hypersensitivity to neuroleptics
4. **Dementia with 1 year of Parkinsonism**
- Otherwise called Parkinson's Disease Dementia (PDD)

• **Multiple System Atrophy (MSA):**
Also an α-synucleinopathy, but instead with astrocytic/glial inclusions.
Incidence 3/100k, onset ~60 years, mean survival 6 years.
Clinical Manifestations (often predated with sleep apnea/stridor)

- **Autonomic failure** is the hallmark of ALL presentations (so-called Shy-Drager/MSA-A no longer recognized).
  -Urinary symptoms, early erectile dysfunction first.
  -Orthostatic hypotension with recurrent syncope.
- **MSA-P** (previously called striatonigral degeneration, SND)
  -Parkinsonism is hallmark
  -Only 30% dopa responsive (even then only a little)
  -50% have axial dystonias (orofacial/craniocervical).
- **MSA-C** (previously part of olivopontocerebellar atrophy)
  - Cerebellar atrophy/dysfunction is the hallmark feature.
  - Gait ataxia and scanning dysarthria.
  - Cerebellar oculomotor problems.

MRI Findings: -"Hot cross bun sign"- cruciform degeneration of pontocerebellar fibers. Cerebellar atrophy in MSA-C.

• **Progressive Supranuclear Palsy (PSP)**
Tauopathy (typically 4R variety) with aggregates in neurons and glia of basal ganglia, brainstem, and cortex. Onset ~60's, life expectancy ~7 years.
Clinical Features

- **Classic (Richardson) phenotype**
- **Parkinsonism:** Symmetric unlike PD, axial>appendicular rigidity, tremor rare, early frequent falls/gait difficulty (often the presenting issue).
- **Visual:** Starts with slow vertical saccades. Later hypometric saccades and square-wave jerks. Eventually supranuclear vertical gaze palsy (but overcome with VOR).
  Typically late in disease.
- **Bulbar symptoms:** Dysarthria/growling speech, pseudobulbar affect.
- Other: Neck extension (rather than flexion in PD), dystonia of extremities.

• Other clinical phenotypes:
PSP-Parkinsonism (mostly PD-like), **PSP-pure akinesia** (isolated akinesia w/ gait freezing), **Asymmetric Parkinsonism** (overlaps with CBD), **Frontal-Predominant Dementia** (PSP with FTD features)
MRI Findings: Midbrain atrophy
Mickey Mouse sign (axial view)
or hummingbird sign (sagittal view)

• **Corticobasal Syndrome (CBS):**
"CBD" (cortical basal degeneration) is a tauopathy (usually 4R variety) inclusion disease, but cortical basal syndrome (CBS) can be due to a host of pathologies including CBD, PSP, AD, DLB and prion disease. Asymmetric frontoparietal cortical atrophy occurs grossly. Onset usually >60 years.
Clinical Syndrome

- **Unilateral parkinsonism** (L-dopa unresponsive)
- **Other lateral motor features:** Ideomotor apraxia, dystonias, myoclonus, alien limb syndrome
- **Non-motor features:** Aphasias, cortical sensory syndromes, visuospatial deficits

MRI: Classically posterior parietal and frontal cortical atrophy

Other Potential Causes of Parkinsonism

• **Medications:** Neuroleptics

• **Toxins:** Carbon monoxide, manganese, MPTP

• **Vascular parkinsonism:** Often legs> arms (attributable ischemia on MRI)

• **Infections:** HIV/AIDS, encephalitis lethargica

• **Wilson's Disease:** +/- psychosis, dystonia, tremor, seizures
(Workup: Ceruloplasmin, 24-hour urine copper LFTS, slit-lamp)

• **Fahr's Disease** & **↑PTH:** Both may have basal ganglia calcifications best seen on CT

• **Diseases with iron deposition in brain:** (PKAN, etc)

• **Other neurodegenerative diseases:** CJD Huntington's (Westphal Variant), FTD

• **Numerous more obscure diseases:** Primary dystonia syndromes (Segawas [DYT5a & 14] DYTs 9,11,12, 18), parkinsonism-dementia-ALS complex of Guam, spinocerebellar ataxias (SCA 2,3,12,17, 21).

Pharmacologic Management of Parkinson's Disease:

NOTE: PD inpatients are often very ill and will decompensate easily if they miss their medications (e.g. for surgeries or NPO status, use an NG tube)

• **Carbidopa/L-dopa (Sinemet):** The main focus of treatment.
The old standard of care was to "save" this drug until the end to limit dyskinesias but this may decrease the ability to store dopamine later (so OK to use early).
Side effects: Sleepiness, GI upset, orthostatic hypotension, psychosis.
- Have about 2-5 years before onset of fluctuations and dyskinesias.
- Sudden withdrawal may look like NMS.
NOTE: At least 30min before, 60min after protein rich meal (or else↓ absorption):
Dosing:
- Start ~25mg/100mg TID
(10/100, 25/100, 25/250 mg available & pills can be cut)
- Titrate 50-100mg L-dopa per week (start lower and slower in elderly).
-Max 2,000 mg of L-dopa.
General concepts in dosing: (Increase dose or frequency?)

First ask your patient about the following topics each visit:
• Ask if and when current is "wearing off"
• Ask if patient is getting dyskinesias after dosing.
• Ask if current dose is even sufficient when initially taken.
Then tailor titration to efficacy and on/off symptoms.
• For "off symptoms," increase frequency (do this early in disease) to limit off periods w/out increasing dyskinesias
  • Ex: TID→QID → ...
  (may even go up to Q2 hours!).
• For dyskinesias consider lowering L-dopa dose and spread it over more doses (trade off with efficacy).
• increase L-dopa dose if insufficient efficacy after dose

Newer formulations:
• **Rytary:** True long acting oral form, typically TID dosing
• **Duopa:** Continuous via tube in duodenum. Higher dose, limits on-off.

Dopamine receptor agonists: ONLY FOR YOUNG PATIENTS W/O DEMENTIA.
• **Ropinirole (Requip):**
IR: 0.25 mg TID, titrate up 0.25TID weekly, max 24mg/day.
XR: 2mg/day, may titrate 2mg Qwk, max 24mg/day.
•**Pramipexole (Mirapex):**
IR: 0.125 mg 3 TID, titrate Q 5 to 7 days,
usual ~0.5- 1.5mg TID.
XR: 0.375mg/day, titrate Q 5 to 7 days, maximum 4.5 mg/day.
•**Rotigotine (Neupro):**(Transdermal patch)
2 mg/24 hours patch (may increase 2mg Q weekly), max 8 mg.

• **Apomorphine (Apokyn)** (limited by orthostatic hypotension)

Injectable 0.2ml/day (max 0.6ml/day).

Must monitor for the following:

• Sedation, nausea, peripheral edema.

• Dopamine dysregulation syndrome: (Avoid in elderly)

Obsessive/compulsive behaviors, punding, increased reward seeking (hyper sexuality, gambling), paranoia.

-Patients rarely admit compulsive behaviors (poor insight), screen with direct/specific questions

COMT inhibitors (↓dopamine removal→ ↑L-dopa half-life)

• **Entacapone (Comtan):** Adds ~30 minutes to each L-dopa dose, decreases "off" time

-200mg with Sinemet (max 1600/day, not much more effect after 5x daily)

• **Stalevo:** Available combined carbidopa/L-dopa/entacapone - 25/100/200

• Tolcapone: Start 100mf TID (Max ~200mg TID) - seldom used due to hepatotoxicity

MAOi: (↓dopamine removal→ ↑endogenous dopamine and L-dopa half-life)

• **Rasagiline (Azilect):** Reasonable monotherapy in early/minimally symptomatic PD.

- May also use as adjunct to decrease off time on Sinemet.
- Start 0.5mg/day x 1 month then increase to 1 mg/day (if Sinemet adjunct use 0.5).

• **Selegiline**: 5mg/day (max 5mg QAM and QNoon).

Oral disintegrating: 1.5 mg/morning, max 2.5mg/morning.

SE: Caution patients about use of MAOI's and dextromethorphan and ephedrine.

Tremor Management in PD

• **Trihexyphenidyl (Artane):**
0.5-1mg BID, may gradually increase to 2mg TID
SE: Anticholinergic side effects, dry mouth, confusion (avoid use in elders given their greater loss of anticholinergics)
• **Amantadine:** **Also used to limit dyskinesias**
Start 100mg QAM and Q Noon (up to 100mg TID in younger patients)
SE: Livedo reticularis, ↑stimulation (don't give at bedtime), hallucinations, confusion.

Surgery
• **Deep Brain Stimulation (DBS)**: Really only good for limiting patient's at titration limit due to on-off symptoms, and makes person only as good as their best on Sinemet. Not good for postural instability (will not improve) or demented patients.

Management of Orthostatic Hypotension
(More of an issue in MSA than PD)

• **First non-pharmacologic:** Compression stockings, high salt diet, staying well hydrated, getting up slowly.

• **Fludrocortisone:** 0.1mg/day (may titrate 0.1 mg/ week, max 1 mg).
SE: Monitor for hypotension, ↓K at doses over 0.3mg.

• **Midodrine:** 10mg TID (beware supine hypertension).

• **Droxidopa**: (Hard to get approved but better efficacy than midodrine).
100mg TID (may titrate 100 mg TID/day every 24-48rs, max 1800 mg).
Beware supine hypertension.

*Can also consider **pyridostigmine** if supine hypertension is an issue.

Depression Management:

• **Escitalopram** (Lexapro): good first choice

• **Paroxetine**(Paxil): Good for anxiety but anticholinergic

• NOT Prozac: Most interaction with MAOi.

CEREBELLAR ATAXIAS

Edited by Peter Ljubenkov, MD

Sources: - Continuum.2013 Oct; 19(5 Movement Disorders): 1383–1396
- www.uptodate.com
- Lectures by Doctors Litvan, Song, and Nahab

Initial Differential Diagnosis in a Patient with Gait Disturbance/ Falls:
- Peripheral Sensory Ataxia (poor proprioception, positive Romberg)
- Weakness
- Parkinsonism
- Ataxia from Vertigo
- Myelopathy (long track signs, sexual dysfunction, incontinence)
- Cauda Equina
- Ataxia from Disorders of Cerebellum and afferents to Cerebellum (Detailed in this chapter)

Cerebellar Findings on Examination:

• **Visual:** Poor fixation, poor pursuit, nystagmus, overshoot/hypermetric saccades.
• **Speech:** Scanning, slow, slurred/dysarthric.
• **Motor:** Decreased tone, titubation, kinetic tremor, intention tremor (only end point).
• **Coordination:** Dysmetria/overshoot (finger-to-nose, heel-to-shin), at end point, rebound phenomenon, slowed/irregular alternating movements (dysdiadochokinesia).
• **Gait:** Often wide based and unsteady (especially on tandem gait).
• **Cognitive:** Primarily executive dysfunction.

Differential Diagnosis for Cerebellar Ataxias in Adults

DDX includes any cerebellar injury or injury to inputs to cerebellum (anterior internal capsule, numerous brainstem locations, spinocerebellar in the cord tracts, etc.)
• **Vascular:** Stroke, ICH, AVM
• **Infectious:** Viral encephalitis/cerebellitis, vCJD
• **Inflammatory:** Demyelinating diseases, anti-GAD-antibody-positive cerebellar ataxia, celiac disease, SLE, Sjögren's, Hashimoto's encephalopathy/SREAT
• **Trauma:** Contusions, hematoma, etc.
• **Neoplastic:** Posterior fossa tumors (more common in children)
• **Paraneoplastic:** (Subacute) small cell lung CA, breast, ovarian, lymphoma
• Nutritional: ↓thiamine, ↓B12, ↓vit E
• **Drugs/Toxins**: **Ethanol, phenytoin are the big offenders.** Metronidazole (& other azoles), calcineurin inhibitors, amiodarone, lithium, chemotherapy (especially cytarabine), heavy metals
• **Metabolic: Wilson's Disease**
• Neurodegenerative causes (detailed next page)

- **Neurodegenerative**
  - **MSA-C:** Most common primary cause of cerebellar atrophy.
  - **Friedreich's ataxia:** (GAA triplet repeat in the FXN gene)
    - Usually childhood onset but can be 2nd decade.
    - Import to diagnose b/c DM, arrhythmia, CHF.
    - Cerebellar & posterior column findings (poor vibration, proprioception).
    - Weakness and ↓DTRs, but toes up-going.
    - Vision and hearing loss.
  - **Fragile X-associated tremor/ataxia syndrome** (FXTAS)
    - -Ataxia, intention tremor, parkinsonism, memory changes
    - -permutation of FMR1 (55 and 200 CGG repeats)
    - X-linked, usually men
  - **Spinocerebellar Ataxias:**(See chart below)
    - Largely autosomal dominant repeat diseases.
    - The list is huge (don't commit to memory), but other clinical features can narrow down diagnosis.

SCA Subtypes (Don't memorize this!)	
Clinical Features	SCA Type
***MOST common**	**1, 2, 3, 6**
***MOST common sporadic &>50yrs**	**6**
Pyramidal features	**1, 3**, 23, 28
Motor neuron involvement	**2, 3**, 36
Peripheral neuropathy	**1, 2, 3**, 4, 12, 18, 25
Slow saccades	**2**, 7
Ophthalmoparesis	**1**, 28
Retinal macular degeneration	7
Eyelid retraction	**3**
Tremor	12, 15/16, 27
Parkinsonism	**2, 3**, 12, 17, 21
Dystonia	14, 15/16, 27 (orofacial), 31 (torticollis)
Myoclonus	**2**, 14, 19/22
Chorea	17
Dementia	**2**, 7, 10, 19 (executive dysfunction)
Intellectual disability	13
Seizures	10

Workup for Cerebellar Ataxias in Adults
History: • If acute in onset, **TREAT FOR STROKE/CALL STROKE CODE.** • Discuss time course/associated symptoms. • Discuss alcohol intake, medication history. • Replete thiamine empirically if deficiency possible; don't trust labs.
• MRI brain w/wo contrast, and MRA including posterior circulation. +/- MRI of relevant spinal level if myelopathy suspected - Look for structural lesion, neoplasm, stroke, demyelination, etc. - May alleviate the need for further workup.
First Tier Labs: - BMP, CBC w/ smear, LFTS, A1C, lipid panel - B12 (+folate, MMA, homocysteine), vit E, copper, TSH - ESR, CRP, ANA, SPEP (+ immunofixation), anti-GAD antibodies, Anti-gliadin/endomysium antibodies (IgA), - HIV, RPR
Second Tier Labs Based On Clinical Suspicions - ANA, SSA/SSB, anti-TPO, Anti-thyroglobulin - Ceruloplasmin - Heavy metals screen - Lactate, pyruvate (if mitochondrial disease suspected) - Paraneoplastic panel: (Subacute) Yo, Hu, Ri, CV2 - **CSF studies:** Cell count, glucose, protein, culture, VDRL +/- MS panel, 14-3-3, total tau - Urine studies: Heavy metals, 24-hour urine copper, UPEP - Slit lamp study: If Wilson's disease suspected
Genetic studies: • Rarely needed. • May be considered if FXTAS, Friedreich's ataxia, or SCA are considered and genetic counseling may be needed.

DEMENTIA/ MAJOR COGNITIVE DECLINE

"Cognitive decline sufficient to result in social or occupational impairment"

Edited by Peter Ljubenkov, MD, and Mike Rafii, MD, PhD.

Sources:

-Mckahnet all 2011.The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011 May;7(3):263-9

-Galasko D. The diagnostic evaluation of a patient with dementia. Continuum 2013 Apr;19 (2 Dementia):397-410

-Seltman R & Matthews B, Frontotemporal Lobar Degeneration: Epidemiology, Pathology, Diagnosis, and Management CNS Drugs 2012; 26 (10) 841-870

-Apostolova, L. G. Alzheimer Disease. Continuum (Minneap Minn) 22.2 Dementia (2016): 419-34. Print.

Dementia Incidence: 1% @ 65yo →10-15% @80yo→40% @90yo

Prevalence: 26.6 million worldwide

	5 Steps to Diagnosis of Dementia of all Causes (Mckahn et al 2011) **-Best over 2 visits: history, exam, discuss safety→ discuss dx, etiology, goals, support, legal issues** **-verify history from a reliable collateral, often in separate room**
1	**Rule out encephalopathy from a medical condition or active psychiatric illness**: -You can't evaluate dementia in the context of acute medical or psychiatric illness! (typically, not an inpatient diagnosis)
2	**Establish a decline in previous level of function:** •establish a baseline, onset, time course (insidious? sudden? rapid?)
3	**A. Establish an inability to perform common daily tasks:** •**ADLs:** hygiene, toileting, feeding, and other self-maintenance tasks •**IADLs:** - Taking/managing medication (important!) - Managing finances - Driving/getting lost, - Housework: cooking, cleaning, etc. - Telephone & technology use (multistep processing) **B. Establish that deficits interfering with dysfunction in patient's usual sphere of activities:** •Job performance •Other executive function indicators: Complicated hobbies (building things, knitting, etc.) **•In particular you must attempt to cover safety issue** -Safe to drive, take meds, use a stove, etc. -If there was a fire what would you do?

4	**<u>Establish Dysfunction in at least 2 cognitive domains:</u>** **•<u>Memory encoding:</u>** repetitive questions, Poor recollection of conversation details, appointments, bills, movies/TV show details **•<u>Executive function:</u>** starting activities, making plans, multistep processes, technology **•<u>Visual-spatial abilities:</u>** faces, finding stuff, objects in space, hallucinations **•<u>Language:</u>** hesitations, word finding, paraphasic errors circumlocution, poor reading **•<u>Behavior</u>:** mood Δ, apathy, decreased empathy, compulsion/obsession, agitation, withdrawal, social taboos , Sleep changes
5	**<u>Objectively verify cognitive decline:</u>** -**MOCA**** (AD & MCI under 26 - very sensitive but not specific) -more false positives but allows some assessment of individual domains -**MMSE** (severe dementia [0-9], moderate [10-18], mild [19-24], normal [26-30]) insensitive to mild dementia, high retest variability, also not free -F**ormal Neuropsych Testing:** You should especially consider referral in atypical cases, unclear cases, or serious implications w/ tenuous DX **<u>Mental Status</u>** (poorly localizing, but necessary for validation remaining exam). Alertness / Orientation / Attention / Memory (verbal and nonverbal) **<u>Speech</u>** Screen: "mama, tip-top, fifty-fifty, baseball player, huckleberry" Localize: ma ma (ant lip), pa pa (post lip), la la (tongue), Localize: ca ca (ant pharyngeal), ga ga (post pharyngeal) **<u>Language</u>** (dominant hemisphere) Fluency / Repetition "no ifs and or buts" Comprehension complex commands Reading/Writing/Prosody **<u>Parietal</u>**/Neuropsychological 3D construction (dominant side does detail and non-dominant does 3D Calculation (dominant left parietal angular gyrus) Neglect (sensory, spatial, motor, anosognosia) Apraxias (prefrontal or parietal) **<u>Frontal</u>** / Frontal release signs Emotional disinhibition (orbital frontal) Working memory (Dorsolateral prefrontal) Abulia (Mesio-frontal) Snout (tap upper lip) Glabellar (tap nose bridge) Palmo-mental Grasp hand Luria sequence Semantic listing Categorical listing Graphomotor sequencing (alternating pattern figure)

******Diagnostic Studies for a Patient with Suspected Dementia******

First Tier Dementia Workup:

•**General lab panel:** CBC, BMP, LFTS (and possibly A1C)

•**Reversible dementia labs:** HIV, TSH, RPR, B12 (+/-MMA), Thiamine (often misleading, treat if suspected)

•**Imaging:** MRI Brain w/wo contrast (or CT if can't get MRI)

Second Tier Optional Dementia Workup: Biomarkers of Alzheimer's (AD) and other Dementia Syndromes. These are typically done in conjunction with involvement of a dementia sub specialist

•**Marker's of Aβ accumulation:**

CSF Aβ:

- in AD: CSF ↓Aβ 1-42
- CSF tau/Aβ ratio (AD>1 & normal<1 [FTD also <1]

Amyloid PET: radio linked thioflavins - PiB, 18F florbetapir (FDA approved for AD). Good negative predictive value for AD, no insurance coverage

- Use in amnestic neurocognitive disorder, atypical AD, and EOAD < 65
- BUT can be positive in other kinds of dementia!

•**Marker's of Neurodegeneration:**

- **CSF Tau**: in AD - ↑CSF tau (particularly p-tau)
- **Volumetric MRI:** Can objectively measure hippocampal atrophy (and other regions)
- **FDG PET:** - Bilateral wings of parietal-temporal hypometabolism in AD
- Currently, FDG-PET and SPECT use is only covered by Medicare for differentiating AD from FTD
- Occipital Hypometabolism in DLB

•DAT scan: Brightness ≈density of intact dopaminergic synapses

- low density suggests an α-synucleinopathy (PD, PD+D, DLB)

(only FDA approved for ET vs PD diagnosis , but broader implications)

Field Guide to Alzheimer's Disease (AD) Variants (Adapted from Galasko 2014)			
Type	**Symptoms**	**Exam**	**Imaging/notes**
Typical Amnestic AD	•Insidious onset of Forgets conversations, plans, appointments •Early retention of social graces	•**Poor encoding** (can't recall 50% of items even w/ cues) •Relative sparing of rest of exam early in disease •Often look deceptively normal until tested	(see diagnostics section) The most common form of dementia
Logopenic AD variant	•word finding issues •pauses in speech	•poor single word retrieval •poor repetition of longer phrases	•Left posterior perisylvian or parietal atrophy (MRI) and/or hypometabolism (FDG-PET)
Executive/ Frontal Variant	↓ reasoning, judgment & multitask	May have aspects of bvFTD	•May have frontal atrophy
Posterior cortical Atrophy (PCA)	•visual agnosias +/- prosopagnosia •difficulty reading •difficulty locating & manipulating objects •poor judgment of distance	•Visual field cut •Simultagnosia •Baling Syndrome •Eastman syndrome •poor reading •difficulty drawing intersecting figures •poor understanding of complex images	**MRI:**Occipital Atrophy **Typically an AD variant** (but can be due to other pathology subtypes including tau & DLB)
Lewy Body Dementia (DLB) **VS** **Parkinson Disease Dementia (PDD)**	•Visual hallucination •"Fluctuations" in alertness & attention •hypersens to neuroleptics • **Dementia in 1st year of Parkinsonism** (otherwise PDD)	•executive impairment (memory may be relatively spared) • visuospatial impairment •parkinsonism	**MRI:** less prominent atrophy **FDG-PET/fMRI**: occipital hypometabolism **DATscan:** ↓dopaminergic synapses **Path:** SN and cortical Lewy bodies (intracellular α-synuclein aggregates) (PPD may have classic DLB or mixed path)

FTD subtypes (60% of dementia in 45-60 year old bracket)			
Behavioral Variant Frontotemporal Dementia (bvFTD)	*Disinhibition •inappropriate interpersonal behavior •loss of decorum •rash/impulsive •Apathy/Inertia •loss of empathy •rituals/repetition •obsession/compulsion •hyperorality •poor hygiene	•Poor executive tasks -relative preserve memory (but poor recall w/o cues) •ALS in some cases •occasional parkinsonism	**Imaging:** Frontal or anterior temporal atrophy (MRI &CT) and hypometabolism (FDG-PET & fMRI) **CSF tau/Aβ<1** (distinguish from AD) **3 main pathology types of FTLD** (frontotemporal lobar degeneration) **1. FTLD-tau :** (3R tau inclusions in frontal & temporal regions) •**Pick's Disease** (PiD) - have '"pick bodies" •(FTDP-17: MAPT gene-tau filaments -occurs with parkinsonism) **2. FTLD- TDP** - ubiquitinated TDP43 inclusions •**Progranulin deficiency** (PGRN) (a neuro-inflammatory state?) •**C9 Orf 72:** also the major cause of familial ALS 3. (FTLD -FUS)
Primary Progressive aphasias (PPA): **Semantic Variant (Semantic Dementia)**	•Difficulty thinking of words (naming objects) •Fluent language output	•Poor confrontational naming & single word comprehension •Loss of object knowledge (forgets name & purpose!) •Surface Dyslexia (misreads irregular words)	**Imaging:** anterior temporal atrophy (MRI &CT) and hypometabolism (FDG-PET & fMRI) **Mostly TDP-43** pathology (type C) (but not PGRN or C9 mediated)
Non-fluent Variant (PNFA)	•slow, halting speech	•halting speech •paraphasic errors & speech sound distortions •spared word knowledge	**Imaging:** Dominant Frontal Insular atrophy (MRI &CT) and hypometabolism (FDG-PET & fMRI) Typically a tauopathy (3R)

MORE DEMENTIAS

TYPE	Symptoms	Exam	Imaging/pathology/notes
VASCULAR DEMENTIA (VAD) **(OFTEN MIXED WITH ANOTHER DEMENTIA)**	Possible hx of stroke/episodic decline	•subcortical dementia •some aspects of hypofrontality •focal feature related to stroke locations	**MRI:** increased ischemic burden, ↑subcortical/white matter disease **Treatment:** mitigate vascular risk (A1C, BP, LDL, smoking)
WERNICKE KORSAKOFF (WKS)	Falls, diplopia and confusion in the contest of alcoholism	•**Wernicke** -Ophthalmoplegia (CN VI) -Nystagmus -Ataxia -Confusion •**Korsakoff:** Amnestic + ↓executive= confabulation	**MRI:** • mamillary body atrophy •T2 Hyper. & diffusion restriction in mesial dorsal thalami & periaqueductal day **Lab:** thiamine is only informative if low, (but normal after a meal) Treat empirically w/ IV thiamine.
NPH	**Wacky, Wet, Wobbly** •Dementia • Incontinence • Gait disturbance	•Subcortical & hypofrontal •Magnetic gait -the only thing reliably helped by tap/shunt	**MRI:** Ventriculomegaly (flow study and cisternography not too helpful) **Timed gait test**, before and after 30-50cc tap (spec, not sensitive) -predicts response to shunting
PSP	•early falls*>gait issues •visual issues (poor eye movement) •dysarthria, dysphagia •stiffness	•hypometric saccades •poor vertical gaze •rigidity & akinesia (parkinsonism) •poor cog. & executive function	MRI: **"hummingbird sign**" of shrunken midbrain on sagittal view Pathology: 4R Tau inclusions (4 repeated exons included instead of 3R)
CBS	•clumsiness •stiffness, movement complaints •Visual or language symptoms	(often starts on one side) •Apraxias (early limb sub) •Alien limb •cortical sensory loss (neglect & parietal syndromes) •Rigidity, Dystonia •Reflex focal myoclonus	**MRI:** Asymmetric parietal atrophy Pathology: -**Cortical Basal Degeneration (CBD**) is a 4R Tauopathy (like PSP) -BUT "CBS" is more often a different pathology type (**AD**, etc.) (see page 73 for more)

ADDITIONAL DEMENTIA ETIOLOGIES:

•VITAMINS: **↓B12, PELLEGRA**
•ENDOCRINE: **HYPOTHYROID, ↓↑PTH**
•ORGAN FAILURE: **RENAL, LIVER, PULMONARY**
•TRAUMA: **CTE, POST-ANOXIA, CHRONIC SDH**
•INFECTION: **HIV, SYPHILIS, PML, CJD, WHIPPLE'S**
•NEOPLASTIC: **METS, 1° TUMORS**
•PSYCH: **DEPRESSION, SCHIZOPHRENIA, CONVERSION**

•**Inflammatory:** Sarcoid, vasculitis, MS/demyelinating
•**Toxic:** iatrogenesis, narcotics, heavy metal (Thallium), Dialysis (aluminum)
•**Metabolic:** Wilson's, leukodystrophies, lipid storage, mitochondrial, PKAN, porphyria
•**Degenerative:** Huntington's, MSA, some hereditary ataxia
•**Misc:** sub-clinical seizure, CADASIL, sleep apnea

DEMENTIA MANAGEMENT PSYCHOPHARMACOLOGY

Edited by Peter Ljubenkov, MD, March 2015

Source: [1] Schneider L. Alzheimer Disease Pharmacologic Treatment and Treatment Research. Continuum 2013 Apr;19(2 Dementia):339-357

[2] Lectures by Daniel Sewell, Director of UCSD Senior Behavioral Health, January 2015

•MILD AD PHARMACOTHERAPY: Cholinesterase inhibitors [1]
Side effects: diarrhea, nausea/vomiting, anorexia, abdominal pain, muscle cramps, dizziness, fatigue, bradycardia
Withdrawal: may cause confusion and acute worsening of cognition in some patients if abruptly stopped

Drug	Titration (maintenance dose in bold)	Notes:
Donepazil	**5mg daily→10mg** (can increase in 4-6 wks)	GI upset (consider stopping in severe patients)
Rivastigmine	(1.5daily)→**3mg→4.5→6mg daily** (can titrate every 2wks)	**(Can't take w/ food)** Good trial data for **DLB**
patch	**4.6mg daily→9.5→13.3 daily** (can titrate every 4 wks)	-better tolerated than oral
Galantamine	4mg BID →**8BID →12BID** (can titrate every 4 wks)	**(Can't take w/ food)** Also an ER form
•SEVERE AD PHARMACOTHERAPY (MMSE under 10) →add weak NMDA agonist (↓glut mediated excitotoxicity?)		
Memantine	5mg QD→5BID→ 5/10 →10mg BID (can titrate Q wk)	Adjunct to cholinesterase inhibitors
Donepezil SR	(23mg/day currently marketed for sever AD)	↑ adverse (must tolerate 10mg > 3 months

Dementia Psychopharmacology

Try to utilize**" The Psycho-Behavioral Metaphor"** when choosing which medication to begin:

Ask the following: **"If my patient wasn't demented, what would I call the symptoms they are exhibiting?"**

-Treat symptoms as you would their analogous psychiatric illness (depression, mania, anxiety, psychosis, etc.)

