Management of Immunotherapy Related Adverse Events in Solid Tumors

Alga S. Ramos Morales, PharmD, MS, BCPS, BCOP

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Doral, FL
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Disclosures

- I have nothing to disclose

Objectives

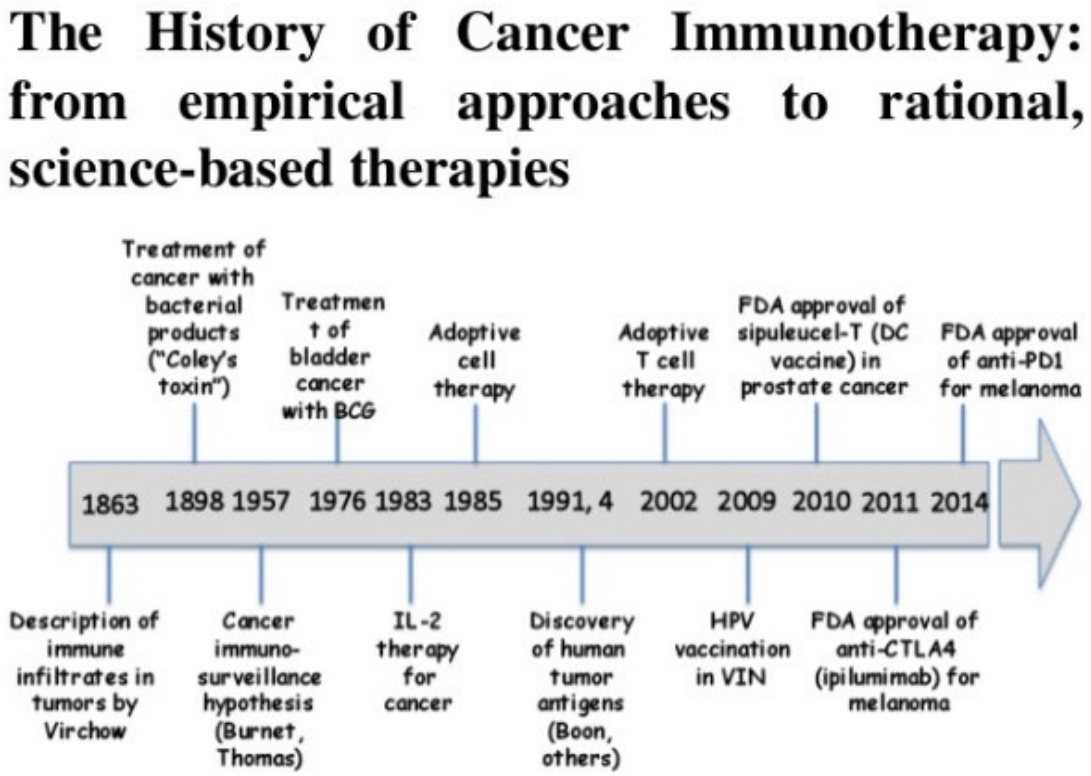
- State the definition and types of immunotherapy
- Describe immune mediated adverse events (irAEs)
- Discuss monitoring and treatment of irAEs

