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# Identification and Management of Immune-Related Adverse Events in the Emergency Setting

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American Academy of Emergency Medicine

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# Disclosures

- No relevant financial relationships to disclose
- I will not be discussing non-FDA approved indications during my presentation.

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# Mechanism CTLA-4 &PD-1

- Involved in maintaining appropriate immune response
- Downregulates & prevents inappropriate activity


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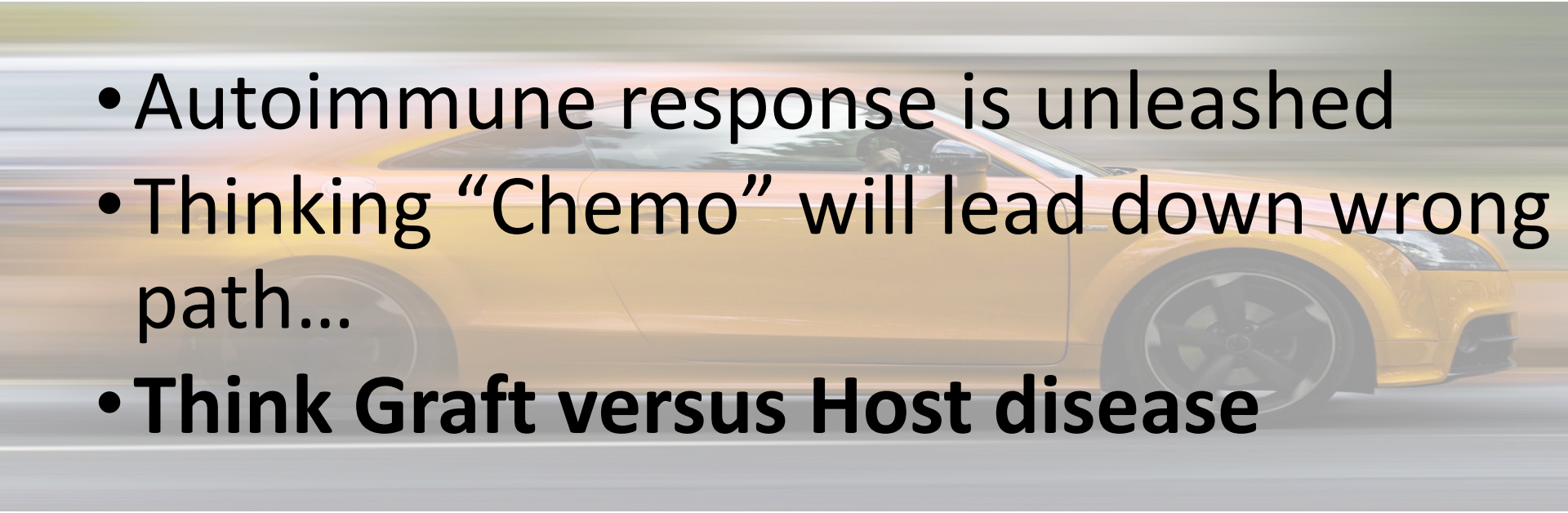
# CTLA-4 &PD-1 Blockade



- Autoimmune response is unleashed
- Thinking “Chemo” will lead down wrong path…
- **Think Graft versus Host disease**

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# Common Medications used to Treat irAE

- Corticosteroids
  - Prednisone
  - Dexamethasone
  - Methylprednisolone
  - Hydrocortisone
  - Cortisone
- Mycophenolate mofetil (CellCept)
  - Standard BID
- TNF inhibitors
  - Infliximab
  - Adalimumab
  - Others

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# irAEs include:

Ophthalmic toxicity

Dermatologic Toxicity

Hepatotoxity

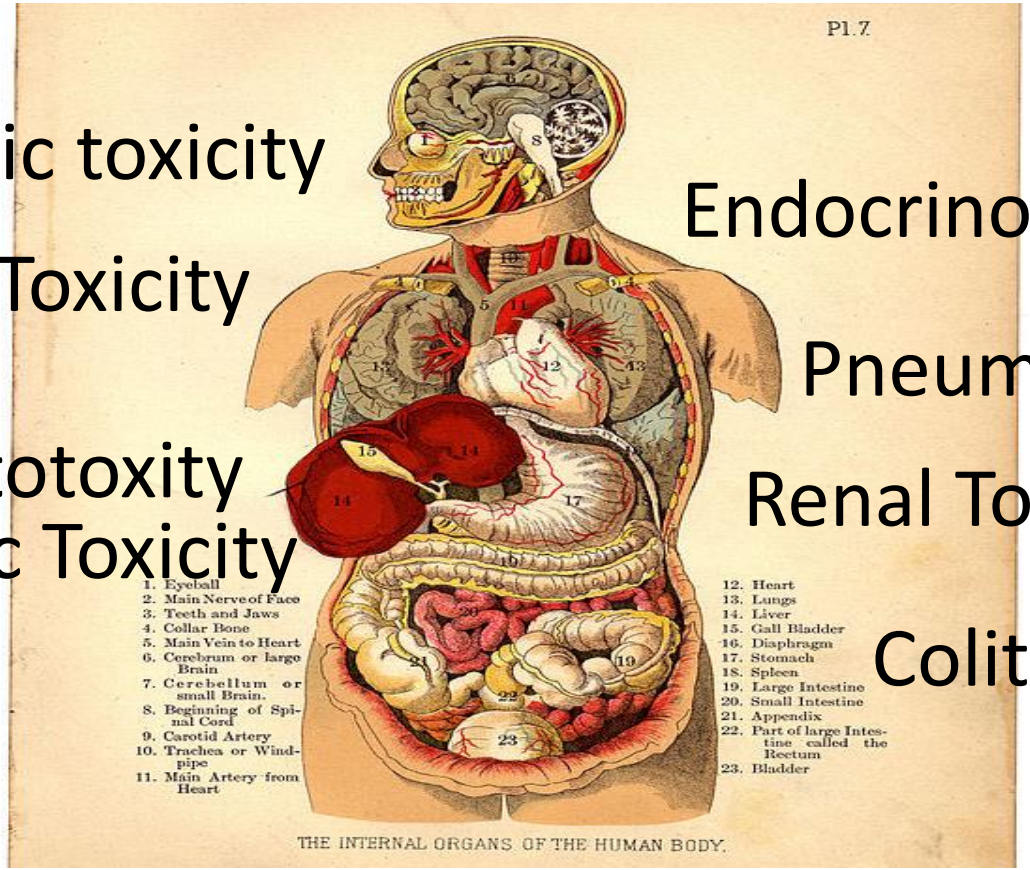
Pancreatic Toxicity

Endocrinopathy

Pneumonitis

Renal Toxicity

Colitis

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# Timing of irAE

- Most occur within first 3 months
- May occur after final dose
- Some dose dependent
- Grade 3-4 toxicity is rare- 10% overall

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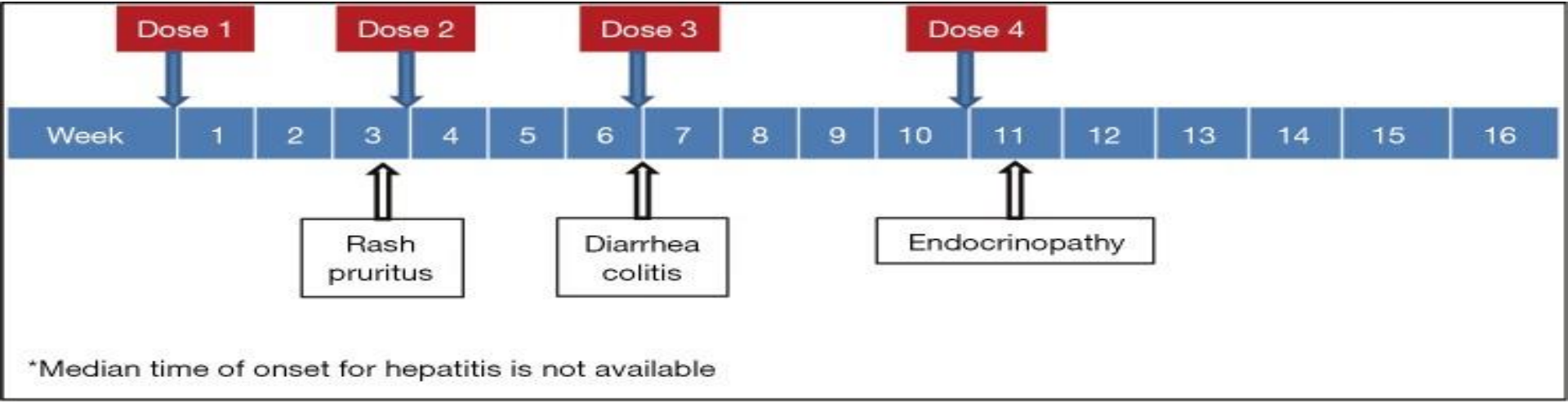