•Treatment of Depression

First Tier/ Senior friendly SSRIs: **Lexapro, Celexa, Zoloft**

Second Tier: Bupropion, Venlafaxine, Cymbalta, Remeron

Third Tier: TCAs, desipramine and nortriptyline are the least anti-cholinergic

Paroxetine is the most anticholinergic & fluoxetine has most drug interactions.

•Treatment of Mood Disorders and Mania

Valproic Acid (preferable given side effect profile)

Lithium: The most efficacious but hard to manage level

•**Treatment of Anxiety**
Prophylaxis: Senior friendly SSRIs as listed above
Benzodiazepines, but NEVER for confusion, delirium or psychosis
Senior Friendly Benzos (**O.L.T.**): **Oxazepam, Lorazepam, Temazepam**
Avoid the following: Xanax (addicting) and Valium (anticholinergic)
Off-label Gabapentin: sedating, but great side effect profile

•**Treatment of Psychosis:**

Haloperidol: good choice for acute management

Atypical Antipsychotics: best choice for prolonged use, less TD

- **Seroquel:** Best for Parkinson's and (low D2 affinity, least EPS) causes over-sedation (use at night) and hypotension
- **Risperidone:** highest association with earlier death
  Avoid in Parkinsonian patients (high D2 affinity)
- **Olanzapine:** Worst offender for metabolic syndrome
- **Aripiprazole:** slightly better than olanzapine for metabolic
- **Ziprasidone:** worst arrhythmia offender!

RAPIDLY PROGRESSIVE DEMENTIAS

Edited by Peter Ljubenkov, Source: Geshwind et al. Rapidly progressive Dementia *Ann Neurol*. 2008 July ; 64(1): 97–108.

RPD demographics (out of N of 178)	
Breakdown	Notes
46.9% **Sporadic CJD**	**~62 % of RPD Some form of CJD** annual incidence ~ 1/1 million
13.6% **Genetic CJD**	
1.7% **Acquired CJD**	
~38%**Non CJD RPD**	**Greatest to least occurrence, Geshwind et al 2008:** 1. Rapid presentation neurodegenerative diseases (CBD>FTD>DLB>AD>PSP) 2. Autoimmune: (Hashimoto/SREAT*>MS>sarcoid>antibody/paraneoplastic) 3. Unknown 4. Infection 5. Psychiatric 6. Malignancy (PCNSL, non-antibody mediated paraneoplastic) 7. Toxic / metabolic (EtOH, methylmalonic acidemia, MTX) 8. Vascular

NOTE: Rule out delirium first!!!

RECOMMENDED WORKUP		
Type	**FIRST TIER WORKUP**	**SECOND TIER WORKUP (tailored to clinical suspicion)**
Blood	CBC, BMP, LFTs Rheum Screen: (ESR, ANA, CRP) -HIV, RPR, TSH, B12 (+MMA, folate, & homocysteine) -Lyme, Anti-thyroglobulin, anti thyroperoxidase, -Paraneoplastic panel (see page 107-109)	-Tumor markers -peripheral smear -Ceruloplasmin & Copper (if suspect Wilsons) -Hypercoag (if vascular) -Additional Rheum: SLE, ACE -Mycoplasma serology -Thiamine (treat empirically if deficiency suspected as labs may be misleading)
Urine	UA + Culture	24 Hr Urine copper (if suspect Wilsons) 24 Hr Heavy Metal Screen
Continued on next page...		

RAPD workup continued		
	1st tier work up	(2nd tier based on clinical suspicion)
CSF	Protein, glucose, cell count/diff, culture, VDRL MS panel: IgG index, OCBs **<u>If CJD if truly suspected:</u> (coordinate w/ lab & cjd surveillance.com)** •**RT-Quic** (98-100% specific) • General neuron destruction markers: - **14-3-3** (sensitive for some subtypes, but NOT specific) - **tau** (more specific if in the thousands)	Fungal culture, AFB, Cryptococcal antigen Cytology & flow (PCNSL) Bartonella serology, Whipple PCR <u>Viral PCR</u> -HSV, CMV, West Nile -JC & BK PCR (if immunocompromised)
Image	<u>MRI w/wo contrast & MRA</u> • **<u>DWI</u>** +ADC ~91% sensitive & 94% specific for CJD -often first thing positive in CJD when other workup is negative <u>Possible findings:</u> -Cortical ribbon -Basal ganglia (Caudate and Putamen) -Occasional Thalamic "Pulvinar sign" (vCJD)	-MR Spectroscopy (clarify lesions) -Formal Angiogram (if vasculitis suspected) -CT Head (useful in Fahr's) -Cancer screen (suspect paraneoplastic syndrome) -CT chest, abdomen, pelvis w/wo contrast). Body PET. Mammography -Vascular workup: echo, Carotids

ALTERED MENTAL STATUS / DELIRIUM

Edited by Michelle Van Noord, MD and Peter Ljubenkov, MD, January 2015

Sources: [1] Adapted from UCLA Neurology Resident Handbook
[2] Plum and Posners's Diagnosis of to Stupor and Coma, 4th edition
[3] AAN Continuum 2010; 16(2)

Delirium risk factors: old age, underlying dementia, cardiac or orthopedic surgeries, ICU setting, decreased vision or hearing.

Key historical points in Evaluation of Delirium:

- **Previous functional status** (is this truly an alteration?)
- **Acuity** (acute/subacute/chronic)
- **Onset** (gradual/sudden/stepwise)
- **Progression** (waxing and waning/fixed)
- **Associated features** (hallucinations, hemiparesis/focal features, general medical issues, medication schedule)
- **Recent complaints** (severe headache, neck or chest pain).
- **Drug changes**
  -Worst Offenders: anticholinergic medications (especially in elderly), benzodiazepines, opiates, antihistamines, anesthesia, neuroleptics
  -Other drugs to consider: antiepileptics, muscle relaxants, dopamine agonists, L-dopa, steroids, fluoroquinolones, cephalosporins, beta-blockers, digitalis, lithium, calcineurin inhibitors, chemo, MAOi/serotonergic medications in excess
- ****Any Current Primary Medical Issues: ****
  Why is patient in hospital? Any suggestion of cardiac, renal, or liver disease? Any recent surgery? Any change in medication? Any changes in vitals?

Key physical exam points:

- **Vital signs:** ↓↑Temperature? Tachypnea? ↓↑ HR? ↓↑ BP?
- **General:**
  -Signs of trauma?
  -Meningismus (photophobia, stiff neck, Kernig's/Brudzinski's)
  -Rash (e.g. meningococcal or viral exanthema)?
  -Stigmata of heart failure (crackles)? Lung disease (clubbing)? Liver disease (caput, icterus/jaundice, asterixis)?
- Key features in your full neuro exam:
  -Attention*(days of week or months backward)
  -Level of awareness, orientation
  -basic language (following commands, repetition, naming)
  -Pupil: blown pupil (think herniation but only if comatose!!!), big pupils(anticholinergic), small pupils(opiates?)
  -Papilledema, $4^{th}/6^{th}$ nerve palsies)**:** ↑ICP?
  -Abnormal movements: subtle twitching/eye deviation (seizures?), positive myoclonus & asterixis)
  -Focal findings on neurologic exam?

Basic Clinical Approach to delirium: (2010 continuum)

Step 1: Stabilize acute contributing issues

-ABC: assess/manage airway, breathing and circulation
-Check vital sign
-blood glucose level.
(if low, 100mg IM thiamine 1st→1amp D50)
-consider naloxone if suspect opiates (only temporary!)

Step 2: Initial Assessment

-History (especially baseline cognitive status, meds, infection symptoms).
-Physical examination (special attention to infection or focal signs),
Thorough review of medication list***
Initial Labs: CBC w/diff, BMP, Ca, Mg, Phos, LFTs, ammonia, UA and culture, blood cultures, urine tox, EtOh, **ESR**
(also include an LP if fever on unknown origin)
Other Studies: CXR, EKG (don't miss arrhythmias!)
Head imaging: (CT or MRI)

Step 3: Use workup above to select amongst the following

MRI Brain w/ DWI and w/wo Gad: if not done previously
Lumbar Puncture: (If signs of increased ICP, *scan before LP*)
Must have: Opening pressure, cell count (1&4), protein, glucose, gram stain, fungal /bacterial cultures
Consider: VDRL, HSV-PCR, viral culture, lyme ab, cocci ab, AFB stain/culture, India ink prep base on clinical suspicion.
EEG: Consider sooner if seizure history or high suspicion of seizure

Step 4: consider additional labs based on the initial evaluation

Second Tier Labs: morning cortisol, TSH, T4
Third Tier Labs: autoimmune serologies, anti-tpo and anti -thyroglobulin
Reversible Dementia Labs (for chronic cases):
B12/folate (+/- MMA, homocysteine), RPR
Consider Rapidly Progressive Dementia w/u if above negative
Extended tox screen if they have access/exposure to harmful medications: phenobarbital, phenytoin, carbamazepine, valproic acid, lithium, tricyclic antidepressants, diltiazem, etc.

Step 5: Treatment of Delirium

- **Treat underlying cause if known**
  - -antibiotics, O2, AED's, etc.
  - - Low threshold for **Thiamine 100mg IM** in alcoholics
- **If febrile, consider empiric CSF coverage** (Don't hold for LP)
  - -Ceftriaxone 2mg Q12H, Vancomycin 15-20 mg/kg Q12hrs
  - -acyclovir
  - +/- ampicillin (Listeria for elderly)
  - +/-steroids (dexamethasone 10mg IV Q6h, x4 day, prior or w/ first antibiotic dose, ↓ mort/morbid in pneumo. Meningitis)
- **Treatment of agitation:** Antipsychotic
  - - Haldol best first line but lots of EPS
  - - Risperidone is longer acting, but also lots of EPS
  - - Seroquel has least EPS, but very sedating

- note Neuroleptics have black box warning for mort. in elders
-Watch out for NMS
- Avoid benzos – result in disinhibition, paradoxical worsening

•**Mitigate hospital issues!!!**
- Limit awakenings, and promote appropriate sleep/wake times
- Limit restraints
- Place room with window
- Frequently reorient patient (unfamiliar environment is deleterious)
- Limit urinary catheters (infections)
- Limit Multiple procedures
- Treat pain, constipation, infection, etc.

Important Parts the Differential Diagnosis of AMS
The big 3 acute things you can't miss! **1. Strokes:**(ischemic and ICH): aphasia may look like confusion **2. Non-convulsive status epilepticus:** eyes deviated? subtle twitching? **3. Increased ICP/herniation:** (comatose with blown pupils?)
The big 3 categories you will see most **1. Toxic:** (particularly meds, recreational drugs, opiate excess, EtOH) **2. Metabolic**: (↓↑ glucose, ketoacidosis, HHNK, hepatic encephalopathy, uremia/azotemia, Wernicke's) **3. Infectious:** (UTI, PNA)

Expanded Differential Diagnosis for Delirium

•**Vascular:** Ischemic Stroke (typically bi-hemispheric or reticular activating), ICH or SAH, PRES, Vasculitis,
•**Infection:** UTI, PNA, sepsis, encephalitis, meningitis, abscess
•**Trauma:** concussion, SDH, EDH
•**Autoimmune:** ADEM, Vasculitis, SLE, Hashimoto's/SREAT, paraneoplastic limbic encephalitis (see separate section)
•**Metabolic/systemic**:
-Electrolytes: ↑↓Na^+, ↑↑Ca^{2+}, ↑↑Mg, ↓phos
-Endocrine: ↑↓ **glucose,** ↓ PTH, ↑↓ cortisol, ↑↓ Thyroid
-Hepatic encephalopathy (↑**NH3**) & poor drug clearance
-Uremic encephalopathy (↑**BUN**) & poor drug clearance
-Respiratory Failure: Hypoxia and hypercarbia
-Vitamins: ↓thiamine, ↓B12, Malnutrition (albumin <2), ↑ vit D
-Dehydration: BUN/creatinine ratio > 18
•**Seizures:** non-convulsive status epilepticus, postictal state
•**Structural:** hydrocephalus (especially in shunt cases), herniation
•**Degenerative:** (usually just a risk factor, needs other inciting issue) Rapidly Progressive Dementia (pg 89) & DLB (pg 70,83) may mimic delirium
•**Psychiatry disease**: psychosis, mania, catatonia, malingering
•**Neoplastic:** vasogenic edema, ↑ICP, carcinomatous meningitis, Paraneoplastic limbic encephalitis (see separate section)
•**Toxic:** Alcohol intoxication, recreational drugs (LSD, PCP, meth, cocaine, etc.), medication (previous page), environmental exposures, (carbon monoxide), anticholinergic plants, acidic poison (ethylene glycol, methanol, paraldehyde)

-**Withdrawal:** (etoh, benzos, barbituates)

•**Iatrogenic precipitants:** (a huge deal for inpatients!!!)
-See list of offending drugs on previous page

•**Other contributors to hospital acquired delirium:** Sleep deprivation (disrupted circadian rhythm), Untreated pain Surgery (thoracic [cardiac and noncardiac], vascular, hip replacement), Constipation

PRES: "Posterior Reversible Encephalopathy Syndrome

Edited by: Amanda Yu, DO and Dr. Mike Rafii. MD. PhD, June 2014

Despite the name, it can be in other regions than posterior, may not be reversible, may not always cause encephalopathy.

Pathophysiology: Assumed to be disruption of blood-brain barrier (endothelial dysfunction) or autoregulatory failure that is more likely to occur in posterior circulation (and in patients on PRES-inducing drugs).

Etiologies:

- Chronic immunosuppression, tacrolimus, sirolimus; cyclosporine
- Severe HTN
- Pre/post-partum (eclampsia = PRES).

DDx:

- Basilar infarct
- CVT
- Demyelination (tumefactive MS, ADEM)
- Vasculitis
- Other encephalitides

Symptoms:

AMS, visual field loss/aura, headache, seizure, gait disturbance
*May also developed symptoms due to a secondary ICH.

Characteristic MRI: FLAIR hyperintensities, DWI hypo or isointense, +/- hemorrhage.

Treatment: depends on cause

- if on immunosuppressant, need to hold them, check level, supportive care
- if hypertensive, treat like hypertensive emergency: bring BP down 25% in minutes to 2 hrs with IV drugs.
- if eclamptic and seizing, treat with magnesium sulfate 4·6grams IV over 15 mins followed by 2·3 grams/hr for 24 hr
- Treat seizures in non-eclamptic patients with IV Ativan +/- Dilantin or Keppra load depending upon the clinical scenario. Risk of seizures diminishes as the structural changes resolve over 3 mos therefore not necessitating long term AEDs.

APHASIAS AND LANGUAGE

Edited by Peter Ljubenkov. Adapted from lectures by Mark Kritchevsky, MD.

Hemispheric Dominance of Language

	Left hemi	Right Hemi	Bilateral
Right Handers	96-99%	1-4%	0%
Left Handers	70%	15%	15%

Laterality of Hemispheric Function

Left	vs	Right
verbal	vs	non-verbal communication
analytical	vs	holistic thinking
temporal	vs	spatial processing (at synaptic level)

Definitions

- **Aphasia**: an acquired deficit in speech production or comprehension due to brain damage or dysfunction
- **Anomia**: an inability to name something
- **Alexia**: an acquired disorder of reading due to brain damage or dysfunction
- **Agraphia**: an acquired disorder of writing due to brain damage or dysfunction.
- **Agrammatism**: impaired word conjugation and syntax. May have telegraphic speech
- **Prosody**: intonation, tone, stress and rhythm of speech that sometimes conveys emotion content or meaning not encoded by grammar, syntax or vocabulary
    - **Aprosodia:** impaired prosody; may be seen in non-dominant lobe lesions
- **Paraphasic error**
    - **Literal** (phonemic): substitutions of wrong/similar sound/phonemes
    - **Verbal** (includes semantic type): substitutions of wrong/unrelated words
- **Neologism**: made up word that obeys typical word rules
- **Spoonerism**: syllable transposition between words ("bood goy for good boy")
- **Circumlocution**: excess of words instead of a more discrete word or phrase (May explain the word rather than saying it)

Language in Physical Exam

- **Output**: - **Content**
    - **Fluency**: Decreased fluency manifests as agrammatism, paucity of speech, shortened phrases, effortful (loss of melodic rhythm), & errors in speech praxis (pa/ta/ka, artillery/catastrophe)
        - May check letter fluency (F words)
        - May check categorical fluency (animals, etc.)
- **Repetition**: Start simple; more complex examples include:
    - *"No if's and's or but's*."
    - *"You know how."* [and other sentences on NIHSS]
    - *"I only know that John is the one to help today."*
- **Naming**: Use confrontational naming to assess for anomia, word retrieval

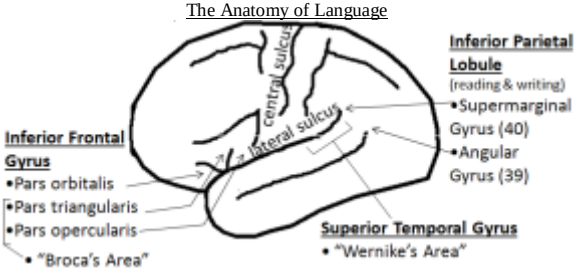
& word production
- items on the NIHSS card
- pen/pen tip
- watch/watch dial

• **Comprehension**: evaluate with sequence of commands starting simple, midline, followed by more complex, such as activity crossing midline and 2 step commands.
- *"Please point to the ceiling after pointing to the floor."*

You should also ask a question that requires interpretation of complicated grammar:
- *"Is my aunt's uncle a man or woman?"*
- *"Do you put on your shoes before your socks?"*
- *"The lions was killed by the tiger; which animal is dead?"*

• **Reading**: NIHSS cards.
• **Writing**: write a sentence of their own choosing.

The Anatomy of Language



Perisylvian Aphasias

• **Broca's Aphasia**: Agrammatic, telegraphic, effortful speech (decreased fluency), with anomia and poor repetition. There is relative retention of comprehension, though deciphering complex syntax and grammar may be impaired (e.g. they may answer "The tiger" when asked, "The lion was killed by the tiger; which animal is dead?"). Comparable issues in writing. Sometimes treated with melodic intonation therapy.

• **Wernicke's Aphasia**: Fluent speech (including some grammar) with normal cadence and normal tone but with poor content (marred by paraphasic errors and neologisms), anomia, poor repetition, and relatively poor comprehension. Patients also exhibit comparable issues in writing and poor incite (i.e. they might think you have the problem).

• **Global aphasia**: Involving both Broca's & Wernicke's area; mute, nonword utterances.

Extrasylvian Aphasias

• **Conduction aphasia**: Destruction of arcuate fasciculus connecting Broca's and Wernicke's areas. Fluent, paraphasic with impaired repetition*, normal comprehension.

• **Transcortical Motor**: Resembles Broca's but repetition is intact. May be cortical and deep structures adjacent to Broca's area, including the caudate.

• **Transcortical Sensory**: Resembles Wernicke's but repetition is intact. May be cortical and deep structures adjacent to Wernicke's, including the thalamus.

• **Transcortical mixed**: Similar to global aphasia except that repetition is intact

• **Anomic aphasia**: (Angular gyrus or improved Wernicke's). Mostly anomia with marked circumlocution (e.g. may say "thing" and "do" rather than specific pronouns and verbs), with rest of language.

Neurodegenerative Aphasia Syndromes:
Primary Progressive Aphasias (PPAs)

• **Logopenic Aphasia**: Left parietal lobule and posterior temporal atrophy, typically due to Alzheimer's pathology. Poor naming but some retained output with slowed/dysfluent speech. Patients also show poor repetition, and poor comprehension of syntax.

• **Progressive Non-Fluent Aphasia**: Left posterior frontal atrophy, typically due to FTD spectrum pathology. Marked decrease in fluency (hesitant and effortful) with relative retention of word meaning. May also have speech apraxia, anomia, paraphasia and agrammatism.

• **Semantic Dementia**: Left temporal lobe atrophy, due to FTD spectrum pathology. Marked anomia, often starting with low frequency words, including loss or meaning and conceptual knowledge of the things they are trying to name.

Other Syndromes

• **Alexia and Agraphia**: Can't read or write but intact speech. Usually angular gyrus.

• **Alexia without Agraphia**: Left occipital and splenium (e.g. PCA stroke).

• **Gerstmann Syndrome**: (Inferior parietal lobule)
1. Agraphia/dysgraphia
2. Acalculia/dyscalculia
3. Finger agnosia
4. Left-right disorientation

MULTIPLE SCLEROSIS

Edited by Peter Ljubenkov, MD, Walter Heine, MD, PhD, and Revere Kinkel, MD

2011 McDonald Criteria for Diagnosis of MS	
Clinical Presentation	**Additional Data Needed for MS Diagnosis**
•2 attacks with objective clinical evidence of 2 lesions •**OR** objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	None
2 attacks with objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: •1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) • **Or** Await a further clinical attack implicating a different CNS site
1 attack with objective clinical evidence of 2 lesions	Dissemination in time, demonstrated by: • Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time • **Or** a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; • **Or** Await a second clinical attack
1 attack; objective clinical evidence of 1 lesion (clinically isolated syndrome)	**Dissemination in space and time**, •For DIS: 1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord) or Await a second clinical attack implicating a different CNS site. • For DIT: Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time; or A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan. or Await a second clinical attack.
Insidious neurological progression suggestive of MS (PPMS)	•1 year of disease progression (retrospectively or prospectively determined) plus 2 of 3 of the following criteria: 1. Evidence for DIS in the brain based on T2 lesions in the MS-characteristic regions (periventricular, juxtacortical, or infratentorial) 2. Evidence for DIS in the spinal cord based on 2 T2 lesions in the cord 3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

•**"Dissemination in Space and Time":** The diagnosis of MS requires evidence of symptoms and signs of inflammatory demyelination in different anatomical regions at different points in time

• **Radiologically Isolated Syndromes (RIS):** only MRI evidence strongly supportive of MS, but no clinical findings, even if CSF is findings are consistent with MS.

• **Clinically Isolated Syndromes (CIS):** Symptoms of an attack who do not satisfy dissemination in time criteria are called

What is a Typical MS Attack?

• May be subjective report or objective observation of focal neurologic deficit
• At least 24 hours duration in absence of fever or infection
• Exclude pseudo attacks (single paroxysmal symptoms) or acute onset (query stroke) classic MS symptoms such as trigeminal or glossopharyngeal neuralgia, Lhermitte's phenomenon, tight band sensation around trunk, Uhthoff's phenomenon is evidence of an MS lesion not an attack if objective evidence is supportive (typically MRI, exam findings or electrophysiologic testing)
• Determine Time Between Attacks 30 days between onset of event 1 and 2
• Some historical events with symptoms and pattern typical for MS can provide reasonable evidence of previous demyelinating event(s), even w/o objective findings. Vague neurological symptoms (eg. forgetfulness, brain fog, fatigue, multifocal paresthesias, pain syndromes, heat sensitivity are at best supportive of MS but carry no weight without objective evidence of MS

Syndromes/symptoms	Exam Findings
Optic Neuritis	
• 90 % unilateral: Bilateral more common in children, Asians, South African blacks and other etiologies (NMO) • 90 % pain on eye movement • 90 % have decreased acuity, contrast sensitivity and color vision; • Photopsias common • Often pain with eye movement	• **Decreased acuity**: 20/25 to NLP • **Decreased color vision** or red desaturation • **Central scotoma** most common but all field defects described. (Think AION with inferior altitudinal defects) • **RAPD** /Afferent pupillary defect if other eye not involved • Fundus normal or papillitis; 35 % disc swelling (AION if peripapillary hemorrhage)
Acute Brainstem & Cerebellar Syndromes	
• Virtually every BS syndrome possible. (more incomplete than strokes) •**INO:** Classic syndrome is a bilateral INO, but unilateral is more common. •**Cerebellar syndromes**: usually asymmetric ataxia out of proportion to degree of dizziness •**Trigeminal neuralgia** under the age of 40 is MS till proven otherwise but requires MRI evidence of MS to count as attack •Refractory nausea/vomiting; -thinkNMO	•**INO:** slowed saccade of adducting eye, often with end gaze nystagmus of abducting eye. - Convergence is relatively preserved • **Irritative phenomenon** such as periorbital/ perioral myokymia or hemifacial spasms are common • **Pseudo-cranial nerve palsies** mimicking extra-axial process from involvement of CN exit zone. Most commonly pseudo Bell's palsy or pseudo 6th nerve palsy
Internal Capsule Syndrome usually large T2 lesion rostral to the internal capsule & abutting posterior lateral ventricle	

•Incomplete numbness and weakness on one side of body	Incomplete loss of primary sensory modalities and weakness on one side
Sensory Myelitis (Posterior cord usually thoracic)	
• Ascending numbness from distal LEs to a torso level (may be asymmetric) • Macrosomatic illusions • Distal tight band sensation chest • Mild imbalance	Mild to severe decrease vibration in the toes (often minimal findings in proportion to symptoms) Brisk reflexes
Asymmetric Sensory Myelitis (posterior cord usually above C5)	
Windmill pattern of numbness (hand → leg → leg→ hand)	• Asymmetric posterior column dysfunction (again often mostly vibration sense) • Imbalance • Dysmetria especially in initial limb involved • Asymmetric ipsilateral weakness if it begins more laterally in cord
Useless Hand Syndrome of Oppenheim (lateral posterior C3/4 cord level)	
• Unilateral clumsiness of a hand • Difficulty identifying objects in pocket	•poor stereognosis in hand w/ relatively preserved 1º sensory modalities and strength •joint position and graphesthesia usually less affected
Conus Medullaris Syndrome	
•Saddle anesthesia sometimes down posterior legs (can't feel while wiping and numb perineal region) •B/B function often not affected	•Decreased 1º sensation in saddle distribution •Decreased cremasteric reflex but rectal tone usually good unless severe

Initial Evaluation of Patient with MS

•Obtain a history with particular focus on:

- Age and Duration of MS symptoms
- Baseline function (walk unassisted or require a walker? Do they work?
- Bowel and bladder function? etc.)
- Current symptoms and temporal course of symptom onset
  -usually over several days or hours, not stroke-like. >24 hours
- R/O pseudo exacerbation from common triggers (see below)
- Typical prior exacerbations and last exacerbation
- Response to steroids and date of last treatment
- Current/Past Disease modifying therapy/ duration

•Physical exam with particular attention to:

- Optho exam: ↓acuity, color desat, APD, pale optic disc, pain with INO
- Motor exam: look for weakness and spasticity
- Coordination–dysdiadochokinesia, intention tremor (end tremor on FTN), dexterity (9 hole peg test)
- Gait and mobility timed 25 ft-timed gait on clinic patients)
- Long tract signs such as up-going toes & hyperreflexia

Initial Workup of MS/Suspected MS

• **MRI Brain w/wo contrast** and often **C-spine w/wo** (get T-spine if lesion suspected)

2D FLAIR, T2 weighted images for posterior fossa evaluation, DWI, GRE, and T1 (pre and post gadolinium). The UCSD MS protocol includes 3D FLAIR and 3D T1 weighted images for volumetrics and image analysis.