Agenda

- Definitions and History
- Checkpoint Inhibitors
- Management of Toxicities

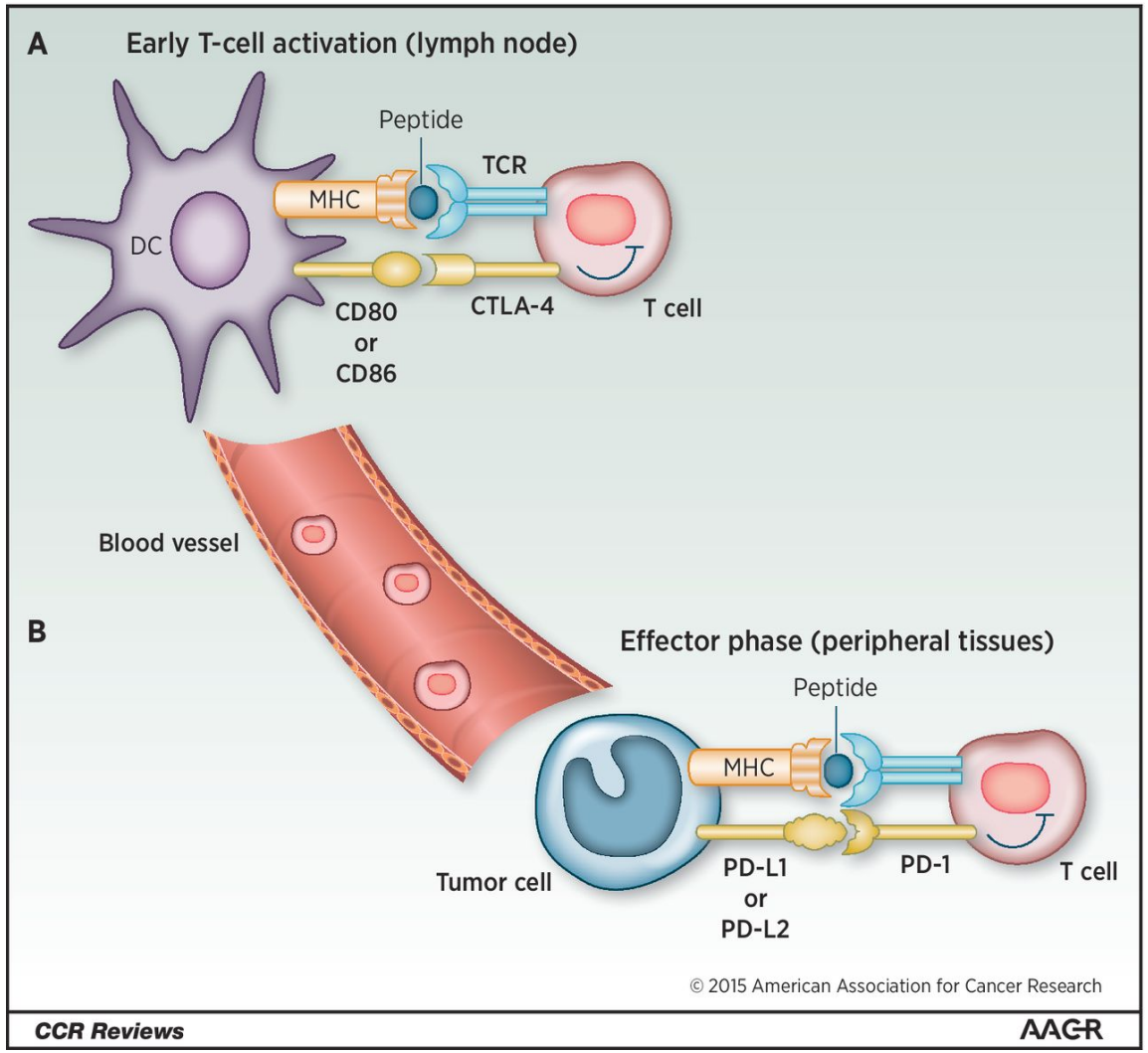
Immunotherapy

- Treatment that uses the body's own immune system to help fight cancer

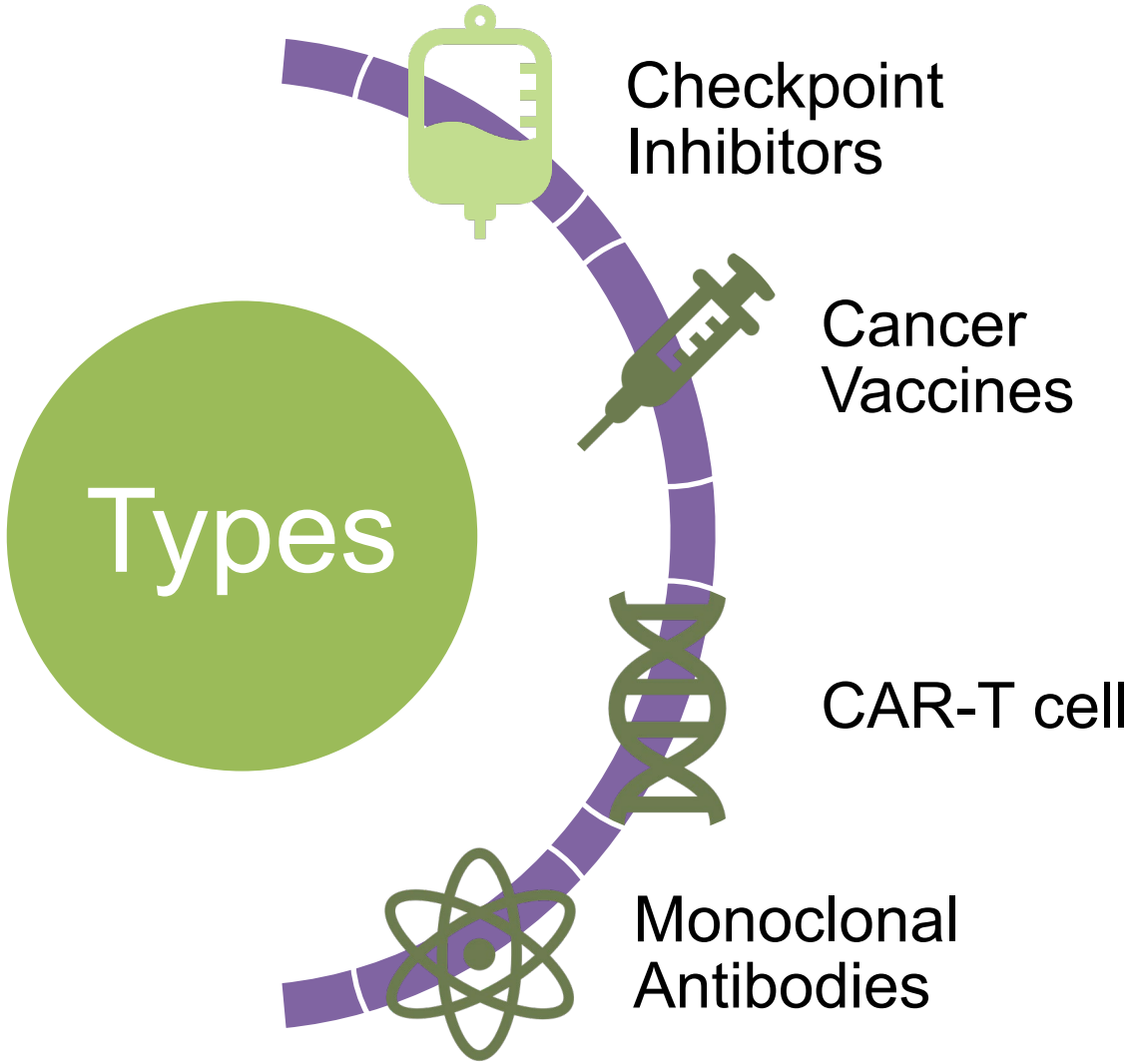


