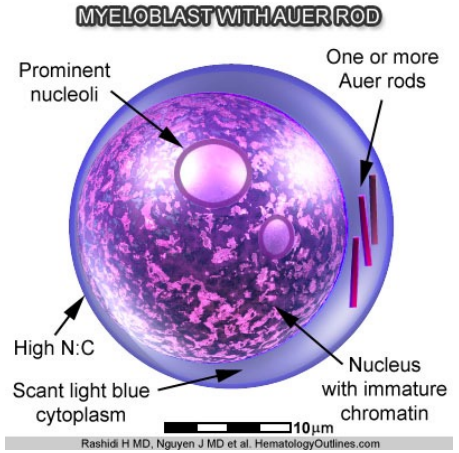
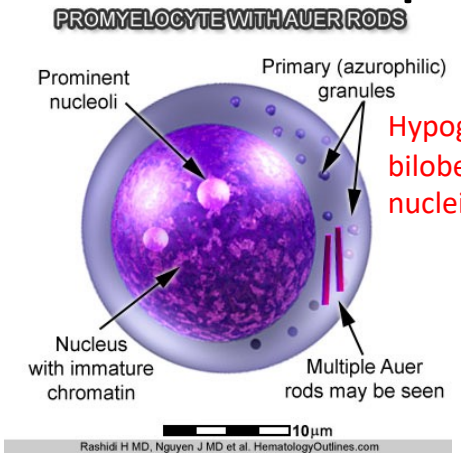
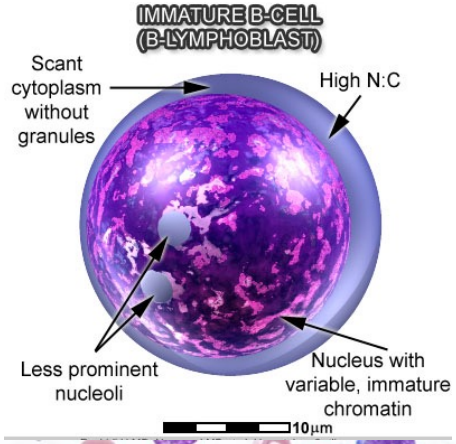
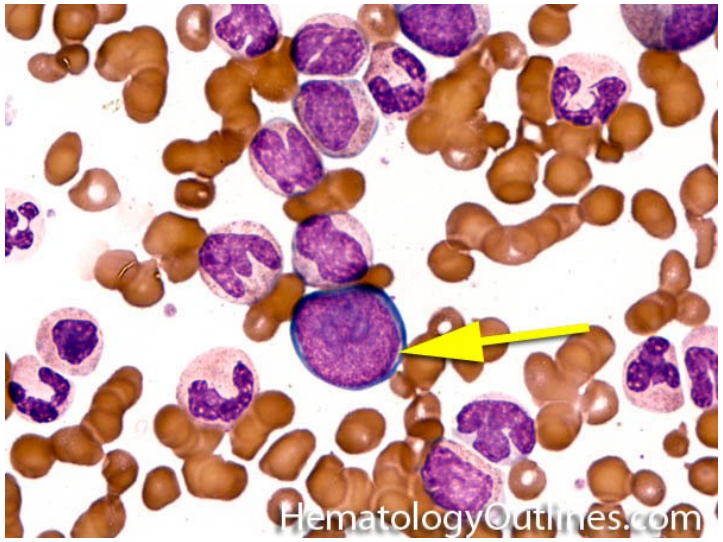
Acute Leukemia: Blast morphology