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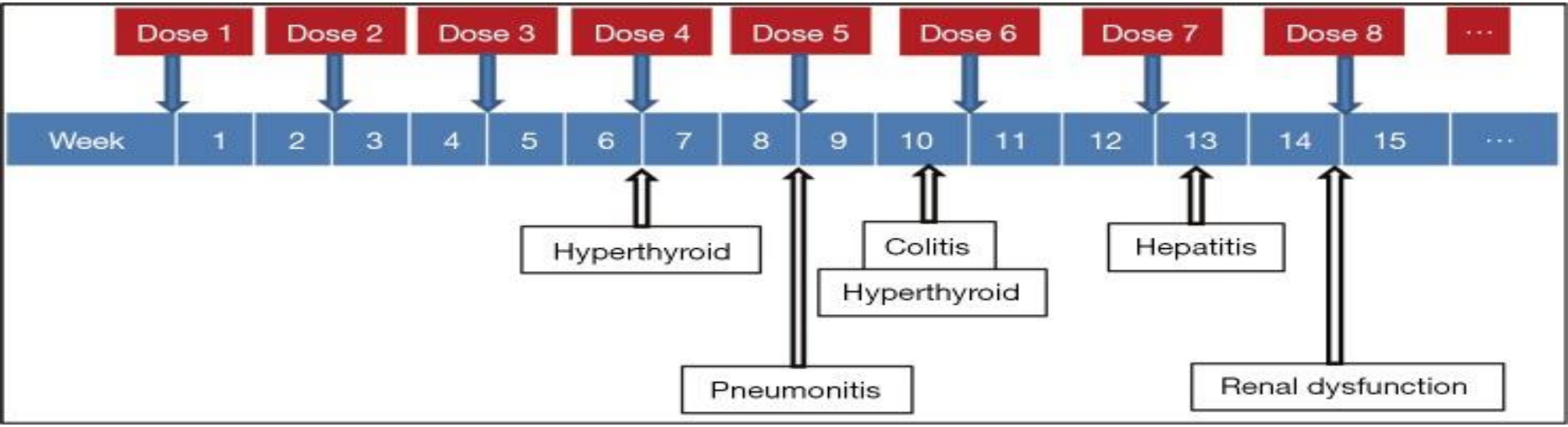


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# Dermatologic Toxicity

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# Dermatologic Toxicity

- Presents **three weeks** into therapy
- **Mild** – maculopapular rash with or without symptoms
  - Pruritis, burning, tightness
  - 10%-30% TBSA
  - Limiting ADLs
  - Tx: Topical steroids, hydroxyzine, diphenhydramine
- **Moderate** – diffuse, nonlocalizing rash
  - 30-50% TBSA
  - Tx:
    - Topical corticosteroids, hydroxyzine, diphenhydramine
    - Consider systemic corticosteroids if no improvement in one week (0.5-1mg/kg/day)

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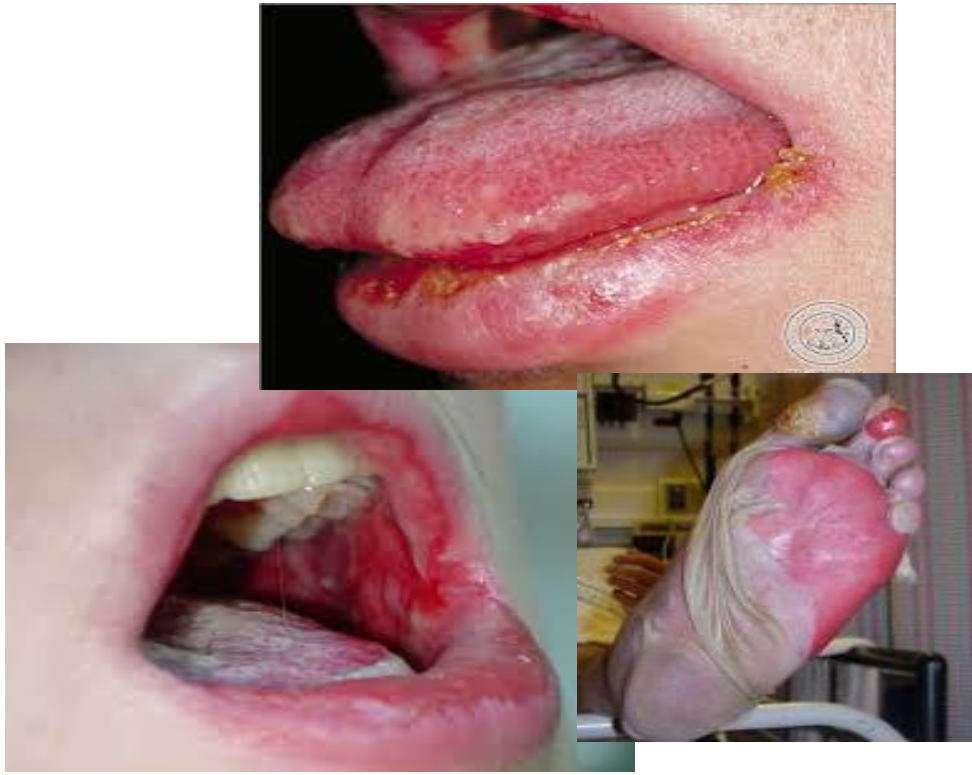
# Dermatologic Toxicity

**Severe -**

- Blisters, dermal ulceration, necrotic, bullous or hemorrhagic
- Most severe- Stevens Johnson Syndrome (SJS)/Toxic Epidermal necrolysis (TEN)
- Systemic corticosteroids 1-2 mg/kg/day prednisone equivalent
- Taper over one month following improvement
- Manage like a burn!



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# Dermatologic Toxicity

- Vitiligo
- Most cases permanent
- No treatment

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# Patient 1

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# 45 yo M
# HTN, DM, NSCLC
# on nivolumab

