2023 Patient 2023 Patient Conference
Co-Hosted with Adrenal Insufficiency United

Friday, March 31, 2023

What Happens Before and After Surgery for Patients with Cushing Syndrome?

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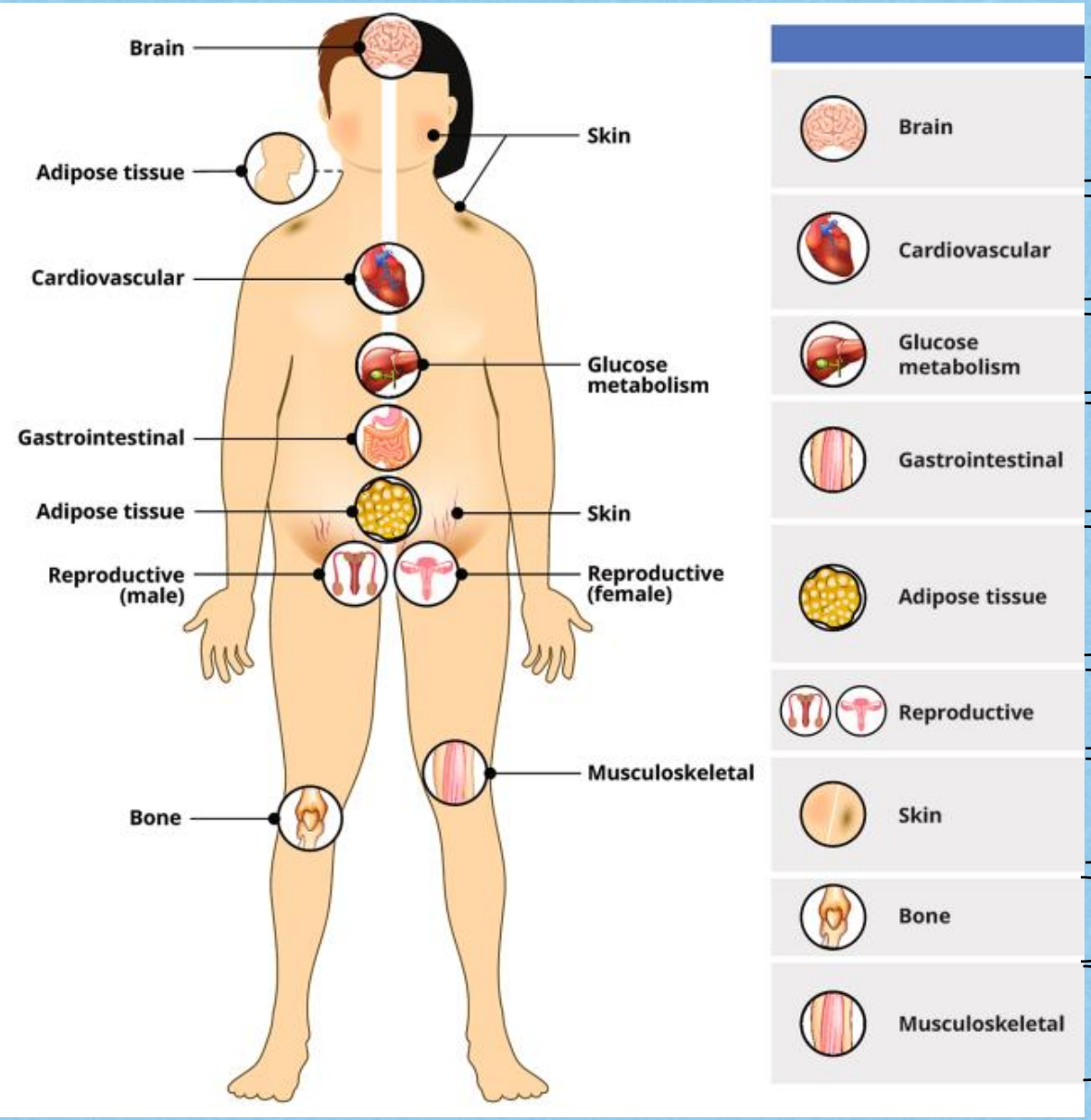
Disclosures

- Received research grants to Barrow Neurological Institute from Crinetics, Ascendis, Corcept, Sparrow and Amryt
- Served as an occasional advisory board member for Novo Nordisk, Ascendis, Corcept, Ipsen, Amryt, Strongbridge, Crinetics, Recordati and Xeris
- Served as occasional speaker for Recordati, Novo Nordisk and Corcept

Clinical features of CS



Mood and cognitive dysfunction
Sleep disorders

High BP and dyslipidemia
↑clots

High blood sugars

↑appetite

Central obesity and facial roundness
Swelling around the neck and shoulders

Infertility/subfertility

Infections
Stretch marks, skin thinning and easy bruising

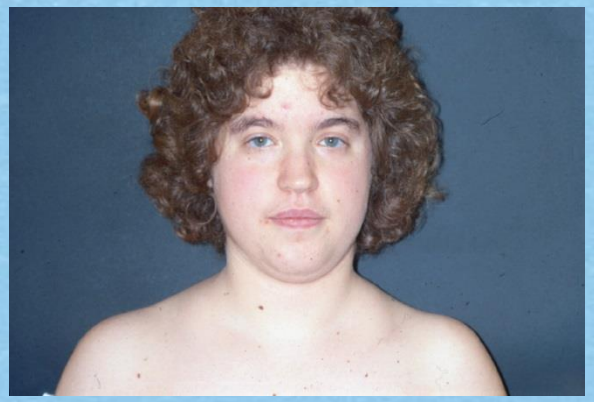
Osteopenia/osteoporosis
Fractures

Muscle weakness
Fatigue and physical deconditioning

He X, et al. Pituitary. 2022 Jun;25(3):393-403.