•MRI Evidence of Dissemination in Space (DIS)?

• ≥1 T2 lesion in at least two out of four areas of the CNS:
-periventricular (actually abutting ventricle!)
-juxtacortical(U shaped configuration following sulci),

-infratentorial lesions typically abutting edge of brainstem or 4th ventricle as well as ovoid cerebellar DWM lesions
-spinal cord (Ovoid and < 2 vertebral body levels)

• Gadolinium enhancement of lesions is not required for DIS

•MRI Evidence of Dissemination in Space (DIS)?

•A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI

OR

•Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions at any time

•Lumbar Puncture

• Cell count, protein, glucose
• MS Panel (IgG synthrate, Ig index, oligoclonal bands, MBP)
Positive if:
-Oligo clonal IgG bands in CSF (and not serum) (80% sensitive) -***or*** elevated IgG index
note: different labs have different reference values for Oligoclonal bands; some report > 2 as abnormal but > 4 by isoelectric focusing is more commonly considered abnormal)

• MS Mimic Workup

• Consider obtaining the following only if dictated by demographics, history and/or exam: **Aquaporin 4 antibody Ab (for NMO), ESR, ANA, Lyme, ACE, RPR, HIV, HTLV 1/2, B12 (+/- MMA homocysteine), Vit D**
(ANA not helpful w/o systemic signs of Lupus - High false pos)
• May also consider vasculitis labs if indicated
• See separate DDX for transverse myelitis
• Notch 3 if imaging/history more concerning for CADASIL

•Baseline Visual Evoked Potentials:

Positive studies have delayed but well-preserved waveform

Common Causes of Worsening MS symptoms/ Pseudo Exacerbations	
Category	Examples
Medications	Baclofen used for spasticity: increased weakness, transfer problems and mental dulling AEDs (CBZ, Gabapentin, lyrica, lamotrigine, PTH) for neuropathic pain: ataxia and dizziness Interferons: Pseudo relapse from flu-like effects Fingolimod (Gilenya): PRES Fingolimod (Gilenya): Macular edema, shingles Natalizumab (Tysabri): PML, shingles Benzos, narcotics, gabapentin and others: increased confusion, mental dulling sedation Antimuscarinic (Oxybutynin, tricyclic antidepressants etc): blurred vision, urinary retention, impaired heat tolerance from impaired sweating, constipation Topiramate: paresthesias
Infections	UTI, Cellulitis & abscess (especially injection sites), decubitus and aspiration
Pain / noxious stimuli	Increased spasms, autonomic dysreflexia, distended bladder, severe constipation)
Hyperthermia (Uhthoff's phenomenon)	Hot weather/broken air conditioner (worse in late afternoon and evening), Medications (anticholinergic medications inhibiting sweating, neuroleptics)
Hypothermia	MS involvement of preoptic nucleus of hypothalamus causing decline in function, confusion and sometimes encephalopathy
Co-morbid medical conditions	• Thyroid disorders (hypo and hyperthyroid) common in MS especially post interferon use • Hyponatremia from SIADH (meds; primary disease) • Diabetes Mellitus and complications • Adrenal insufficiency from chronic steroids • Nutritional deficiency especially with gastric surgery and inflammatory bowel disease (↓B12, ↓ Copper) • Renal failure from Neurogenic bladder Frozen shoulder, entrapment neuropathies, bursitis hip or shoulder, Avascular necrosis

Acute MS Flare Management

•ABCs: watch respiratory fxn if cervico-medullary junction involved

•RO pseudo-exacerbation from infections/ medical conditions above
- UA, CXR CBC BMP
- symptoms usually improve with treatment of underlying cause
- If pseudo-exacerbation from infection, treat infection first (may give steroids if no improvement in 1-2 weeks
-Treat symptoms (pain, spasticity) regardless of etiology (see next page)

• MRI w/wo contrast of relevant level?:
- Only If you are unsure if this is a true exacerbation
- NOTE: Not all flares enhance (particularly in elderly), and some enhancing lesions don't confer obvious symptoms
- enhancement predicts steroid response but is not a required for steroids.

• Methylprednisolone 1 gm IV q day for 3-5 days:
for actual suspected flares
• May sometimes follow with **Medrol dose pack** or **prednisone taper:** starting 40-60mg, taper over 11 to 14 days
• Prepare patient for insomnia and steroid induced behavioral changes (anxiety, panic, restlessness, hypomania/mania, psychosis, depression)
-**zolpidem 10 mg qhs prn** or **lorazepam 0.5 mg bid prn**

For anxiety/ agitation
- **olanzapine 5 mg QHS:** for current acute psychosis or preemptive in patients w/ hx of acute psychosis on steroids

• No rush on admission night to start IV steroids if you are unsure of true exacerbation - ok to admit and decide next day.
- Treat the symptoms in the meantime

•Reasons to admit
(NOTE: patients can sometimes get steroids via infusion center):
- Patient seems to be fairly sick or incapacitated
- First time use or complicating medical condition (e.g. DM)

CHRONIC MS MANAGEMENT

Initial Platform Disease Modifying Drugs for RRMS (↓ relapses ~ 30%)

• **Glatiramer Acetate (Copaxone)**: ----**SC 20mg qday Or SC 40 mg MWF**
Myelin Basic protein analog
SE: injection site reaction, lipoatrophy, idiosyncratic reaction (like a panic attack), lymphadenopathy; very rarely cardiac

• Interferon Therapies (note there is little sense in switching amongst these)
- **SE (all):** Flu like symptom**,** Hepatotoxicity (trend LFTs), skin reactions with subcutaneous shots; rarely increased depression or suicidal ideation, autoimmune thyroid or hepatic dysfunction, cardiovascular disease, seizures

Interferon B 1-alpha
•**Avonex:** (5% get neutralizing Abs in 6-18 mo, don't resolve)
-Start 7.5 & titrate by 7.5 Qwk----------**IM 30mcg/wk**
•**Rebif:** (25% get neutralizing Abs in 6-18 mo, don't resolve)
• 4.4mcg 3x wk (wks 1 & 2) →11 mcg 3x wk (wks 3 & 4)
SC 22mcg 3x wk
or 8.8 mcg 3x wk (wks 1 & 2) →22 mcg 3x wk (wks 3 & 4)
SC 44 mcg 3x wk

Interferon B 1-beta
•**Betaseron** and **Extavia** ----------**SC 250mg QOD**
62.5mcg QOD wk1-2 →125mcg QOD wk3-4 →187.5mcg QOD wk5-6 then ↑
(note: INFs may have lower utility in African Americans)
Important: avoid interferon in Ab mediated disorders such as SLE, NMO

Salvage Disease Modifying Drugs for RRMS:

• **Dimethyl Fumarate (Tecfidera)**----------**Oral 240mg BID w/ meals**
Very short half-life, hence BID dosing
SE: Nausea, vomiting, abdominal pain, anorexia, diarrhea, flushing/scalding skin with dose : aspirin 81-325 mg in am decreased flushing; loperamide 2 mg bid for diarrhea and metoclopramide for upper GI symptoms
- Rare cases of clostridium difficile infections and GI bleeding
- Rare cases of PML no known utility of JC antibody screening for PML risk especially with low incidence of PML
Note: This PML risk increases in context of sustained lymphopenia and +JC
→ Trend CBC w/ diff
→ DC with sustained absolute lymphocyte count < 500
→ Consider stopping for absolute lymphocyte counts between 500 and 900 if significant increase in CD4/CD8 (> 5) ratio as a result of selective depletion of CD8 + lymphocytes

• **Teriflunomide (Aubagio)**----------**Oral 7mg or 14 mg / day**
Inhibits DHODH, ↓pyrimidine synth. in proliferating B & T cells
SE: Hair thinning (10 % that recovers in 6 months), Acute Hepatitis

(check LFTs), GI Upset
Category X for pregnancy (men and women): stays in system for 18 months recirculated in enterohepatic circulation; remove rapidly with cholestyramine 4-8 mg three times a day for 11 days (lower dose only if higher dose not tolerated; may also use activated charcoal but not as well tolerated)

•Fingolimod (Gilenya) ----------> **Oral 0.5mg /day**

-phosphorylated to Analog to sphingosine-1-phosphate (S1P)
Derived from a parasitic fungus that feeds upon cicada larvae
RISKS: (check CBC and LFTs every 6 months)
- AV Nodal block (~11 deaths to date< 1/2500) –ECG at baseline must be normal with no evidence of cardiac disease; monitor 6 hrs after 1st dose and stop if greater than 1st degree AV block
- Macular edema - Ophthal eval every 3 months X 2
-Shingles, very rare VZV encephalitis: Must get titer first, must wait 4 wks post immunization
-Rare cases of PML (2 cases in first 110,000 treated); no known utility for JCV antibody screening for PML risk given low incidence of PML

• **Natalizumab (Tysabri)** ----------> **IV 300 mg every 28 days**

Antibody to α-1-integrin only 0.16 to 0.18 relapse rate - may start outright in severe cases but may require initial or repeat IV Methylprednisolone at onset or induction therapy with Rituximab if highly active at onset because it takes up to 3 months for full effect
Risk of PML in JC virus antibody positive patients (55% of people) and patients with any prior immunosuppression other than steroids
-MD must register w/ REMS (see risk stratification table on next page for interpretation of index values)
-Screen serology every 4 months → PLEX to remove if evidence of PML
-Concurrent steroids or additional therapies rarely needed except at onset of therapy; avoid concurrent use of immunosuppressants

Ocrelizumab

Anti-CD20 Ab **approved for primary progressive MS and RRMS**
Contraindicated in Hep B
IV infusion 300mg IV x2 separated by 2 weeks then 600mg IV q6mo

Additional Chronic MS Management

- **Controllable Risk Modification:** ↓smoking, ↓obesity
- **Vitamin D3:** 5000 international units/day (possible cofactor in MS?)
- Fatigue Management:

Amantadine 100mg BID is first line (also consider fluoxetine for depression)

• Gait Dysfunction:

Dalfampridine (Ampyra) 10mg BID, low efficacy, may cause SZ

- Must do 25-ft timed gait before & after initiation **(typically only approved for ambulatory patients with normal renal function, no history of seizures and 25-foot ambulation time > 8 secs)**

•Pain management: (Neuropathic pain rarely responds to narcotic or analgesics; narcotics are to be avoided)

-1st line: gabapentin & pregabalin.

-2nd line and carbamazepine & oxcarbazepine treatment

-3rd line: PTH and lamotrigine

•Spasticity: • **Baclofen**: start 5 mg 2-3 times daily; titrate 5 mg per dose every 3 dat. Do not exceed 80 mg daily

• **Tizanidine**: start 2 mg up to 3 times daily. Titrate 2-4 mg increments per 1-4 days maximum: 36 mg daily. (beware of hypotension!)

• Others: Gabapentin, Valium, Botox (for discrete region up to 3 months)

PARANEOPLASTIC NEUROLOGICAL SYNDROMES

Edited by Peter Ljubenkov, MD, and Mike Rafii, MD, PhD, January 2015

Sources: [1] Dalmau J & Rosenfeld M, Autoimmune encephalitis update. Neuro-Oncology 16(6), 771–778, 2014
[2] Lancaster et al. Encephalitis and antibodies to synaptic and neuronal cell surface proteins. Neurology 2011; 77:179

Autoimmune Encephalitis with Autoantibodies Against Neuronal Cell Surface Synaptic Proteins

• Better prognosis that T-cell mediated paraneoplastic syndromes: ~70-80% recovery w/ therapy (~20% relapse)

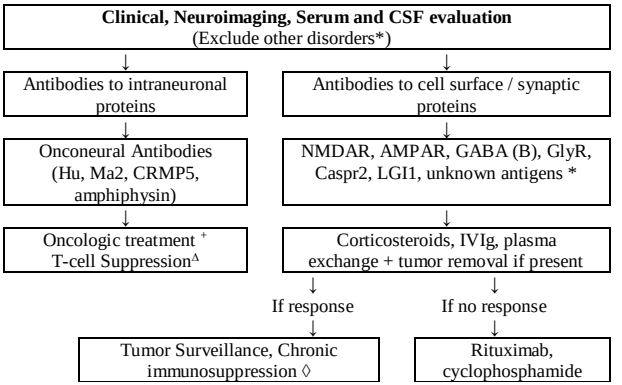
• **All of these syndromes can occur with or without neoplasms*****

Target Antigen	Syndrome	"Typical "Neoplasm (if present)	Notes
NMDA Receptor -most common	**Neuropsychiatric syndrome movement disorder, seizures, coma, autonomic instability**	**Typically teratoma (if any at all)**	**-Often young adults (women), adolescents and children.Antibody may also complicate HSV encephalitis cases**
AMPA Receptor	Limbic encephalitis, psychosis	~70% have lung, breast, thymus tumors	-often coexisting autoimmunities
LGI1 (formerly VGKC)	Limbic encephalitis, seizures, hyponatremia, myoclonus	~10% have thymoma	-"Faciobrachial dystonic seizure" -Often misdiagnosed as myoclonus or startle
Caspr2 (formerly VGKC)	Encephalitis and seizures, +/- peripheral nerve excitability & neuromyotonia	Rarely thymoma	-"Morvan's syndrome" -misdiagnosed as myasthenia or motor neuron disease
$GABA_B$ Receptor	Limbic Encephalitis & early, prominent/severe seizure	~50% SCLC /other lung neuroendocrine tumors	- often coexisting autoimmunities
$GABA_A$ Receptor	Status epilepticus or refractory seizures, encephalitis	None	-extensive multifocal MRI changes -often coexisting autoimmunities
DPPX	-Encephalopathy agitation, tremor, startle rigidity, seizure - Severe GI symptoms	None	Severe GI symptoms may mislead diagnosis
Dopamine-2 receptor	Basal ganglia encephalitis, Sydenham chorea	None	
mGluR1	Cerebellar Ataxia	Hodgkin Lymph.	
mGluR5	Limbic Encephalitis	Hodgkin Lymph.	Ophelia Syndrome

+Stiff-person syndrome			
Glycine Receptor	Stiff person, hyperekplexia, PERM, Encephalitis	Rarely w/ cancers	
Amphiphysin	Stiff person syndrome	Breast, SCLC	
GAD	-Stiff person syndrome -sometimes cerebellar ataxia and refractory seizures	Rarely thymoma and other tumors	-Reported in other syndromes with limbic encephalitis and epilepsy -often coexisting autoimmunities
Classic Antibody Associated Paraneoplastic Encephalitis, Associated with Intracellular Targeting Antibodies			
•All rare syndromes mostly older adults (an unusual presentation of something else should be considered first) •Almost always associated with a cancer •Intracellular targets w/ T-cell mediated response →**monophasic course w/ limited response**			
"Associated" Auto Antibody	Typical Neoplasm	Syndrome	
Anti-Hu	SCLC, other	-Paraneoplastic Encephalomyelitis (PEM) -Limbic Encephalitis -Brainstem encephalitis -Paraneoplastic Cerebellar Degeneration (PCD) -Paraneoplastic Sensory Neuropathy (PSN) -Autonomic Dysfunction	
Anti-Yo	Gynecologic, Breast	-Paraneoplastic Cerebellar Degeneration (**PCD)**	
Anti-Ri	SCLC, Gyn, Breast	**PCD**, brainstem encephalitis, opsoclonus-myoclonus	
Anti-CV2/CRMP5	SCLC, Thymoma, other	PEM, PCD, chorea, peripheral neuropathy	
Anti-Ma proteins	Germ cell (testis), lung, other solid Ca	Limbic encephalitis, hypothalamic encephalitis, brainstem encephalitis, (rarely PCD)	
Anti-Recoverin	SCLC	Cancer-associated retinopathy	
Anti-Tr	Hodgkin Lymph	PCD	
Anti-Zic	SCLC	PCD	
Other Autoantibody Syndromes Associated with Neoplasms			
Antibody	**Syndrome**	**"Typical " Neoplasm**	**Notes**
Anti-VGCC	Lambert Eaton Syndrome Cerebellar dysfunction	SCLC	Some autonomic features too (ganglionic CA channels)
Anti-AChR	Myasthenia Gravis	Thymoma	(less commonly Anti MuSK)
Anti-nAChR	Subacute dysautonomia	SCLC, others	

VGKC= Voltage-Gated Potassium Channel, VGCC=voltage gated potassium channel, AChR=Acetylcholine Receptor, nAChR=Nicotinic Acetylcholine Receptor

Diagnosis and Treatment of Paraneoplastic and Autoimmune Encephalitis



Workup and Treatment Guide for Immune Encephalitis:

***Start RPD workup first** (See section on RPD for detailed workup) including MRI w/wo contrast and lumbar puncture.
(may have CSF lymphocytic pleocytosis, elevated CSF protein, elevated peripheral inflammatory markers [ESR, CRP], and occasionally anti-thyroid antibodies as bystander autoantibodies.

→**Athena Diagnostic panels**

-Paraneoplastic Encephalitis (447): NMDA-R, VGKC (Caspr2, LGI1), Amphiphysin, GAD, CV2, Hu, Ma, Ta

-NeoComplete [467]: also includes Zic4 & CAR/Recoverin)

-Cerebellar Degeneration (438): CV2, Hu, Ma, Ta, Ri, Yo

-Neuropathy Panel (436): Amphiphysin, CV2, Hu

→Tumor screen: CT Chest, Abdomen, Pelvis (+/- mammography)

Legend:

• "Unknown antigens": not yet identified but visible using immunohistochemistry

Δ T-cell suppression strategies:
-decreasing T-cell activation (rituximab)
-cytotoxic T-cell mechanisms (cyclophosphamide, tacrolimus, or cyclosporine).

◊ Consider tumor surveillance and chronic immunosuppression in groups with High relapse: AMPA-R, $GABA_B$-R, Caspr2 & NMDAR (w/o tumor)

NEURO-ONCOLOGY

Edited by Peter Ljubenkov and David Piccioni, MD, PhD
(Source: Lectures by Dr. David Piccioni. Dr. Larry Hansen, and First Aid for the Neurology Boards Review)

Basic demographics:

Adults: 70% Supratentorial.
Common types: metastases (100k/ year)>> glioma (13k/year)> meningioma > schwannoma
Common mets: lung > breast > melanoma > renal > colorectal > lymphoma
→Hemorrhagic mets: (melanoma, choriocarcinoma, renal cell)> (thyroid, lung)

Children: 70% infratentorial
Common types: pilocytic astrocytoma>medulloblastoma>ependymoma.
Common mets: neuroblastoma, sarcoma, germ cell tumors.

Midnight Troubleshooting
(for the late night GBM case with declining neurological status)

1) Seizure management caveats: *Get EEG if change in mental status*
-Empiric prophylaxis not recommended (1B) w/o Hx of Sz (brief post-op course ok)
-After 1st seizure: Non enzyme inducing AEDs are preferable: **keppra & vimpat** typical (lamictal, topiramate, zonisamide, & gabapentin ok)
-depakote works but suppresses chemo metabolism (↑med) & theoretic bleed risk
-Treat status epilepticus (see pages 52-53)
-2mg ativan q5min, up to 8mg, 20mg/kg PE fosphenytoin, etc.

2) Mass effect and ICP issues:
-Vasogenic edema management: Load 10mg IV decadron, then start 4-10 mg BID
-Starting dose should be at least double patient's outpatient dose (max 40mg/day)
-GI and endocrine issues: start PPI & ISS (metformin as outpatient)
-side effects: psych., osteoporosis(bisphosphonates), spinal lipomatosis, infection
-**Herniation:** BRAIN CODE - (ventilate, head up, osomol, CT, nsrg)

3) ID: neutropenic fever workup:
-**EMERGENCY**! Blood culture x2, urine culture, CXR, KUB,
-CSF cultures (esp if recent surgery),
-immediate broad-spectrum antibiotics after blood cultures drawn, w/in 1 hr
•If afebrile and ALC < 600:
Bactrim DS MWF, or dapsone 100 mg QD, or Mepron QD
•If afebrile and ANC < 500
Cipro 500 mg BID

PRIMARY CNS TUMOR SUBGROUPS	
1. Glial	Astrocytic: Circumscribed astrocytomas: (I), pilocytic astro, SEGA Diffuse astrocytomas: -low grade astrocytoma, PXA (II) -anaplastic astrocytoma (III), -high grades: GBM (IV), gliomatosis cerebri, gliosarcoma Oligodendroglial: oligodendroglioma (II), anaplastic oligodendroglioma (III) Mixed: oligoastrocytoma (II), anaplastic oligoastrocytoma (III)
2. Meningeal	-Meningiomas: (I) benign, (II) atypical, choroid, clear cell, (III): rhabdoid, papillary, anaplastic -Hemangiopericytoma
3. Embryonal	Medulloblastoma, PNET, (pineoblastoma is a pineal PNET)
4. Sellar region	pituitary adenoma, pituitary carcinoma, craniopharyngioma, rathke's pouch cyst
5. Pineal region	pineal cyst, pineocytoma, pineal tumors of intermediate diff., pineoblastoma, pineal parenchymal tumors (II), (pineoblastoma (III) a PNET variety)
6.Ependymal	Myxopapillary ependymoma (I), ependymoma (II), anaplastic ependymoma (III)
7. Germ cell tumors:	Germinoma, Embryonal carcinoma, yolk sac tumor, choriocarcinoma, teratoma, mixed germ cell
8. Neuronal	DNET, ganglioglioma and gangliocytoma (I-II), central neurocytoma (II)
9. Choroid	choroid papilloma (II), choroid carcinoma (III)
10. Nerve Sheath	Schwannoma, malignant peripheral nerve sheath tumor (MPST)
11. CNS lymphomas	PCNSL, intravascular lymphoma
12. Other:	Hemangioblastoma, chordoma (clivus or sacrococcygeal), lipoma

Ward Field Guide to Primary CNS Tumors:
4 steps of tumor identification: 1) What is the age of the patient? 2) Where is it? (anterior or posterior fossa? intra or extra axial?) 3) Generate list of possibilities (given answers from 1 and 2) 4) Look at tumor appearance

Common Adult CNS Tumors By Location

I. Supratentorial Region Tumors

A. Glial tumors

•Low-grade astrocytoma (grade II):

Rads:-Infiltrates white matter (deficit<image)

-Don't enhance (except pilocytic astrocytoma)

•Anaplastic astrocytoma (III):

(+mitosis →may enhance [most don't])

Genetics: If IDH1 & IDH2 mutation (isocitrate dehydrogenase) then↑survival (grade II, III & 2ºIV)

•**Oligodendroglioma** (grade II and "anaplastic" grade III)

R: T1 hypo, T2 hyper, rarely enhance (+/-dark calcific blooming),

P: fried egg (perinuclear halo), uniformed cellularity,

-mixed type known (look like oligo early, and GBM later)

-1p/19q loss of heterozygosity: signature for in oligos→ better survival, radiation +"PCV chemo" (procarbazine, CCNU, vincristine)

T: (no cure, but can be treated well): chemo, radiation, grade III, median survival >14 years

•**Glioblastoma/GBM (IV)** (Most common 1º adult brain malignancy)

Radiology: enhancing, heterogeneous (necrosis), may cross corpus callosum ("butterfly glioma") ↑blood volume on MR perfusion

Pathology: "pseudopalisading necrosis" and endothelial proliferation.