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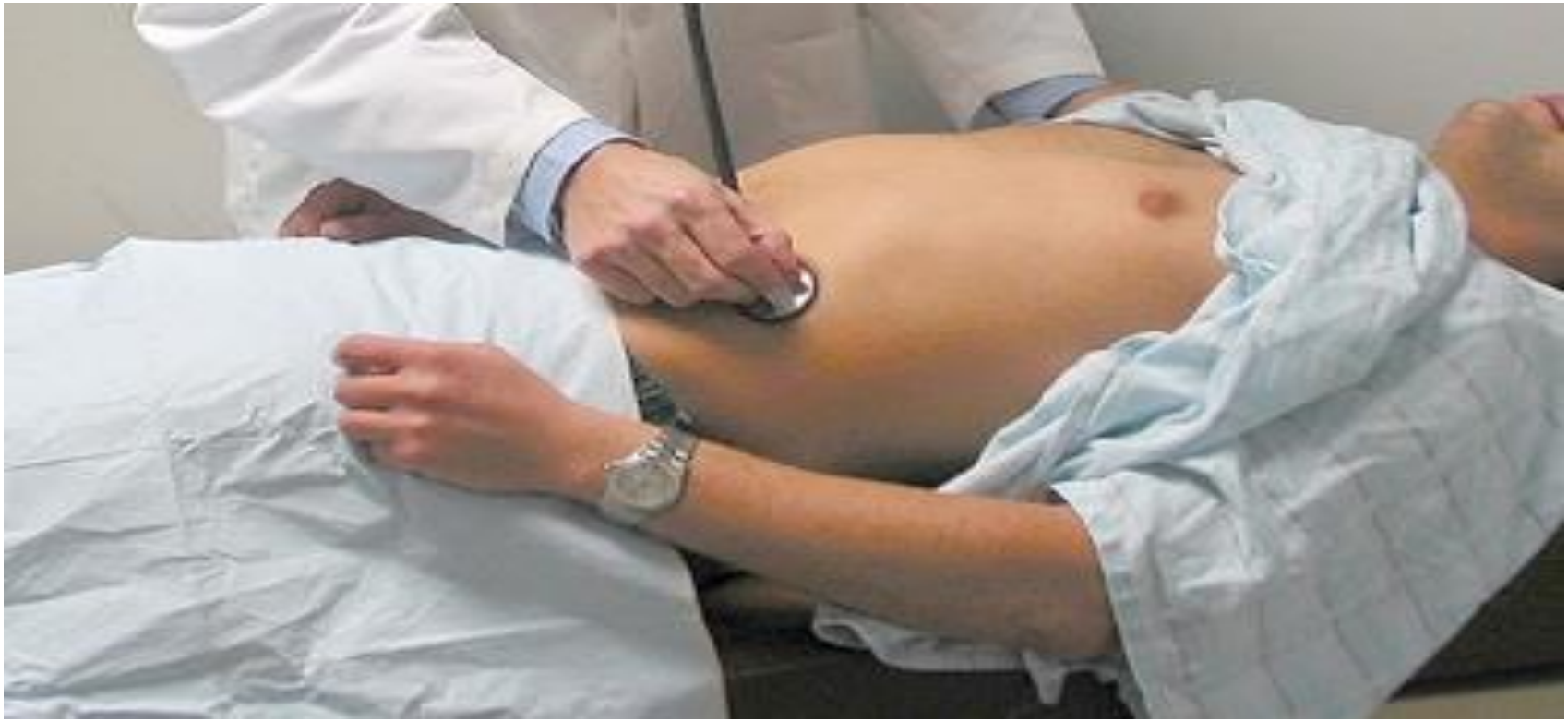

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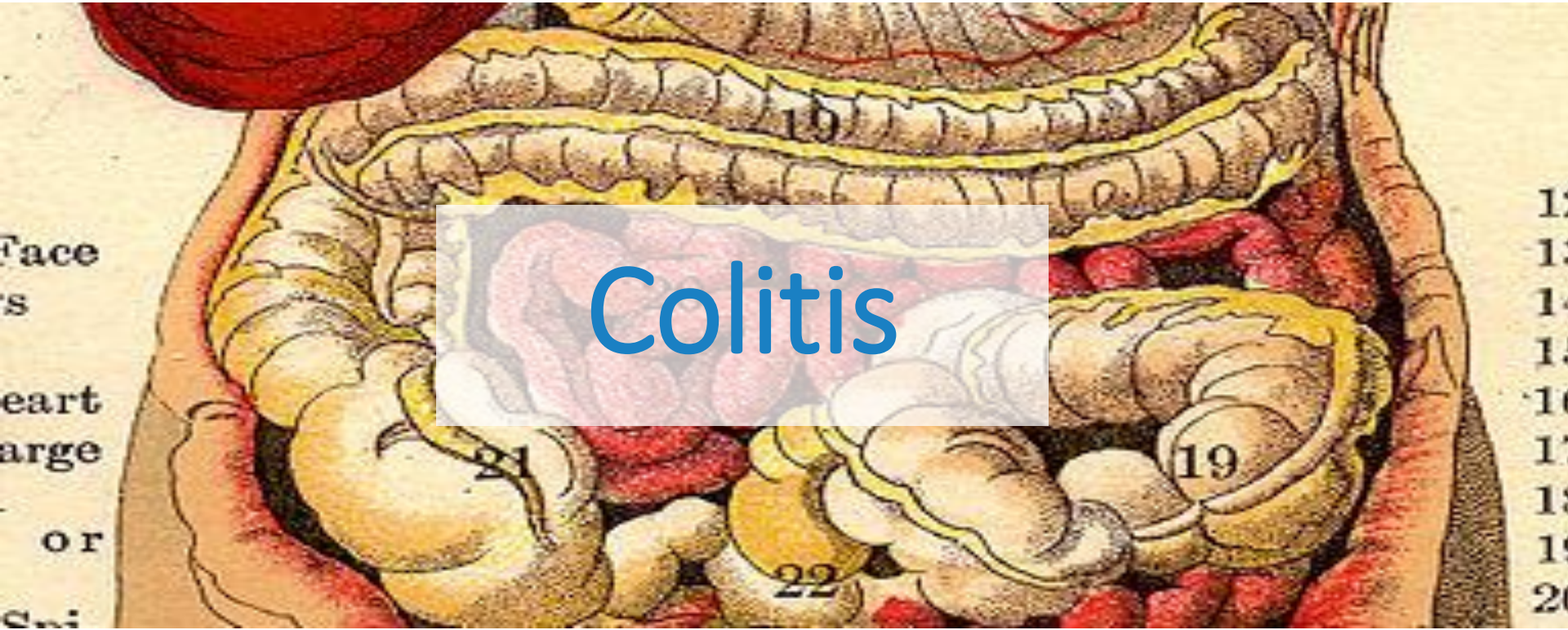


# Colitis

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# Colitis

- **Mild** - <4 stools above baseline/day

- Testing: C. diff., lactoferrin, O & P, stool culture

- Treatment
  - Symptomatic: oral hydration & bland diet
  - No corticosteroids
  - Avoid antidiarrheal meds
  - Budesonide – no significant difference

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# Colitis

- **Moderate** – 4-6 stools above daily baseline
- Abdominal pain, blood or mucus in stool
- Testing - C. diff., lactoferrin, O & P, stool Cx
- Systemic corticosteroids 0.5/mg/kg/day equivalent if symptoms > one week

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# Colitis

- **Severe –** 7 stools above baseline/day
- Peritoneal signs, ileus or fever
  - Rule out perforation
- IV hydration
- Stool studies
- Admission

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# Colitis

- **Severe continued -**
- Systemic corticosteroids 1-2mg/kg/day equivalent, if no perforation
  - Hold if clinically stable until stool studies available (24hrs)
- Unstable – High dose corticosteroids: methylprednisolone 125 mg IV daily x 3 days to evaluate responsiveness
- Consider empiric antibiotics for fever or leukocytosis

- Infliximab 5 mg/kg if no response to corticosteroids
- Consider mycophenolate mofetil for select patients

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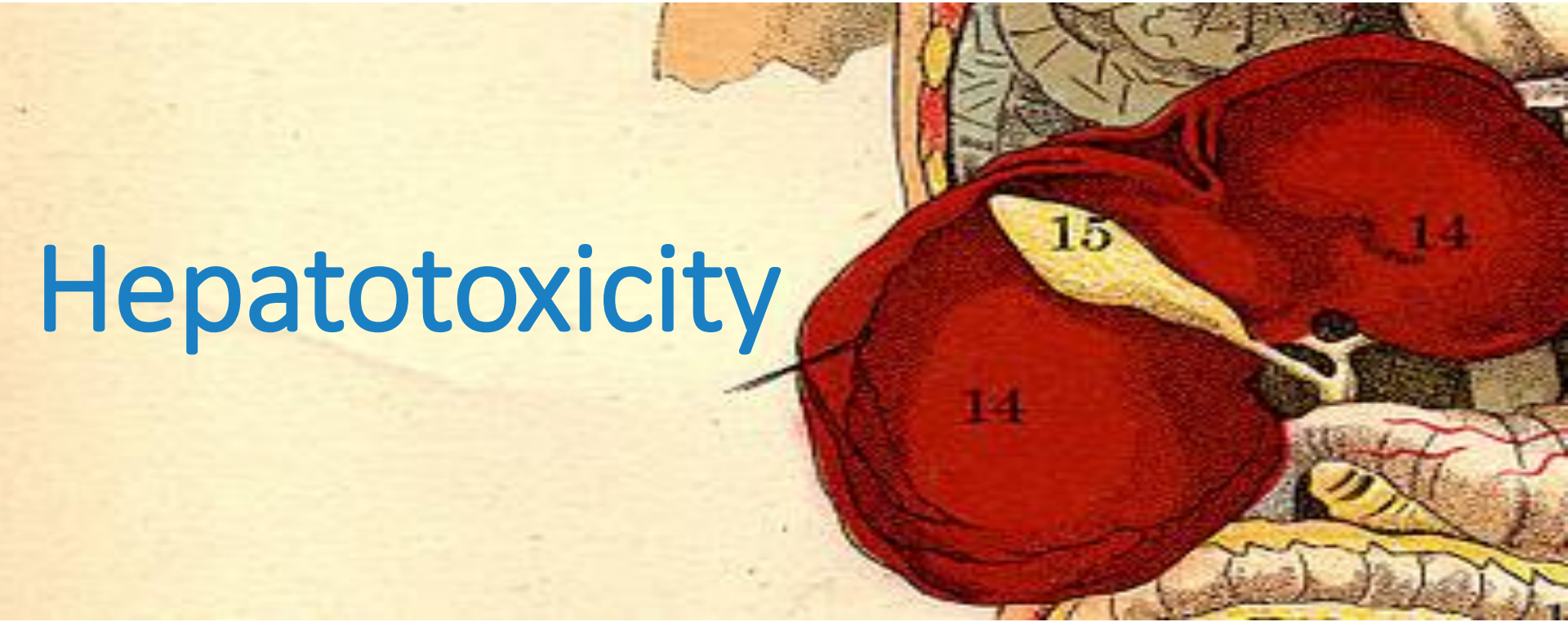
# Hepatotoxicity