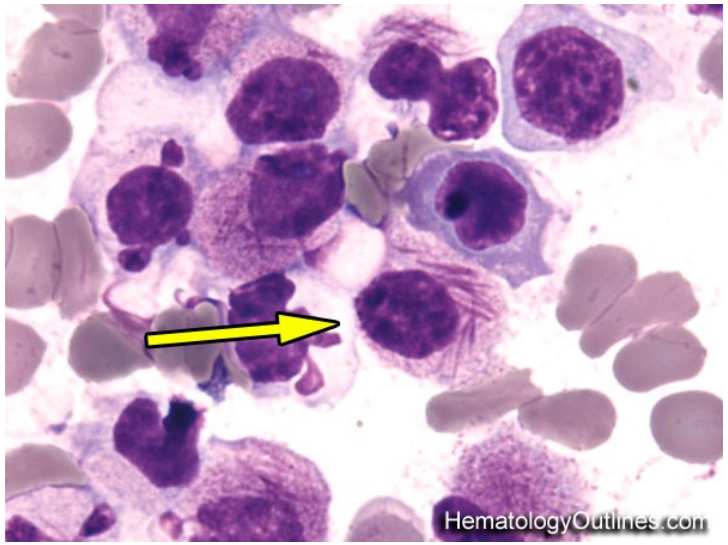


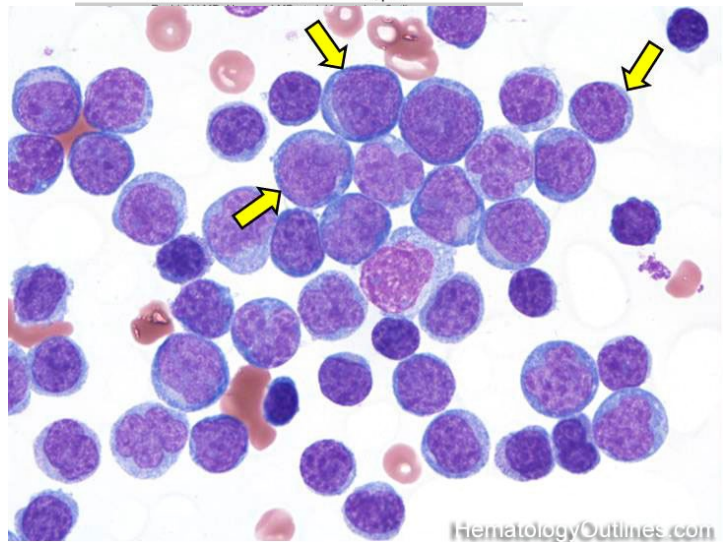


Hypogranular APL: bilobed or folded nuclei







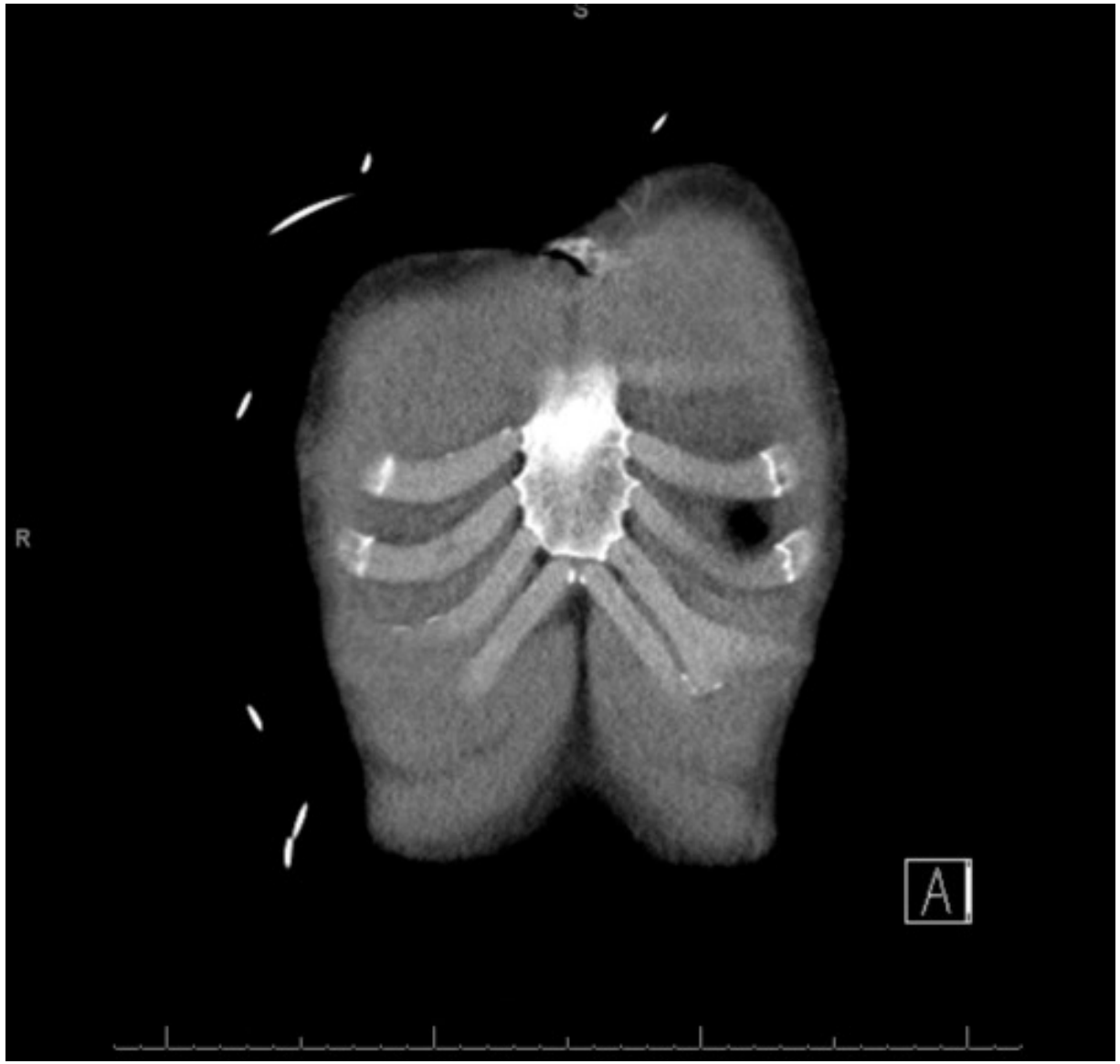


- Blasts cannot be reliably distinguished from each other based on morphology alone.
- The exception are blasts with Auer Rod(s) which are unique to abnormal Myeloblasts and abnormal promyelocytes as noted in some AMLs and APL.

HematologyOutlines.com

Case

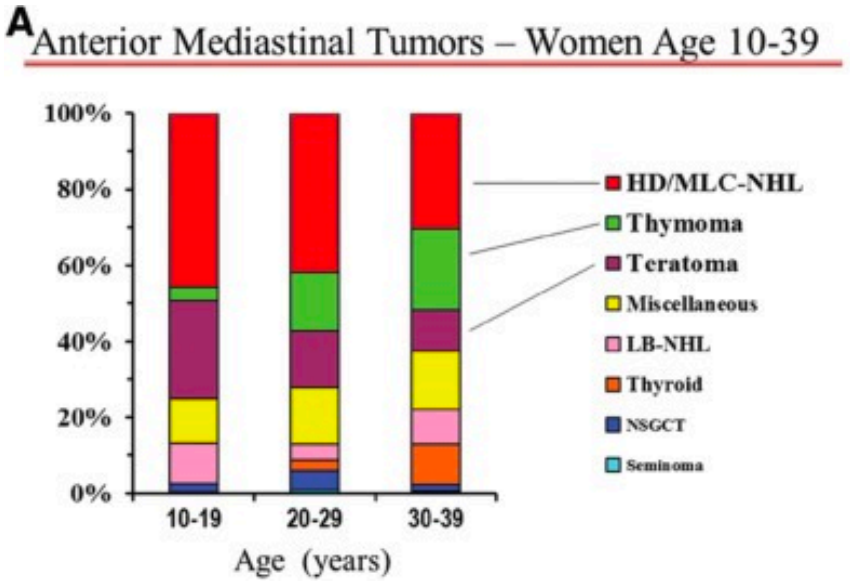
- 29M p/w 2 weeks of fatigue and syncope with leaning forward
  - HR 120s, BP 110s/70s, on RA.
  - CMP/CBC/PT/PTT wnl.
  - Sitting up at 90º, dyspneic with laying flat or leaning forward
  - CTA chest shows a 20cm mediastinal mass with SVC compression, moderate pericardial effusion, and mass effect on the heart, aorta, trachea, carina, right PA, and right PVs
  - Transferred from Fargo, ND to HCMC ICU for thoracic surgery evaluation
- ICU calls you and asks **“Should we start steroids?”**
  - What other clinical info do you want to know?
  - Which oncologic emergencies are you thinking about?