Genetics:

-**MGMT promoter methylation** - predicts better outcome/ survival w/temodar

-2˚ GBM pathway: p53 mutation, IDH 1/2 mut

-1˚ GBM pathway: PTEN mutation, EGFR amplification EGFRvIII variant, p16 deletion

GBM Treatment:
(1) maximal safe resection (depends on location)
(2) then concurrent temodar & XRT daily for 6 weeks with PCP prophylaxis
(3) then pulsed temodar, 1st 5 days of every 28 day cycle for 6-12 month. ANC nadir at day 21.
(4) if recur: Clinical trial, CCNU or Avastin (anti-VEGF). q2 weeks.
Avastin side effects: HTN (treat with ACEi, ARB or norvasc), hemorrhage, (ICH, colon if diverticulitis) PRES, stroke, clots (need to anticoag if DVT/PE develops)
Survival: 3 months w/o treatment, median 16 months w/ (longest if MGMT)

B. Meningioma:
(demographics: older adults, females [estrogen responsive ↑size], people post radiation*)

R: Heterogeneously enhancing* with dural tail* (may also be near brainstem, spinal canal, optic nerve, choroid plexus)
T: Follow with imaging at 3, 6, 12 months to see if lesion is growing →follow clinically if stable.
-resect if growing or symptomatic (→high dose XRT if recurs or anaplastic)
-may need AEDs

C. Primary CNS Lymphoma (PCNSL):

R: Ring-enhancing lesions (if HIV positive, homogenous enhancement if immunocompetent), Isointense on T2, often periventricular with subependymal enhancement (note: pure subependymal pure intravascular variants exist)
Thallium 201 chloride spect + (distinguish from look-alikes)
Diagnostic workup NO steroids prior to biopsy! PCNSL is very sensitive to steroids)
-HIV screen (considered an AIDS-defining condition) & CSF EBV PCR (+)
-CSF:
-flow cytometry (must call lab to coordinate first) & cytology
-r/o others stuff: CSF toxo serology (-), CSF CMV
-LDH, plus ILR2 & β2 microglobulin (specific, not sensitive)
staging exam: Neuro-optho *(get ocular lymphoma!), neuraxis, chest/abdomen/pelvis
- biopsy, off steroids preferred
-consider bone marrow bx and/or testicular US
P: perivascular cuffing w/ malig. lymphocytes, usually B-cell
T: treat the HIV (may be sufficient alone)
→Methotrexate+rituximab +/- temozolomide (hold out on whole brain radiation, especially if old)
→frequently remission

D. Lipoma: T1 Bright** - only blood and fat do this. Benign but can get big. Often attached to quadrigeminal plate

II. Peri-sellar Region Tumors: (Note: 3rd vent. masses rarely arise from 3rd vent., may be pineal or peri-sellar)

A. Pituitary adenoma

(may present with apoplexy or bitemporal hemianopsia

Rad: contrast enhancing, can look like dumbbell or "snowman" (pinched between dura)

Dx: prolactin >200ng/m (prolactinoma), IGF-1↑ (if acromegaloid) 24 hr urine cortisol (if ACTH secreting), also check TSH, T3, T4, FSH, LH, prolactin

Tx:-transsphenoidal surgery, cabergoline or bromocriptine for prolactinoma

surgical complications:

-cavernous sinus involvement (may have CN VI palsy)

-triple phase response (DI→SIAH→DI)

-residual pituitary tissue.

B. Meningioma – see page 113

C. Giant carotid aneurysm- may look like a tumor

D. Craniopharyngioma – (occasionally also 3rd ventricle)

R: 95% are cystic (fluid-fluid level) with solid enhancing components, often proteinaceous

P: Cholesterol rich "crankcase oil"

Tx: resect and XRT (subtotal resection= worse prognosis, frequent recurrence)

III: Posterior Fossa

A. Schwannoma: (CN VIII >> CN X, VII, V >> all others) BL in NF2

B. Brain Stem Glioma (see glioma discussion above): location determines feasibility of treatment

-Diffuse T2 hyperintensity, increased diameter of pons. Occasionally enhancing. Treat as GBM

C. Hemangioblastoma: cystic with enhancing nodule. Can confirm with angiogram. Tx with resection.

IV: Common Spinal Tumors

A. Extradural: Mets

B. **Intradural Extramedullary:** schwannoma, meningioma, leptomeningeal mets, neurofibroma

CSF "goblet sign" on imaging

C. **Intramedullary**

(often w/ 2º caudal cyst): ependymoma, astrocytoma, GBM

(**Note:** myxopapillary ependymoma is the most common cauda equina tumor, tx with surgery + XRT)

Common Pediatric CNS Tumors by Location

I. Posterior Fossa (**the hot spot for primary CNS tumors in kids!**)

A. Pilocytic astrocytoma (grade I)

~1/3 of tumors in posterior fossa

R: Cerebellar hemisphere (95%) > (brainstem, hypothalamus, optic nerve)

– usually cystic + solid enhancing mural nodule.

P: Rosenthal fibers, eosinophilic granular bodies,

Treatment: 95% completely resectable/curable

B. Medulloblastoma ~1/3 (just under pilocytic astrocytoma)

R: Midline (4th ventricle, often from vermis), rounded w/ mass effect

***heterogeneous on T1 & T2 and enhances

***Drop mets common: MR spine survey w/wo contrast

-Followed by LP for cytology (8-10 ml) and

G: WNT group: good survival, (treat less)

Treatment:

surgery if possible→ combo chemo & screen CSF

-SSH group: use vismodegib

C. **Ependymoma** (~1/6)

R: Midline (4th ventricle), heterogeneous enhancement

Soft mass: tends to take shape of ventricle with inferior point & growth through foramina

P: perivascular pseudorosettes

Treatment: MRI spine survey c/s contrast plus CSF for cytology (LP after spine MRI) resection + RT (No RT in the very young to avoid developmental delay, chemotherapy instead)

D. **Brainstem glioma** (1/6)

-Brainstem. diffuse intrinsic pontine glioma(DIPG)

II. Supratentorial Region Tumors

A. Primitive Neuroendocrine Tumor (PNET) -

(see medulloblastoma discussion/workup)

histology of a medulloblastoma but different outcomes

-Cerebral **neuroblastoma** subtype: - associated with paraneoplastic opsoclonus-myoclonus

B. Dysembryoplastic Neuroepithelial Tumor (DNET)

-looks like a cortical dysplasia: can cause seizures that are cured with resection

C. Ganglioglioma/Gangliocytoma: Cyst with enhancing mural nodule. Intractable seizures can be cured w/resection

Path: mixed glia and neuron w/ proliferating ganglion cells + eosinophilic granular bodies

III. Perisellar Region Tumors (in order of occurrence)

A. Craniopharyngioma – Far and away most likely (see discussion in adult section, page 114)

B. Hypothalamus/chiasm glioma – Pilocytic enhances / low-grade fibrillary does not enhance

C. Germinoma– (M>>F in this region; dense on CT, enhances on MRI) -↑ β-HCG
-High cure w/ resection

IV: Pineal Region Tumors (in order of occurrence)

- Difficult to differentiate on MRI, but vast difference on path
- Note, the pineal gland should not calcify before age 6 (otherwise think tumor)
- May present with **Parinaud's Syndrome**
  1. Paralysis of upgaze
  2. Light-near dissociation (respond to near but not to light)
  3. Convergence -retraction nystagmus
  4. "Setting-sun sign" - eyes in conjugate down gaze in primary position
  5. Eyelid retraction

1. Germinoma: (10-20:1 M>>F in this region; dense on CT, enhances on MRI) (markers negative or very low) High cure w/ resection, multi-agent chemotherapy + XRT
2. Pineocytoma:
3. Pineoblastoma (PNET of the pineal gland): needs aggressive multiagent chemo +XRT
4. Teratoma (look for fat – bright on both T1/T2)
5. Other germ cell: - ↑**β-HCG**: choriocarcinoma
   - ↑**AFP:** yolk sac/endodermal sinus, embryonic cell
6. Astrocytoma (see earlier discussion)

Neurocutaneous Syndromes Associated with Neoplasms				
	genetics	Tumors associated	Findings	Treatment
NF1 (Dx as kids) ~1/3K	Ch. 17 Auto. dom.	**"NO"** -**N**eurofibromas (spine, peripheral nerve, skin) -benign**O**ptic gliomas (15%) (also rarely the NF2 tumors)	-cutaneous neurofibromas -cafe au lait spots -Axillary/inguinal Freckles -Lisch nodule (iris)	"watch & wait" -neurofibromas: Surgery only for symptoms -Optic gliomas: Surg. and XRT only for aggressive growth or vision compromise; may self-resolve
NF2 (Dx as adults) ~1/30K	Ch. 21 Auto. dom.	**"MISMEG"** -**M**ultiple **I**nherited **S**chwannoma -**M**eningiomas -**E**pendymomas -Rare **G**liomas	-hearing loss -cataracts -NB: skin findings very rare	Surgery or XRT for tumors
TS Tuberous Sclerosis	Ch 9 &16 TSC1 & TSC2 Auto dom.	**SEGA** (subependymal giant cell astrocytoma) **Renal Angiomyolipomas** -can bleed! Cardiac Rhabdomyomas	**Clinical** •Vogt's Triad (~50%) - Mental retardation -Seizures -Facial Angiofibromas •Shagreen patches •Ungal fibromas **Rads:** -Cortical tubers -periventricular nodules	Everolimus for SEGA Treat Seizures -vigabatrin in infantile spasms

Cancer Syndromes with CNS tumors			
Syndrome	**Genetics**	**Tumors associated**	**Clinical Notes**
Li-Fraumeni	p53 auto dom.	25% have malig. by 50 Breast> GBM> leuk> sarcoma> others	
Von Hippel-Lindau	VHL gene	-multiple Cerebellar & cord hemangioblastomas -RCC -Pheochromocytoma	-Surgery & XRT for symptomatic lesions -consider Avastin -look like pilocytic astrocytomas on MRI (but not the same path)
Gorlin	PTCH gene	-early medulloblastoma -early non-melanoma skin cancer	Early ectopic falx calcifications
Turcot	MMRCS (mismatch repair)	"Brain Tumor Polyposis Syndrome" -gliomas -medulloblastoma -colorectal tumors	(Lynch syndrome if bi-allelic)
Cowden	PTEN	-Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos) -Colon polyps -breast & thyroid cancer	

MYELOPATHY & SPINAL CORD INJURY

Edited by Peter Ljubenkov, MD, David J. Lee, MD, PhD, and Ross Mandeville, MD

Sources: [1] Beh et al. Transverse myelitis. NeurolClin. 2013 Feb; 31(1):79-138.
[2] Bracken MB. Steroids for acute spinal cord injury. Cochrane Database SystRev. 2012 Jan 18;1:CD 001046.
[3] Uptodate.com
[4] Bradley's Neurology in Clinical Practice, 6th edition

Initial Evaluation:

• ABCs and stabilization: see neuromuscular emergency (page 123)
-call neurosurgery early if trauma or compressive condition likely

• **H&P:** -breathing difficulty, bowel/ bladder incontinence, ataxia, sexual dysfunction.
-obtain history of vaccination, recent illness, past radiation
-Exam: sensory level, motor (UMN pattern weakness), ↑ reflexes (↓ if acute), ASIA level.

•MRI relevant spine level w/wo contrast + DWI (+MRI brain if likely demyelinating)

Differential Diagnosis for Myelopathy [1]

(This is not an exhaustive list)

• **Compression/ Anatomic Injury:** Acute trauma, spondylosis, epidural abscess (fever), epidural hematoma, syrinx

• **Transverse myelitis** (will be apparent on imaging)

- **Acquired Demyelinating:** **
  - **Multiple sclerosis**
  - **NMO** (multiple segments, +/- BL optic neuritis)
  - **ADEM**
- **Infectious/parainfectious:** West Nile virus (polio-like syndrome), herpes viruses (HSV, CMV), HIV, HTLV-1 (in Asia), Lyme, Mycoplasma, syphilis, Tuberculosis.
- **Paraneoplastic:** Necrotizing myelopathy (NMO-spectrum?), Motor neuron syndrome, anti-Hu, anti-CRMP5 /CV2 antibodies, (often antibody negative)
- **Systemic autoimmune:** Neurosarcoidosis, Ankylosing spondylitis, Antiphospholipid antibody syndrome, Behçet disease, Mixed connective tissue disease, Rheumatoid arthritis, Scleroderma, Sjögren syndrome, SLE

• **Metabolic and nutritional:** ↓B12, ↓ Vit D (MS risk?), ↓Vit E, ↓Copper (may be Zinc supplement induced), hypothyroidism

• **Primary neurological diseases**: ALS, hereditary spastic paraparesis, adrenoleukodystrophy/adrenomyeloneuropathy

• **Neoplasms**: Spinal ependymoma, Glioma, Primary CNS lymphoma, Intravascular lymphoma

• **Drug/toxin-induced:** NO toxicity, neurolathyrism, neurocassavism, radiation

• **Vascular myelopathies**: Anterior spinal artery infarction, Spinal-dural arteriovenous fistula, AVM (compressive), aortic aneurysm, artery of adamkiewicz injury (anterior cord syndrome), ischemia from severe hypotension, fibrocartilaginous embolism, vasculitis

Workup for Transverse Myelitis:

First Tier Work -up

• **Serum Labs:** Serum anti-aquaporin 4 IgG, serum B12, methylmalonic acid, HIV, syphilis serologies, serum
ANA, Ro/SSA, and La/SSB antibodies, TSH, ESR, CRP

• **Lumbar Puncture:** cell count and differential, protein, glucose, VDRL, gram stain, bacterial/fungal cultures, AFB, Cytology, MS panel (oligoclonal bands, IgG index)

Second Tier Workup

Serum Vit E, Copper, CSF Herpes PCR (HSV, CMV), CSF flow cytometry

For patients with longitudinally extensive spinal cord lesions:

Anti-RNP, Anti Scl-70, Anti Jo1 anti-phospholipid Ab, P-ANCA, C-ANCA
-Chest CT to evaluate for evidence of sarcoidosis, ACE (serum +/- CSF)
- consider repeat anti-aquaporin 4 IgG if high pretest probability for NMO

Additional Testing for select patients

• CSF cytology and flow cytometry (CNS lymphoma)
• Neuro-ophthalmologic evaluation
• Paraneoplastic panel (especially CRMP5/CV2), Infectious serologies, VLCFA
• Spinal angiogram (if suspect AVM)
• VLCFA: if suspect adrenomyeloneuropathy

Management of Myelopathy

Spinal Cord Trauma and Acute Compressive Myelopathy

- If acute injury suspected, don't hesitate to start treatment before imaging.
- Neurosurgery/Orthopedics evaluation STAT.
- **Steroids for traumatic cord injury:** Bracken high-dose protocol [1]
  - •If<8Hr, methylprednisolone 30mg/kgx1 over 15min, then 5.4 mg/kg/hx 23H.
  - •If >8Hr, steroids not effective.

NOTE: Some neurosurgical and cord societies recommend steroids only as an option rather than the standard.

Acute Management of Transverse Myelitis

(Note, will depend heavily on etiology)

- **Methylprednisolone** 1g daily x 3-5 days
- **Plasma exchange: for NMO or for other demyelinating disease that fails to respond to steroid**
  - you don't need to wait until steroids finish if very bad
  - 5 treatments, each with exchanges of 1.1 to 1.5 plasma volumes, every other day for 10 days
- Some disorders, such as NMO, may require Rituximab
- (See separate chapter for MS management, page 104-106)

Cord Compression Due to Neoplasm
- Neurosurgery/Orthopedics evaluation STAT
- Dexamethasone 10 x1 IV bolus (depending on severity)
then 4 mg Q6H IV/PO, gradually tapered after more definitive treatment

Chronic Cord Compression from Spondylosis
(no good evidence based guidelines)
• Error on the side of neurosurgical consultation
• Mild, non-debilitating myelopathy (possibly can defer surgery?)
  •Neurosurgery may opt for close neurologic follow-up along with **Conservative measures** (intermittent neck immobilization, pain management, and restriction of high-risk or aggravating activities), rather than surgery
• **Severe myelopathy or progressing deficits →surgical decompression**

General Myelopathy Management Issues
- **Telemetry- potential autonomic dysfunction**
- GI PPx if giving steroids.
- check PVR, intermittent bladder catheter or foley as needed
- Assess EtOH/substance withdrawal, and give empiric thiamine (trauma patients_
- PT/OT

SPINAL CORD SYNDROMES: [4]

symptoms are distal to the lesion (ie there's a level).

• Central cord syndrome (neck hyperextension): weak Arms>Legs, variable sensory disturbance, loss of bladder control.

• Anterior cord syndrome (neck flexion, anterior spinal art): weakness (corticospinal); hyperesthesia + hypoalgesia (spinothalamic); spares dorsal columns.

• Posterior column syndrome (neck hyperextension): loss of proprioception and vibration, retained spinothalamic (pain/temperature).

• Brown-Sequard syndrome (penetrating injury, disk herniation, hyperextension, compression): Ipsilateral deficits of corticospinal, dorsal column; contralateral deficits of spinothalamic tract.

• Cervicomedullary syndrome (atlantoaxial injury/fx, herniated disc): respiratory failure, hypotension, tetra-paresis, hyperesthesia, onion-skin pattern sensory loss of face (spinal trigeminal nucleus).

Conus Medullaris Syndrome [4]	Cauda Equina Syndrome [4]
Upper and lower motor neuron involvement	**Lower motor neuron** involvement
Symmetrical motor impairment (weak legs)	**Asymmetrical** motor impairment
Vertebral column injuries between T12-L2	Vertebral column injuries distal to L2
Absent deep tendon reflexes in legs, though patellar may be spared	Absent deep tendon reflexes in legs
Permanent areflexic bladder (low-pressure, high PVR)	Permanent areflexic bladder, usually later onset than in CM
Absent bulbocavernosus reflex	Absent bulbocavernosus reflex

NOTE: Cauda Equina Syndrome is a neurosurgical emergency. If it is suspected get a STAT MRI and call neurosurgery if confirmed

Complications of Myelopathy

Neurogenic bladder:

• LMN lesions: (lesion below the conus medullaris):
areflexic/hyperreflexic detrusor
→ normal external sphincter→ intact detrusor-sphincter coordination
→ low bladder pressure + high PVR (treat with intermittent cath).

• UMN lesions: (lesion above the conus):
Disrupted pontine modulation (detrusor-external sphincter dyssynergia),
→ detrusor over activity
→ high bladder pressure + high PVR (can injure upper urinary tract).

Delayed post-traumatic spinal cord syndromes and complications:
• syringomyelia
• neuropathic pain
• spasticity
• sexual dysfunction
• autonomic dysreflexia
• DVT/PE.

ACUTE NEUROMUSCULAR EMERGENCIES

Edited by Peter Ljubenkov, MD, David Lee, MD, PhD, and Chamindra Konersman, MD

Source: The Washington Manual Neurology Survival Guide, 2004; On Call Neurology 2nd Ed,

I. General Rules for Neuromuscular Emergencies

Common for GBS, myasthenic crisis, Botulism, acute myelopathy, crashing/decompensating ALS, etc.

1) Respiratory monitoring for ALL patients

- **STAT:** immediately check negative inspiratory force (NIF) and forced vital capacity (FVC) and
- Check FVC and NIF q 2-6 hours (often q4), depending on patient's respiratory values (O2 and ABG not reliable)

2) Have a very low threshold for ICU:

- tenuous respiratory status/hard to clinically assess
- possible associated **cardiopulmonary instability, autonomic issues**-Must monitor on telemetry (especially GBS)

3) Intubate early and preferably electively:

(they decline quickly, are too tired to show distress)

TYPICAL CRITERIA FOR INTUBATION

- **NIF <-20** cm H2O (start discussing elective intubation @ -25)
- reduction of **FVC to 15ml/kg** ideal body weight (approximately 1L in a 70 kg person) or rapid decline

Other criteria for intubation:

- PO2 < 70 mm Hg on room air
- PCO2 > 50mm Hg associated with acidosis (pH<7.35)
- Positive expiratory force < 40 cm H2O
- Tidal volume < 5ml/kg
- Severe dysphagia /inability to protect the airway, or strider

II. Specific Acute Management of Guillain-Barré syndrome/AIDP:

-acute (<2 mos), monophasic, rapidly progressive polyneuropathy, symmetric weakness (typically ascending), absent/depressed DTR's.
-May be preceded by surgery, vaccination or illness: Respiratory (mycoplasma pneumoniae), GI (c.jejuni), viral infection (CMV, HIV, EBV).

- Treatment -**Don't wait:** Treat clinical diagnosis not labs/ NCS (studies might be negative)
  -**Cardiac and respiratory** monitoring as discussed above
  -**PLEX of IVIG** as discussed in Myasthenia section (NOT steroids)
- Workup (aside from basic labs)
  -CSF: may have albumino-cytologic dissociation (↑ protein, normal WBC)
  Also useful to rule out infectious mimics
  -Serum: anti-GQ1B for miller-fisher or Bickerstaff presentations
  -EMG/NCS: may be normal in acute presentation or just loss of H-reflex. Eventually decreased velocities in demyelinating variants and decreased amplitude in axonal variants

• GBS Subtypes/variants:

•AMAN/AMSAN: axonal, Asians, preceded by campylobacter jejuni in summer (antibodies to gangliosides GM1, GD1a, GalNac-GD1a, and GD1b of nerve axons).

•Miller Fisher syndrome (MFS): ophthalmoplegia, ataxia, areflexia. Anti-GQ1b (IgG).

•Bickerstaff brainstem encephalitis: encephalopathy, hyperreflexia. Overlaps with MFS (ophthalmoplegia, ataxia). Anti-GQ1b.

•Pharyngeal-cervical-brachial weakness: oropharyngeal/dysphagia, neck, shoulder. Overlaps with MFS. Legs usually spared. Anti-GT1a, Anti- GQ1b, or Anti-GD1a.

III. Specific Acute Management of Myasthenic Crisis

• Stabilize clinically and trend respiratory status, per discussion on page 123
-may also trend neck flexion/extension (correlates with respiratory ability), sustained upward gaze, counting numbers, etc.

•**Eliminate triggers**:
-Treat infection, metabolic derangements
-Avoid culprit drugs: Magnesium, aminoglycosides, other antibiotics, steroids, anti-arrhythmics, beta-blockers, succinylcholine, increased doses of cholinesterase inhibitors) (see page 131 for larger list)

•**Direct Intervention:** plasmapheresis vs IVIG (note, all are transient)
-**Plasmapheresis (PLEX):** typically 5 exchanges. More rapid but may cause hypotension, coagulopathies, electrolyte derangements, removal of protein- bound drugs.
-**IVIG:** 2 g/kg total (usually 0.4g/kg x 5 days)

•**Other possible interventions**:
-**Steroids**: prednisone 1 mg/kg/day IV. Good for more sustained effect, but paradoxical acute worsening (must give after PLEX or IVIG)
-**Cholinesterase inhibitors**: May initially ↑ weakness, ↑secretions, and cause cholinergic crisis w/ pyridostigmine>120mg PO Q3Hrs

IV. Specific Management for Botulism

•Same initial stabilization as discussed on page 123

•Diagnosis: progressive bulbar weakness, unreactive pupils, and descending weakness

-Serum studies/mouse bioassay: Call CDC and toxicology fellow and send serum BEFORE treatment (DO STAT!)
-may also perform analysis on stool and vomit

-EMG/NCS: (may be useful but are not generally required)
NCS: CMAPS small, but normal SNAPS
Repetitive nerve stimulation: Decrement at 3Hz, Increment at 40Hz (50% to 60% of patients)
EMG: CMAPs Small & short. Recruitment:

Normal, or mildly reduced. Muscle denervation; Fibrillations & Positive sharp waves

-Examine for wound botulism (especially IV drug users)

-LP if any signs of meningismus

• Botulism Treatment: (You should send off serum studies first, but don't wait for studies to result. They take to long and may be negative)

- **Antitoxin:** Call State Health Department and they will contact the CDC to request release of botulism antitoxin. The regional Poison Center State Health Department representatives after hours (calling 1-800-222-1222 automatically forwards the caller to the regional Poison Center). If there is no response, the CDC Director's Emergency Operations Center should be contacted (770-488-7100)

- **Antibiotics for wound botulism:**

Penicillin G - 3 million units IV Q 4 hrs in adults or

Metronidazole 500 mg IV Q8 hrs if penicillin allergy

Expanded DDx for acute/subacute generalized neuromuscular weakness

- **Brainstem lesion:** stroke, ICH, central pontine myelinolysis
- **Acute Myelopathy:** acute compression and transverse myelitis (persistent asymmetry, bladder/bowel, sensory level)
- **NMJ disorders:** MG, LEMS, paralytics (especially in ICU patients in renal failure).
- **Inflammatory neuropathy:** GBS/AIDP, AMAN, AMSAN, vasculitis, paraneoplastic
- **Myopathic:** CIM, Medication-induced (steroids, statins, colchicine, HIV meds), inflammatory, rhabdo, Acid maltase deficiency, acute Myosin deficiency (drugs, steroids, transplant, critical illness), Periodic paralysis, mitochondrial.
- **Electrolytes:** (hyper/hypo-K, hypo-Na, hypo-Ca, hyp**er**-Mg).
- **Infectious:** Viral (polio, JC, WNV, HIV, rabies). Bacterial (diphtheria, brucellosis)
- **Toxin:** Venom (snake, spider, fish, tick). Botulism. Metals (arsenic, lead, thallium). organophosphates.
- **Meds:** lithium, gold, vincristine, vecuronium, succinylcholine etc.)