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# Hepatotoxity

- **8-12 weeks** after therapy initiation
- Avoid ETOH & acetaminophen

## Grade 2 toxicity

- AST/ALT 2.5 -5 times ULN
- Bilirubin 1.5-3 times ULN
- Corticosteroids 0.5-1 mg/kg/day & 1 mo. taper

## Grade ≥3 toxicity

- Admission
- Methylprednisolone IV 125mg/day
- Consider mycophenolate mofetil 500mg PO Q12hrs

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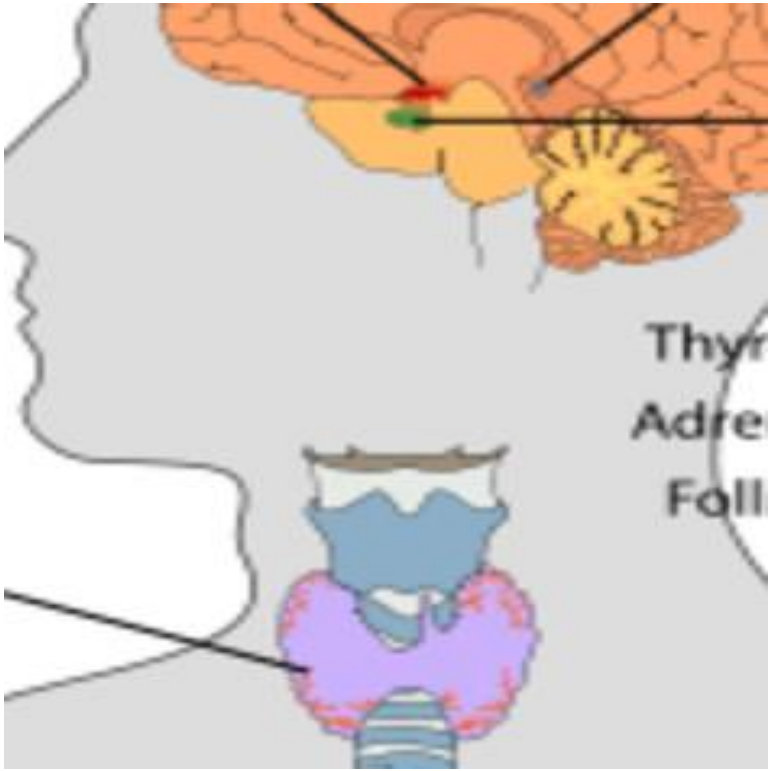
# Endocrinopathy

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# Endocrinopathy

- <10%
- **6 weeks** after initiation of therapy
- Dose-dependent

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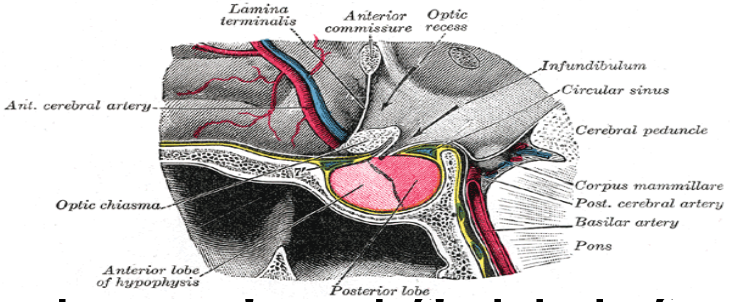
# Endocrinopathy

**Hypophysitis –**




- Fatigue, headaches, visual field defects
- ACTH, TSH, FSH, LH, GH, prolactin
- Imaging – enlarged pituitary gland
- Treatment:
  - Corticosteroids 1 mg/kg/day OR
  - IV dexamethasone 6 mg Q6hr x 3 days OR
  - Methylprednisolone 125 mg daily

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# Endocrinopathy

- **Hypothyroidism**
  - 1 wk-19 months onset after therapy initiation
  - Appropriate levothyroxine replacement
- **Hyperthyroidism**
  - Check TSH level
  - Acute thyroiditis secondary to immune activation
    - Corticosteroids 1 mg/kg for symptomatic patients
- **Adrenal Insufficiency**
  - Admission
  - Corticosteroids 60-80 mg prednisone or equivalent

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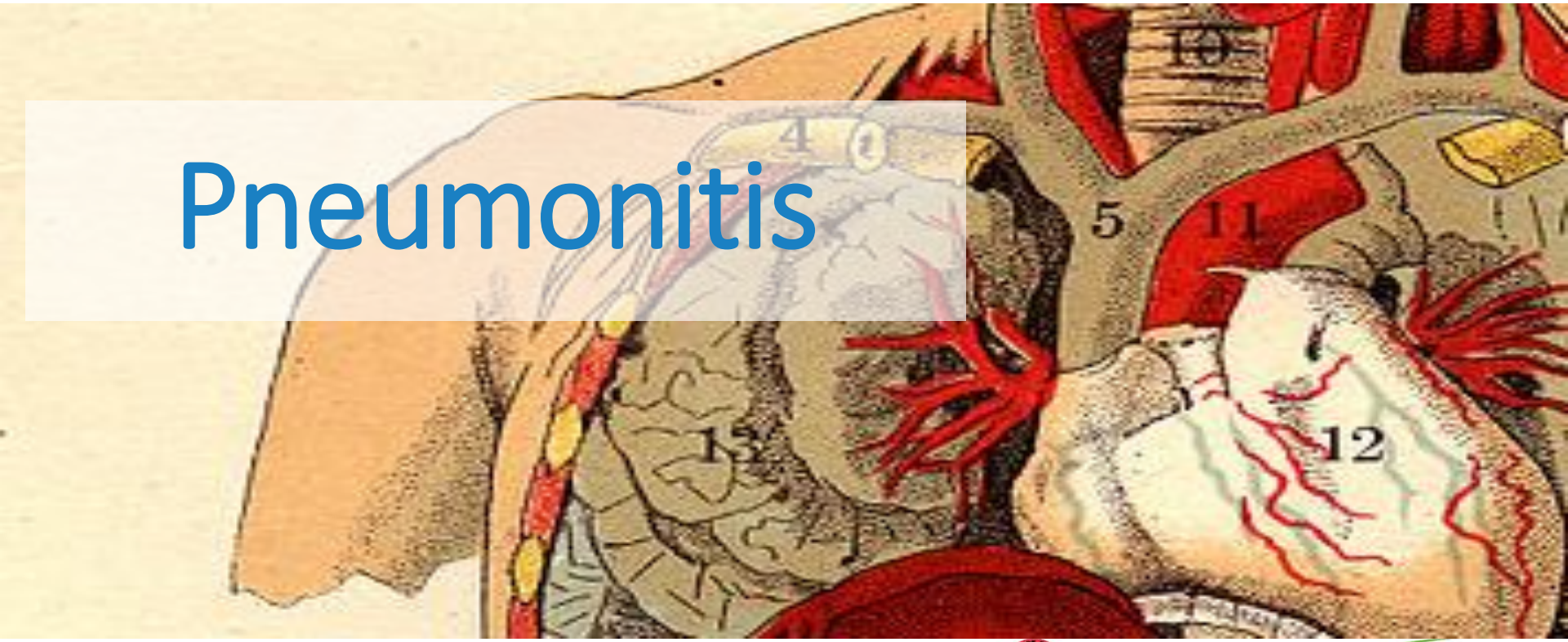
# Pneumonitis