Mechanism of Action

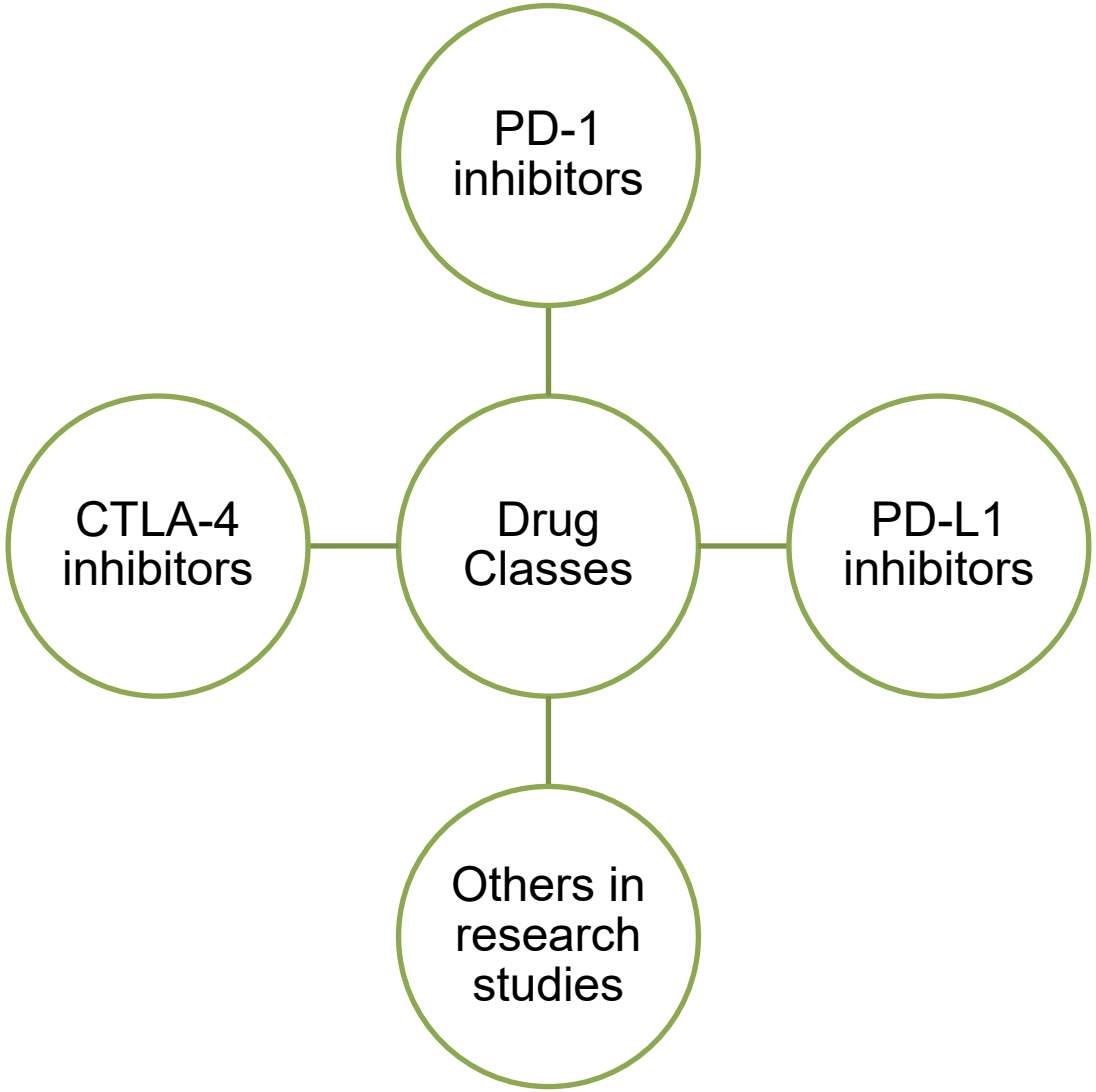
- An efficient T-cell-mediated adaptive antitumor immune response requires two phases:
  - Priming phase (generation of antitumor T cells)
  - Effector phase (destruction of the cancer by T cells)