MYOPATHIES

Edited by Peter Ljubenkov, MD, Amir Sabouri, MD, PhD, & Chamindra Konersman, MD

10 Clinical Patterns of Myopathies

1. Limb Girdle: proximal and symmetric weakness
- -Difficulty rising from a chair, climbing stairs, reaching up
- -Most Myopathies follow this pattern (acquired and genetic)
  - -[CK↑] Becker's (BMD), Duchenne (DMD), polymyositis, dermatomyositis
  - -drugs (steroids, statins, colchicine, HIV meds), toxins, endocrine (hypothyroid)

2. Distal: distal symmetric weakness
- -May mimic periph neuropathy or NMJ issue, but spare EDB
- - Myofibrillar myopathies, Desmin, Miyoshi's, Myotonic Muscular dystrophy type 1 (DM1)

3. Proximal Arm and Distal Leg: scapuloperoneal
- -Periscapular Muscle (winging), anterior distal leg (foot drop sparing EDB)
- -FSH (+face, and asymmetric), Emery Dreifuss (contractures, arrhythmia)
- (also acid maltase deficiency, congenital scapuloperoneal)

4. Distal Arm and Proximal Leg: (may spare face but dysarthria common)
- (IBM) Inclusion Body Myositis (quads & finger flexors worst)
- Myotonic muscular dystrophy type 2(also consider ALS)

5. Ptosis and/or Ophthalmoplegia:
- Oculopharyngeal Muscular Dystrophy (OPMD), Mitochondrial (including Kearn-Sayer), POLG alpha, Myotonic muscular dystrophy

(also consider NMJ issue/myasthenia – more symptomatic diplopia)

6. Neck Extensors:
- -ALS & Myasthenia >INEM (isolated neck extensor myopathy)

7. Bulbar: (tongue and pharynx)
- -OPMD
- -also consider myasthenia/NMJ disorders, and motor neuron disease (ALS, Kennedy's if male w/ gynecomastia)

8. Episodic Weakness + Rhabdo/Pain + Trigger:
- -Mcardle's Disease [episodic myoglobinuria, ↑CK], Drugs, Toxins,
- CPT (carnitine palmitoyltransferase)

9. Episodic Weakness, with delay from or no relation to exercise:
- - Primary Periodic paralysis [↑↓K]
- (with cold, heat, stress, carbs)
- - Secondary periodic paralysis (hyperthyroidism)

10. Stiffness/unable to relax:
- -Myotonias [worse w/ cold]: Myotonia congenita (worse with exercise), paramyotonia (better with exercise)
- -Myotonic muscular dystrophies (DM1 and DM2/PROMM-more proximal) (also consider SPS & dystonia)

NEUROMUSCULAR JUNCTION DISORDERS

Edited by Peter Ljubenkov, MD and Chamindra Konersman, MD

Myasthenia Gravis

Auto-Ab mediation postsynaptic NMJ attack → ↓ AChR available →fatigable weakness

Presentation: fatigable, weakness, diplopia, dysarthria, and dysphagia worse with stress, with heat, and especially at the end of a day

Bimodal distribution: 20-30y→mostly ♀; 40-50y→♀=♂; if 50-60y→mostly ♂

Precipitating factors: (especially bad at end of day)

sustained exercise/exertion, systemic infection/fever/any cause of elevated temperature, hypo/ hyperthyroidism, pregnancy (may trigger first presentation), and drugs that interfere w/ NMJ transmission (pg 131)

Clinical variants and associated features- **Mostly driven by AChR Abs**

• **Ocular MG**: isolated to extraocular muscles (not pupils) & eyelids: ptosis and diplopia

-if it remains ocular ≥ 2 years, it won't generalize

-will reports difficulty watching TV

-eye closure weak - may note Bell's phenomenon w/blinking

- Ptosis worse with upgaze ≥30s

• **Ice pack test:** will temporarily improve ptosis (89% sensitive)

• **Cogan's lid twitch**: lid overshoots and falls back to ptosis again when looking rapidly from downward to primary position

• **Generalized MG**: ocular features & generalized fatigable weakness

- Oropharyngeal: dysarthria, dysphagia, nasal speech, breathy voice. May have absent palate elevation, tongue weakness,

-Facial: look depressed' or 'expressionless'

-myasthenic snarl w/smiling only middle lip contracts

-weakness in pursing lips, puffing out cheeks

-Axial: neck flexor/extensor muscle weakness - may have dropped head

-difficulty climbing stairs & overhead tasks

-smooth/cardiac muscle not sparred

- **May have respiratory weakness/failure**

-Appendicular muscles: (proximal > distal muscle weakness)

-any muscle group, usually asymmetric, but normal DTRS

-no muscle atrophy, DTRs normal

• **MuSK Ab + MG:** distinctive pattern from AchR positive MG

- bulbar and cranial muscles weakness, but often sparing of ocular muscles. Mostly neck, shoulder, respiratory weakness

- ↑ respiratory crisis

- improvement w/ PLEX and variably to mestinon

- NO response to IVIG or thymectomy

•**Neonatal MG**: passive transfer of Ab from mom w/MG→ transient neonatal weakness

•**Congenital myasthenic syndrome** = genetic mutations to NMJ (not an Ab)

MG Workup: Perform tests in the following order
1) Confirmatory antibody testing for "Seropositive MG": • **1st: Anti- AChR antibodies:** (always IgG) -may be binging, modulating or blocking. Sens. 92% in generalized & 58% in ocular. Specificity is 99% • **2nd:** Anti-Musk antibodies (+ in ~40% AChR negative patients • Only ~9% of suspected MG pts will ultimately be "seronegative MG (-Anti-striatal Ab: rarely tested- positive in 75-80% of pts with thymoma)
2) NCS/EMG - not needed if Ab positive and clinical picture correct (note: Must stop mestinon prior to test) - **Single fiber EMG**: (most sensitive test for MG, but not many MDs do it) 90% sensitive for ocular, 99% for generalized MG - **Repetitive Nerve stimulation** - (decrement with 2-3Hz) - 60% sensitive for generalized
Chest CT - to look for thymoma if MG diagnosis is
(Tensilon test - almost never done anymore. ~60-95 sensitive for ocular)
Outpatient Treatment of Myasthenia Gravis:

• **Pyridostigmine (Mestinon):** first line for symptomatic relief, works fast
Dosing: 60mg po tid/qid (max ~ 1,500 mg/day, divided 4-6x/day)
SE: cramps, diarrhea, ↑bronchial secretions, arrhythmias
Note: Limited utility in decompensating patient & may make them worse
Note: symptom management is not sufficient to avoid long-term permanent weakness, and should not be sole treatment in patients with night dyspnea

• **Prednisone:** 1st line agent to avoid irreversible weakness
Dosing: start 5-10mg po/day, may titrate 5mg/week until weakness is controlled
high dose regimen—60-80mg po qd - 10-20% will get paradoxical ↑↑ weakness in 2 wks
titrate off: extremely slowly (many months) only if stable on steroid sparing alternative
SE: Myopathy (try to avoid doses over 40mg), adrenal suppression, HTN, weight gain, osteoporosis, cataracts, acne, thin skin, PUD, insomnia, DM, buffalo hump, moon facies
Mitigating side effects:
-Calcium (1200-1500mg/d) with Vit D (600-800IU) to minimize osteoporosis
-get flu & pneumococcal shot
-low calorie, high protein, low fat diet

Steroid sparing agents: Consider starting simultaneously to steroids to limit steroid exposure. These are highly recommended, even in children with ocular myasthenia requiring prednisone. Ultimate goal in most patients is to cross -titrate prednisone with a steroid-sparing agent. Only consider titrating SLOWLY off if stable over 2 years.

• **Azathioprine (Imuran**) The most typical 1st line steroid sparing agent
Dosing: start 50mg po daily; stay on lowest necessary dose (1-3mg/kg/d)
takes ~ 6-12mo for full effect
SE: GI upset (most common) marrow suppression/leukopenia, ↑ infection risk, ↑malignancy risk, pancreatitis, megaloblastic anemia (expected if efficacious)
Hepatotoxicity (avoid use w/ allopurinol). idiosyncratic high fever, teratogenic
Labs: CBC (weekly x 1 month →biweekly x 1 month→ every 1-2 months)
LFTs every 3 months if thiopurine S methyltransferase deficiency => ↑ bone marrow toxicity

• **Mycophenolate mofetil (MM) (CellCept):** Also 1st line (but less used than Imuran)
Dosing: 1g po bid; can ↑to 1.5g po bid if needed (6-9 mo for full effect)
SE: diarrhea, nausea, leukopenia
Labs: routine CBC

• **Cyclosporine [Sandimmune, Neoral**]: used when above drugs fail
Dosing: start 3-6mg/kg/d spaced at q12h intervals
SE: vasoconstricts afferent arteriole→**nephrotoxic** (↓ed nephrotoxicity w/diltiazem & verapamil)**, neurotoxicity** (hand tremor)**, HTN,** hyperlipidemia, hyperglycemia**,** cholelithiasis

• **Cyclophosphamide [Cytoxan]** Last ditch - ablates marrow/reboots immune system
can get in infusion center
SE: GI distress, pancytopenia, hemorrhagic cystitis (give w/mesna & hydrate)

Surgery: Thymectomy: the only true indication is the a thymoma
Should be considered in younger patients, especially females
(not helpful if MuSK+)
Generally <65yo should be done within first 3 yrs of onset if at all.

Other Interventions: (see typical dosing in neuromuscular emergency section)
• **IVIG:** Usually only in decomposition, but rarely uses monthly **(1st line in pregnancy)**
• **PLEX**: Usually only in decomposition, but rarely used as a sched therapy

Lambert-Eaton Myasthenic syndrome (LEMS)

P/Q type voltage gated calcium channel antibodies (presynaptic cell) in 90%
50% are paraneoplastic (usually SCLC, but can be others)
clinical triad:
1) **Proximal muscle weakness**: legs>arms, proximal>distal, rarely bulbar)
2) **Autonomic features:** dry mouth, impotence, hypotension, constipation
-pupils dilated & poorly reactive
3) **Areflexia**
Precipitants: neuromuscular blocking agents, Calcium Channel blockers

LEMS Workup - in this order

1) Repetitive Stimulation NCS
- 3Hz accessory nerve→30% decrement in CMAP
- Posts exercise or high frequency (50Hz) of ulnar nerve
→ CMAP amplitude increases >100

2) Labs: Serum anti-VGCC antibody (90%) - rarely needed
3) Malignancy Screen: CT Chest/ Abdomen/ Pelvis w/wo contrast

Treatment/Management:
- Remove/treat malignancy ASAP
- **Pyridostigmine:** 30-60mg TID or QID
- **Guanidine** (↓ mitochondrial Ca^{2+} uptake)
  - 5mg/kg/d divided doses, may titrate slowly every 3days to 30mg/kg/d,
  -there is a delay of a few days before full effect is seen
  -**SE**: bone marrow suppression, hepatic/renal toxicity
- Corticosteroids or azathioprine in pts who fail symptomatic agents
  -improves strength modestly (not as good as MG)
- IVIG & PLEX may improve symptoms over several days in patients not responsive to other management

NMJ Toxins

- **Presynaptic: botulinum toxin** steroids, Magnesium (competes with Ca), aminoglycosides, Calcium Ch Blockers, ticks venom
- **Synaptic:** AChE Inhibitors (edrophonium, pyrido-/neostigmine), organophosphates.
- **Postsynaptic:** tetrodotoxin (fugu), ciguatoxin (other reef fish,) α-bungarotoxin (snake venom), succinylcholine, curare

Drugs That May Worsen/ Unmask Myasthenic Syndromes	
Cardio.	β blockers, Verapamil, Procainamide, Quinidine
Antibiotics	Aminoglycosides (Neomycin, Gentamicin, Streptomycin, Tobramycin), Ciprofloxacin, Macrolides (Erythromycin, Azithromycin, Clarithromycin), Tetracycline, Sulfonamides, Ampicillin
CNS drugs	Lithium, Chlorpromazine, Phenytoin, Trihexyphenidyl, Botox
Rheum.	D-Penicillamine, Chloroquine, IFN α
Anesthetics	Neuromuscular blocking agents: curare (and other non-depolarizing agents), succinylcholine (and other depolarizing agents).
Other	Magnesium

PERIPHERAL NEUROPATHIES

Edited by Peter Ljubenkov, MD, David Jin Lee, MD, PhD, Chamindra Konersman, MD, and Ross Mandeville, MD

Sources: [1] Bradley's Neurology in Clinical Practice, 6th edition
[2] R. Baron, A. Amato. Pattern recognition approach to Neuropathy and Neuropathy. NeurolClin 2013 May: 31 (2): 341-361
[3] http://neuromuscular.wustl.ed

NOTE:

Always localize first: Muscle-NMJ-Nerve-Plexus-Root-LMN-Cord-Brain

Selected Upper Extremity Nerves			
Nerve	Site of injury or subdivision	Methods of injury	Syndrome/deficits
Long Thoracic			Winged scapula (Serratus anterior C5,6,7)
Upper Trunk (C5-6)		Breech delivery, shoulder dystocia	Erb's palsy: "waiter's tip" position due to deltoid, biceps, infraspinatus, supinator weakness
Suprascapular (C5, C6)	Suprascapular notch	Blunt trauma	Supraspinatus and Infraspinatus (C5, C6) paresis
Musculo-Cutaneous			Weakness of elbow flexion -biceps & brachialis (C5, C6)
Axillary, C5,6		Shoulder dislocation	Decreased Shoulder abduction: -Deltoid (C5, 6), teres min.
Median C6-T1	**Carpal tunnel**	repetitive wrist flexion, arthritis, tenosynovitis	CTS: **paresthesia/pain +/- numbness (palmar digits 1-4)**, late APB weakness/thenar atrophy
	Anterior Interosseous Nerve	Strenuous exercise, trauma	Abnormal "pincher sign"&"benediction sign" (weak 1, 2, 3 DIP joint flexion and pronation)
	Elbow (pronator teres syndrome)	Repetitive elbow motions	Tenderness resisting pronation, + deficits like CTS and anterior interosseous syndromes

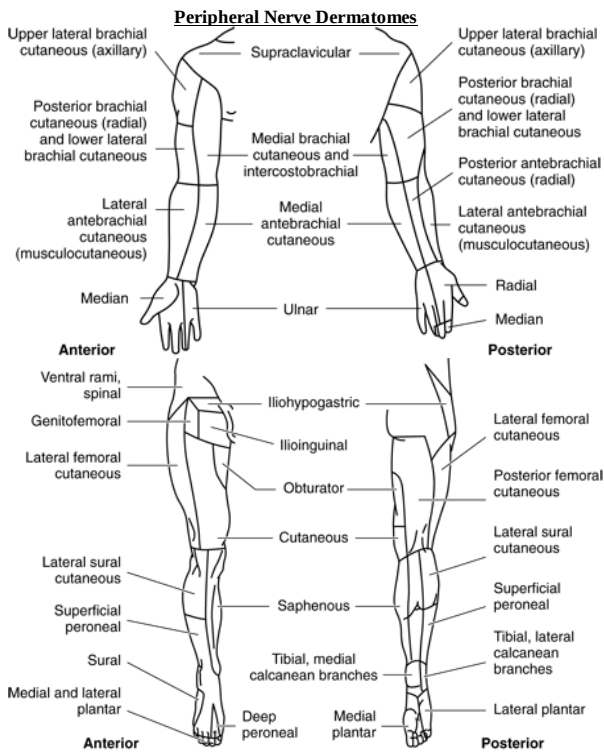
Ulnar C8-T1	**Elbow (cubital tunnel)**	Elbow leaning/bending, trauma	**↓ sensation digits 4 (split) & 5, interossei weakness,** (also sometimes lumbrical & FDP 4&5)
	Guyan Canal	Mechanics, cyclist	Interossei (FDI is C8, T1) & ADM weak (C8, T1)
Radial C5-C8	Axilla	Crutches	Wrist drop. **Triceps (C6, 7)** & supinator weakness. Sensory loss over extensor forearm and hand.
	Spiral groove	Abnormal sleep, compression	Saturday night palsy: Wrist drop, sensory loss
	Posterior interosseous	Elbow synovitis, trauma, neuritis	Paresis of finger extensors (EDC [C7, 8], EIP [C7, 8]), & radial wrist dev (ECRL spared).
	Superficial sensory	Wrist band, hand cuffs, IV lines	Paresthesias/numbness over dorsum of hand (cheiralgiaparasthetica)
Lower trunk (C8-T1)	Thoracic Outlet	C7 rib or process	Atrophy of hand intrinsic muscles, paresthesias of hands and forearms similar to C8 and T1 dermatome
Selected Lower Extremity Nerves			
Sciatic Nerve L4-S3	Hip>Sciatic Notch > Popliteal fossa	Fracture, dislocation, "piriformis syndrome"	Pain down thigh, flail foot, absent ankle jerk. Mix of tibial & peroneal dysfunction, but often pure peroneal – check SH biceps femoris.
Common peroneal (L4-S1)	**Fibular Neck**	**Leg crossing, squatting**	**Foot Drop, weak eversion, sensory loss over foot dorsum (short head biceps femoris L5, S1 is spared)**
	Deep peroneal		Foot drop (↓Dorsiflexion-Tibialis anterior), ↓ toe extension, ↓Foot eversion, ↓dorsal sensation between digits 1&2.
	Superficial peroneal		Sensory loss, foot dorsum and distal lateral shin, eversion (Peroneus brevis and longus L5, S1)

Tibial (L4-S2)	Tibial fossa		Gastroc. (**S1-2**) and soleus. Inversion/Tibialis posterior (L5). (LH biceps femoris-L5, S1)
	Medial Malleolus syndrome	Ankle fracture, tenosynovitis	"tarsal tunnel" – CTS of the foot, likely very rare. Sensory loss over sole of foot
Femoral L2-4	Inguinal ligament, Psoas muscle	Lithotomy position, Psoas hematoma	Weak knee extension/Quads (Vastus lateralis/medialis-absent knee jerk); medial thigh and Saphenous sensory loss
Lateral - fem. cutaneous (L2,3)	Inguinal ligament	Tight clothing weight gain/loss, utility belts	"Meralgiaparesthetica": sensory loss/ paresthesias external thigh
Illio-inguinal L1	Abdominal wall	Trauma, surgery	Sensory loss in iliac crest, crural area
Obturator L2-4	Obturator canal	Tumor, surgery, pelvic frac.	Sensory loss in medial thigh, weak hip add.

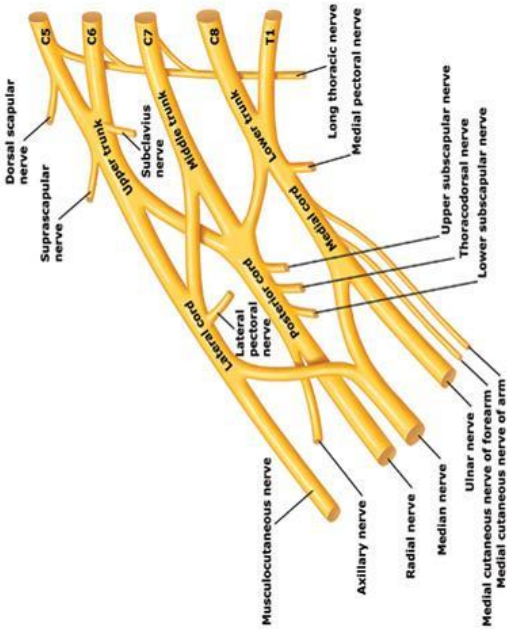
Important Roots

	Dermatome	Myotome Summary	Associated reflex
C5	Radial forearm	Deltoid, biceps	None
C6	Digits 1 and 2	Biceps, brachioradialis	Biceps (musculocutaneous) Brachioradialis (radial)
C7	Digits 3 and 4	Wrist extensors, triceps	Triceps (radial)
C8	Digit 5	intrinsic hand muscles	Hoffman's (med/ulnar)
L2	Lateral and anterior upper thigh	Psoas, quadriceps	None
L3	Lower medial thigh	Psoas, quadriceps	Patellofemoral
L4	Medial lower leg	Quadriceps, Tibialis anterior	Patellofemoral
L5	Lateral lower leg, dorsal foot	Gluteus medius, Tibialis anterior, toe extension, foot inversion (compare peroneal neuropathy),	None, possibly Biceps femoris tendon

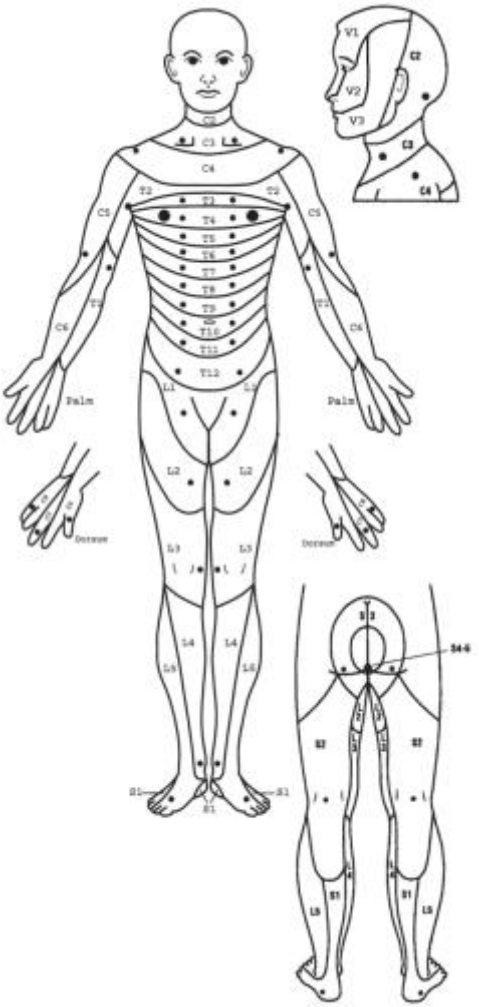
		Peronei	
S1	Lateral foot, digits 4 and 5, outside of sole.	Gastrocs, gluteus maximus, Peronei	Achilles (tibial)



The Brachial Plexus



American Spinal Injury Association (ASIA) Spinal Root Dermatomes



Diagnostic Workup of Peripheral Neuropathies

FIRST TIER WORKUP (Depending on clinical picture)

•**LABS:**(CBC, BMP, LFTs, Ca, Mg, Phos) **A1C** (+/- glucose tolerance test), **B12** /folate (MMA and homocysteine more sensitive) **TSH**, Serum Protein Electrophoresis (**SPEP**) with immunofixation (more sensitive than SPEP alone for finding M-proteins), +/- **HIV**, **RPR**, **ESR/CRP**, Lyme, EtOH

•**EMG/NCS**: Localization, Pattern, Severity, Chronicity.

-**Demyelinating features?** Conduction velocities <75% normal, prolonged distal latencies, conduction blocks, absent F waves. likely treatable!

-**Axonal features?** (↓amplitude) Majority are axonal, length dependent, symmetric, small and large fiber, sensorimotor polyneuropathies.

-**EMG:** Should be neuropathic. Consider primary muscle issue if myopathic

+/-MRI of relevant region: if you suspect myelopathy, polyradiculopathy, plexopathy or cauda equina on DDx

SECOND TIER WORKUP (Consider depending on clinical picture)

NOTE: Unless there is rapid progression, purely demyelinating pattern (usually treatable), multifocal distribution (also treatable), severe disability, abnormal lab tests, or young, you may consider observation after the first-tier workup (falling into the mild and cryptogenic category).

•Possible Second Tier Labs to consider – if no obvious pattern as below, and, again, depending on clinical/EMG:

B1, B6, Vit E, Cu, ACE, ESR/CRP, Lyme, HTLV, TB, heavy metal, Celiac studies (anti-Gliadin IgA IgG, anti-transglut.), Hep panel, Cryoglobulins, Porphyrins, Triglycerides, Paraneoplastic. (just replete thiamine)

•If GBS/AIDP Suspected: (again, treat syndrome, not labs)

-**CSF studies**: MAY have albumino-cytologic dissociation [↑ protein, ↔WBC] in GBS after days

-GQ1b antibody if suspect Miller-Fisher (ataxia, ophthalmoplegia, areflexia)

•In Cases of Multiple Mononeuropathies:

-Vasculitic/mononeuropathy multiplex labs (usually axonal):

Cryoglobulins, Hep C, HIV, RF, ANA, ESR, ANCA, dsDNA, SSA/SSB, SPEP, UPEP, Lyme, Celiac studies, (PMP22 deletion if HNPP family hx)

•Nerve biopsy if vasculitis is truly suspected

-If polyneuritis cranialis/accumulating cranial neuropathies:

- HIV, Lyme, Quantiferon, serum ACE
- CSF: cell count, protein, glucose, ACE, culture, AFB smear + MTD PCR
- CSF cytology and flow cytometry **x3** (r/o meningeal malignancy)
- MRI w/wo contrast with thin cuts through brainstem

-If rapidly accumulating/progressing polyradiculopathies:

- MRI w/w contrast of relevant region
- Also consider CSF cytology and flow cytology **x3**

•If pure demyelinating NCS pattern:

- **Non-uniform:** IMPORTANT to think about acquired autoimmune processes as these are treatable! Think GBS if acute. If chronic think CIDP and chronic acquired/autoimmune processes (see pages 139-140)
- **Uniform (think Genetic)**: PMP22 for CMT (MPZ, Connexin 32 rarely sent). (leukodystrophy [MLD], Refsum, Krabbe disease and workup considered if given clinical picture)

Etiologies of Toxic Neuropathy:

***EtOH* &** Drugs/vasculitic (amphetamine, heroin, cocaine), Industrial (hexane, organophosphates) Metals (arsenic, lead, mercury, thallium) Medications (amiodarone, cisplatin, oxaliplatin, taxol, vincristine, adriamycin dapsone, disulfiram, hydralazine, INH, linezolid, Flagyl, nitrofurantoin, HIV meds, phenytoin, pyridoxine (B6)

Demyelinating Immune Polyneuropathies [3]

•**CIDP: C**hronic **I**mmune **D**emyelinating **P**olyneuropathy
Chronic/Relapsing Motor > Sensory, Proximal & Distal Symmetric
NCS: Motor + Sensory Δ, ↓ conduction velocity, Conduction Block, ↑Distal Latency, Slow F- wave
Labs: 15% have m proteins
Treatment: IVIG, PLEX, T-cell suppression (Prednisone, Cyclosporine, Methotrexate)

•**Multifocal CIDP variant: (MADSAM)** Multifocal Acquired Demyelinating Sensory & Motor
Chronic, Motor >Sensory, Distal> Proximal, Arms > Legs, Onset: 15 -75 yrs
NCS: like CIDP but multifocal
Treatment: T-cell immunosuppression, Prednisone, IVIG

•**MMN: M**ultifocal **M**otor **N**europathy with conduction block
Motor only,** slow progressive, Distal > Proximal, Arms > Legs, Asymmetric
NCS: Motor only, **Conduction Block**
EMG: Denervation with disease progression
Labs: Anti GM1 antibody 35-50% sensitive, 20% have m-protein
Treatment: IVIG, B-cell suppression, Cyclophosphamide ± PLEX, Rituximab (may worsen with prednisone)

•**Anti MAG: M**yelin-**A**ssociated **G**lycoprotein
Sensory > Motor, Distal; Symmetric, **Gait disorder/ataxia, Tremor**
Onset age > 50 yrs, slowly progressive
NCS: Motor + Sensory Δ, ↑ Distal Latency, ↓NCV, no blocks, occasionally Axon Loss: Distal legs
Labs: anti-MAG Ab (Class IgM), 85% have m-protein
Treatment: B-cell suppression, Cyclophosphamide ± PLEX, Rituximab

•**GALOP**: **G**ait Disorder **A**uto-antibody **L**ate **O**nset **P**olyneuropathy
Gait Disorder, Sensory (with ataxia) > Motor, Distal; Symmetric
Onset age > 50 yrs
NCS: Motor + Sensory Δ, ↑Distal Latency, ↓NCV: Slow, No blocks
Labs: 80% have an M-protein

Treatment: Human immunoglobulin,
Cyclophosphamide ± PLEX

(Demyelinating Immune Polyneuropathies continued)

•Anti Sulfatide Neuropathy

Slowly progressive, Sensory > Motor, Distal; Symmetric, Onset: > 45 yrs

NCS: ↑Distal Latency, ↓NCV, some distal Axon Loss
Labs: Anti-Sulfatide Antibody (Class IgM), 90% have M-protein on SPEP
Treatment: Human immunoglobulin,
Cyclophosphamide ± PLEX

•GM2 & GalNAc-GD1a

Slowly progressive Sensory > Motor, Ataxia: Limb & Gait, Distal, Symmetric or Asymmetric, Onset: Adult

NCS: slow NCV
Labs: Anti GM2 or Ga1NAc-GD1a Abs.
Treatment: Human immunoglobulin

•POEMS:

Polyneuropathy, **O**rganomegaly, **E**ndocrinopathy, **M**-protein, and **S**kin changes
http://neuromuscular.wustl.edu/antibody/pnimdem.htmlcauses a Sensory & Motor Symmetric, Onset: 25 to 60 yrs

NCS: slow NCV sometimes with Axon Loss
Labs: 90% have an associated M-protein, most w/high VEGF
Treatment: Localized osteosclerotic lesions and chemo
No bone lesions: Cyclophosphamide + Rituximab,
(IVIG and PLEX?)

•Neurofascin

Progressive Sensory & Motor, Distal, Tremor, Adult Onset

NCS: slow NCV
Labs: Anti Neurofascin antibodies

•Contactin-1

Progressive Sensory & Motor, Distal or Diffuse, Onset: Adult, late

NCS: Prolonged Distal latency, Conduction block
Labs: Anti Contactin-1 Antibody
Treatment: Prednisone

Polyneuropathy Differential Diagnosis Using Clinical Pattern

Pattern 1: Symmetric proximal and distal weakness with sensory loss

AIDP/GBS (nadir ~4wks), CIDP, vasculitis, critical illness neuropathy

Pattern 2: Symmetric distal sensory loss +/- distal weakness

-CSPN (cryptogenic sensory polyneuropathy), diabetes, drugs, toxins, hereditary neuropathies (CMT), amyloidosis, paraproteinemias
(see acquired demyelinating immune page 139-140), Celiac, EtOH abuse

Pattern 3: Asymmetric or focal distal weakness and numbness

(includes "mononeuropathy multiplex" [page 138]**)**
Axonal: Vasculitis (systemic and isolated), Diabetes, Sarcoidosis, Leprosy, HIV, trauma
Demyelinating: Compression neuropathy (entrapment, hypothyroidism, Diabetes, HNPP), trauma, MADSAM (Lewis-Sumner Syndrome, page 139)

Pattern 4: Asymmetric or focal proximal and distal weakness and numbness

Consider polyradiculopathy or plexopathy, in addition to pattern 3 etiologies
-Meningeal carcinomatosis/lymphomatosis*, sarcoid, Lyme, amyloidosis, HNPP, diabetic amyotrophy, acute brachial neuropathy (Parsonage-Turner)

Pattern 5: Motor predominant:

(consider myopathy such as IBM)

-Consider Motor Neuron Diseases: ALS (UMN sings), Kennedy's Disease (lots of bulbar and some sensory issues, X-linked), juvenile monomelic atrophy.
-Also consider NMJ disorders and myopathies
-MMN (multifocal motor neuropathy), West Nile, MAMA (multifocal acquired motor axonopathy)
Note: GBS, CIDP, POEMS, CMT, diabetic lumbar radiculopathy, CMT and lead toxicity [wrist drop] may all look "predominantly motor".