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# Pneumonitis

- **5 months** after treatment initiation
- Symptoms/Signs:
  - **New cough**
  - **Dyspnea**
  - **Chest pain**
  - **Radiographic changes**
- Fatal cases reported
- Management based on grades of severity

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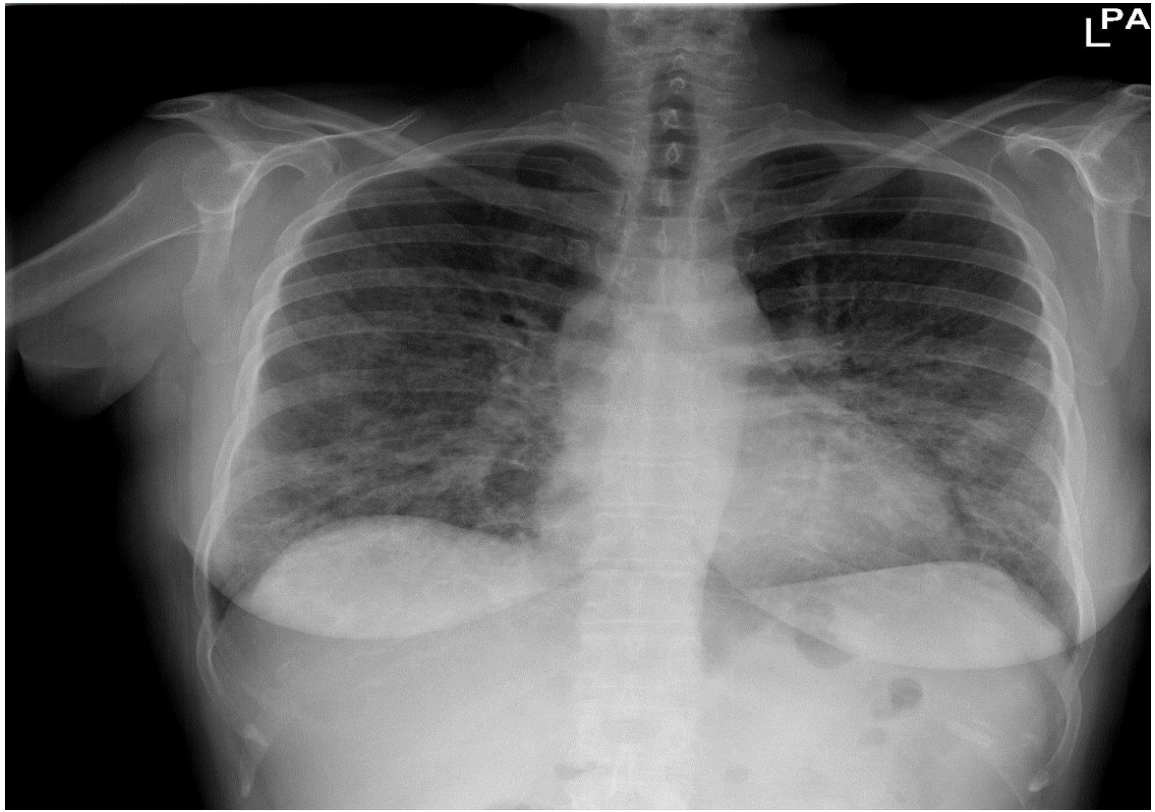


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# Pneumonitis

- **Grade 1** (radiographic changes only)
  - Outpatient, Continue treatment
  - Re-image in 3 weeks
- **Grade 2** (mild to moderate symptoms)
  - Monitor daily or Admit, DC treatment
  - Prednisone/prednisolone
    - Taper over one month after improvement seen
- **Grade 3-4** (severe symptoms, hypoxia)
  - Admission, DC treatment
  - Prednisone/prednisolone
  - Six week taper

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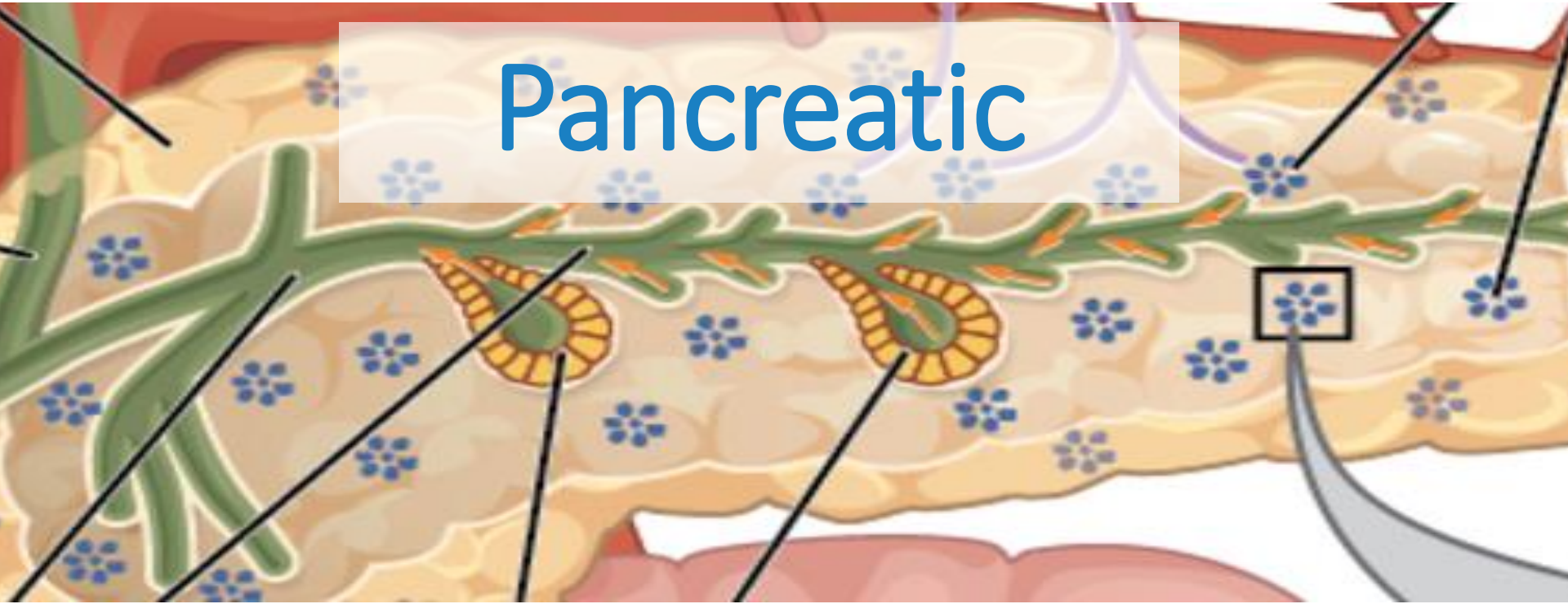
# Pancreatic



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# Pancreatic

- Elevation amylase & lipase
  - With both CTLA-4 &PD1 inhibitors
  - Without overt pancreatitis– monitor
  - Grade 3-4 with symptoms – hold therapy

- New onset diabetes with DKA
  - Normal ED treatment
  - Aggressive treatment of DKA