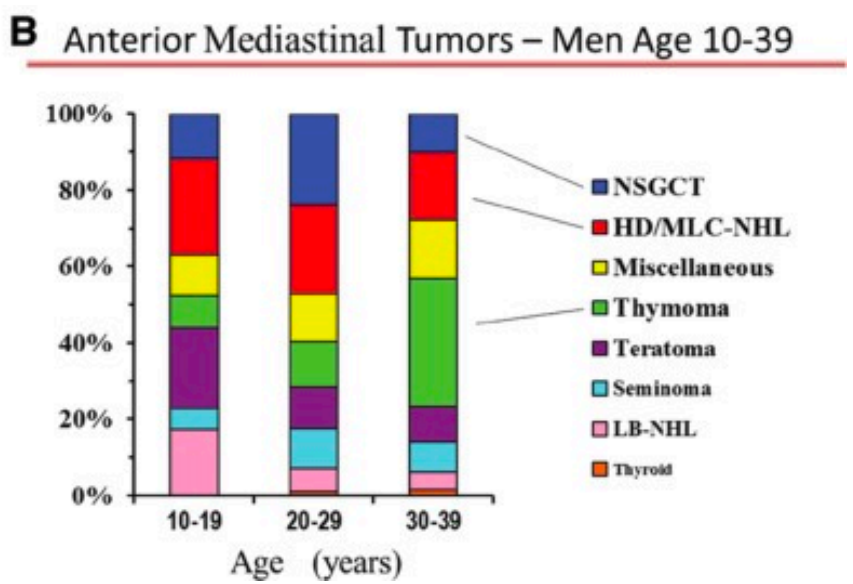


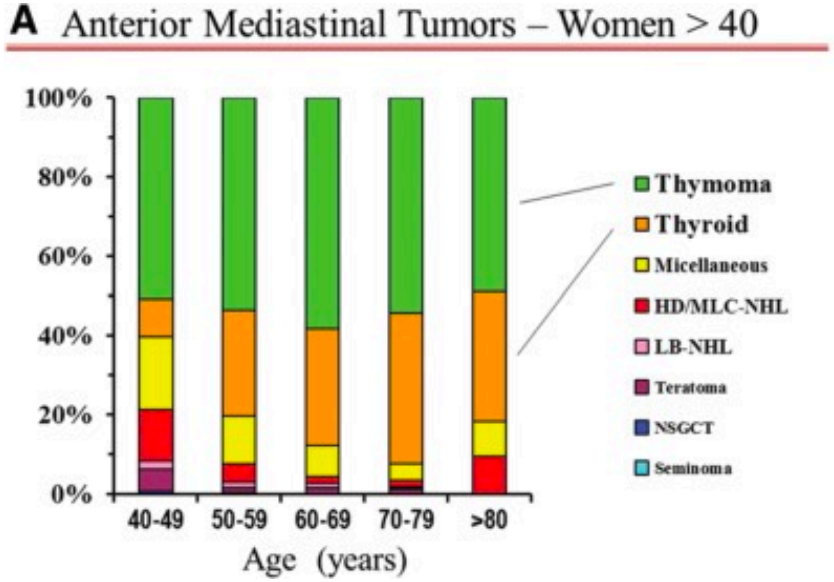
Case

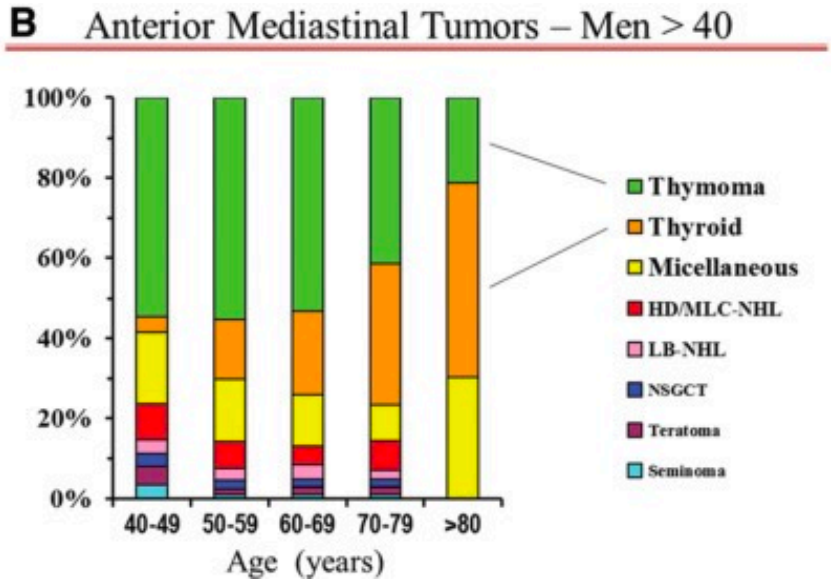
- Exam: AOx3, no stridor. Pulsus paradoxus, Pemberton's sign not assessed
- Labs: LDH, uric acid, AFP, bHCG pending
- ECG: electrical alternans
- TTE:
  - EF 55%
  - moderate to large pericardial effusion
  - Mildly swinging heart and respirophasic tricuspid inflow variation that is consistent with pre-tamponade physiology.
  - No definite mitral inflow variation or echocardiographic pulsus alternans
  - Likely extrinsic compression of the left atrium with distorted anatomy

Anterior mediastinal mass dDx









4 T's
Teratoma/Testicular
Terrible lymphoma
Thymoma
Thymic carcinoma

Anytime lymphoma is on the dDx, treatment with steroids should be avoided as long as safely possible until a diagnosis is confirmed

An inadequate diagnosis can preclude curative treatment

JTO 2014 Sep;9(9 Suppl 2):S102-9.

Cardiac tamponade, SVC syndrome, Malignant airway obstruction

- Short answer: mechanical interventions are faster than chemotherapy or radiation
  - Tamponade – pericardiocentesis vs drain placement vs pericardiotomy
  - SVC syndrome – IR SVC stenting
  - Airway obstruction – surgical airway

SVC syndrome: treatment

- Steroids may obscure a lymphoma diagnosis
- Palliative radiation may preclude definitive radiation later
- Radiation usually requires laying flat

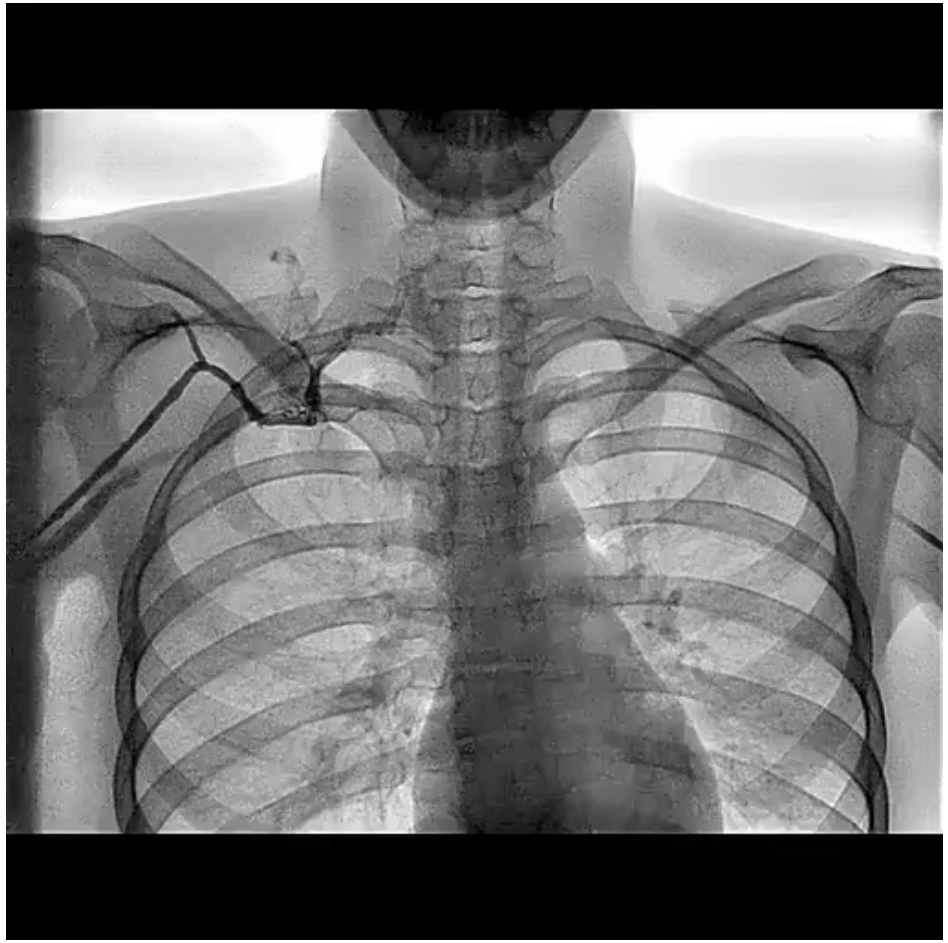
Table 3 Comparison of treatment modalities

	Time to symptom relief	% Chance of partial symptom relief	Can be combined with other therapies?	Treatment-associated mortality
Radiation Therapy	3–30 days (Armstrong et al. 1987; Mose et al. 2006; Ostler et al. 1997; Davenport et al. 1978; Rodrigues et al. 1993)	56–96 (Armstrong et al. 1987; Rodrigues et al. 1993)	Yes	Low
Chemotherapy	1–2 weeks (Rowell and Gleeson 2001)	59–77 (Rowell and Gleeson 2001)	Yes	Low
Stent placement	0–72 h (Hennequin et al. 1995; Rosch et al. 1992)	80–95 % (Uberoi 2006)	Yes	3–4 % (Uberoi 2006)