Hypercortisolism can present in many ways

	Severe Hypercortisolism	Less Severe Hypercortisolism
Biochemical Evaluation	• Biochemically severe based on cortisol secretion patterns • ↑↑ cortisol levels	• Biochemically less severe based on cortisol secretion patterns • Biochemical evidence of autonomous cortisol secretion above diagnostic threshold criteria
Clinical Presentation	• Highly specific phenotypic features (e.g., moon face, buffalo hump)	• May experience multiple progressive metabolic derangements • *Classic features of Cushing syndrome may not be present*



1. Sharma ST, et al. *Clin Epidemiol.* 2015;7:281-293.
2. Di Dalmazi G, et al. *Eur J Endocrinol.* 2015;173(4):M61-M71.
3. Di Dalmazi G, et al. *Lancet Diabetes Endocrinol*. 2014;2(5):396-405.
4. Morelli V, et al. *J Clin Endocrinol Metab*. 2014;99(3):827-834.

FAQs

Why is diagnosing CS so challenging and often delayed?

- Symptoms are often non-specific and can develop over time
- Symptoms overlap with PCOS and other common health complaints
- Not practical to screen every patient
- Doctors may not think about CS
- Many patients use steroids
- Unsure which screening test to use
- Screening tests can be negative
- Unsure how to interpret screening tests
- The process of testing for CS can take time

Examples of other causes of high cortisols

- Excessive exercise
- Hypothalamic amenorrhea
- Pregnancy
- Poorly controlled diabetes
- Sleep apnea
- Chronic pain
- Alcoholism, especially withdrawal
- Psychiatric disorders
- Morbid obesity
- Glucocorticoid resistance syndromes

Types of specialists consulted before the diagnosis of CS was correctly made

	PIT-CS	ADR-CS	ECT-CS	OTH-CS	Overall
General practitioner	198/260 (76)	90/114 (79)	18/22 (82)	5/10 (50)	311/406 (77)
Diabetologist	58/236 (25)	19/98 (19)	9/22 (41)†	2/9 (22)	88/365 (24)
Gynaecologist	47/193 (24)*	21/85 (25)*	1/11 (9)	2/8 (25)	71/297 (24)
Psychiatrist/psychologist	28/226 (12)	10/97 (10)	2/22 (9)	2/10 (20)	42/355 (12)
Rheumatologist/orthopaedist	25/224 (11)	10/96 (10)	2/22 (9)	2/10 (20)	39/352 (11)
Dermatologist	18/227 (8)	5/97 (5)	1/22 (5)	2/10 (20)	26/356 (7)
Other[a]	121/229 (53)	47/90 (52)	10/18 (56)	6/9 (67)	184/346 (53)

Other[a]: 'other endocrinologists', 'cardiologists', 'gastroenterologists' and 'neurologists'

Valassi E, et al. Eur J Endocrinol. 2011 Sep;165(3):383-92.

FAQs

How to test for CS?

- Overnight 1-mg dexamethasone suppression test (DST)
- 24-hour urinary free cortisol (UFC)
- Late-night salivary cortisol test (LNSC)
- *Hair cortisol?*

Challenges associated with interpreting screening tests

Screening tests	False positive	False negative
Dexamethasone suppression tests *(sens 80-95%; spec 80-95%)*	Birth control pills, medications that can alter dexamethasone metabolism, rapid metabolizers, GI malabsorption	Hepatic or renal failure
24-hr urine free cortisols *(sens 45-71%; spec up to 100%)*	Depends on assay, urine volume > 5 L, medications	Dependent on assay, GFR < 30 mL/min, improper collection
Late night salivary cortisols *(sens 92-100%; spec 85-100%)*	Depends on assay, age, shift workers, stress, smokers	Insufficient saliva production

Braun LT, et al. *Front Endocrinol (Lausanne)* 2019 Nov 8;10-766.

What are the treatment goals for CS?

- Normalization of biochemical changes with minimal morbidity
- Reversal of clinical features
- Long-term control without recurrence

Nieman, et al. *J Clin Endocrinol Metab* 2015 Aug;100(8):2807-2831

FAQs

I have been diagnosed with CD and am told I need surgery. What does this mean?

Don't panic!

Call the BNI Pituitary Team!

FAQs

I have been diagnosed with Cushing disease due to a pituitary tumor and am told I need surgery. What does this mean?

- Pituitary tumors are almost always benign
- With the exception of a prolactinoma that can be treated with a medicine, all secretory tumors require surgery
- Surgery is needed to remove such tumors and cause remission with normalization of cortisol

FAQs

How is pituitary surgery performed?

- Most pituitary tumors can be removed through the nose (rarely a craniotomy)
- The opening through which transsphenoidal surgery is performed is very small, and visualizing the tumor is done using a high powered operating microscope, or a fiberoptic endoscope
- Most centers use a direct transnasal approach utilizing the endoscopic technique
- Most patients go home the day after surgery with minimal blood loss and no scars

FAQs

How should I choose a neurosurgeon for my pituitary surgery?

- Success of surgery depends on the experience the surgeon!
- And the TEAM!