Pattern 6: Symmetric Sensory Loss with distal areflexia and UMN signs

B12 deficiency, Copper deficiency (Zinc toxicity), Inherited disorder (adrenoleukodystrophy, Fabry's, Metachromatic Leukodystrophy)

Pattern 7: Small Fiber predominant (may be painful)

Diabetes, Alcohol, Drugs, toxins (arsenic, thallium), HIV, Hep

C, Fabry's, Tangier, Sjogrens/SICCA, Vasculiti, B6 toxicity, Amyloid (early familial and primary), Cryptogenic

Pattern 8: Marked Ataxia or Proprioceptive loss (particularly w/o weakness)

CIDP, Tabes Dorsalis (Syphilis), GALOP, anti-MAG sensory neuronopathies/ganglionopathy/paraneoplastic (Anti Hu, CV2), B6 toxicity, HIV, Sjogrens, toxins (↑B6, Cisplatin, etoposide, nucleoside analogues). (Miller fisher variant of GBS, ataxia but not necessarily proprioception)

Pattern 9: Neuropathies with prominent autonomic features (orthostatic, ↓ sweat, ED, bladder issues, GI, early satiety, photophobic, xerostomia)

Acute: GBS variant, acute panautonomic neuropathy (may be neoplastic or idiopathic), porphyria, toxins (vincristine, Vacor), (also consider botulism and diphtheria if syndrome fits)
Chronic: Sensory neuronopathies (Paraneoplastic), DM, Amyloid neuropathy, HIV, Hereditary sensory & autonomic neuropathy

Pattern 10: Prominent Cranial Nerve Involvement: "polyneuritis cranialis"
Meningeal carcinomatosis/lymphoma *(need CSF cytology and flow x3), GBS variants (especially Miller-Fisher [GQ1B]), Tuberculosis, Sarcoidosis, HIV, Syphilis, Lyme, Diabetes, Sjogrens, diphtheria

Especially facial nerve involvement: GBS variant, Lyme, Sarcoid, HIV, Tangier disease, Gelsolin familial amyloid neuropathy (Finish)

BASIC NERVE CONDUCTION STUDY/ EMG PRIMER

NCS MOTOR STUDIES

Nerve	Distance (cm)	Distal Latency (ms)	Amplitude (mV)	Velocity (m/s)	F latency (ms)
Median	7	4.4	4.0	**49**	32
Ulnar	7	3.6	5.0	**49**	32
Peroneal	8	6.2	2.0	**39**	58
Tibial	8	6.0	3.0	**39**	58

•Demyelinating pattern: Decrease in velocity by 25% (36 m/s in arms & 29.5m/s in legs)
→Conduction Block:
Decrease in amplitude by 50% across a region
•Axonal Pattern: Decrease in amplitude, relatively intact velocity

NCS SENSORY STUDIES

Nerve	Stim	Record	Distance (ms)	Peak latency (ms)	Peak amp (uV)
Median	Wrist	Dig II	14	3.6	15
Ulnar	Wrist	Dig V	11	3.1	10
Radial	Forearm	Wrist	10	2.9	15
Sural	Calf	Lat Mall	14	4.4	5
Superficial fibular	Lat Leg	Ankle	14	4.2	5

EMG STUDY BASICS:

•**Normal Muscle:**

Spontaneous activity: NONE after initial insertion activity/quiet at rest
MUAPs (motor unit action potentials)
Duration 8-12ms
Amplitude 0.2mV-5mV
Recruitment: 1 new motor unit added every 5Hz

•**Neuropathic MUAPS**: (Muscle losing innervation)

Spontaneous activity: fasciculations**, fibrillations, positive sharps
MUAPs:↑ amplitude, ↑ duration, ↓ recruitment
Sounds like a helicopter (scant loud units firing very fast)

•**MyopathicMUAPs**:
(Sick muscle for a variety of reasons including myopathy)

Spontaneous activity: fibrillations, positive sharps
MUAPs:↓ amplitude, ↓ duration, ↑ recruitment
Sounds like crinkling cellophane
(high pitch, small, numerous units)

•**Spontaneous Activity by Localization**

-Muscle Membrane Derived: (inappropriate membrane depolarization)

•**Fibrillations (fibs):** quick positive (down) and negative deflections. Sounds like regular raindrops on a tin roof
•**Positive Sharp waves:** primarily a positive deflection (down), these basically represent a fib in muscle deformed by the needle. Sounds like a soft regular ticking clock
•**Myotonic discharge:** seen everywhere in myotonic muscular dystrophy, myotonia congenita, paramyotonia, & Pompe's, but can happen as an isolated finding in numerous muscle diseases. Sounds like "dive bomber" (up & down w/ amp. of MUAP)

-Multiple Muscle Derived:

•**Complex repetitive Discharge** (CRD): an inappropriate circuit between muscle cells. Myopathic or chronic neuropathic process. Sounds like a "jack hammer."

-NMJ derived:

•**End Plate Noise:**"sea shell"sound of individual quanta of ACh causing mini endplate potentials without reaching

threshold

-Terminal axon derived:

•**End Plate Spikes:** Sounds like "fat on a frying pan"

-Lower Motor Neuron Derived:

•**Fasciculations:** General LMN damage, sounds like irregular "popcorn"

•**Myokymic discharge:** originated from a group of adjacent demyelinated axons, classically radiation. ("marching soldiers")

•**Neuromyotonic discharge:** Due to voltage gated potassium channel dysfunction in Morvan's syndrome.

•**Cramps** & •**Tetany**

COMMONLY TESTED MUSCLES (EMG) (Krarup et al Brain.)

Upper Limb

- Rhomboid (C5)
- Deltoid (**C5**-C6) [Infraspinatus, supraspinatus]
- Biceps (C5-**C6**) [Brachialis, Pec. Major clavicular head]
- Triceps (C6, **C7**, *C8*)
- Pronator teres or flexor carpi radialis (C6-C7) [EDC]
- Extensor indicis proprius (C7-**C8**)
- APB (**C8**-T1) [FPL, PQ, FDP]
- FDI (C8-T1)

Lower Limb

- Tibialis anterior (L4 and **L5**, 10% only L4, 20% only L5, 20% some S1)
- Peroneus tertius (L5-S1)
- Peroneus longus/brevis (**L5** and S1, 67% S2)
- Tibialis posterior (**L5**-S1)
- Medial gastrocnemius (L5 and **S1**, 67% some S2)
- Lateral gastrocnemius (L5 and **S1,** 67% some S2)
- Vastus lateralis and medialis (L2, L3, L4)
- Sartorius (L2-L3-L4)
- Tensor fascia lata or gluteus medius (L4-S1, largely **L5**)
- Biceps femoris (**L5** and S1, 30% L4, 20% small S2)
- Adductor hallucis (S1-**S2,** 30% with small L5, 30% only S2)

4 Common Mononeuropathy Consults

 # Carpal Tunnel Syndrome:

Syndrome of symptoms from compression of median nerve in carpal tunnel.

• *Pain or paresthesia* in distal palmar first three digits and the radial half of the fourth digit (wide range of variability, bilateral common).

• *Typically worse at night*, provoked flexing or extending the wrist or raising the arms. Relieved by hands flick and changing position.

•If severe: weakness thumb intrinsic muscles (APB) and atrophy of the thenar eminence.

Tests:

- Provocative maneuvers: Phalen, Tinel, carpal compression, hand elevation.
- NCS: slow of blocked conduction across carpal tunnel.

Treatment/Management:

•Mild-Moderate CTS (≤10 months duration):

- Nocturnal wrist splinting in neutral position (try for at least 1 month)
- Occupational therapy, carpal bone mobilization, or yoga
- May consider glucocorticoids:
    - Methylprednisolone 40mg injected into carpal tunnel
    - Alternatively (less optimal) oral Prednisone 20 mg QDAY x10-14 days.

• Moderate-Severe CTS/refractory to conservative measures: surgical decompression
• Ineffective treatments for CTS: NSAIDs, B6, diuretics.

#Ulnar neuropathy: Usually compression at elbow/cubital tunnel (occasionally compression at Guyon's canal / handlebar palsy at wrist - mostly motor)
• numbness & tingling in 4th (split) & 5th digits, medial elbow pain.
•Worse at night and with elbow and/or repeated wrist flexion
DDX: C8 radiculopathy or thoracic outlet syndrome
Treatment:
- elbow padding/avoid leaning on the elbows
- splints/wrappings limiting elbow flex to 45 to 90^{o} at night
- Translocation surgery: generally poor efficacy

#Peroneal neuropathy: typically compress across the fibular head numbness/tingling over dorsum of foot. Foot drop and weak eversion
DDX: L5 radiculopathy (look for foot inversion as this is done by L5, not peroneal)
Treatment: Avoid provocation (tight boots, squatting excessively, etc.)

#Bell's Palsy:

Lower motor neuron injury to facial nerve/ CN VII in facial canal.

Clinical presentation: acute (often hours) unilateral facial weakness (upper and lower)

+/-ipsilateral pain behind ear, hyperacusis (stapedius), loss of taste on anterior 2/3 of tongue, decreased lacrimation.

Differential Diagnosis:

Usually just transient inflammation of CN VII, may be post viral

Other diagnoses to consider is complicated/atypical cases)

- CPA or IAC neoplasm/mass: (associated auditory deficit)
- Ramsay-Hunt (VZV): vesicles in ear
- Other Infections: Acute HIV, Lyme, Otitis Media
- Inflammatory: Neurosarcoid (hilar adenopathy, uveitis), Sjögrens, (see page 142, pattern 10 for more)
- Stroke (usually UMN pattern +/- dissociation of volitional & emotional. (Nuclear lesions look LMN [usually neighborhood signs, e.g CN6 palsy])

Workup (clinical assessment is good enough for typical incomplete cases): Consider if progression beyond 3 weeks, no improvement in 4 months, or f the patient has other focal findings:

•MRI w/wo of brain (brainstem), IAC, temporal bone, parotids & CXR (for adenopathy)

•Lyme serology, CBC, ESR, ACE, HIV (see polyneuritis cranialis)

Treatment: •artificial tears, ointment, eye patch (avoid corneal ulceration)

•**prednisone 60-80 mg**, x 1 week (start within 3 days of sx onset)

•**valacyclovir 1000 mg TID x1wk** for severe facial palsy or Ramsay-Hunt.

Prognosis: ~85% signs of recovery within 3 weeks, 71% complete recovery, 13% slight sequelae, 16% residual weakness, synkinesis and/or contracture.

•Incomplete lesions: 94%f return to normal function

•Complete lesions: 60% return to normal function.

•Zoster: worse prognosis & 7-15% recurrence.

NEURO-OPHTHALMOLOGY

Edited by Peter Ljubenkov, MD Amanda Yu, DO, PhD, and Revere Kinkel, MD

Sources: Bradley's Neurology in Clinical Practice, 6th edition
First Aid for the Neurology Boards Review

Evaluation of Vision Loss

Central Retinal Artery Occlusion (CRAO):

"Sudden, profound, painless monocular vision loss", usually due to carotid embolus (cholesterol, calcific, or fibrin-platelet)

But may be related to GCA & other vasculitides

Fundoscopy: retinal pallor and macular "Cherry red spot"

Treatment: - ocular massage
- stat Optho & Neuro IR consult – tPA?
- stroke workup

Amaurosis fugax: If symptoms transient.
Like a TIA- needs stroke work up

Branch Retinal Artery Occlusion (BRAO): if incomplete territory. Whitening in area of ischemia on fundoscopy

Anterior Ischemic Optic Neuropathy (AION)

Acute painless vision loss, usually altitudinal (usually inferior)

Arteritic (AAION): 2/2 GCA/temporal arteritis (↑ESR)
(see temporal arteritis management, page 165)

Non-Arteritic (NAION): controversial mechanism but disc crowding, HTN, Diabetes, and high cholesterol are all risk factors

Optic Neuritis: Acute/subacute demyelination of CN II, unusually unilateral. Bilateral or rapidly sequential case are NMO till proven otherwise

Exam: Typically central visual loss, may or may not have loss of acuity depending on degree of central visual loss, loss of color vision.

- Relative afferent pupillary defect required (unless contralateral eye involved), pain on eye movement (>90%), occasional disc swelling (35 %)

Workup: Order MRI Brain w/wo con + T2 fat sat of orbits: may have optic disc swelling/ enhancement.

Tx: Methylprednisolone 1 gIVx 3-5days
(oral alone will ↑recurrence)
-Follow w/ or prednisone 40-60mg, taper over 11 to 14days

MS Risk

- **At 5 years:** 16% if 0 lesions, 37% if 1-2, 51% if ≥3 lesions
- **At 15 years**: 22% if 0 lesions, 56% if ≥ 1 lesion
- Avonex, betaseron, copaxone all demonstrated to decrease risk of relapses involving optic nerve or other CNS territories by 50% in patients with typical MRI findings of MS at onset (2 or more typical asymptomatic T2 lesions on cranial MRI)

Toxic/Nutritional Optic Neuropathies:

(typically slow in onset except with acute poisoning; typically bilateral and symmetric)

• ↓B12 (will have ↑MMA)

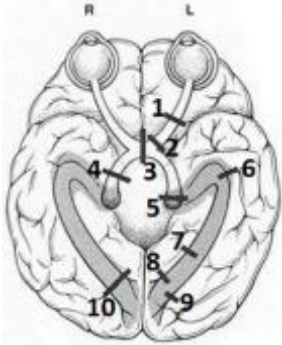
• Methanol (converts to formaldehyde within 24 hr)
• ethmabutol
• amiodarone
• linezolid

Hereditary Optic Neuropathies
• **Autosomal Dominant Optic Neuropathies**: slow BL vision loss over decades starts in childhood but frequently unnoticed for a long time
• **Leber Hereditary Optic Neuropathy (LHON)** - Rare with mitochondrial inheritance. Acute to subacute vision loss in one eye, followed by another ≤ 1 year. Males to females 9:1; typical age 10-30 but any age reported. Central or centrocecal scotoma with normal or pseudo-swelling associated with peripapillary telangiectasia
    •**LHOH plus**: cardiac conduction defects & MS-like syndrome

Paraneoplastic Retinopathies: Subacute onset
• **Melanoma Associated Retinopathy** (MAR)
    - Only rods: Poor night and peripheral vision
• **Cancer-associated Retinopathy** (CAR)
    - Rods and cones: poor acuity, color, night & peripheral
    - Usually small cell lung cancer, but also other CA
    - steroids may help for short time

Neoplasms/ Compressive neuropathies:
•**Foster- Kennedy Syndrome:** due to frontal lobe mass most commonly meningiomas of olfactory groove or sphenoid wing or falx cerebri
    -Ipsilateral optic disc pallor, contralateral papilledema, +/- anosmia
• **Optic nerve meningioma** (usually middle-aged women)
    -best viewed MRI Brain w/w con + T2 fat sat/ thin orbital cuts
    TX: typically stereotactic radiation w/o biopsy
•**Pituitary Adenoma**: typically chiasmatic lesion (bitemporal hemianopsia
    May result in life-threatening pituitary apoplexy (see page 163)
• **Optic Nerve glioma**: typically under age 15, associated with NFT1
    Usually slow growing/ little visual progression

Evaluation of Visual Field Cuts



L R			
	1	Left optic Nerve	No light perception in left eye
	2	Left proximal optic nerve	"Junctional Scotoma"
	3	Optic Chiasm	Bitemporal hemianopsia
	4	Right optic tract	Incongruous left homonymous hemianopsia
	5	Left Lateral Geniculate Nucleus (LGN)	• Right homonymous sectoropia (lateral choroidal artery) Or • Incongruous right homonymous hemianopsia
	6	Left Temporal Lobe (Meyer's Loop)	Right homonymous quadrant defect ("pie in sky")
	7	Left Parietal Lobe (Baum's loop)	Right homonymous defect, denser in inferior quadrant
	8	Upper bank of Left Occipital lobe	Right homonymous lower quadrantanopia w/ macular sparing
	9	Lower bank of Left Occipital Lobe	Right homonymous upper quadrantanopia w/ macular sparing
	10	Right Occipital Lobe	Left homonymous hemianopsia with macular sparing

Evaluation of Papilledema and Idiopathic Intracranial Hypertension

Work Up for a Patient with Papilledema

MRI Brain w/wo contrast to rule out mass lesion and
CT wo contrast + CTV (w/con) or **MRI w/ contrast + MRV**
-MUST R/O VST before making pseudotumor diagnosis!!!
LP w/ opening pressure (after excluding herniation risk): Cell count, protein, glucose
Optho eval ASAP: check visual fields

Symptoms/ signs of elevated ICP in an ambulatory patient with papilledema
- Headache (worse in AM, worse w/ valsalva, wore when dependent)
- Nausea / vomiting
- Pulsatile tinnitus
- Transient visual obscurations (w/ cough, valsalva, changes in position)
- Cranial Nerve VI palsy / diplopia

Differential diagnosis of papilledema in an ambulatory patient with ↑**ICP**
(also see ICP chapter, 44-46) (Note: this list is not exhaustive)
- Mass occupying lesion
- VST (Venous sinus thrombosis): especially if pregnant, hypercoag, OCPS
- Infection

Idiopathic Intracranial Hypertension (IIH, Pseudotumor Cerebri)
Risk factors: women, obesity, tetracycline, vitamin A/accutane

Diagnosis exclusion using Dandy criteria
1) symptoms/signs of raised ICP (see above)
2) no localizing signs, except for sixth nerve palsy
3) No cause on MRI for ICP (VST or mass)
4) **opening pressure > 25 cmH2O** w/ normal CSF composition
5) no alternate explanation for the raised ICP

IIH Findings on MRI
-Empty sella (can be incidental finding too)
-Dilated optic nerve sheaths on T2
-Posterior globe flattening
-Protruding optic nerve heads on T1 w/ con.

Treatment:
- Weight loss & stop offending agents
- **Optho referral** to follow visual fields ASAP**
  -Pt may not notice & fundoscopy not reliable
  -↑physiologic blind spot → late central vision loss
  - rapidly central vision loss
  →emergent surgical intervention!
- **Diamox**: start 250 mg BID, increase 250mg weekly to 500mg BID max 2g Daily. (may also use **topiramate**)
  SE: paresthesias, altered taste sensation, lethargy
- Avoid opioids/ excess analgesics - ↑↑↑rebound headache risk
- **Furosemide**: 20-40mg daily may be adjunct to CA inhibitors
- **Surgery** (for refractory or rapidly progressing cases)
  - **VP or LP shunting:** if headache
  - **optic nerve sheath fenestration (ONSF):** if severe visual loss, but minimal or no headache

Evaluation of Anisocoria:

NOTE: ONLY consider uncal herniation if they are altered!

History:
- Recent trauma?
- Check old photographs
- Use of topical medications
- Exposure to toxins, drugs
- Other associated ocular or neurologic symptoms
- DO THEY HAVE GLASS EYE?

IS IT WORSE IN THE DARK?

→The small pupil is abnormal/ dilates poorly in dark

•**Horner's syndrome:**
- -Will reverse with 0.5-1 % Apraclonidine
- - 1% hydroxymethamphetamine dilates preganglionic, not post ganglionic
- -typically associated ipsilateral ptosis (upper lid, sometimes lower too), dilation lag, and possibly anhidrosis
- -Think **carotid dissection** first, but can be anywhere along pathway, including apical lung path, superior cervical ganglion, lateral medulla, etc.
- • Preganglionic or central: dilates with 1% hydroxyamphetamine
- • Postganglionic: no dilation with 1% hydroxyamphetamine

•**Physiologic/ Simple Anisocoria**
- -unlike Horner's, won't reverse with 0.5-1 % Apraclonidine
- -may alternatively look similar equal or worse in light

IS IT WORSE IN THE LIGHT?

→ The large pupil is abnormal/constricts poorly w/ light

• Is pupil irregular/is margin torn?

→**Damaged Iris** (surgery, etc.)
- -May fail to respond to pilocarpine

• Is there associated ptosis & ophthalmoplegia? (down & out)

→**3rd Nerve Palsy:**
- -If pupil involved in 3rd nerve palsy, must r/o compression (due to aneurism, etc. see page 151)

•Do they have the following associated features?
- - There is no ptosis or ophthalmoplegia (isolated anisocoria)
- - Pupil is just sluggish to light
- - Light/near dissociation

→**Adie's Tonic Pupil:** * Will constrict with 0.1% pilocarpine
- -May be associated with a syndrome of decreased DTRs
- -likely post viral/ immune mediated

→**Pharmacologic Anisocoria:** * Will not constrict with 0.1% pilocarpine

Other Pupil abnormalities

• RAPD (Relative Afferent Pupillary Defect/ "Marcus Gunn Pupil") CNII or any ocular pathology limiting afferent signal during "swinging flashlight" test, both eyes dilate when swinging from good eye to bad eye (BL Edinger Westphal have BL afferents & efferents)

• Light-Near Dissociation: "accommodates but does not react"

90% of fibers for constriction are devoted to accommodation (preserved)
→**Argyll Robertson Pupil**: Small, irregular w/ light-near dissociation. Classically neurosyphilis, but DM or old Adie's more common.

Evaluation of Acquired Eye Movement and Alignment Abnormalities

Differential Diagnosis For Abnormal Eye Movements
(see respective Myopathy, 126-127, and NMJ disorder 128-131, sections)

- **Myopathy:** (mitochondrial, OPMD, Myotonic),
- **Neuromuscular Junction Disorders:** (Myasthenia, LEMS, Botulism)
- **Cranial Nerve Palsies** (peripheral and nuclear)
- **Orbital pathology**: granuloma, malignancy, etc
- **Internuclear vs. Supranuclear disorders**

Varieties of Alignment Abnormalities
(exo = abducted, eso = adducted, hypo = down, hyper = up)
-**"Phoria"**: Latent deviation only obvious when binocular vision interrupted
- Patient fixates & you alternately cover up each eye

→Abnormal eye can be seen correcting back to target when uncovered.
- **"Tropia":** Persistent deviation of one eye

• **CN3 Palsy:** "Down and out" (impaired adduction & vertical movement when abducted)
•Often small vessel ischemia/DM → will spare pupil
•May be compressive (tumor, aneurysm located at the junction of the internal carotid and posterior communicating arteries or, less commonly, at the apex of the basilar artery or its junction with the superior cerebellar or posterior cerebral arteries) → dilated pupil
-STAT brain imaging including vessels if pupil involved!
Superior CN3 branch: superior rectus & levator palpebrae
Inferior CN3 branch: medial, inferior, superior rectus, inferior oblique & parasympathetics (on the outer portion of nerve)

• **CN4 Palsy:** vertical and torsional diplopia (often post traumatic)
Eye elevates/depresses poorly in adduction. Head tilts away from lesion
Path: Exits the dorsal midbrain, decussates, and innervated the superior oblique muscle.

• **CN6 Palsy:** Horizontal diplopia due to poor abduction
DDX: ↑ ICP, ischemia, and demyelination.
Path: Exits the pons, travels along the clivus bone, cavernous sinus, to lateral rectus.

Multiple CN Palsies:

• **Consider workup for neoplasms, granulomas, infections** and other pathology within the cavernous sinus, Meckel's cave,

petrous apex, orbital apex, or pons may all give rise to multiple cranial nerve palsies.

-MRI brain w/wo, +T2 fat sat orbits, MRA, MRV

•**Consider meningeal process/ polyneuritis cranialis**

-MRI w/wo contrast with thin cuts through brainstem

-HIV, Lyme, Quantiferon, serum ACE,

-CSF: cell count, protein, glucose, ACE, culture, AFB smear + Tb PCR (MTD PCR)

-CSF cytology & flow.**x3** (r/o meningeal malignancy)

• **Internuclear Ophthalmoplegia (INO)**: palsy of medical rectus on adduction of lateral gaze +/- nystagmus of abducting eye.

-Damage to MLF which sends fibers from PPRF /abducens nucleus to the contralateral medial rectus.

DDX includes MS & stroke.

• **1 and a half syndrome:** lesion to PPRF and ipsilateral MLF

INO + ipsilateral CN6 palsy

ipsilateral eye fixed, contralateral eye abducts but won't cross midline

• **8 and a half syndrome:** posterior pons lesion hits PPRF, MLF, and CN VII fibers making hairpin turn around abducens nucleus

INO + ipsilateral CN6 and CN 7 palsy

• Horizontal Gaze Paralysis: Usually associated with damage to the ipsilateral pons (PPRF or CN6 nuc) or contralateral frontal eye field.

•**Vertical Gaze Paralysis**: Usually associated with midbrain lesions involving the riMLF or midbrain vertical gaze center (nucleus of Cajal).

• **Supranuclear Palsy:** Cortical or cortical-bulbar lesion usually only has paralysis of voluntary gaze therefore VORs are intact. Usually seen in PSP or s/p cardiac arrest.