Properties of various treatment modalities used in superior vena cava syndrome

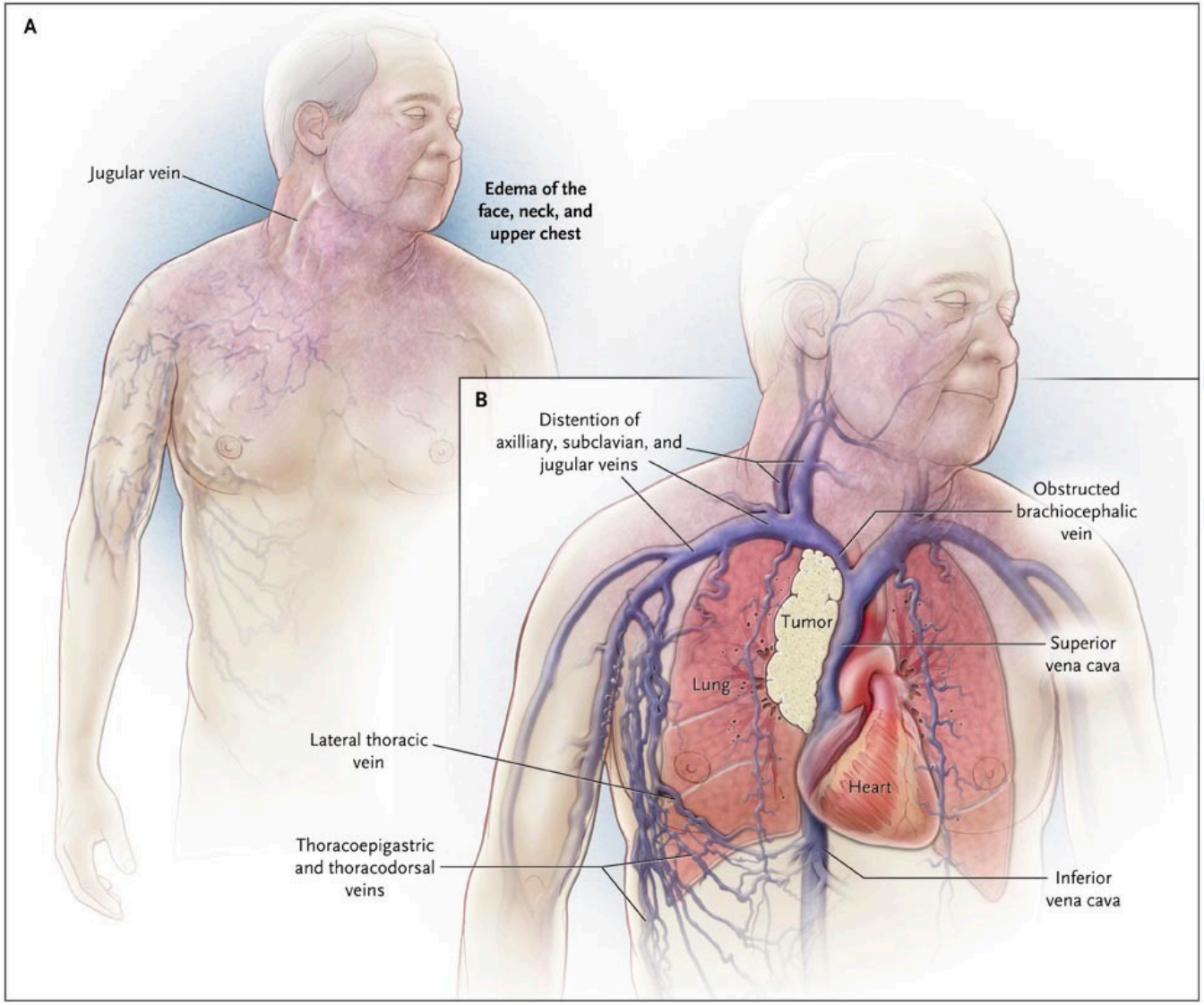
Springerplus. 2016; 5: 229.

Pemberton’s sign (thoracic outlet obstruction)