Pituitary (2018) 21:545–555
https://doi.org/10.1007/s11102-018-0904-4

The experience with transsphenoidal surgery and its importance to outcomes

Jürgen Honegger[1] · Florian Grimm[1]

Published online: 31 July 2018

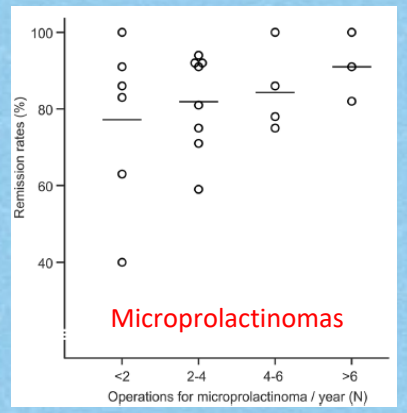
Abstract

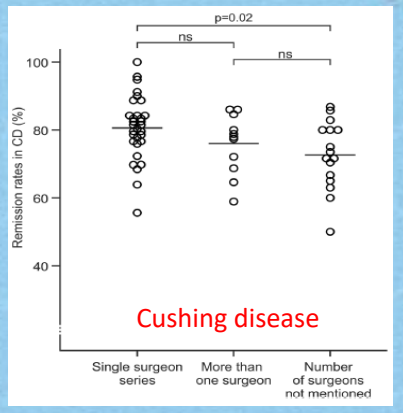
Purpose Surgical experience is considered paramount for excellent outcome of transsphenoidal surgery (TSS). However, objective data demonstrating the surgical success in relation to the experience of pituitary surgery units or individual experience of pituitary surgeons is sparse.

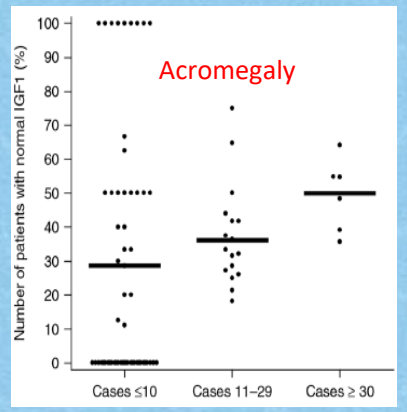
Methods Based on literature data, we have investigated the influence of experience with TSS for pituitary adenomas on endocrinological remission rates and on operative complications. The surgical experience was assessed by calculating the number of transsphenoidal operations per year.

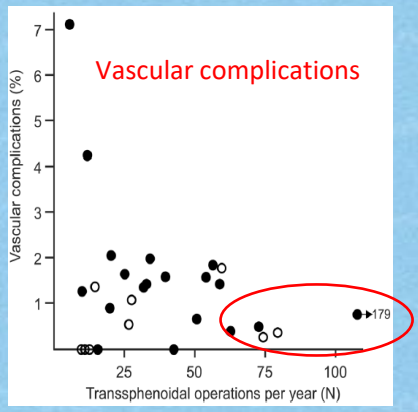
Results For TSS of microprolactinomas, mean remission rates were 77% in centers with < 2 operations per year for microprolactinomas, 82% with 2–4 operations, 84% with 4–6 operations, and 91% with > 6 operations. A yearly experience with more than 10 initial operations for Cushing's disease (CD) warrants a remission rate exceeding 70%. Remission rates in CD exceeding 86% have only been reported for single surgeon series. Extraordinarily high complication rates were found in some series with < 25 yearly total operations for pituitary adenomas. Major vascular complications were less than 2% and revision rates for rhinorrhea usually < 2.5% in centers performing > 25 transsphenoidal operations per year.

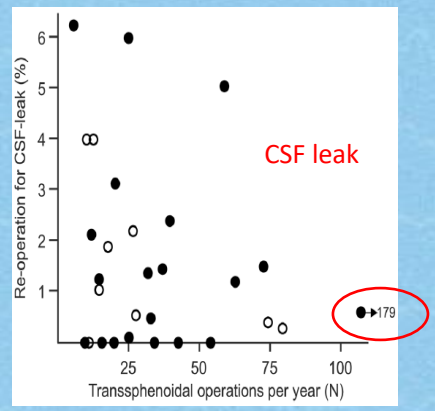
Conclusions We conclude that a center with experience of > 25 transsphenoidal operations for pituitary adenomas per year provides a high likelihood of safe TSS. Surgery for CD requires a particularly high level of practice to guarantee excellent remission rates. The endocrinologist has the unique opportunity to audit the surgical success by hormone measurement and to refer patients to neurosurgeons with proven excellence.