Evaluation of Nystagmus		
Nystagmus	Description	Localization
Downbeat	Fast phase down, most noticeable in down or lateral gaze	BL cervicomedullary junction (flocculus), floor of 4th vent.
Upbeat	Fast phase up	BL pons-midbrain junction, BL pons-medulla junction, Cerebellar vermis
Periodic Alternating	Horizontal, firs one direction then the other (cycles over 3 min)	Cervicomedullary junction (nodulus)
Pendular	sinusoidal oscillation, often with elliptical trajectories	Paramedian pons, Deep cerebellar (fastigial) nuclei
Seesaw	Eyes alternate like a seesaw	Chiasm
Rebound	Horizontal, gaze evoked with a few beats in opposite direction with return to primary position	Cerebellum
Brun's	Large Amp, low frequency ipsilateral gaze and small Amp, high frequency contralateral gaze	Cerebellopontine angle
Torsional		Central vestibular system
Sensory		Blindness
Latent	Only with other eye occluded	Congenital (usually impaired binoc. pathways (amblyopia, strabismus)
Spasmus Nutans	Dissociated, asymmetric, high frequency, low amp, pendular Age 6-12, lasts ~2 years Often w/ torticollis and titubation	Unusually benign, but rule out visual pathway lesion
Induced	Tulios, Dix hallpike, Valsalva, etc.	Usually vestibular

Evaluation of Additional Ocular Oscillations		
Name	Description	Localization
Square Wave Jerks	Paired saccade with brief inter saccade latency	Cerebellar disease, PSP, MSA
Opsoclonus	Continuous random saccades	-Posterior fossa -Paraneoplastic w/ neuroblastoma -other toxic and paraneoplastic syndromes of pons and cerebellum
Ocular Flutter	Back to back horizontal saccades	Posterior fossa: cerebellum or paramedian pontine reticular formation
Ocular Bobbing	Fast down beat with slow upward return	Pons
Oculo-palatal Tremor	Pendular oscillations of eyes and palate (patient reports clicking noise)	Interior olive hypertrophy after insult within Mollaret's triangle (inferior olive, red nucleus dentate nucleus

VERTIGO & NEUROTOLOGY

Edited by Peter Ljubenkov, MD, Jaehoon Cho, MD, and Revere Kinkel, MD

Sources:
[1] UCLA Neurology Residents Manual
[2] Bradley's Neurology in Clinical Practice, 6th edition
[3] Oxford American Handbook of Neurology
[4]Kattah et al. HINTS to Diagnose Stroke in the Acute Vestibular Syndrome. Stroke. 2009;40:3504-3510
[5] UpToDate.com

Differential Diagnosis in a subjectively "DIZZY" patient

• **Near Faint/ Presyncope** (↓blood to brain) most common cause
Light-headed, swimming sensation, blackout spells

Causes: Orthostatic hypotension, hyperventilation, vasovagal syncopy, cardiac arrhythmia, anemia, autonomic insufficiency, POTS, dehydration, BP meds
DO ORTHOSTATIC VITALS (ask ED to do before consult)
Labs: CBC, TSH
Cardiac w/u: CXR, EKG, Holter monitor, Echo, +/-Stress test
(Head and neck vessel imaging only needed if suspect VBI)

• **Hypoglycemia** (insulin OD, alcoholism, insulin -secreting tumors)
Light-headedness, disorientation, confusion
Blood Glucose Check - correct if low

• **Psychophysiology-induced dizziness**
Report Disorientation, being "spaced out" or "out of body"
Impaired central integration from anxiety, phobia, panic

• **Ataxia**

• **Vertigo:** The pathologic illusion of movement.
-Vestibular causes are far more common
-but don't miss a central cause!

II. Common Peripheral and Central Vertigo Syndromes [2]

Common Central Causes of Vertigo (don't miss strokes!)				
Etiology	Recur	Onset	Duration	Associated features
Cerebellar stroke	-	Sudden	Days-months	Unilateral dysmetria, central nystagmus
Brainstem stroke: particularly **Lateral medullary stroke** (classically a PICA stroke)	-	Sudden	Days-months	Wallenberg syndrome • Vertigo (fall ipsilateral) •↓ ipsilateral gag • ipsilateral Horner's • ipsilateral ataxia •↓ ipsilateral face pain/temp •↓ contralat. body pain/temp
Vertebro-basilar Insufficiency	+	Sudden	Minutes	Other Transient cranial neuropathies, long-tract symptoms & signs
Multiple Sclerosis	+/-	Sub-acute	Minutes - weeks	Usually "central" features (but may look peripheral), + other focal neuro signs
Migraine	+	Gradual	Sec-days	Young female, HA, aura, may be tumbling vertigo; usually just vague dizziness
Common Peripheral Causes of Vertigo (more common than central)				
Etiology	Recur	Onset	Duration	Associated features
BPPV	+	Sudden	<1 min	Elderly, induced by position change (roll over, get up)
Meniere's Disease	+	Gradual	Hours	Ear fullness, tinnitus, low frequency hearing loss
Vestibular Neuritis	-	Sudden or gradual	Days-weeks	50% preceding viral illness, +hearing loss = "labyrinthitis"
Perilymph fistula	+	Sudden	seconds	Tulio's Phenomenon: Nystagmus w/ loud noise & pressure change

III. Differential diagnosis of vertigo by anatomical locations:

A. Cochleovestibular/ Peripheral Lesions

1. **Infection:** otitis media, serous otitis media, bacterial labyrinthitis, viral labyrinthitis, vestibular neuronitis, syphilis, herpes zoster otitis
2. **Trauma:** Perilymph fistula, Temporal bone fracture, Labyrinthine concussion, Barotrauma
3. **Tumor:** schwannoma, or meningioma or the acoustic nerve: Brain stem glioma, Primary or met to posterior fossa
4. **Vascular:** Infarction of labyrinthine artery, Intra Labyrinth Thin Hemorrhage
5. **Benign positional vertigo** (cupulolithiasis): (↑ w/aging, trauma)
6. **Meniere's disease** (endolymphatic hydrops)
7. **Perilymph fistula** (if pt complaint of dizziness with cough/sneeze)
8. **Disorders of bone metabolism**: Otospongiosis, Osteopetrosis
9. **Peripheral neuropathy**: Diabetes mellitus
10. **Head Trauma**: including temporal bone fracture

B. Drugs/Ototoxins: (usually a peripheral nystagmus)

- Anticonvulsants: Phenytoin, Phenobarbital, carbamazepine
- Aminoglycosides
- ETOH
- Salicylates
- Loop diuretics: furosemide, ethacrynic acid
- Antineoplastics: nitrogen mustard, bleomycin, cis-platinum
- Heavy metals: mercury, gold, lead, arsenic drugs

C. Central Processes

1. Infection: Meningitis, Encephalitis, Brain abscess
2. Demyelinating disorders: **Multiple sclerosis**
3. Tumor: Cerebellopontine angle tumors: benign and malignant
4. Vascular: vertebrobasilar insufficiency, migraine variants, **brain stem or cerebellar stroke or ICH**
5. Congenital conditions: e.g, Arnold-Chiari
6. Familial ataxia, neurodegenerative cerebellar issues (usually more ataxia than true vertigo)
7. Seizure disorders

D. Other Systems: Acute ocular palsies are sometimes interpreted as vertigo

VI. Focus Points for Examination of Patient with Vertigo:

Acute Peripheral vs Central Nystagmus [3]	
Acute Peripheral	**Central**
Unidirectional, Jerk Nystagmus Fast beat away from affected labyrinth Slow beat toward affected labyrinth	Uni- or Multi-directional (particularly direction changing) on eccentric gaze
Horizontal >> Torsional Pattern	May be Pure vertical (often downbeat) or pure horizontal
Fatigable	Persistent
Alexander's law: ↑ Amp. with gaze toward fast phase ↓ Amp. with gaze opposite direction	May be gaze evoked
Suppresses with Fixation	Doesn't suppress with fixation
Severe vertigo & nausea +/- vomiting	Variable, often more mild symptoms
+/- associated hearing loss only (walking uncomfortable but usually spared)	+/- other focal finding (brainstem, cerebellar, long tract) & inability to walk
HINTS Criteria for Acute Vertigo Exam	
#1. *Negative* Horizontal **H**ead **I**mpulse testing test (Note: *Positive* = prob. peripheral [high specificity unless criteria #3 is met]) #2. Direction-changing **Nystagmus** in eccentric gaze #3. **T**est of **S**kew deviation (with cover/uncover) reveals vertical disconjugate gaze. Upright-supine test 80% sensitive for skew dev (vertical strabismus ↓ ≥50% w/change from upright to supine)	

A. Vitals: **DO ORTHOSTATIC VITALS** - ED should do before you see Pt

B. **Mental status:** Altered mental status suggests drug toxicity, metabolic abnormalities, large posterior fossa hemorrhage, or postictal state.
(Note: think about subclinical seizures/status if AMS and "nystagmus")

C. **Cranial Nerves + HINTS exam:** (see above)
- CN palsies in general suggests brainstem injury
- **Head Impulse testing:** (diagram page 160)
  - catch up saccade is highly specific for peripheral cause
- EOM and evaluate for **Nystagmus** (see above and page 153)
- **Vertical Skew deviation** (see HINTs discussion above)

D. **Dix-Hallpike:** ~79% sens. and 75% specific for posterior canal **BPPV** (page 160.) consider prophylactic Zofran (or you might induce vomiting)

E. **Query for Wallenberg syndrome**: Lateral Medullary Stroke
- Vertigo (fall ipsilateral)
- ↓ ipsilateral gag
- ipsilateral Horner's
- ipsilateral ataxia
- ↓ ipsilateral face pain/temp
- ↓ contralateral body pain/temp

F. **Detailed Gait and coordination (cerebellar) exam**
Always walk your patients!! Assess severity of ataxia
- Central: often more severe, unable to walk

- Peripheral*:* uncomfortable, but usually can walk with encouragement

V. Workup in Patients with Vertigo:

•**MRI (w/ DWI) including MRA or CTA Head & Neck**: only if suspect central lesion - needed for focal findings, inability to walk or direction-changing -stroke code protocol if suspect stroke onset within 12 (see stroke chapter) • **MRI with/without contrast**: if suspect multiple sclerosis or tumor. + IAC protocol if asymmetric hearing loss • **Head CT:** is test of choice to evaluate for temporal bone fractures
• **Audiology Eval:** for evidence of hearing loss (Low frequency loss suggests Meniere's)
• consider **Lumbar Puncture** with MS panel

VI. Vertigo Management

A. **Central Causes:** see separate stroke (page) and MS (page) chapters

B. **Migraine:** See management section pages 166-168

(Note: Verapamil is 1st line and Topiramate is 2nd for basilar migraine)

C. **Vestibular Neuritis & Labyrinthitis:**

- **Prednisone** starting at 60, with 10-day taper
- or **Methylprednisolone** starting 100 mg w/ 2-3 wk taper
- Acyclovir is rarely given as it is NOT efficacious in trials

D. **BPPV: Epley maneuver, most common use, but may also use Sermont.** meds offer scant relief

E. **Meniere's Disease:** (note: limited established efficacy of medical interventions)

-low salt diet (1-2g Na daily), and avoid caffeine, avoid alcohol.
-May try Diamox + meclizine or Phenergan for symptoms

F. Stop ototoxic agents (see chart on previous page)

G. Commonly used Antivertigo and Antiemetic Drugs [2]

Agents	Dosage Comments
Antihistamines	
dimenhydrinate	50 mg orally q4-6h or 100- mg suppository q8h
meclizine	25-50 mg orally q4-6h
Promethazine	25-50 mg orally, IM, or suppository q4-6h
Benzodiazepine	
diazepam	2-4 mg orally q6-8h (high dose only if non-responsive)
Phenothiazine	
prochlorperazine	5-25 mg orally, IM, or 25mg suppository q4-6h
Benzamide	
metoclopramide	5-10 mg orally, IM, or IV q4- 6h

VIII. Maneuver Diagrams [5]

A. Horizontal Head Impulse Testing (specific for peripheral, unless skew dev. noted)

Normal Side
- Tell patient to fixate on distant object
- Eyes remain fixated during rapid random horizontal thrust

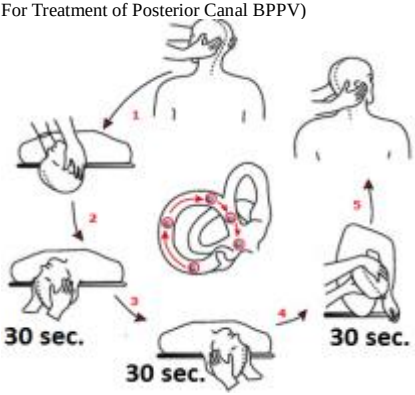
Side of Peripheral Lesion:
- Eye will move will head during horizontal thrust to side of lesion [D] (may be subtle)
- Catch up saccade seen when patient fixates again on distant object [E]

B. Dix Hallpike Maneuver
~79% sensitive and 75% specific for Posterior Canal BPPV (most common)
-consider prophylactic Zofran or you might induce vomiting

- Turn head to tested side
- Bring patient back in controlled but fairly quick
- Make sure their head hangs over edge of bed

- **Nystagmus= positive NOT symptoms**
-usually ≤ 30s latency (must observe 30 seconds)
-usually beats upward and torsionally

C. Epley Maneuver:
For Treatment of Posterior Canal BPPV)



D. Modified Semont Maneuver
- Picture illustrates treatment of LEFT posterior canalithiasis.

1) Turn head 45º to right & quickly drop the trunk to the left
-Hold 30 seconds or until any provoked vertigo subsides.
2) Quickly sit up and lie down on the right side without stopping in the upright position (keep head turned 45º to right)
-Hold for 30 seconds or until vertigo subsides. Then patient returns to down position. Repeat 3x/day until asymptomatic.

HEADACHE

Edited by Peter Ljubenkov, MD, Amanda Yu, DO, PhD, Josh Alexander, DO, MS

[1] Schwedt et al. Thunderclap headache. Lancet Neurol. 2006 Jul;5(7):621-31.
[2] The International Classification of Headache Disorders.Headache Classification Committee of the International Headache Society (IHS) 3rd edition. Cephalalgia 33(9) 629–808
[3] Silberstein et al. Neurology. 2012 Apr 24;78(17):1337-45

LIFE-THREATENING CAUSES

- **SAH:** worst, acute/thunderclap, meningismus, photosensitivity, and occasionally "orgasm ha"
- **VST:** focal finding, OCP/pregnant women, papilledema, elevated ICP
- **Meningitis:** fever, meningismus, toxic appearance
- **Herniation:** decreased consciousness, focal finding, [bleed/mass]

Acute Evaluation of Headache

A. Sick or not sick? -R/o life-threatening causes in anyone who looks sick.
B. Past History: History of similar HA fitting a primary syndrome?
C. Exam: fever, ↓consciousness, papilledema, meningismus, focal findings
D. Tests:

1. When to get imaging? CT Head or MRI
"first, worst, or cursed (focal neurologic signs or fever)"
- new HA > 40-year-old
- focal neurological signs
- orbital bruit
- exertional headache, tussive headache, or orgasm headache
- headache progressively worse
- change in character
- history of malignancy or HIV
- evidence of increased ICP (mass/lesion)
- evidence decreased ICP (meningeal enhancement on MRI)

2.**CTA or MRA:** if SAH or other vascular headache on differential
3. **CT wo contrast + CTV (w/ con)** if suspicion for venous thrombosis.
-or **MRI w/wo contrast + MRV**
4.**Lumbar Puncture** if suspicion for SAH or meningitis, even if CT is negative. (see separate chapter on CSF interpretation, page 173-174)
-Standard of care/ gold standard for SAH
-CT is negative in 10-15% of SAH. (Much higher sensitivity combined with FLAIR, but LP still standard)
- **xanthochromia**: most sensitive for SAH 12 hrs post onset
-**Note: Must get CT prior to LP in patient with any of the following:**
a) depressed level of consciousness
b) focal neurologic signs
c) papilledema.
(Also consider CT first in AIDS patients)
5.**ESR** if suspect Temporal arteritis: Pts over 50 +/- vision loss, jaw claudication, tender temporal artery with loss of pulse
Adjusted ESR limit by age = (age [+10 for women])/ 2

Additional Specialized Headache Workups:

- **Suspected Intracranial Hypotension:** (see discussion of thunderclap HA)
  - **MRI Brain and Spine w/wo contrast**: may have subdural collections, small ventricles, central sagging, tonsil herniation, pituitary engorged
  - **CT Myelogram: test of choice to identify source of leak**
  - **Radioisotope cisternography (indium-111**)- may help for slow leaks not seen on CT myelogram
  - **LP:** can confirm opening pressure <6cm, but not needed if imaging classic, and may exacerbate situation (even possible herniation)
  - Get anesthesia on board early RE blood patch
- **Suspected Intracranial Hypertension** (see page 150)
- **Suspected Reversible Vasoconstriction Syndrome (RCVS):** (see discussion of thunderclap HA below)
  - **Formal angiogram/DSA**
  - Consider LP/ other labs to rule out vasculitis (page 29)

Differential Diagnosis of Thunderclap Headaches [1]

- **Subarachnoid Hemorrhage (SAH)**: 10-25% of thunderclap headache
  -LP with xanthochromia is gold standard/standard of care (but combined CT head + MRI w/ Flare is similar sensitivity)
- **Spontaneous intracranial hypotension:** orthostatic headaches and some combination of nausea/vomiting, dizziness, auditory changes, diplopia, visual blurring, interscapular pain, and/or upper extremity radicular pain. 2/2 meningeal diverticula or instrumentation.
- **Venous Sinus Thrombosis:** uncommon presentation, but consider in at risk patients (pregnancy, hypercoag state, OCPs)
- **Dissection:** Query history of trauma, chiropractic manipulation, etc.
- **Hypertensive Emergency** (may have AMS, blurred vision, ataxia)
- **Pituitary Apoplexy**: AMS (24%), Vomiting, Visual field cut (75%, temporal), diplopia (75%), pupil dilation
- **Retroclival Hamartoma**: Usually post trauma
- **Stroke**: (25% have headache but a thunderclap headache is RARE, make sure they have stroke syndrome before considering
- **Colloid Cyst of the Third Ventricle**: Presents has positional headache +/- and LOC when the cyst shifts and blocks CSF flow
- **Reversible Cerebral Vasoconstriction Syndrome** (RCVS)
  -confirmed via angiogram- beading similar to vasculitis
  -resolves on serial angio & normal LP (otherwise consider vasculitis)
  -May occur spontaneously or in context of pregnancy, SSRIs, triptans, sympathomimetics (recreational and pharmacologic)
  -Typically treated with calcium channel blockers (Verapamil, nimtop)
- **CNS vasculitis**
- **Spontaneous Intracranial Hypertension**
- **1º Cough headache, 1º Excertional Headache, & 1º Sexual/Orgasmic**

Headache (vascular headaches related to a specific straining event)
•"1° Thunderclap Headache"- a diagnosis of exclusion

General Overview of Primary Headaches Syndromes [2]

•Migraine: typically 4-72 hours (untreated) unilateral, pulsatile, aggravation by routine physical activity, and associated with nausea (+/- vomiting), photophobia, phonophobia.

- **•Migraine with aura:** aura may be visual (scintillating scotoma is the most common aura), sensory, language, motor (as in familial hemiplegic variant), brainstem, and retinal
  -Aura typically unilateral, gradual onset over 5 minutes, lasting 5-60 minutes, and occur during or up to 60 min before HA.
  -Risk factor for stroke. Avoid OCPs with estrogen
- **•Chronic Migraine**: more than 15 day/mo ≥ months

•Tension Headache:("band-like") bilateral (frontal and occipital), pressing (not pulsatile) and not aggravated by routine activities

• Trigeminal Autonomic Cephalgias: (always unilateral in onset)
All may have some of the following ipsilateral autonomic features: miosis, conjunctival injection, lacrimation, nasal congestion /rhinorrhea, eyelid edema/ptosis, facial flushing/sweating, ear fullness

- **• Cluster:** unilateral orbital, supraorbital and/or temporal, lasting 15–180min.
  -get a sense of restlessness or agitation (run around room)
  -Often circadian, at night, and clustering (days to weeks).
  -provoked by alcohol, histamine and nitroglycerin
  -NOT indomethacin responsive, but try
- **•SUNCT:** lasting seconds w/prominent tearing/lacrimation (may be mimicked by posterior fossa lesion)
- **•SUNA:** w/o prominent tearing/lacrimation, lasting seconds
- **•Indomethacin Responsive Headaches: (**exquisitely responsive)
  - **•Paroxysmal hemicrania:** 2-30 min (may look like cluster)
  - **•Hemicrania Continua:**>3 months

General Overview of Common Secondary Headache Syndromes

- Vascular Bleeds – SAH, ICH Ischemic stroke/Sinus Thrombosis
- Infectious – meningitis, sinusitis, post-herpetic neuralgia
- Headache 2/2 neuralgias/ neuropathies:
  - **-Trigeminal Neuralgia:** sharp, intermittent shooting pains, usually V2 or V3 distribution. (may have tortuous vessels abutting CN V on imaging)
  - **Occipital Neuralgia:** Jabbing pain in occipital region
- Posttraumatic headache
- Cervicogenic Headache
- Increased ICP – mass lesions (tumor, hemorrhage), pseudotumor cerebri
- Decreased ICP – spontaneous, post-LP. Positional component.
- Temporal arteritis– temporal artery tenderness, jaw claudication, older men, ↑ESR
- HTN

• Drugs – caffeine withdrawal, nitrates, Aggrenox, opiates, NSAIDs, triptans, barbiturates

Management of Specific Headache Syndromes

A. SAH, ICH or herniation: call neurosurgery and NCC stat (see ICH and SAH chapter)

B. Venous thrombosis:
- MRI- venous strokes may be MRI negative
- Therapeutic anticoagulation initiated in ICU - high ICH risk
- thrombolytic/interventional retrieval sometimes considered

C. Meningitis: LP, antibiotics; (see Meningitis Chapter).

D. Trigeminal neuralgia:

Carbamazepine: First line for lancinating paroxysmal pain
start 100-200 mg BID, maintenance 600-1200 mg.
-May alternatively use oxcarbazepine

Gabapentin:200 mg BID, titrate up to efficacy (better for more steady pain)

Surgical intervention: last resort if tortuous vessel seen abutting trigeminal nerve on MRI

E. Occipital Neuralgia
- **Occipital Nerve Block** (Local anesthetic +/- kenalog)

F. Pseudotumor Cerebri: see page 150

G. Decreased ICP: (see specialized workup on page 163 if spontaneous)
•Bed rest, caffeine intake, fluids
→Epidural blood patch if fails
→ Surgical repair if fails

H. Temporal Arteritis: ESR > (age [+10 for women])/ 2
• Uncomplicated: **prednisone** 40 to 60 mg daily, taper 10mg every 2wks
• If vision loss: **methylprednisolone** 1g IV x 3-5 days.
-follow w/1 mg/kg per day (max of 60 mg/day)
• ASA 81mg
• Call optho and organize temporal artery biopsy w/ surgery

I. TAC headaches
• **Cluster:**
• High flow O2 for all suspected cases
• **triptans** (& DHE) (see migraine section next page)
- avoid in cardiac disease
• **octreotide**: SC 100 mcg
• **prednisone** 60 to 100 mg daily x 5 d, then taper 10 mg qday
• **Indomethacin trial:**
(Consider in TAC heads even if it looks like cluster)
- initially 150 mg daily
increased if necessary up to 225 mg daily.
- Must give PPI - GI upset is a major issue with indomethacin
- Cross titrated with Ca-channel blocker if possible
• **Verapamil**
(First line prophylaxis for cluster and other TAC headaches)
-may start at 240mg Daily, divided TID

(or Daily sustained release)
-titrate 80mg Q 10-14day. ~240-320 mg effective
(may need up to 960mg)

J. **Migraine Management**

Common Treatments for Status Migrainosus:

- **Fluids**: at least 500-1000cc Normal Saline
- **"Migraine Cocktail":** NSAID + anti-emetic + Benadryl, repeat q6-8hr
  - Toradol: 30 mg IV or 60 mg IM
  - Reglan 10mg IV or compazine 10mg IV or Zofran 8mg IV
  - Benadryl 25-50 mg IV
- **Valproate** (Depacon) 500mg IV over 30 minutes, can repeat q6-8hr
- **Mg** IV 1-2gm
- **Steroids**: solumedrol 250-500mg (may help prevent rapid recurrence) and consier short steroid taper (e.g. Medrol dose pack or pred 60mg with 5-10 day taper)
- **DHE** protocol (see below)

Never use opiates for migraines.

Status Migrainosus in Pregnant Women:

- Bolus 1-2L NS
- Tylenol 650 mg dosing should be first tier intervention
- May consider trial of caffeinated beverages
- Reglan 10mg IV (class B) +Benadryl 25mg IV (class B)
- May consider Magnesium load 1 g IV load
- If patient remains refractory to treatment above, consider very short-term coverage with low potency opioids such as codeine (but sustained use will be counterproductive)

(Note DHE is class X)

DHE protocol

-Premedicate with Zofran 4-8mg IV 30min prior to every DHE infusion
-DHE given q8h, each dose over 1 hour: first dose 0.5mg/100mL NS, second dose 0.75mg/250mL NS, all subsequent doses (up to 10) 1mg/250mL NS
-if unable to tolerate: add a second anti-emetic such as Phenergan or Reglan, slow infusion to over 2-3 hours, or reduce DHE dose to highest tolerated dose

Migraine Outpatient Abortive Management: (enough for most patients)

NOTE: Avoid opioids and barbiturates (butalbital). Opioids are not usually effective and both rapidly lead to tolerance/worsened headaches.

- **Analgesics** (note ≥15 days per month → analgesic overuse HA)
  - **NSAIDs:** **ibuprofen** (400 to 1200 mg),
    naproxen (750 to 1250 mg)
    diclofenac (50 to 100 mg) PRN
  - **Acetaminophen** 650mg PRN
- **Triptans** (5-HT_{1B} and 5-HT_{1D} **agonists)**

Contraindicated in: CAD, PVD, hemiplegic migraine, basilar migraine, ischemic stroke, Prinzmetal's angina, uncontrolled hypertension, and pregnancy

Use: Typically within 2 hrs of onset, ≤ 8x per months

•**Sumatriptan**

- Oral: 25mg PRN- 100 PRN. may take a 2nd dose in 2 hours
  - Intranasal (usually 20mg) faster than oral
  - Subcutaneous sumatriptan (6 mg) faster/more effective than oral but associated with more adverse events

Additional Triptan choices

•**zolmitriptan**, **rizatriptan**, **eletriptan**, **almotriptan**

•frovatriptan: slow onset & lower efficacy, but long duration

(DHE also rarely used in some outpatient formulations. Use is limited due to cardiovascular side effects)

Non-Pharmacologic Chronic Migraine Management:

- Headache Journal: Allows clear delineation of course and response
- **CASH** Questions
  - •**Caffeine:** even modest regular use with missed or decreased intake with trigger headache
  - **Activity**: regular sustained cardio will decrease headaches
  - **Sleep**: Sleep deprivation and OSA are huge contributors
    - discuss sleep hygiene
    - consider sleep clinic referral to rule out OSA is patient reports snoring or not feeling rested in AM
  - **Hormones**: find out if there is a relation for cycle in women
- Maintain proper hydration and don't skip meals
- Psych referral for refractory stress/ anxiety

Pharmacologic Migraine Management (Prophylaxis)

Commonly Used Prophylactic Med Dose/Titration

Drug	Start Dose	Titrate by	Maximum	Pearls/caveats
Amitriptyline	10-25mg QHS	10mg q10-14d	150mg	1mg/kg typically effective Good for insomnia
Nortriptyline	10-25mg QHS	10mg q10-14d	150mg	Better tolerated than amitriptyline, can do 1:1 dose conversion
Propranolol	20mg BID	20mg BID q2wk	120mg BID	1mg/kg typically effective
Valproate	250-500mg BID	250mg qwk	1500mg BID	Good for comorbid seizures or

				mood disorder
Gabapentin	300mg QHS	300mg BID x5 days 300mg TID x5 days 300mg TID q3wk	1200mg TID	good for anxiety
Topiramate	25mg BID	25mg q2wk	100mg BID	See side effects
Venlafaxine	37.5mg	37.5mg	75-100mg daily	
Verapamil	40mg BID (ER form better than SR)	40mg BID q2wk	320mg TID	Makes ~10% HA worse
Memantine	5mg daily	5mg q10d	10mg BID	

Non Pharmacologic:
Migraineurs like homeostasis/regularity. Regular sleep, meals, stress mgmt., trigger avoidance
Mg 400-600mg daily – causes dose dependent diarrhea
Riboflavin (B2) 400mg daily – causes bright yellow urine
Co Q10 300mg daily
Butterbur 150mg daily

Side Effects of Commonly Used Prophylactic Meds

Amitriptyline Less so for nortriptyline	Anti-cholinergic (dry mouth, urinary retention), sedation, QT prolongation (overdose can be fatal)
Verapamil	Orthostasis, pedal edema, constipation, lethargy
Propranolol	Blunted exercise tolerance, orthostasis
Valproate	Weight gain, hirsutism, hair loss, teratogenicity, liver toxicity, thrombocytopenia
Topiramate	Weight loss, cognitive slowing, paresthesias (typically self-limited), kidney stones, sweating difficulty, rare glaucoma
GBP/PGB	Weight gain, edema, sedation
Venlafaxine	Sexual dysfunction, GI upset

- **Botulinum Toxin** (Botox):
  - Approved for chronic migraine, may improve Sx ~50% (over 15 day/mo x3 mo)
  -Usually need to fail 3 first line interventions
  - Both UCSD and VA have Botox clinics that you can refer appropriate patients to.