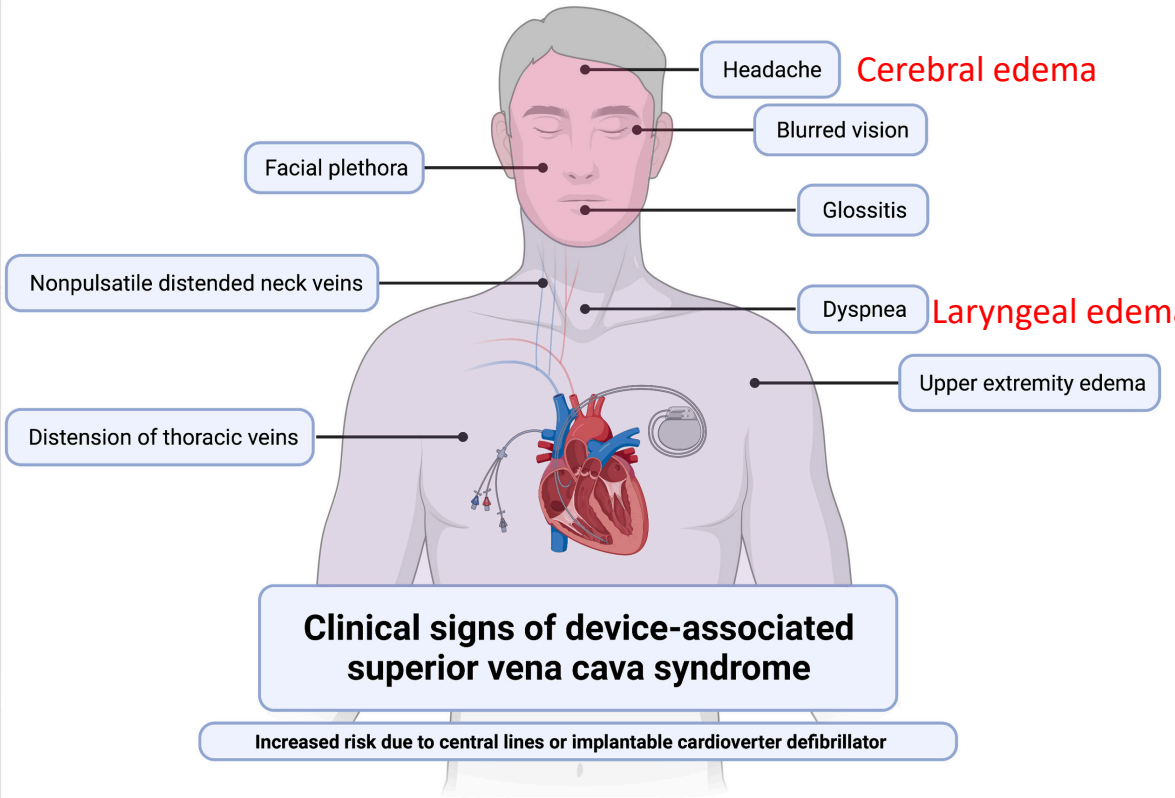


@paulgamboad, @grepmeded

SVC syndrome

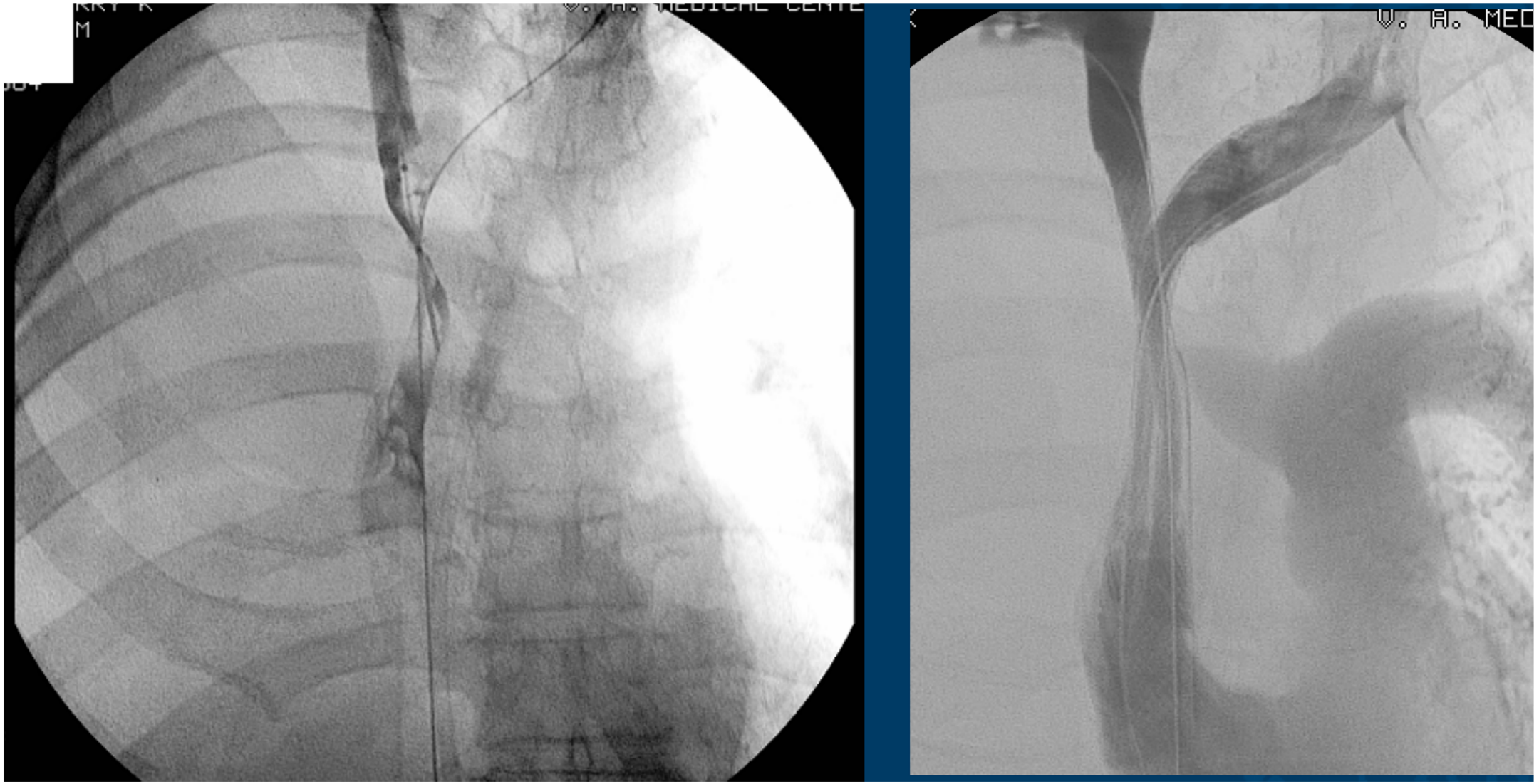


Feared complications:



NEJM 2007; 356:1862-1869,
JACC 2021 Nov, 3 (15) 1690–1693

SVC stenting

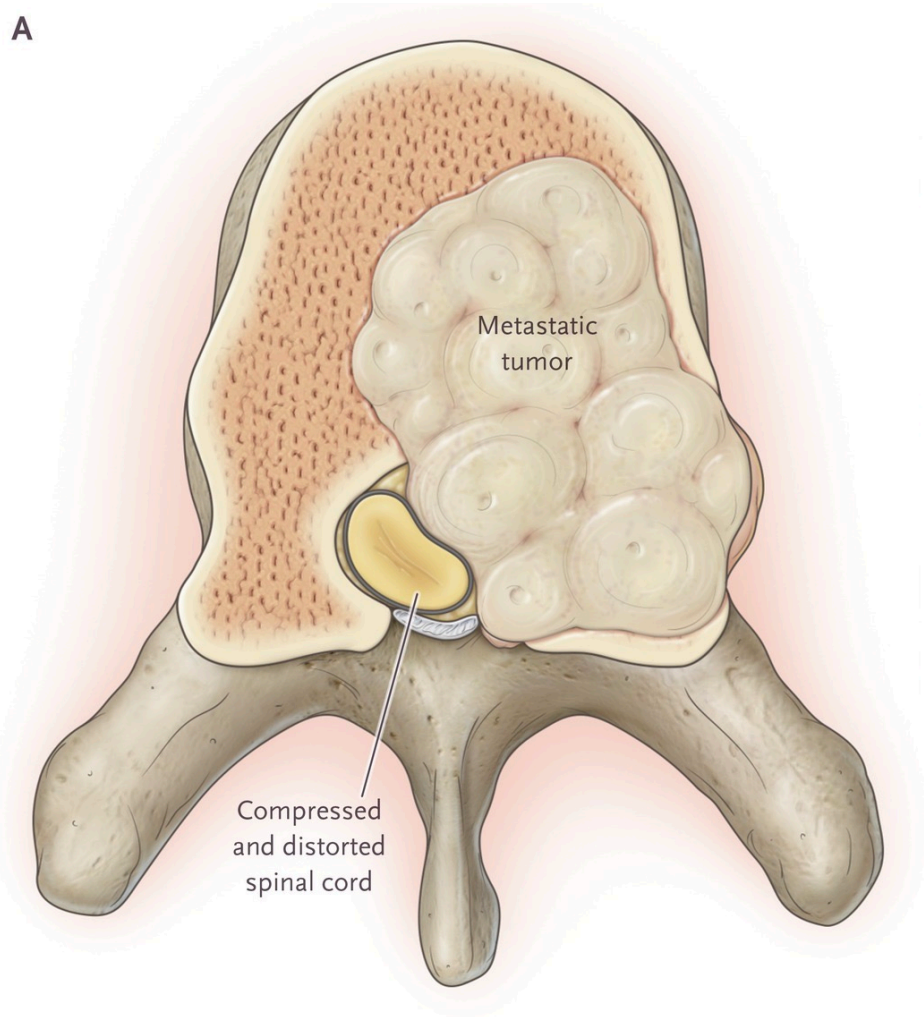


Case:

- 55M correctional officer p/w acute onset of lower extremity numbness and weakness upon getting up from bed 9 days prior to presentation to Regions
  - PSA 150
- What do you recommend?

Cord compression

- Pathophysiology
  - Metastases to the spinal column grow to gradually compress the spinal cord OR cause a vertebral fracture with sudden pain and neurologic deficits
  - 15% cervical, 60% thoracic, 25% lumbar
- Etiology:
  - Most common – breast, lung, prostate
  - Myeloma, NHL, RCC have a proclivity for spine; any cancer can cause it
- History
  - Back pain (85%) with point tenderness, worse at night or with valsalva, radicular symptoms precede neurologic decline by weeks
  - Progresses over days to hours to motor weakness, inability to walk (70%) hyperreflexia, bowel/bladder incontinence, sensory level
- Exam
  - Back/spine exam, percussion for point tenderness
  - Straight leg raise assessing for sciatica
  - Thorough neuro exam including strength, reflexes, Babinski, sensory exam, rectal tone, saddle anesthesia, post void residual