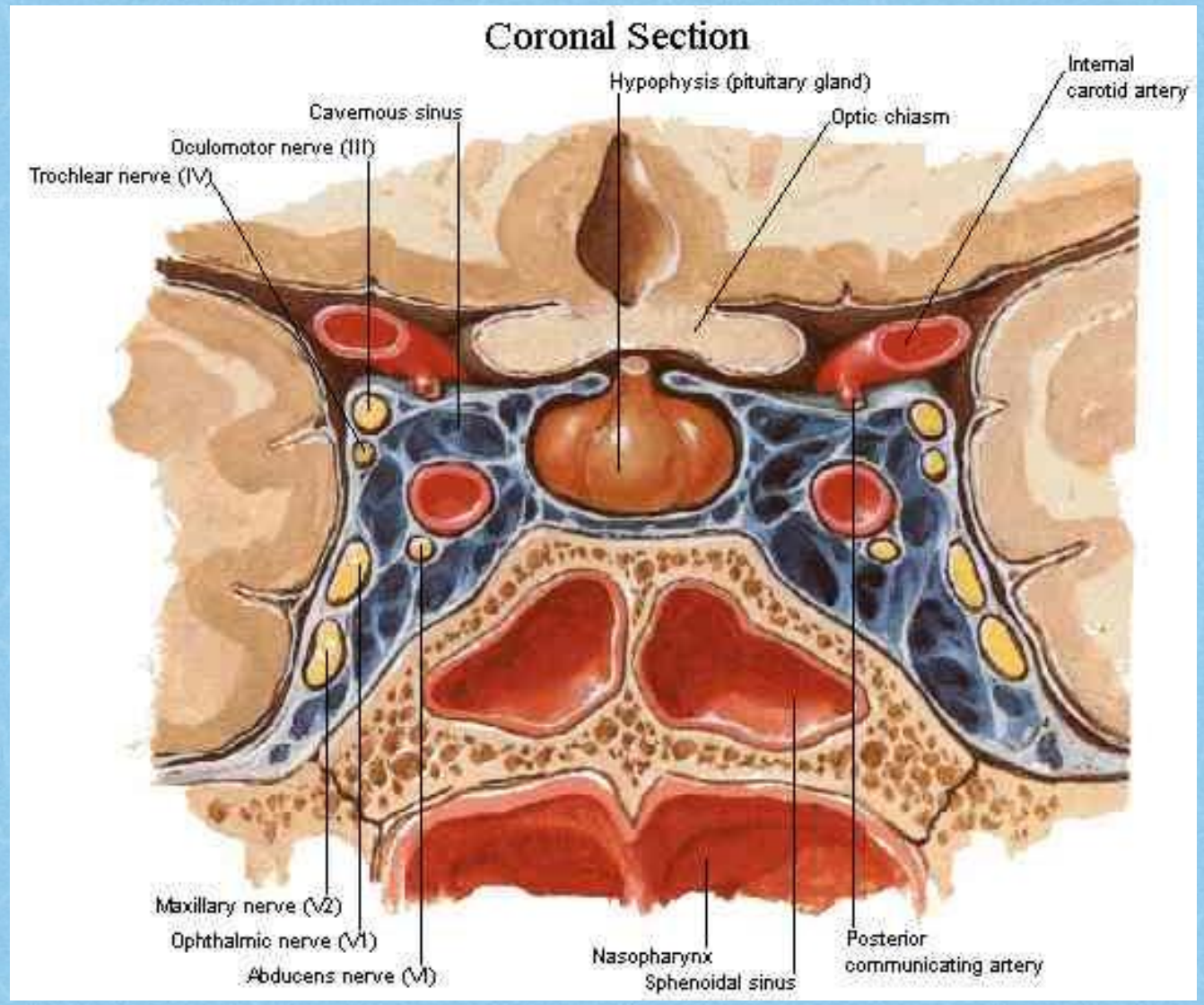
FAQs

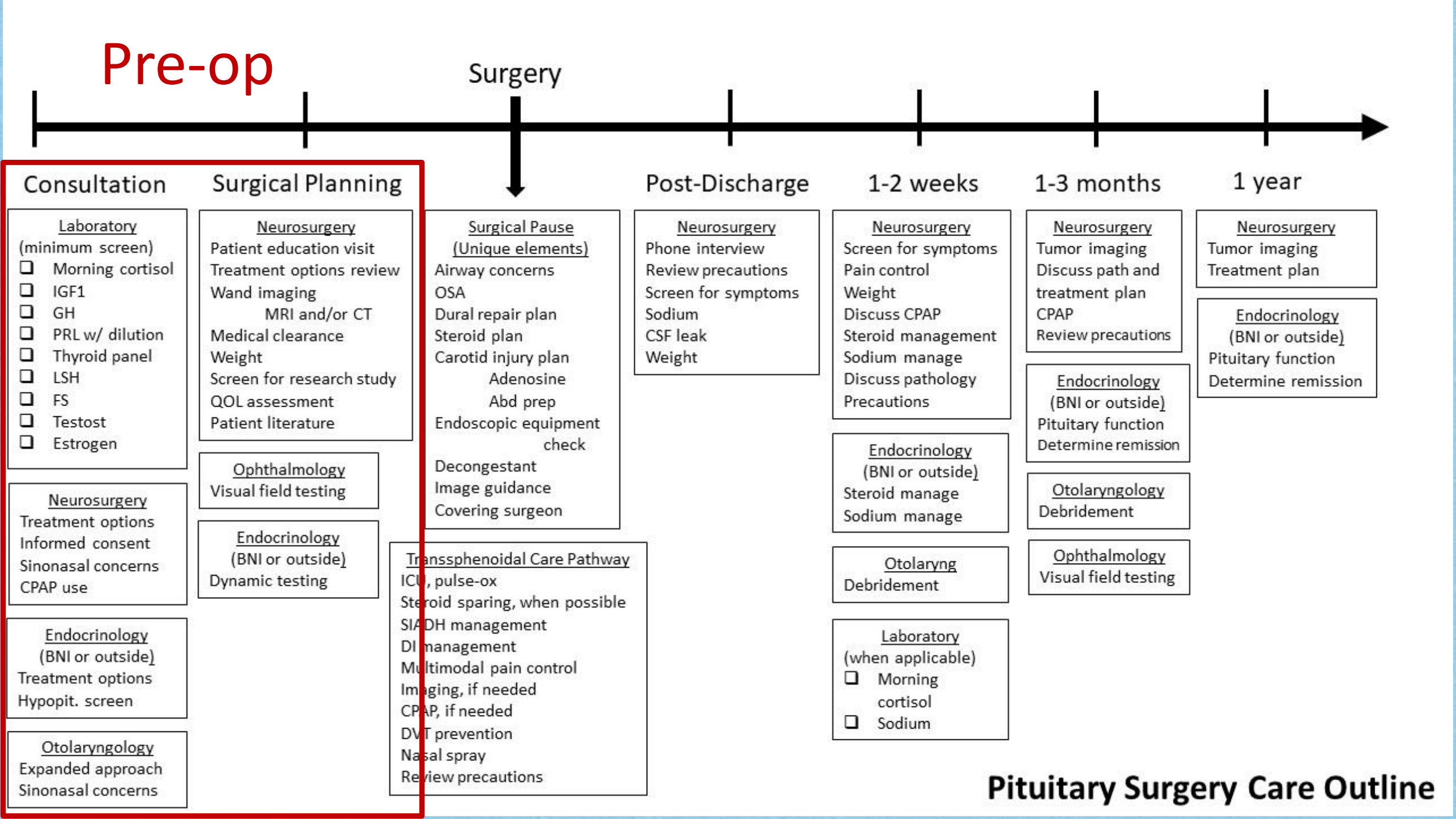
What are the risks of the surgery?