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# Patient 2

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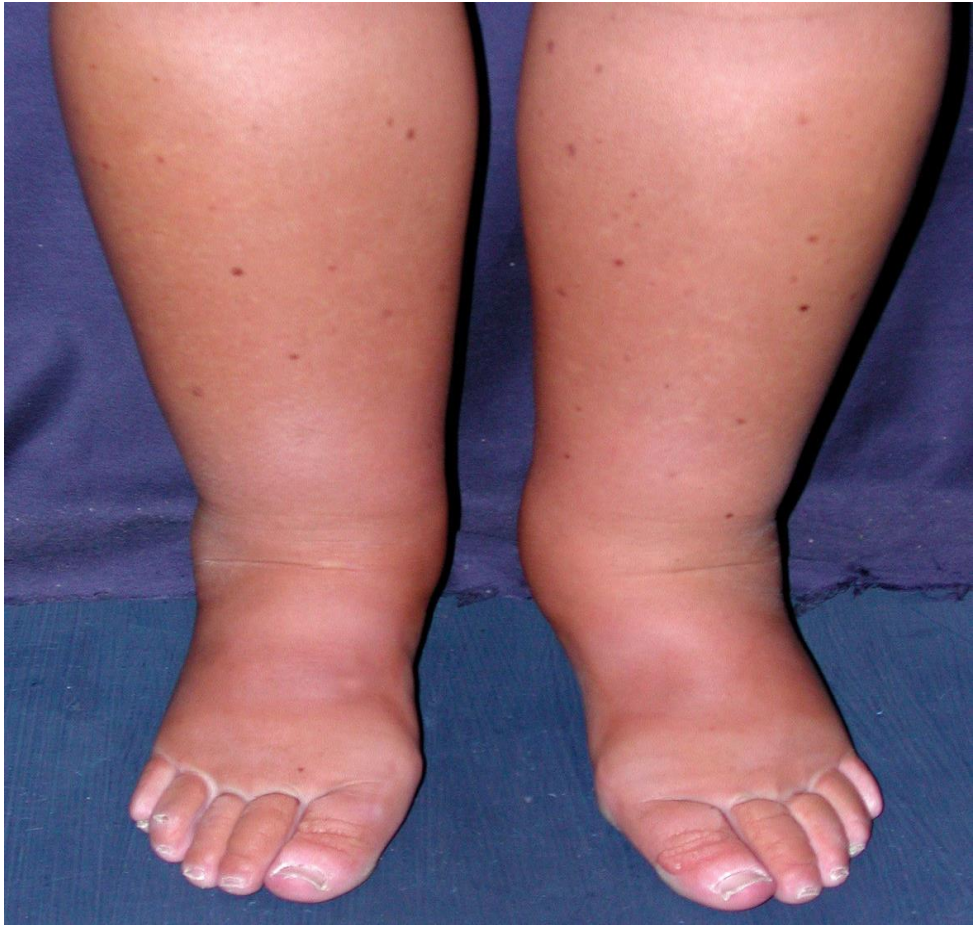

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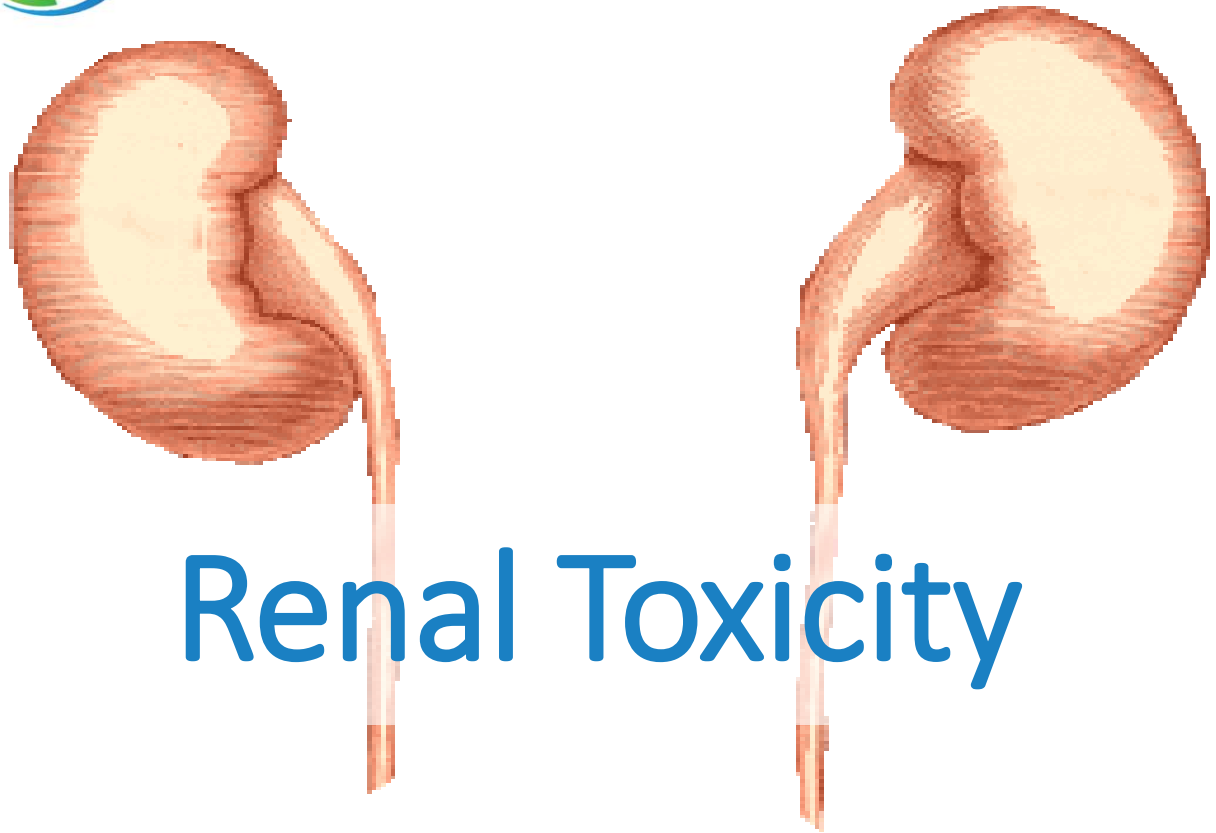

# Renal Toxicity

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# Renal Toxicity

- <1%
- **10-12 months** after initiation of treatment
- **Grade 1**: up to 1.5x above baseline
- **Grade 2 to 3**: 1.5-6x baseline
- Full recovery with high dose corticosteroids. (>40 mg/day)

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# Ophthalmic Toxicity

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# Ophthalmic Toxicity

- <1%
- **6 weeks** after initiation of therapy
- Dose-dependent
- **Episcleritis**
- **Uveitis**
- **Conjunctivitis**
- Treatment:
  - Topical corticosteroids – prednisolone acetate 1%

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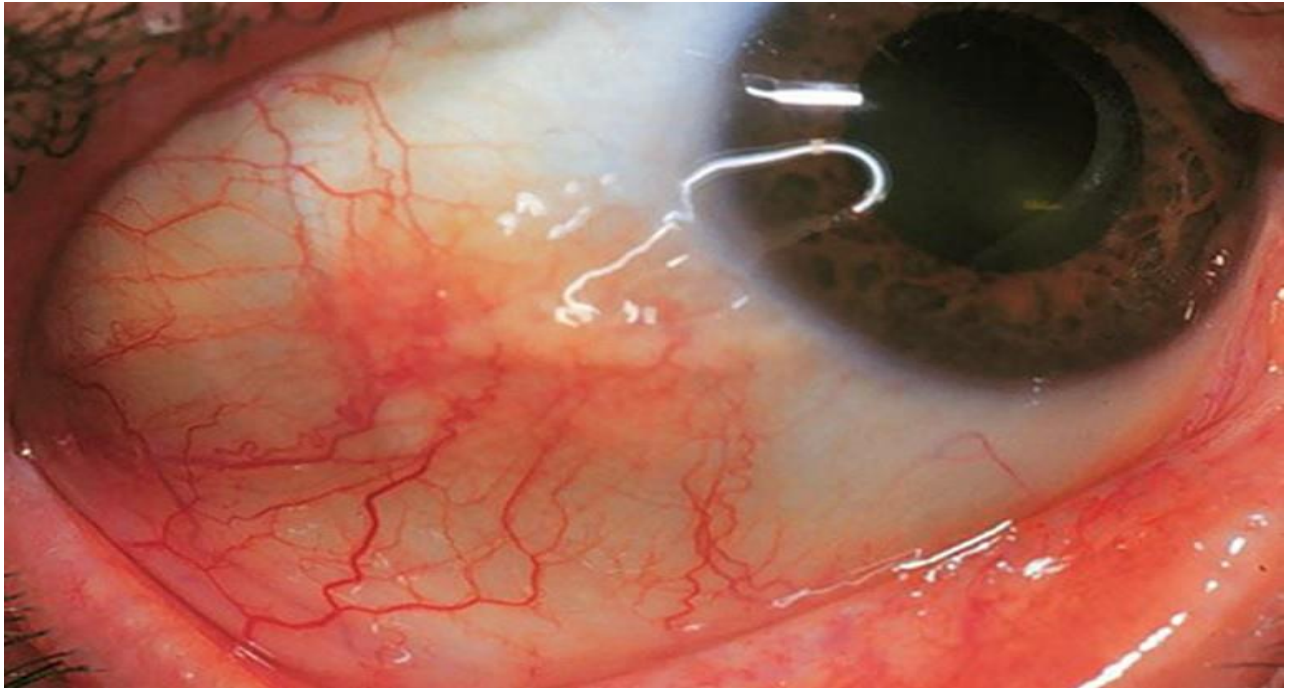