NEJM 2017; 376:1358-1369

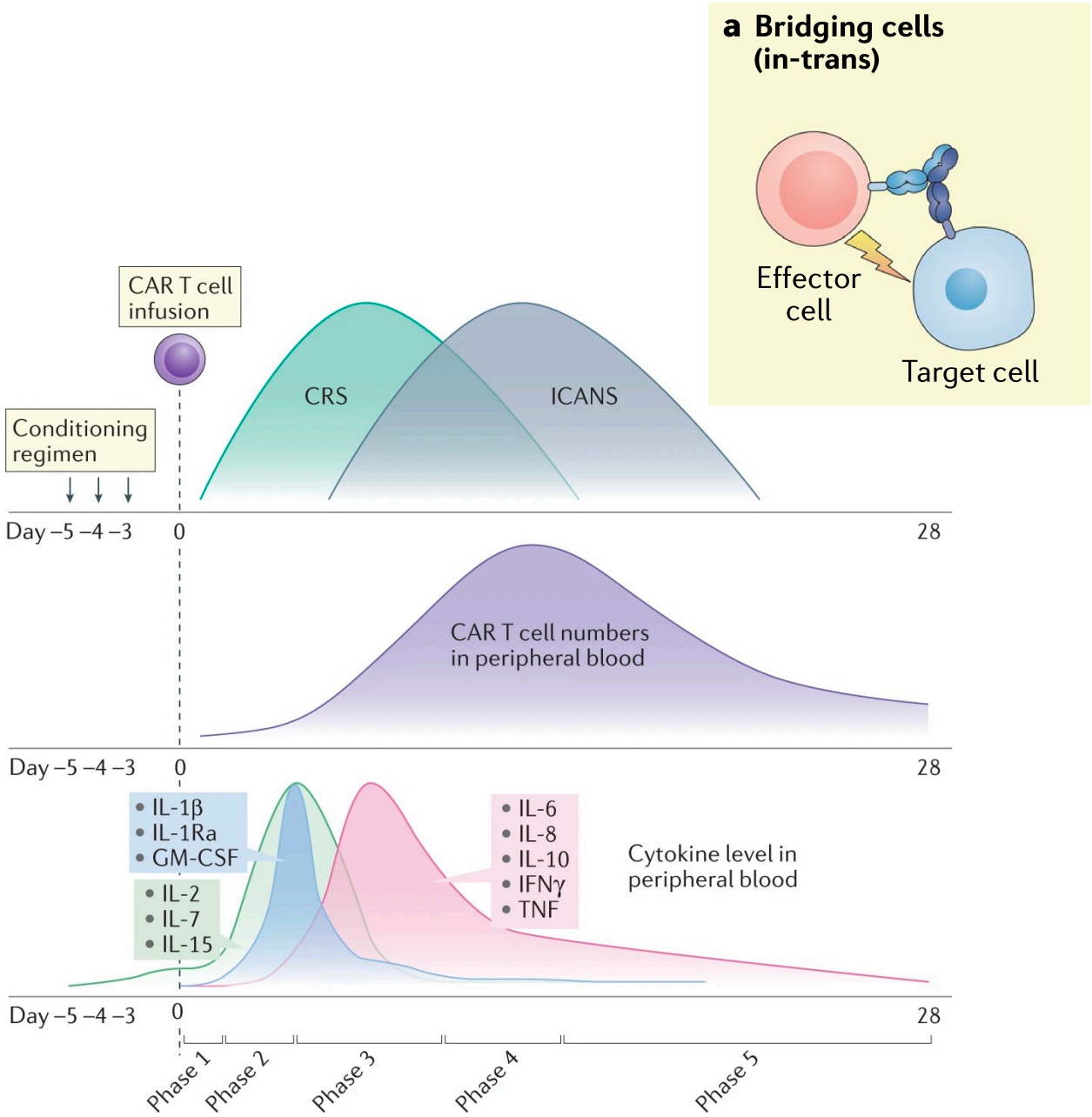
Cord compression

- Diagnosis
  - MRI full spine is the most sensitive and specific test
  - CT is generally not adequate unless MRI cannot be obtained; myelography is uncommon but more sensitive
- Management: consult neurosurgery and radiation oncology
  - Surgery + radiation preserves ability to walk (84% vs 57%) and walking time (122d vs 13d) more than radiation alone
  - Spinal column stability and functional status are important factors in decision for surgery
- Dexamethasone 10mg IV x1, then 4mg PO q6h
- Tumor markers

Lancet. 2005 Aug 20-26;366(9486):643-8.

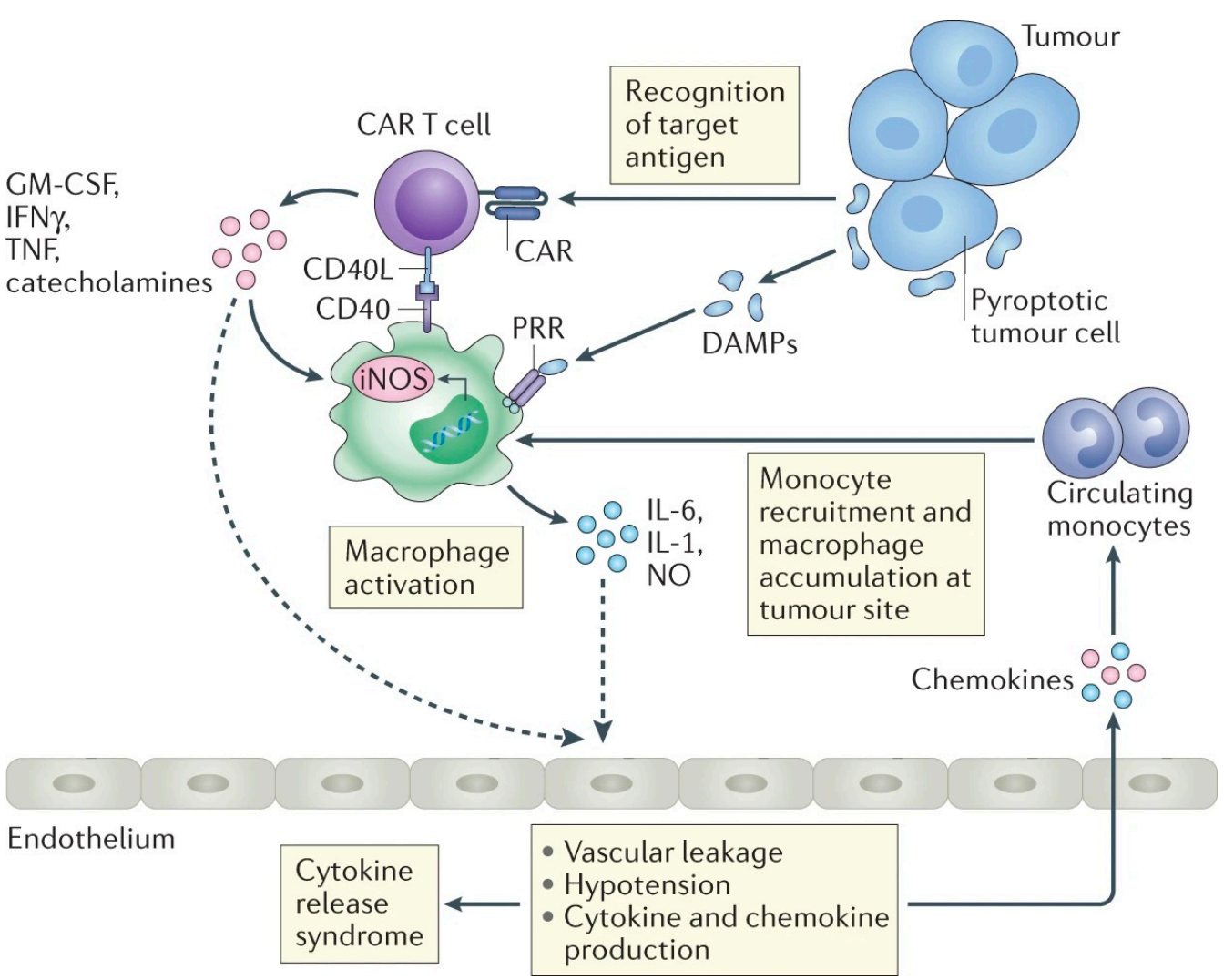
CRS/ICANS

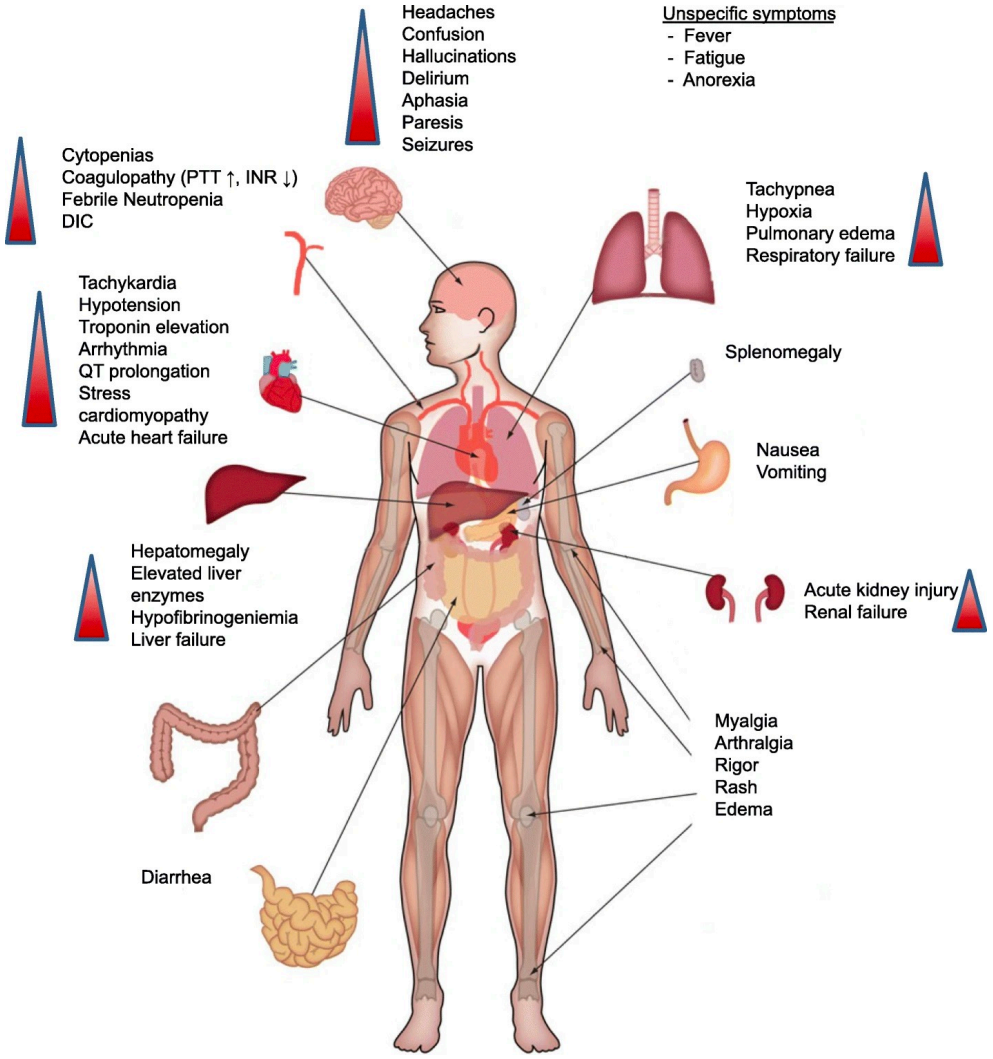
- Initially described with CAR-T
  - Can occur with any T-cell activating therapy e.g. blinatumomab (bispecific T-cell engager)
- CRS 4 cardinal symptoms:
  - Fever
  - Hypoxia
  - Hypotension
  - Organ dysfunction
- Treat grade 2-4 CRS with tocilizumab 8mg/kg IV
  - Treat grade 2-4 ICANS without CRS with Dexamethasone 10mg IV q6h