- Damage to the normal pituitary gland can cause hypopituitarism (rare)
- Damage to the carotid arteries (< 1/1000 cases)
- Post-operative bleeding (very rare)
- Spinal fluid leak (incidence 1%), increasing the risk of meningitis

Risk of complications higher with less experienced surgeon!

Anatomy of the pituitary gland




Pre-op
Surgery
Consultation
Surgical Planning
Post-Discharge
1-2 weeks
1-3 months
1 year
Laboratory
(minimum screen)
❑ Morning cortisol
❑ IGF1
❑ GH
❑ PRL w/ dilution
❑ Thyroid panel
❑ LSH
❑ FS
❑ Testost
❑ Estrogen
Neurosurgery
Treatment options
Informed consent
Sinonasal concerns
CPAP use
Endocrinology
(BNI or outside)
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Hypopit. screen
Otolaryngology
Expanded approach
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Nasal spray
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Phone interview
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CSF leak
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Sodium manage
Discuss pathology
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Pituitary Surgery Care Outline

Pre-op

Consultation

Laboratory
(minimum screen)
- ❑ Morning cortisol
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- ❑ Thyroid panel
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Patient literature

Ophthalmology
Visual field testing

Endocrinology
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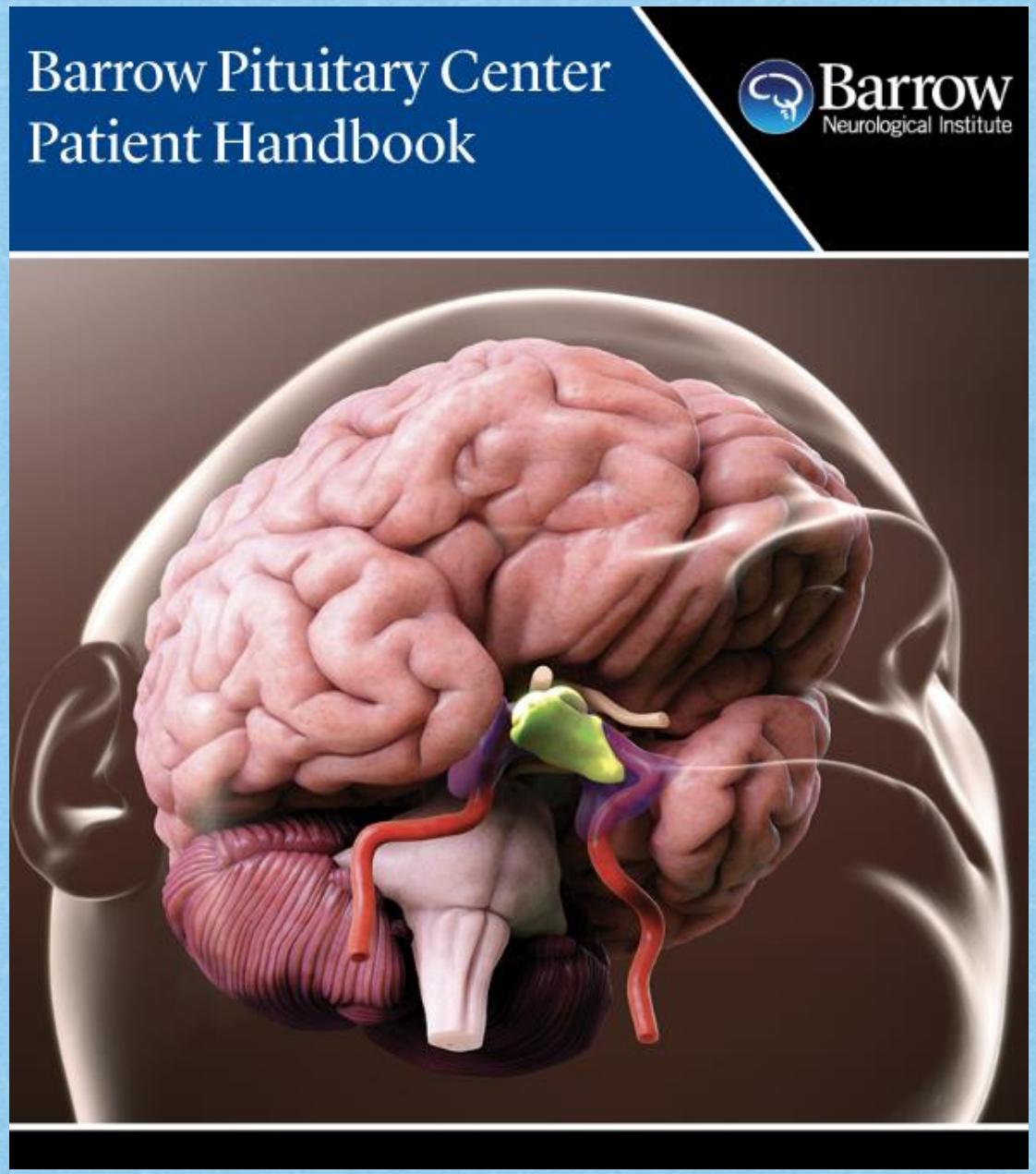
Dynamic testing