SLEEP DISORDERS

Adapted by Walter Heine, MD, PhD, and Mike Rafii, MD, PhD
form UCLA neurology handbook, 2010, Bradley's Neurology in Clinical Practice

Key Questions in the Evaluation

- Do you have problems falling asleep, staying asleep, or awakening?
- Do you feel rested after a night's sleep?
- Do you have discomfort in or jerking of your legs at night?
- Do you snore, gasp, choke, or stop breathing during sleep?
- What time do you go to bed and get up on week days and weekends?
- Do you take naps?
- Do you doze easily or feel sleepy in quiet or monotonous situations?
- What medications are you taking?

Physical Exam of a patient with Sleep Disorders

-Crowded oropharynx, tonsils, soft palate, uvula, tongue Retrognathia or micrognathia, small maxilla, small orals space.
-Nasal/Sinus: Chronic nasal congestion, enlarged turbinates, deviated septum
-Neck circumference: (male > 17 inches, female >16 inches)
Cardiovascular: Hypertension, Heart failure, Ankle edema
Neurologic: Assess for CNS disease (eg, Parkinson's Disease)

Indications for Polysomnography

All night Polysomnogram:
Sleep-related Breathing Disorder, Narcolepsy, REM sleep Behavior disorder, Violent activity during sleep, Sleep-related Epilepsy, Undiagnosed movement /activity during sleep, etc.
CPAP or BiPAP titration, Esophageal PH monitoring, Evaluation of effectiveness of treatment
Multiple Sleep Latency Test: Narcolepsy, test of sleepiness severity
Maintenance of Wakefulness Test: test treatment response

Epworth Sleepiness Scale: Assesses level of daytime sleepiness
0=would never doze or sleep
1=slight change of dozing or sleeping
2=moderate chance of dozing or sleeping
3=high chance of dozing or sleeping

Situation	Chance of dozing or sleeping
Sitting and reading	
Watching TV	
Sitting inactive in a public place	
Being a passenger in a motor vehicle for an hour or more	
Lying down in the afternoon	
Sitting and talking to someone	
Sitting quietly after lunch (no alcohol)	
Stopped for a few minutes in traffic while driving	

Total score	
→ **score of 10 or more is considered sleepy**	

Common Sleep Disorders

• REM Sleep Behavior Disorder

-Often act out dreams, dreams of violent/scary causing violent behavior
-Significant risk-factor for later developing and alpha-synucleinopathy (PD, MSA, dementia with strong association to LBD)
-Diagnosis: Video PSG
-Treatment:
Safety: remove dangerous objects with cushions around bed
Clonazepam
Melatonin (second line) start 3 mg 30 minutes before bedtime

• Sleep Apnea

-Diagnosis: via formal sleep study demonstrating apnea
- Nonpharmacologic treatment:
-CPAP/BiPAP, Cognitive behavioral therapy, surgery, oral appliance, quit smoking, weight loss
- pharmacologic treatment:
-modafinil & nuvigil for residual sleepiness inpatients compliant with their CPAP machine and in whom sleep deprivation is not evident.

• Insufficient Sleep Syndrome

- Non-pharmacologic treatment: naps

• Shift Work Sleep Disorder

-non-pharmacologic treatment: naps, bright lights, avoid AM sunlight, protected sleep environment
- pharmacologic treatment: caffeine, modafinil, melatonin

• Narcolepsy

- Diagnosis: MSLT that demonstrates average sleep latency less than eight minutes. May also have cataplexy, hypnagogic hallucinations, or sleep paralysis.
- non-pharmacologic treatment: prophylactic scheduled brief naps (30 min)
- pharmacologic treatment:
modafinil, dextroamphetamine, amphetamine, methylphenidate, sodium oxybate, antidepressants (for cataplexy)

• Restless Leg Syndrome

- Etiologies/associations: **iron deficiency anemia**, ESRD, DM
- Treatment:
- Iron studies: correct if abnormal
- caffeine, alcohol, and nicotine
- pharmacologic treatment:
-Dopamine Agonists: Pramipexole, ropinirole, Rotigotine
-Gabapentin, Pregabalin
(L-dopa and benzodiazepines occasionally used for intermittent symptoms)

MENINGITIS MANAGEMENT

Edited By Walter Heine, MD, PhD

Sources: UCLA Neurology Handbook, On Call Neurology 2nd Ed, 2001
Infectious Disease, Continuum,2006
Massachusetts General Hospital *Handbook of Neurology* by Alice W Flaherty MD, PhD Natalia S Rost MD, 2007

I. Syndrome: fever (77%), AMS (69%), seizure (5%), meningismus (83%, can also have N/V, photophobia, and lethargy), headache

II. Epidemiology (most common causative organisms): Neonates: group B strep and gram negative bacilli
- Adults 15-50years of age: *S.pneumoniae* and *N.meningitides*
- Adults > 50 years of age: *S.pneumoniae* and enteric gram-negative bacilli but also *Listeria monocytogenes* and *H.influenzae*
- Post neurosurgical procedure: gram-negative bacilli and staphylococci except for shunts: coagulase-negative staph and S. aureus
- Viruses: enteroviruses/ arthropod-borne viruses, HSV, EBV, HIV, VZV

III. CSF profile of meningitis: Refer to section on CSF analysis, page 173.
- CSF workup: Gram stain, AFB, Cultures: bacterial, viral, fungal, AFB
- Depending on clinical scenario, also consider:
  - -India Ink
  - Titers: Cocci, crypto, toxo, cysticercosis, VDRL, lyme, mycoplasma, West Nile, viral meningo-encephalitis panel
  - -PCRs including Mycobacteria, HSV, VZV, CMV, EBV, HTLV, West Nile

-Indications for head CT prior to LP:
- focal neurological deficit,
- new-onset seizure
- papilledema
- abnormal level of consciousness
- immunocompromised state.

-Blood cultures should be drawn in addition to LP

VI: Empiric treatment of bacterial meningitis

- If suspect bacterial meningitis and patient looks very sick, do not hold antibiotics while waiting for CT and LP (LP can be done up to 2 hrs after first dose without destroying cx results).

-**Typical Coverage**
- **Ceftriaxone** 2 gIV q12 or **cefepime** 2 gIV q8,
- **Vancomycin** 1gq12.
- Add **ampicillin** IV 3g q6 if concern for Listeria (>50 years old or immunocompromised).
- -**Dexamethasone**: 10mgIV q6 for 4 days starting before or with first dose of antibiotics.
- -If penicillin allergic: **chloramphenicol** 12.5mg/kgIV q6 or **clindamycin** 900mgIV q8 or **meropenem** 1gIV q8
- -Add **acyclovir** 10mg/kg q8hr empirically until CSF HSV returns negative. If tick season/Lyme suspected: add doxycycline

Adapted by Jaehoon Cho, MD, from UCLA Neurology Resident Handbook

Constipation
Docusate sodium (Colace) 100 mg PO q12 (stool softener).
Senna (Senokot, Ex-Lax) 1-2 tabs PO (pro- motility agent).
Bisacodyl (Dulcolax) 10-15 mg PO (pro-motility agent).
Magnesium hydroxide (Milk of Magnesia) 30-60 cc PO (saline laxative)
Magnesium citrate 150-300 cc PO (saline laxative)
Lactulose 15-30 cc PO (hyperosmolar agent)
Polyethylene glycol c electrolytes (Go-Lytely) 240 cc PO (4L total is used for bowel prep)
Sodium bisphosphate (Fleets enema) or other types of enema

Dyspepsia
Maalox (aluminum hydroxide + Mg hydroxide) 10-20 cc or 1-4 tabs
Mylanta (aluminum hydroxide + Mg hydroxide + simethicone) 10-45 cc
bismuth salicylate (Pepto-Bismol) 2 tabs or 30 cc PO q 30 min up to 8x/day.

Contrast Nephropathy
•Serum Cr starts rising 48-72 hours after contrast administration
•Risk factors: diabetic nephropathy, renal insufficiency, multiple myeloma, large volume of contrast
•Prophylaxis (Use for Cr > 1.2 or CrCl < 50 ml/min):
- 1 liter sterile water + 4 amps sodium bicarbonate, run at 3 cc/kg/hr starting 1 hour prior to procedure. Decrease to 1 cc/kg/hr post-procedure, continue x 6 hours (May alternately use normal saline)
May add Acetylcysteine 600 mg PO bid the day before and on the day of contrast
Treatment: Monitor/observation. Giving fluids does not help. Call renal and dialysis if necessary.

Contrast Allergy
If rash alone: send patient with Benadryl 50 mg IV on call to scan
If reaction is unknown or more severe (but not anaphylactic): give prednisone 50 mg PO q12hr x 3 doses, or SoluMedrol 40 mg IV q12hr x 3 doses, plus Benadryl 50 mg IV on call to scan.
If reaction is severe, consider alternate study.

Home Oxygen To qualify for coverage by Medicare:
$PaO_2 < 55$ mmHg or O_2 sat < 88% at rest
Only nocturnal O_2 will be covered if above conditions met while asleep, but not while awake
If PaO_2 = 56-59 mmHg or O_2 sat = 89%, must also have either dependent edema suggesting CHF, pulmonary hypertension, or cor pulmonale

CEREBROSPINAL FLUID INTERPRETATION

Edited by Michelle Van Noord, MD and Peter Ljubenkov, June 2014
Sources: UpToDate, Mass Gen Handbook of Neurology 2nd edition, Neurology On Call 3rd edition, Mass Gen Handbook of Internal Medicine

Note: Always order cell counts tube 1/4, protein, glucose, gram stain, culture
General: Choroid plexus makes 20 mL/hr CSF. There is 125-150 mL in total, 20% in ventricles.

•**Contraindications to Lumbar Puncture:**
- Coagulopathy)/ therapeutic anticoagulation (risk epidural hematoma)
- Overlying cellulitis (risk introducing infection)
- Space-occupying lesions in brain and spine that increase herniation risk.

•**Pressure:** Normal pressure is 6-20 cm H_2O, usually < 15. This is measured in lateral decub. with legs straight/relaxed.

•**Xanthochromia: (**RBCs lyse in CSF)
Hemoglobin →oxyhemoglobin→methemoglobin→ bilirubin = yellow. Shows up in 2-4 hrs. 90% of SAH will be positive in 12 hrs, remains for 2-4 weeks. Other causes: CSF protein > 150, serum bili> 10.

•**Cells:** 5 WBCs and 5 RBCs are allowed (introduction from tap: CSF is acellular). >3 PMNs abnormal. Need to check w/in 60 min of tap so cells don't settle in tube. **1 WBC allowed for every 500-1500 RBCs in traumatic tap.** Traumatic tap has reduction in RBCs between tube 1 and 4
•**Protein:** usually about 15-40 mg/dL (via pinocytosis); elevation indicates breakdown in BBB or obstructed flow. 1 mg/dL allowed for every 1000 RBCs (check on same tube).
•**Glucose:** CSF: serum 0.6. Ventricles > lumbar. Low: bacterial, mycobacterial, mycoplasma, fungal; rarely sarcoid or malignancy. Usually normal in viral processes.
•**Lactate:** better specificity than WBC count, glucose, protein when diagnosing bacterial vs. viral processes but less sensitive when Abx already on board.

Condition	Appearance	Pressure (cm H_2O)	WBC/mm^3 & Predom. type	Glucose (mg/dL)	Total Protein(mg/dL)
Normal	Clear	9-18	0-5, lymphs	50-75	15-40
Bacterial	Cloudy	18-30	100-10,000, poly	<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

Chart from The Massachusetts General Hospital Handbook of Internal Medicine

Immunoglobulins, oligoclonal bands: Endogenous production of immunoglobulins in the CSF space should not be seen (blood to CSF 500:1). If present, consider CSF leak or production within CNS. Oligoclonal bands (OCBs) are Ig that are seen in CSF but DO NOT match those in serum, classically seen in MS. The CSF Ig index (CSF IgG to CSF albumin ratio compared to the serum IgG to serum albumin ratio) is also commonly elevated in MS (normal 0.00-0.85). However, both OCBs elevated IgG index may be seen in a host of CSF infections, autoimmune conditions, tumors, and lymphoproliferative conditions.

In MS: May have 2 or more oligoclonal bands, lymphocytic pleocytosis, normal or slightly elevated protein. OCB sensitivity only in the 80s for MS, but once they are positive in MS they stay positive. CSF IgG index elevation also has sensitivity on the 80s.

Special tests: TB PCR, AFB culture/stain, viral PCRs (West Nile, CMV, HSV), ACE, crypto antigen, VDRL, 14-3-3, total & phosphorylated tau

Special situations:

•**Suspected CSF/Meningeal Malignancy:**
You must do CSF flow cytometry (for lymphoma) and cytology up to 3 times to rule out malignancy. For both studies you need high volume (10 – 15 mL). Fill tube 4. CSF samples for flow cytometry should be placed directly on ice after they are drawn (or else they must go directly to the flow cytometer). There is some possible utility in doing a cervical tap if studies are negative x2 and there is very high index of suspicion for basilar location of malignancy. If possible, do LP early in the day on a weekday; needs to be processed by path in a timely fashion.

•**Guillain-Barre:** Normal cell count, elevated protein (albuminocytologic dissociation)

•**CSF Block:** Occasionally, particularly in the CSF space around the cord, a space occupying lesion, such as a tumor may obstruct CSF flow, and cause protein to be in the thousands.

Typically LP is avoided in these patients in the first place, as they are at high risk of herniation!

•**Cushing's triad:** Hypertension, bradycardia, ↓RR/respiratory irregularity: impending herniation

•**Skull fracture:** Battle's sign, rhinorrhea, otorrhea (CSF leak)

•**EVD management:** usually open 15 cm above the tragus; lower or "open" at 10 or lower if not draining. Patient fails a clamp trial if ICP > 20. If not antibiotic impregnated, need to cover with Vanc. and 3rd gen cephalosporin.

NEURORADIOLOGY

Walter Heine MD, PhD, Peter Ljubenkov, MD, & James Chen, MD
Sources: -Bradley's Neurology in Clinical Practice, 6th edition UCLA Neurology -UCLA Neurology Resident Handbook

Other resource: **Spinwarp.ucsed.edu** (UCSD neuroradiology site)

Computed Tomography (CT) Modalities:

•**CT, Non-Contrast**: Good for emergencies (available rapidly) or in patients with contraindication to MRI (pacemakers, etc.).

- •Assesses bleeds, masses with edema, fractures, hydrocephalus and old strokes well.
- •CT Shortcomings: acute stroke, small masses, and posterior fossa/brainstem.
- •Differential of Hyper/Hypodensities on CT
  -Hypodensity on CT: air, fat, edematous lesion, gliosis, demyelination, low-grade tumors
  -Hyperdensity on CT: bone, mineralization, contrast, densely packed cells (lymphoma, medulloblastoma, etc.), acute blood, streak artifact.

Appearance of tissue on CT (Hounsfield units)	
Black (hypo-dense)	White (hyper-dense)
(-1000 HU) 0 HU	(+1000 HU)
air→fat→CSF/water→white Matter→ gray matter→acute blood→ bone	

•**CT Angiogram:** Used to assess for arterial blockages (with pseudo-occlusion being a problem requiring catheter angiography), aneurysm, dissections, stenoses. Also good to look at venous thrombosis.

•**CT Perfusion:** Assesses areas of mismatched decreased blood flow, to assess potential "at-risk" areas from vascular stenoses – used often in patients who cannot get MRI.

MRI Sequences:

•**DWI (Diffusion Weighted Image):** Used for acute ischemia, which shows up as white from 15 minutes to 2 weeks. T2-based scan, so can use a poor man's T2, and will also see T2 shine through if old lesions are present.

Differential Diagnosis of Hyperintensity on DWI:

- Infarction (arterial or venous) - ADC dark
- T2 shine through - ADC bright
- Abscess
- Active MS/demyelination
- Densely packed cellular tumor
- prolonged seizure (usually gyriform)
- vasculitis
- epidermoid cyst
- post-anoxic event
- prion disease (pattern discussed on page 90)

•**ADC (Attenuated Diffusion Coefficient)**: Companion to DWI and used to confirm acute ischemia

- Dark/hypointense lesion on ADC: confirms restricted diffusion (stroke, prolonged seizure, hypercellularity, CJD, etc)
- Matched hyperintense ADC map indicates T2 shine through.

•PWI (Perfusion Weighted Imaging): Assesses areas of decreased blood flow –show up as white. Potential to assess "at-risk" areas from vascular stenosis. Assesses angiogenesis in tumors for differentiating high and low-grade.

• **Standard T1 Weighted Imaging:** Anatomic study. Gray matter gray, white matter white, CSF dark. Used with contrast for tumor or other enhancing lesions.

• **Standard T2 Weighted Imaging:** Shows many pathologies that result in edema or increased water content. Gray matter white, white matter gray, CSF white. Best for showing white matter abnormalities like stroke, MS. Use this also to evaluate the posterior fossa.

Differential of Hypo/Hyperintensities on MRI

In general, pathological processes are usually dark on T1 and bright on T2.

	Bright	Dark
T1	Fat, contrast, subacute blood (met-hgb, protein), turbulent flow, free radicals (abscess wall), calcium in suspension	CSF, edema, gliosis, Ca^{2+}
T2	Fat (can also be isointense), edema, CSF	Air, bone, fast flow, acute blood, chronic blood (hemosiderin /ferritin), Ca^{2+}, protein, free radicals, densely packed cells, metal
GRE	Normal blood flow	Deoxygenated blood (thrombus, fat, calcium)

• FLAIR: (Fluid attenuated inversion recovery): T2 with fluid suppressed. Gray matter white, white matter gray, but CSF dark. Allows you to assess cortical and CSF space abnormalities, as well as white matter edema very well (tumor edema, MS, old strokes). Also a good way to look for less old subarachnoid blood, cells or pus in the sulci.

•GRE T2* (Gradient Echo T2*): Assess subacute (at least deoxyhemoglobin) blood, which shows up as dark. Also good or better than CT for intraparenchymal micro-hemorrhage but not acute (oxyhemoglobin) SAH.

• MR Angiogram: Used to assess for arterial abnormalities in aortic arch, neck, or head; tends to overcall severity of stenosis and blockages.

•**MR spectroscopy**: used to identify areas of abnormality such as tumor by spectroscopy, creates metabolite spectra maps.
Note: Normal peaks appear to ascend from left to right ("on the up and up")

•**Choline peak** (seen at 3.2ppms): signal of cellular membrane synthesis; increased peak with of building or tearing down membrane, high choline peak is seen in both infection and tumor and sometimes demyelination.
NOTE: If choline:creatine peak > 2.5, usually tumor.

•**Creatine peak** (seen at 3.0 ppms): creatine associated with cellular energy metabolism, and peak should remain stable.

•**NAA** (seen at 2 ppms): associated with neuronal and axonal integrity, usually the tallest peak, in the center.

•**Lipid and lactate peaks:** seen in metabolic abnormalities as well as with destructive processes, suggestive of necrosis, as in tumor, infarct, dementia or metabolic disorders.

PET Scans:

•**FDG -PET:** Identifies the relative metabolic activity of a region. Used to delineate tumor, surgically respectable focus in epilepsy, and work up of dementia subtype.

•**Amyloid PET:** Used to verify amyloid beta deposition in brain of patients with suspected Alzheimer's disease.

SPECT Scan:

•**DaT SCAN:** Reveals the relative abundance of dopaminergic input from the substantia nigra to the basal ganglia. Useful in verifying suspected Parkinson's Disease.

General Appearance of Tissue on MRI		
	T1 Weighted	T2 Weighted
Air	↓↓↓↓	↓↓↓↓
Free water/CSF	↓↓↓	↑↑↑
Fat	↑↑↑	↑
Cortical Bone	↓↓↓	↓↓↓
Bone Marrow	↑↑	↑
Edema (all kinds)	↓	↑↑
Calcification	↓ if Heavy Ca, ↑ if Little Ca some Fe	↓
Mucinous Material	↑	↓
Gray Matter	Lower than in T2	Higher than in T1
White Matter	Higher than in T2	Lower than in T1
Muscle	Similar to gray matter	Similar to gray

Aging Blood on MRI

A few notes:

• Just remember "**I**t **B**e **I**ddy **B**itty **B**aby **D**oo **D**oo"
• GRE excellent for blood, but can't show acute/ oxyhemoglobin
•The periphery of the hematoma evolves faster
• SAH is best viewed on T2 FLAIR in CSF space (bright instead of dark space)

Age		T1 Weighted	T2 Weighted	GRE
Oxyhemoglobin	Acute<12 hrs	**I**sointense (↔)	**B**right (↑)	*can't see!*
Deoxyhemoglobin	12 hours - 3days	**I**sointense (↔ or ↓)	**D**ark (↓)	Dark
Intracellular Methemoglobin	3-7 days	**B**right (↑↑)	**D**ark (↓)	Dark
Extracellular Methemoglobin	7-14 days	**B**right (↑↑)	**B**right (↑↑)	Dark
Hemosiderin	>2 weeks	**D**ark (↓)	**D**ark (↓↓↓)	Dark

MRI Imaging in Stroke

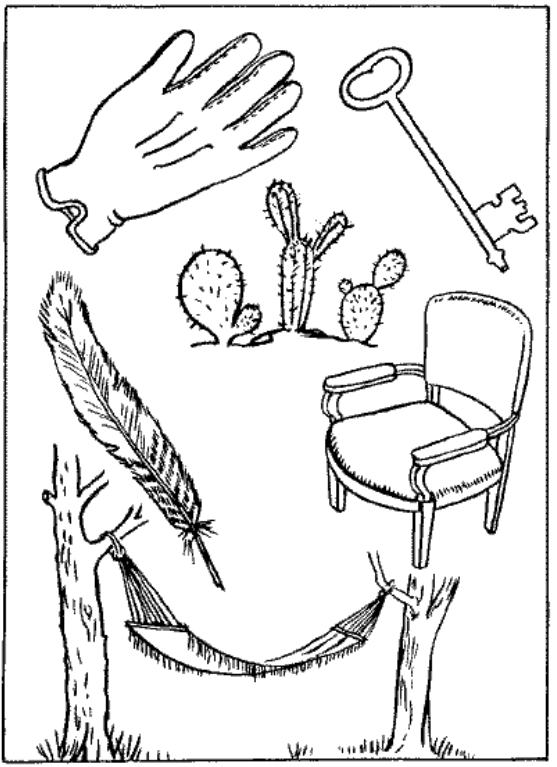
DWI	•Bright "diffusion restriction" within ~15 minutes -**preferred screening MR study for acute stroke** (however, sensitivity sometimes reported in the 80s, especially in the posterior circulation and in first 2 hrs) •Diffusion restriction ~ 2 weeks : However at about 7 days hyper-intensity becomes increasingly due to T2 shine through
ADC	•Dark within minutes •Bright ADC and bright DWI suggests T2 shine through •Good to confirm stroke: more specific from ischemia than DWI •Good to age stroke -reaches nadir at 3 to 5 days, but can be significantly low for ~7 days -return to baseline ("pseudonormalized") in 1-4 wks (usually 7-10 days)
T1/T2:	**•Acute period** -before **6 hours**: both studies may be negative **•Subacute period** (1 day -1 week) - **T2 hyperintensity** increases markedly over 4 days then stabilizes -Cytotoxic edema (T1 hypointense, T2 hyperintense) usually maximal 2-3 days post onset (may be 5 days if malignant MCA syndrome) **•Late Subacute** (1-3 weeks) -T1 hypointensity and T2 hyper-intensity again gradually increase -T1 Post contrast study: gray matter enhancement around this time •Chronic (3 weeks): Eventually cavitary fluid-filled lesions

Appendix

NIH Stroke Scale:		
1a. Level of Consciousness	Alert	0
	Drowsy	1
	Stuporous	2
	Comatose	3
1b. LOC Questions	Both correct	0
(Month, age)	One correct	1
	Incorrect	2
1c. LOC Commands	Obeys both correctly	0
(Open, close eyes, make fist, let	Obeys one correctly	1
go)	Incorrect	2
2. Best Gaze	Normal	0
(horizontal tracking)	Partial gaze palsy	1
	Forced deviation	2
3. Visual Fields	No loss	0
	Partial hemianopia	1
	Complete hemianopia	2
	Bilateral hemianopia	3
4. Facial Palsy	Normal	0
(Show teeth, raise eyebrows,	Minor asymmetry	1
and squeeze eyes shut)	Partial (lower face paralysis)	2
	Complete (upper and lower)	3
5a. Motor Arm-Left	No drift	0
(Elevate extremity 90˚ and	Drift	1
score drift/movement)	Some effort against gravity	2
	No effort against gravity	3
	No movement	4
5b. Motor Arm-Right	No drift	0
(Elevate extremity 90˚ and	Drift	1
score drift/movement)	Some effort against gravity	2
	No effort against gravity	3
	No movement	4
	Amputation, joint fusion	
6a. Motor Leg-Left	No drift	0
(Elevate extremity 30˚ and	Drift	1
score drift/movement)	Some effort against gravity	2
	No effort against gravity	3
	No movement	4
6b. Motor Leg-Right	No drift	0
(Elevate extremity 30˚ and	Drift	1
score drift/movement)	Some effort against gravity	2
	No effort against gravity	3
	No movement Amputation, joint fusion	4
7. Limb Ataxia	Absent	0
(finger-nose, heel down shin)	Present in both upper & lower	1
	Present in both	2
8. Sensory (Pin prick to face,	Normal	0
arm, trunk, and leg-	Partial loss	1
compare side to side)	Dense loss	2
9. Best Language	No aphasia	0
(Name items, describe a picture	Mild-moderate aphasia	1
and read sentences)	Severe aphasia	2
	Mute	3
10. Dysarthria	Normal articulation	0
(Repeating listed words)	Mild-moderate slurring	1
	Severe, nearly unintelligible	2
11. Extinction and Inattention	No neglect	0
	Partial neglect	1
	Profound neglect	2

COOKIE
JAR
Copyright © 1983 by Lee & Felsjow

You know how.
Down to earth.
I got home from work.
Near the table in the dining room.
They heard him speak on the radio last night.



MAMA
TIP-TOP
FIFTY-FIFTY
THANKS
HUCKLEBERRY
BASEBALL PLAYER


DON'T
PANIC