Nat Rev Immunol. 2022 Feb;22(2):85-96, Nat Rev Drug Discov 18, 585–608 (2019).

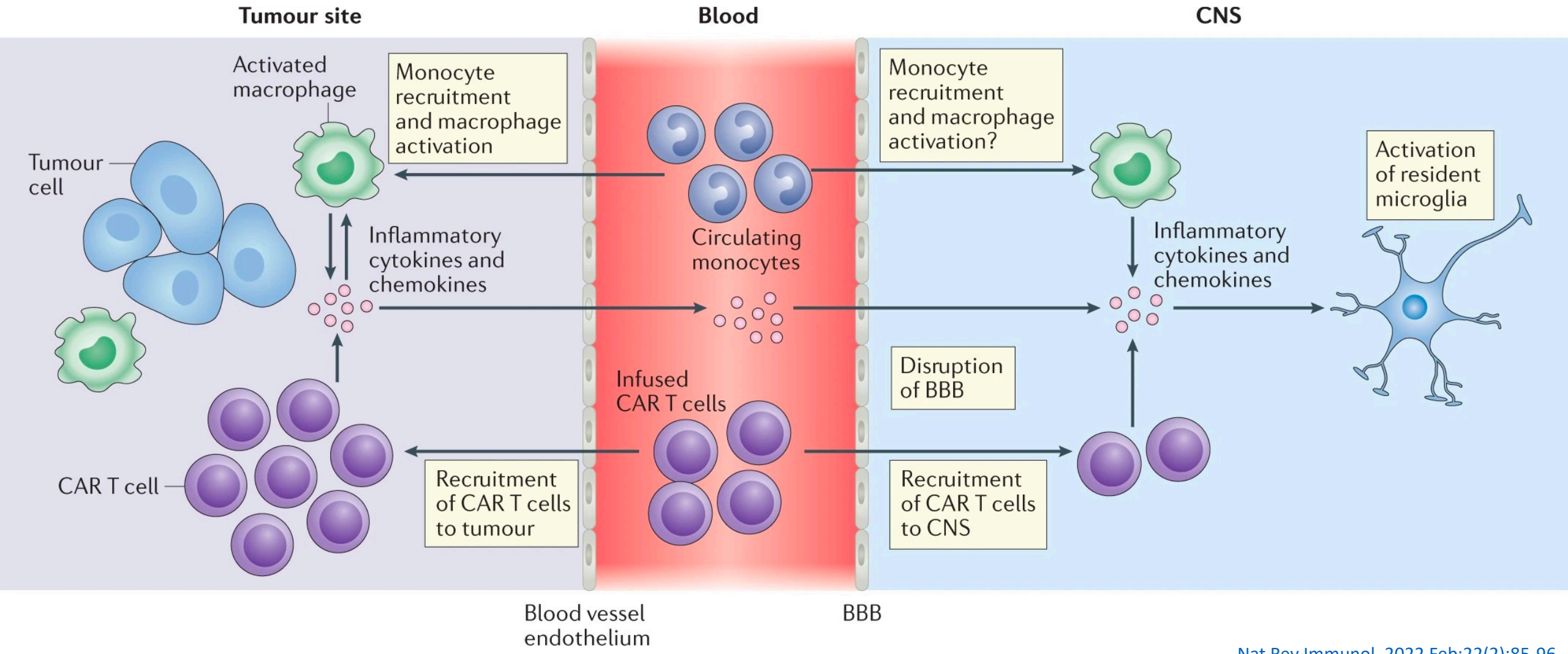
Cytokine release syndrome (CRS)





Nat Rev Immunol. 2022 Feb;22(2):85-96, J Immunother Cancer. 2018 Jun 15;6(1):56.

Immune effector cell-associated neurotoxicity syndrome (ICANS)



Nat Rev Immunol. 2022 Feb;22(2):85-96

CRS: ASTCT grading

ASTCT CRS Consensus Grading

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
			And/or†	
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

* Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

MDACC CARTOX app (apple, android), BBMT 2019 Apr;25(4):625-638.

ICANS: ASTCT grading

Encephalopathy Assessment Tools for Grading of ICANS

CARTOX-10 [12]

- **Orientation:** orientation to year, month, city, hospital, president/prime minister of country of residence: 5 points
- **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points
- **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point
- **Attention:** ability to count backwards from 100 by 10: 1 point

ICE

- **Orientation:** orientation to year, month, city, hospital: 4 points
- **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points
- **Following commands:** ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point
- **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point
- **Attention:** ability to count backwards from 100 by 10: 1 point

ASTCT ICANS Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging§	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as grade 3 ICANS.
N/A indicates not applicable.

* A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

† Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

‡ Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

§ Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

MDACC CARTOX app (apple, android), BBMT 2019 Apr;25(4):625-638.

Anticoagulant reversal

- Indications – life/limb threatening bleeding or emergent surgical procedure
  - Minor bleeding – hold anticoagulant, TXA/ACA (maybe avoid in hematuria)
- Antiplatelets – PLT transfusion or DDAVP used but generally ineffective
- Warfarin – Vitamin K, FFP, PCC
- Heparins
  - UFH, LMWH – protamine sulfate (~60% effective for LMWH)
  - Fondaparinux – none; aPCC/FEIBA or rFVIIa; t½ 17-21h, washout 3-5 days; 77% renal excretion, ?dialyzable
- Oral Xa inhibitors
  - Rivaroxaban, apixaban – andexanet alfa (ANNEXA-4), PCC; ~30% renal excretion
  - Edoxaban, betrixaban – off label andexanet alfa, PCC
- Direct thrombin inhibitors
  - Dabigatran – idarucizumab (REVERSE-AD), aPCC/FEIBA if not available; 80% renal excretion, 50% dialyzable
  - Argatroban – none; t½ 45 mins; hepatic metabolism; 20% dialyzable
  - Bivalirudin – none; t½ 25 mins (up to 3.5h in renal failure); 25% dialyzable

AJH 2019;94:697–709, UpToDate, Blood (2019) 133 (5): 425–435.