MRI
Outside lab draw
Visual field testing
Neuro Infusion Unit testing
Schedule surgery date

https://www.barrowneuro.org/resource/barrow-pituitary-patient-handbook/



Preparing for surgery

Diet

- Eat a balanced diet
- Decrease or stop alcohol, caffeine and cigarettes

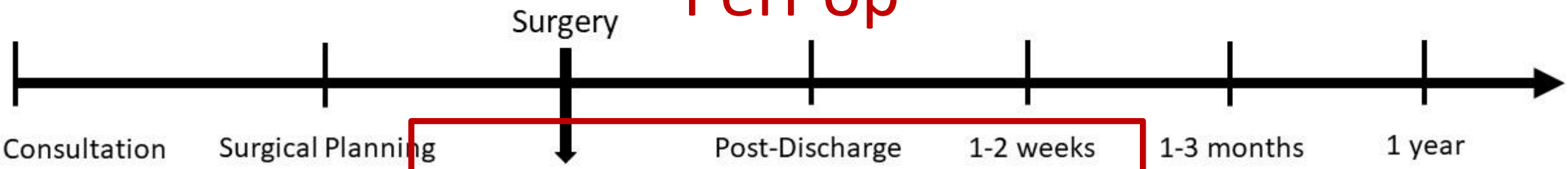
Medications

- Inform your surgical team all the medications and doses you are taking
- You might need to discontinue some medications

Planning on the day and after surgery

- You might need help for a few days after you arrive home
- Arrange transport to and from hospital
- Stock up on food or prepare meals in advance
- Contact your insurance company
- Fill your prescription medications in advance
- Do not eat or drink from midnight the day before surgery

Peri-op



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DVT prevention
Nasal spray
Review precautions

Post-Discharge

Neurosurgery
Phone interview
Review precautions
Screen for symptoms
Sodium
CSF leak
Weight

1-2 weeks

Neurosurgery
Screen for symptoms
Pain control
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Discuss CPAP
Steroid management
Sodium manage
Discuss pathology
Precautions

Endocrinology
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Steroid manage
Sodium manage

Otolaryng
Debridement

Laboratory
(when applicable)
- ❑ Morning cortisol
- ❑ Sodium

1-3 months

Neurosurgery
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Discuss path and treatment plan
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Endocrinology
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1 year

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Post-Discharge

1-2 weeks

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Otolaryng
- Debridement

Laboratory (when applicable)
- ❑ Morning cortisol
- ❑ Sodium

Pi

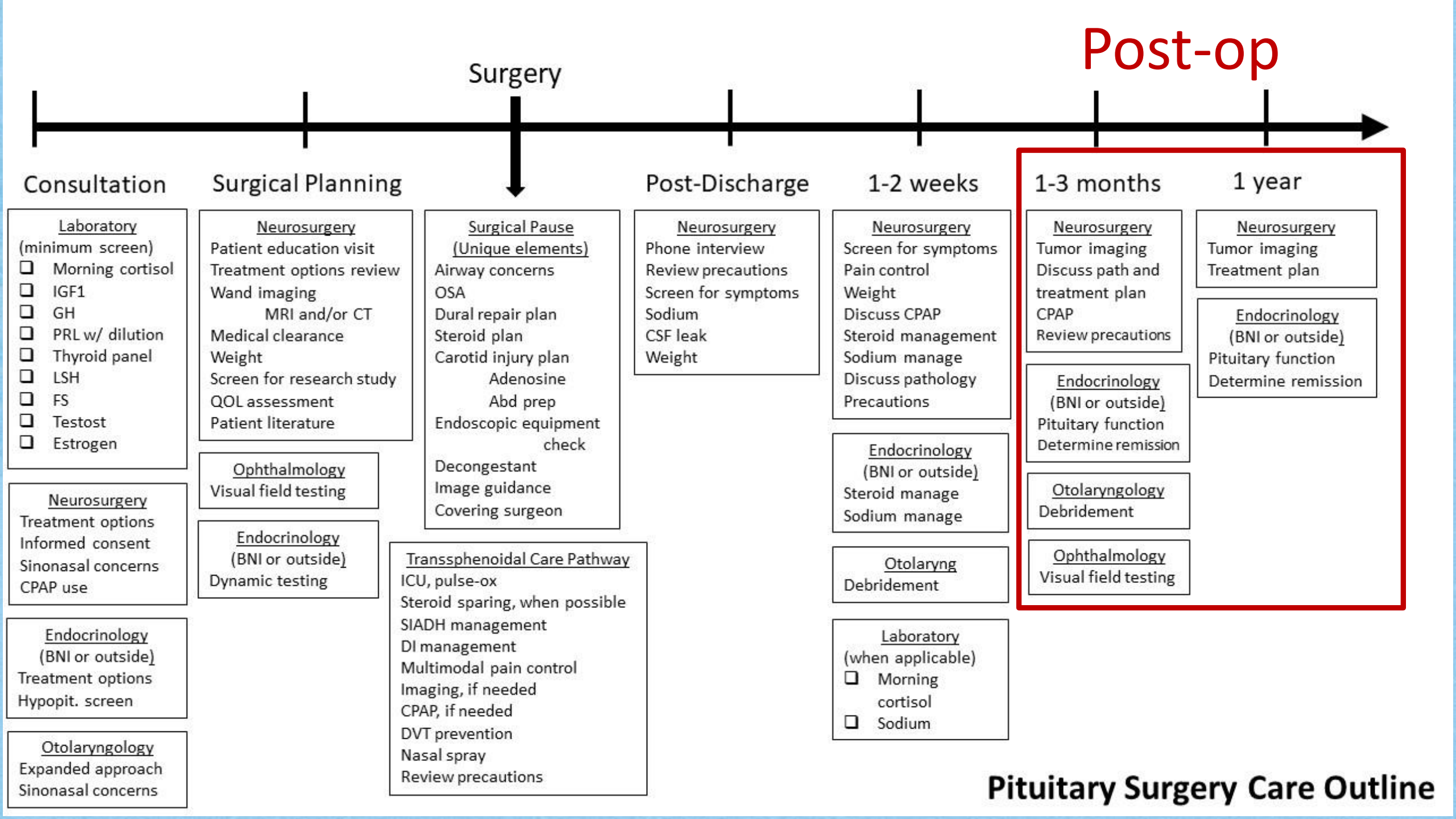
Close fluid and cortisol monitoring (POD1 and POD2 labs)
Home on fluid restriction
Nasal spray
Review precautions