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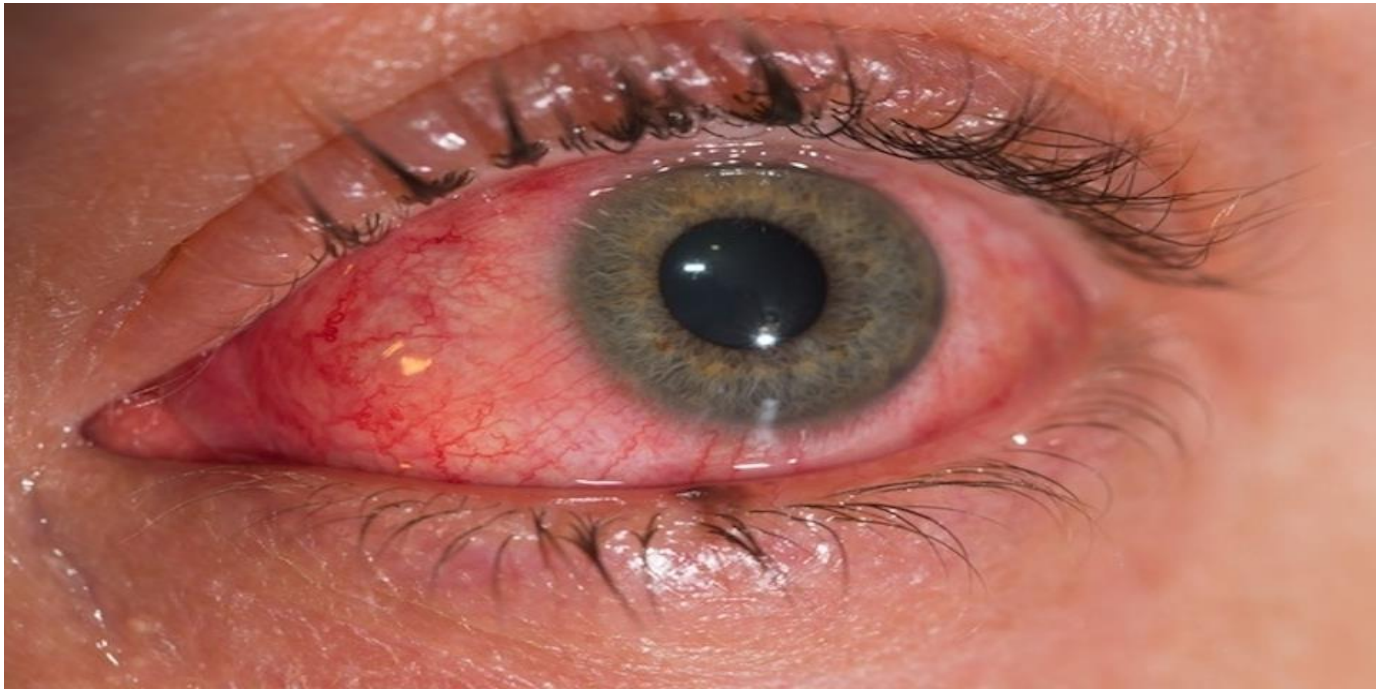

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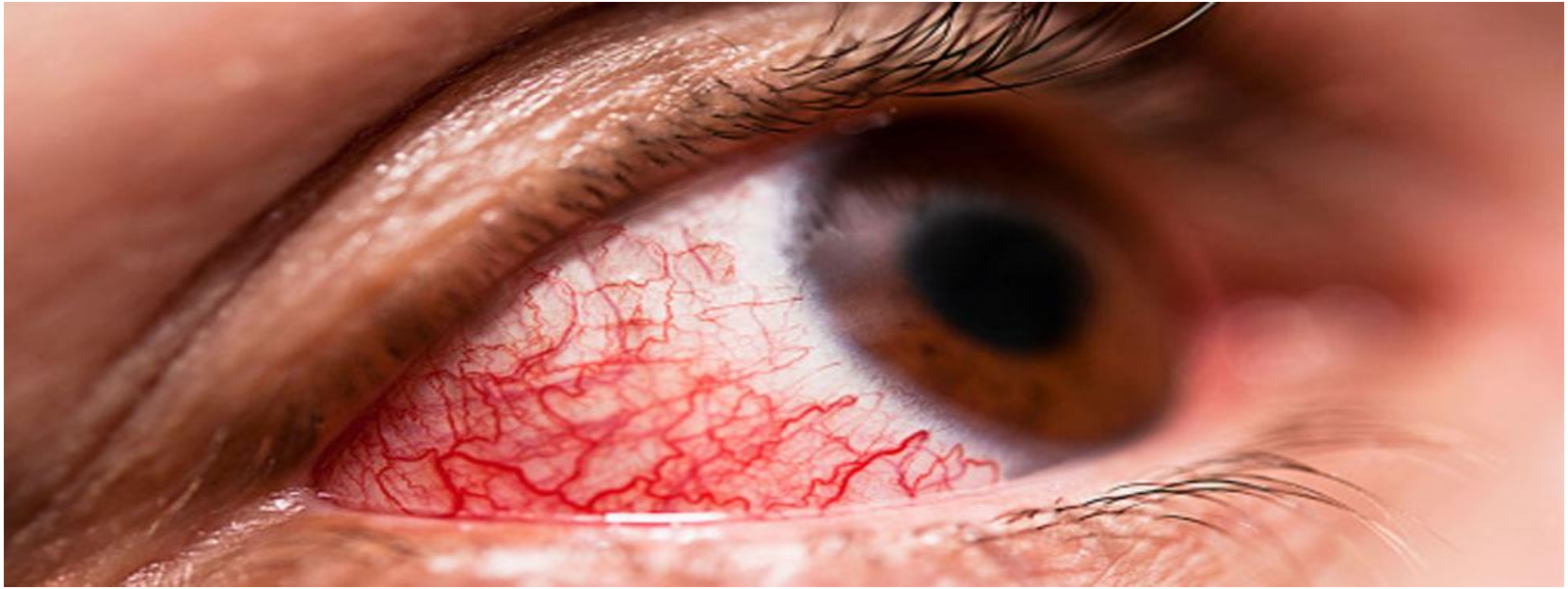

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# Rare irAEs

- <1%
  - Red cell aplasia
  - Thrombocytopenia
  - Hemophilia A
  - Gullian-Barre syndrome
  - Myasthenia gravis
  - Posterior reversible encephalopathy syndrome
  - Aseptic meningitis
  - Transverse myelitis
  - ??