Prothrombin complex concentrates

PCC products available in the United States*

Unactivated prothrombin complex concentrates (PCCs)	
4 factor: ▪ Kcentra	Contains inactive forms of 4 factors: Factors II, VII, IX, and X Also contains heparin
3 factor: ▪ Profilnine	Contains inactive forms of 3 factors: Factors II, IX, and X Contains little or no factor VII Does not contain heparin
Activated prothrombin complex concentrate (aPCC)	
4 factor: ▪ FEIBA	Contains 4 factors: Factors II, VII, IX, and X. Of these, only factor VII is mostly the activated form¶ Does not contain heparin

The table lists 4-factor and 3-factor PCC products available in the United States. Kcentra is available as Beriplex in Canada. Bebulin (a 3-factor PCC) was discontinued in 2018 due to decreased demand for the product. Potency is determined differently for different products; refer to product information. All PCCs are plasma derived and contain other proteins, including anticoagulant proteins (proteins C and S). Unactivated factors are proenzymes (inactive precursor proteins). Activated factors have higher enzymatic activity. Refer to UpToDate topics for use of these products.

US: United States; PCC: prothrombin complex concentrate; FEIBA: factor eight inhibitor bypassing activity.

* Other 4-factor PCCs available outside the US include Octaplex and Cofact Proplex.

¶ Single-factor recombinant activated factor VII (rFVIIa) products are also available.

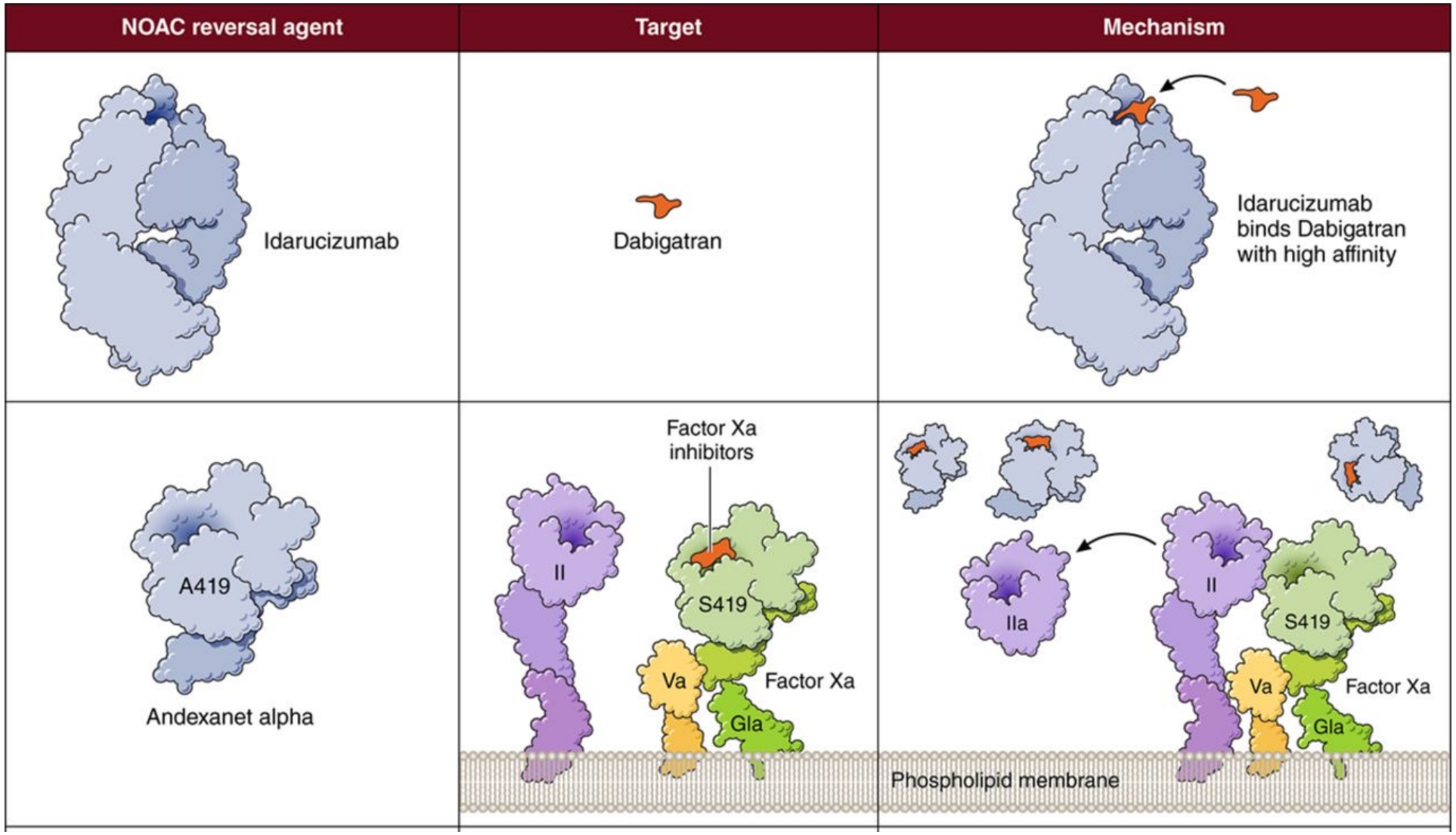
If a patient is bleeding despite activated factor products, look for another problem

None of these products contain fibrinogen, vWF, factors 8 or 13

Workup for DIC, consider cryoprecipitate and/or fibrinolytics

UpToDate

DOAC reversal MOA



"Decoy Factor Xa" Marketing?

Circ 2016;134:248–261

Anticoagulant reversal

Table 8. Cost of reversal agents–based on an 80-kilogram patient.

Generic Drug	Trade Name	Dose	Approximate Cost
Phytonadione	Vitamin K	10 mg IV	$395.00[A]
FFP	N/A	4 units is usual minimum	$1000[B] ($250 each)
4-Factor PCC	Kcentra	25-50 units/kg	$2,540 to $5,080[B]
Activated PCC	FEIBA	25 units/kg	$5,400[B]
Idarucizumab	Praxbind	5 grams	$3,600[C]
Andexanet (Low Dose)	Andexxa	400 mg bolus + 480 mg infusion	$24,750**
Andexanet (High Dose)*	Andexxa	800 mg bolus + 960 mg infusion	$49,500

WJEM. 2019 Sep; 20(5): 770–783.

Apheresis terminology

- Plasmapheresis – removal of plasma (i.e. healthy donors)
- Therapeutic plasma exchange – removal of plasma for a therapeutic purpose, replacement with either albumin/saline or FFP
- Leukapheresis – removal of white blood cells
- Exchange transfusion – removal of RBCs, replacement with transfused RBCs
- Generally requires rigid central access (HD catheter), rarely two large PIVs are adequate

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice – Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Eighth Special Issue

J Clin Apher. 2019;34:171–354.

Phase 1 trial patients – call the attending

- Developmental Therapeutics Clinic at Fairview CSC
- Examples of trials you probably won't be able to google/uptodate
  - Oncolytic virus intratumoral injection
  - Solid tumor CAR-T/TILs
  - CAR-T switch therapy
  - Allo NK-cell and Allo CAR-T therapy
  - BiTEs
- Most common issues are fevers +/- neutropenia, CRS, ICANS
  - Triage as you would for those conditions, call the attending on call
- Trial protocols are on OnCore.umn.edu, but have to request access

Urgencies and emergencies

- Classical Hematology
  - Hemophilia bleeding
  - TMA – TTP, aHUS, CAPS
  - HIT
  - Sickle cell crises
  - Anticoagulant reversal
- Heme Malignancy
  - Acute leukemia and/or APL/DIC
  - TLS
  - Leukostasis/hyperviscosity
  - CRS/ICANS
  - Differentiation syndrome
- General Oncology
  - Cardiac tamponade
  - SVC syndrome
  - Airway obstruction
  - Cord compression
  - Symptomatic brain metastases
  - Hypercalcemia
  - Neutropenic fever
  - Asplenic sepsis
- Phase 1 trial patients

Immediately life/limb threatening without intervention?
Need peripheral smear overnight?