Perioperative monitoring specifically for Cushing disease patients

- Blood draw every 3-6 hours to measure cortisol levels
  - if cortisol < 2, start Hydrocortisone
  - if cortisol 2-5 and symptoms, start Hydrocortisone
  - if cortisol > 5 and symptoms, use Hydrocortisone as needed

  (patients started on Hydrocortisone will be counseled how to taper)

- Monitor how much you drink and urinate
  - if develop diabetes insipidus, treat with DDAVP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1-3 months

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1 year

Neurosurgery
Tumor imaging
Treatment plan

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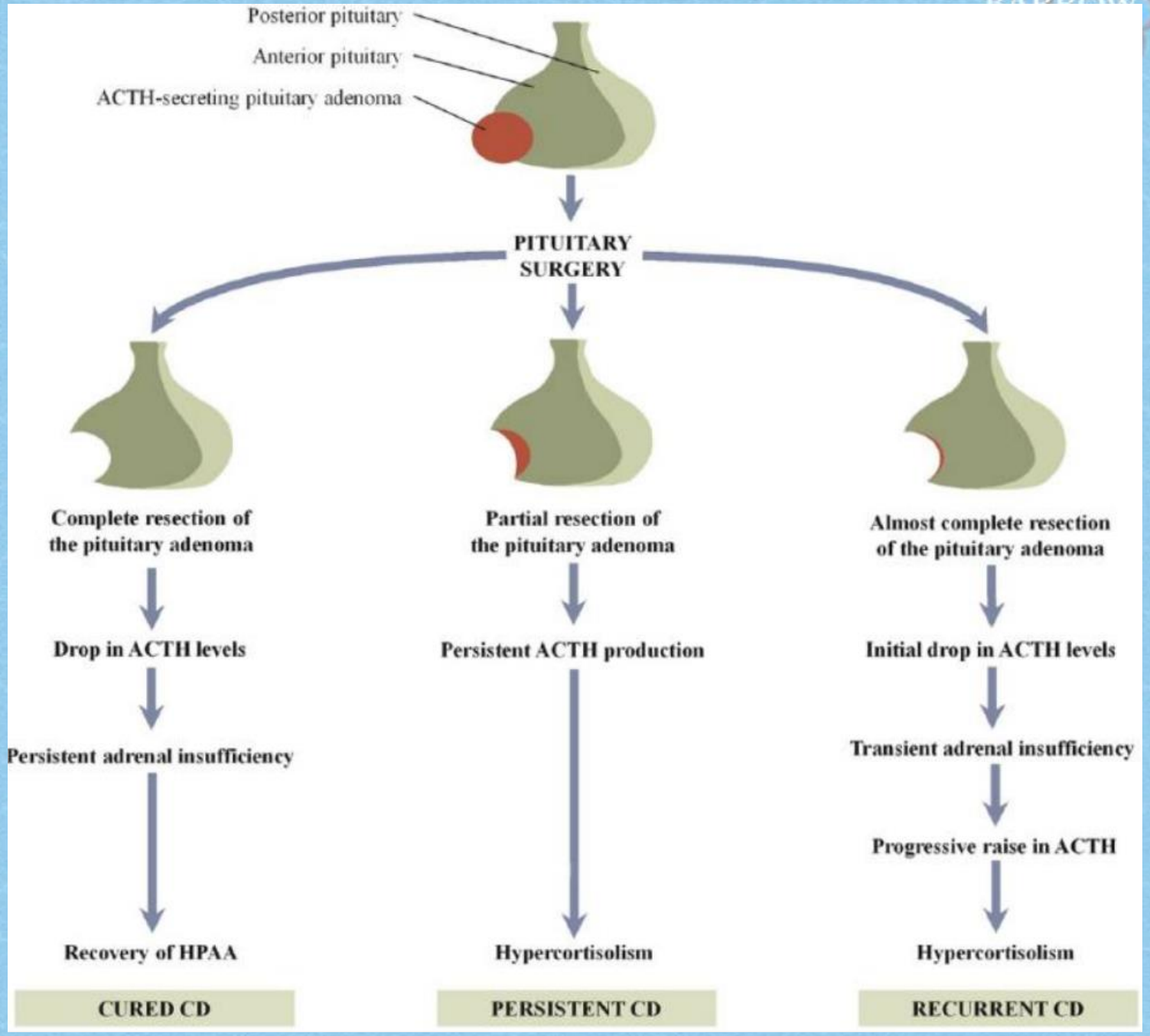
Week 1:
MRI and lab draw
Discuss pathology
Review precautions
Review fluid restriction

Week 6-8:
MRI
Discuss pathology
Neuro Infusion Unit
Review F/U plan
Visual field testing

What to expect after surgery for Cushing disease patients



Prete A, et al. Ther Adv Endocrinol Metab. 2017 Mar;8(3):33-48.