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# Patient 3

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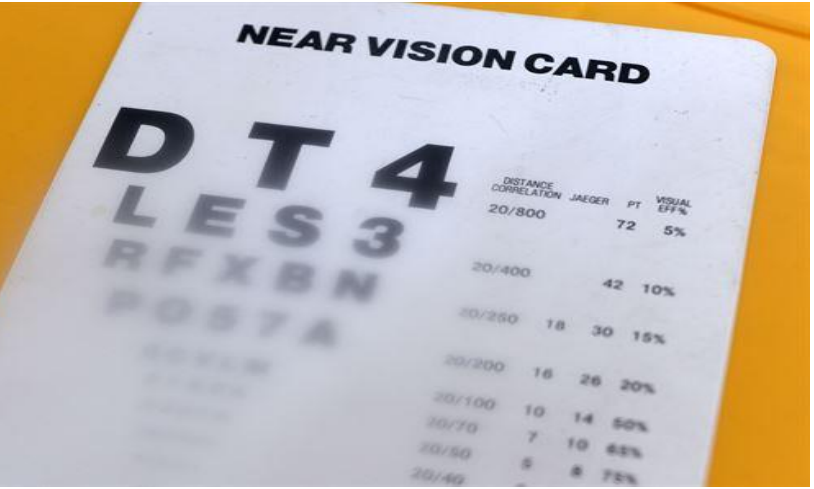
# Exam




- VA w/o correction: 20/25 right eye (OD), 20/125 left eye (OS)
- IOP: 10 mmHg OD, 12 mmHg OS
- Pupils: 5 → 3 mm in both eyes (OU)
- Confrontation visual fields: temporal loss OD, central scotoma OS

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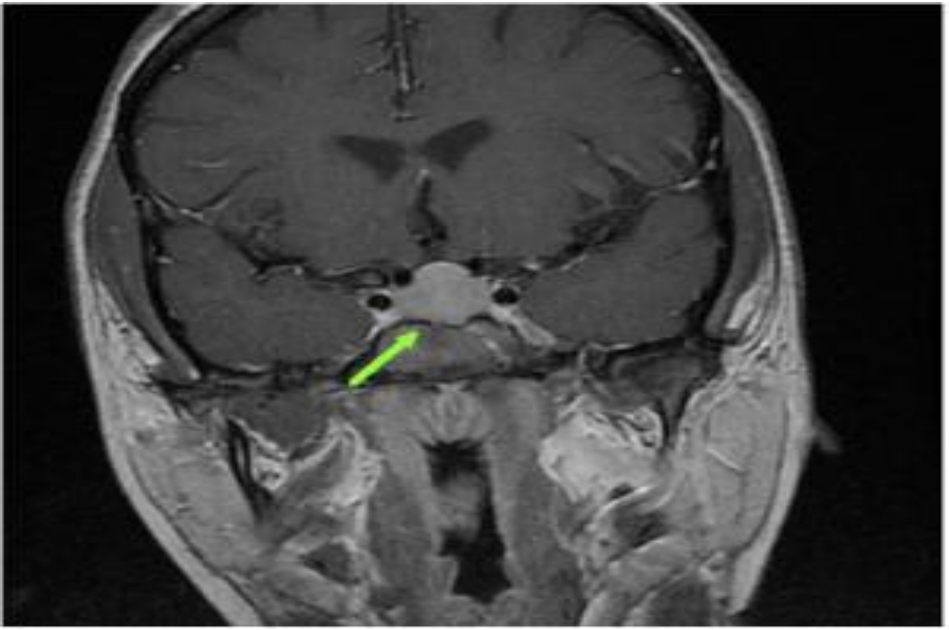

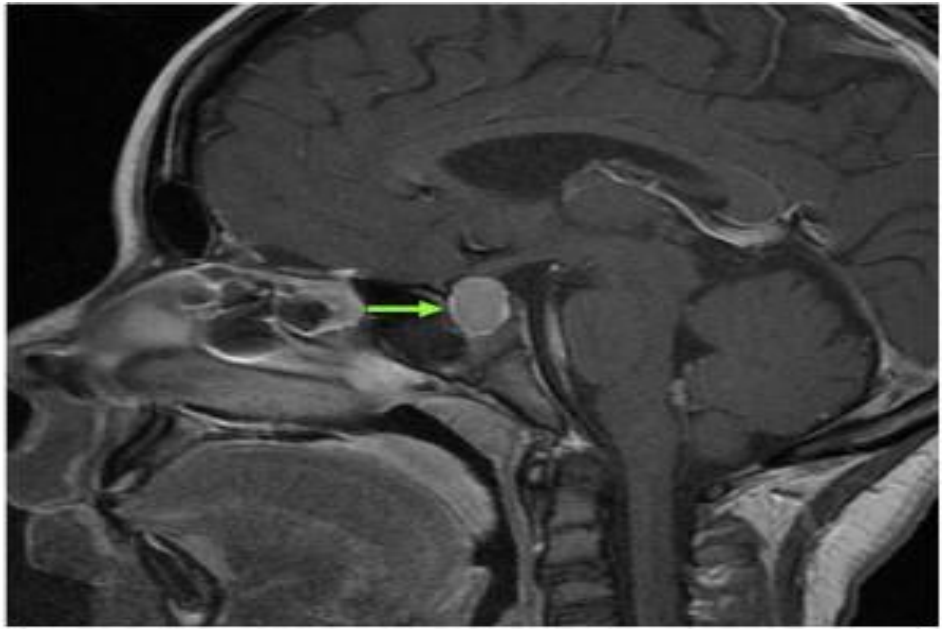

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# Take Home Points

- irAE are autoimmune assaults
- Recognize irAE early
- Management is largely based on grade/severity
- Steroids, steroids, steroids!

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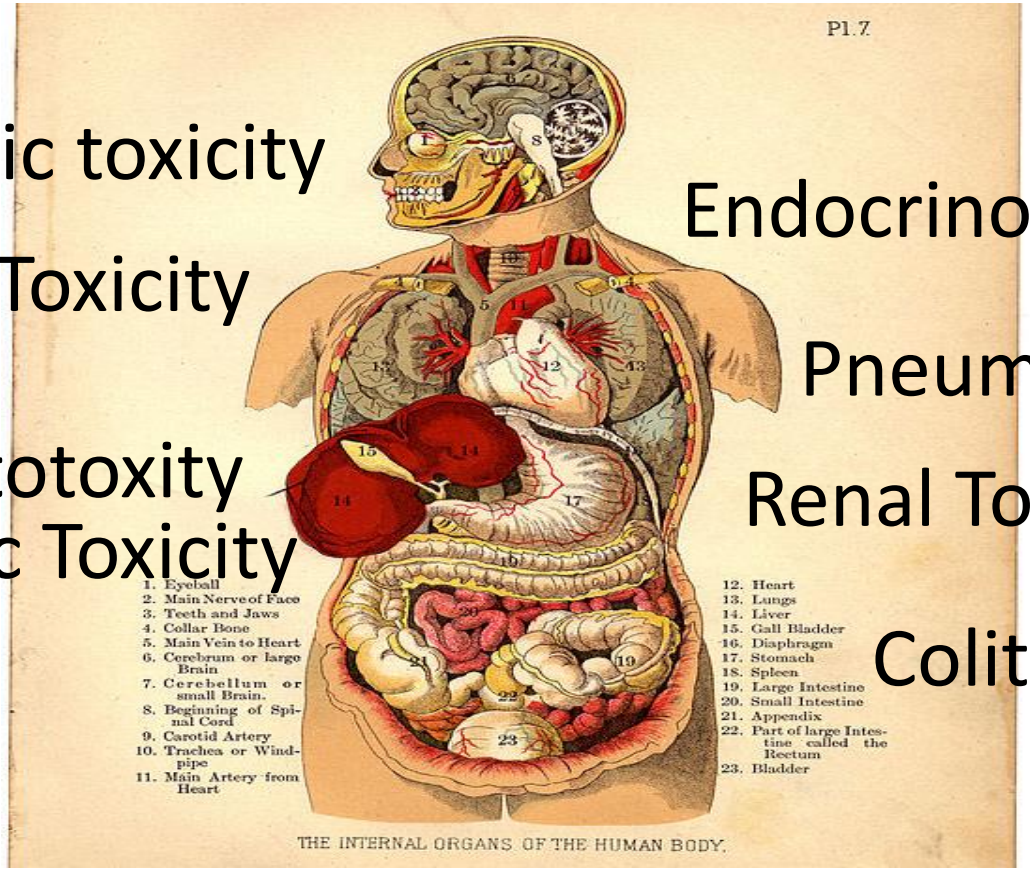
Pneumonitis

Renal Toxicity

Colitis

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