What to expect after surgery for Cushing disease patients: *remission +/- recurrence*

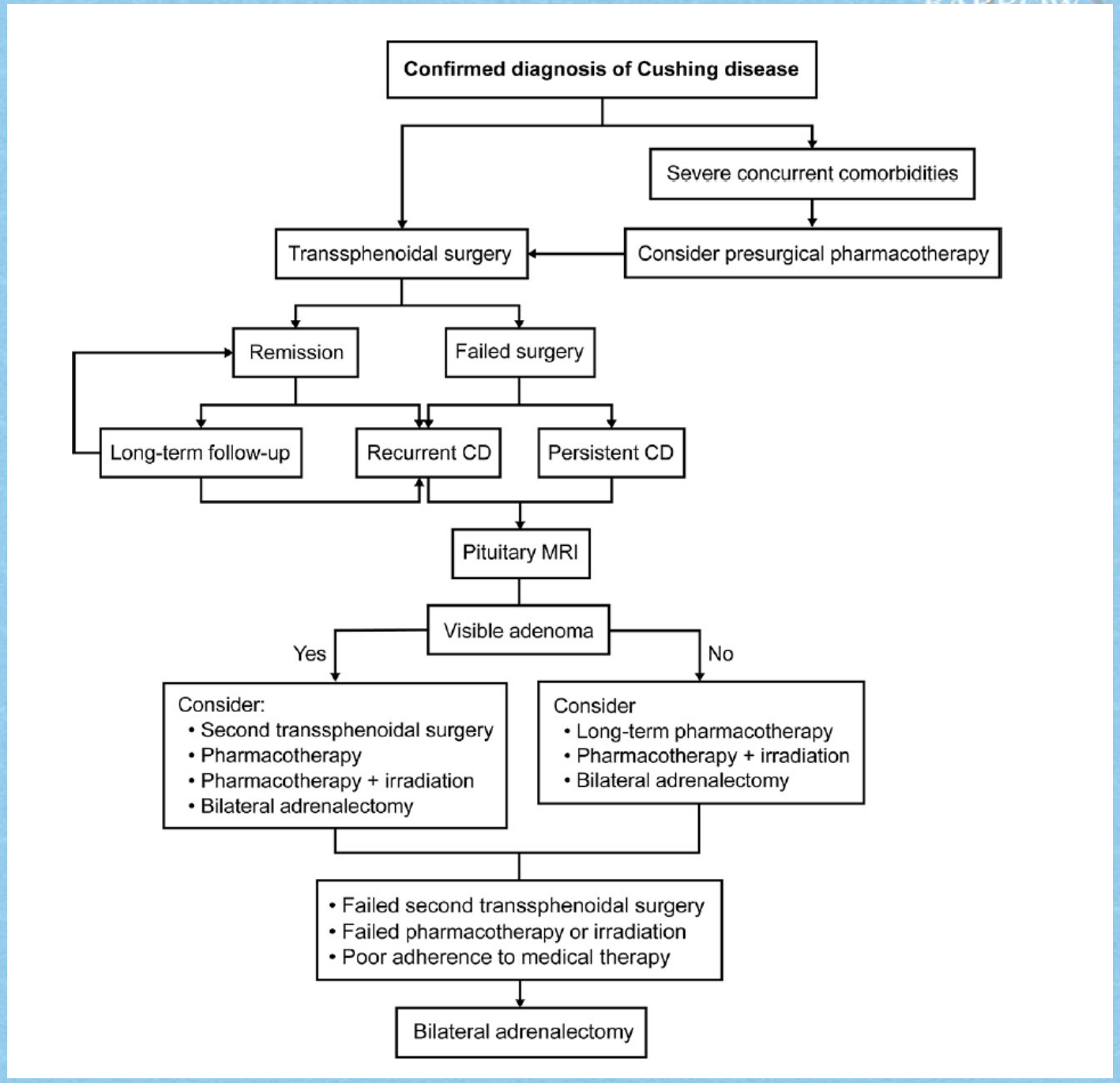
- Adrenal insufficiency with “withdrawal” symptoms
- Treatment with steroids
- Steroid tapering regime varies
- Need to be aware of how to stress dose
- Medical ID card
- Periodic AM cortisol and ACTH checks (+/- ACTH stim test)
- Watch for weight loss, improvement in BP, blood sugars, depression and sleep
- Always test for possible recurrence

Take it day by day and try to remain positive

What to expect after surgery for Cushing disease patients: *persistent*

- May not feel any different after surgery (no “withdrawal” symptoms)
- Further testing to confirm persistent disease
- Treatment with steroids not required
- Optimize treatment for other comorbidities
- Discuss with neuroendocrinologist/neurosurgeon next steps

What to expect after successful surgery for Cushing disease patients: *persistence or recurrence*



Yuen KCJ. Pharmacotherapy options after failed surgery for Cushing disease. In: *Little A, Mooney M, ed. Controversies in Skull Base Surgery. 1st Edition. New York: Thieme; 2019: 70-77.*

Important considerations for management for patients with persistent or recurrent Cushing disease

- Decision tailored to each patient
- Rpt surgery (when feasible) should be 1st choice if postoperative MRI shows a visible resectable adenoma (but lower success rate and a higher risk of complications)
- If rpt surgery is not viable or is expected to be unsuccessful (as judged by an experienced neurosurgeon), 2nd line options (medical therapy, radiotherapy or BLA) have to be considered

Bottomline: Challenging!

Helpful websites

- American Association of Clinical Endocrinologist: https://www.aace.com/
- American Association of Neurological Surgeons: https://www.aans.org/Patients/Neurosurgical-Conditions-and-Treatments/Pituitary-Gland-and-Pituitary-Tumors
- Pituitary Society: https://www.pituitarysociety.org/patient-education
- Cushing's Support and Research Foundation: http://csrf.net/
- Hormone Health Network: http://www.hormone.org
- Endocrine Society: https://www.endocrine.org/clinical-practice-guidelines/diagnosis-of-cushing-syndrome and https://www.endocrine.org/clinical-practice-guidelines/treatment-of-cushing-syndrome
- Magic Foundation: https://www.magicfoundation.org
- Pituitary Network Association: https://pituitary.org/
- Pituitary Society: https://www.pituitarysociety.org/
- Pituitary World News: https://www.pituitaryworldnews.org/

THANK YOU FOR YOUR ATTENTION!