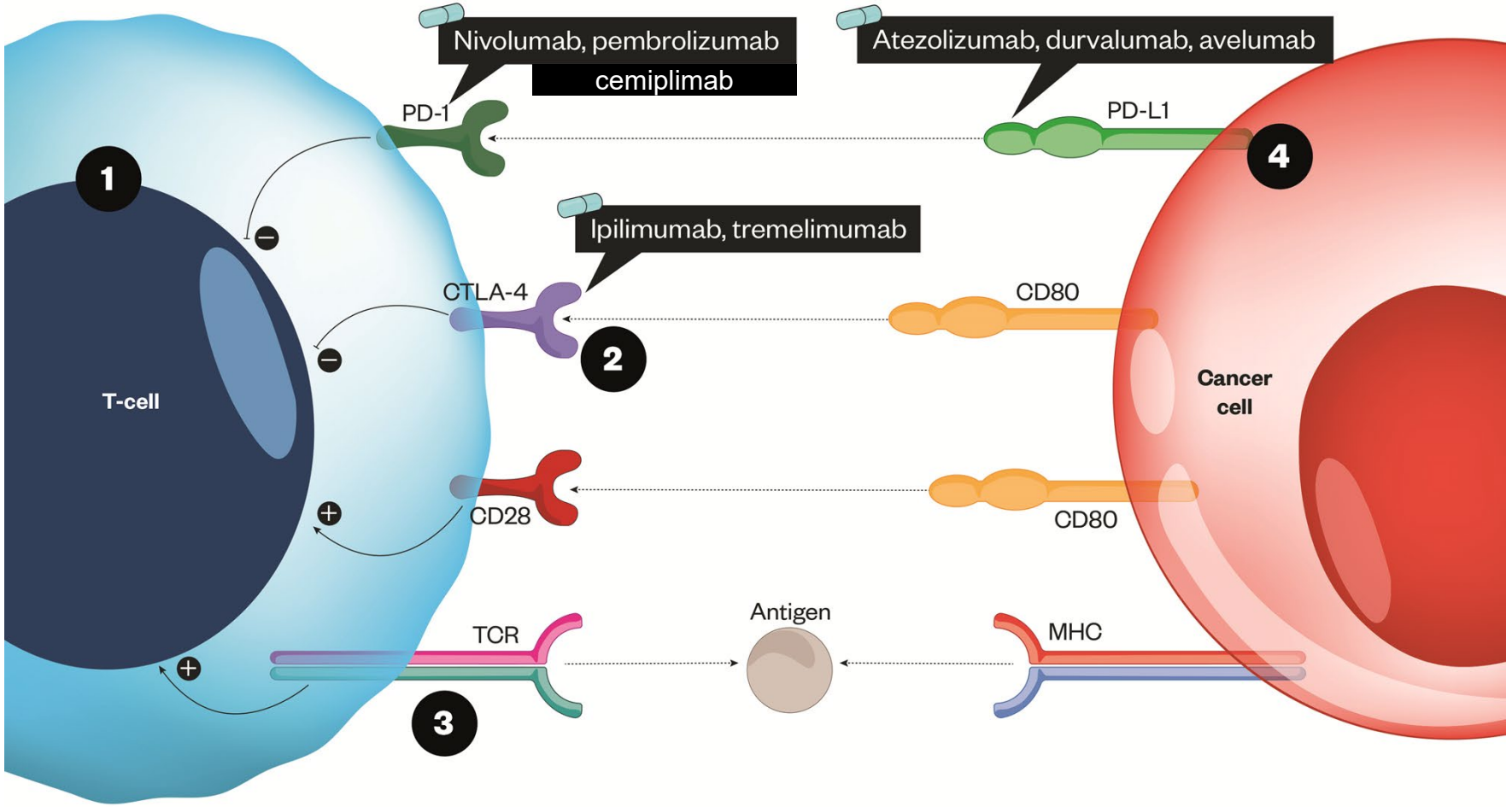
Immunotherapy



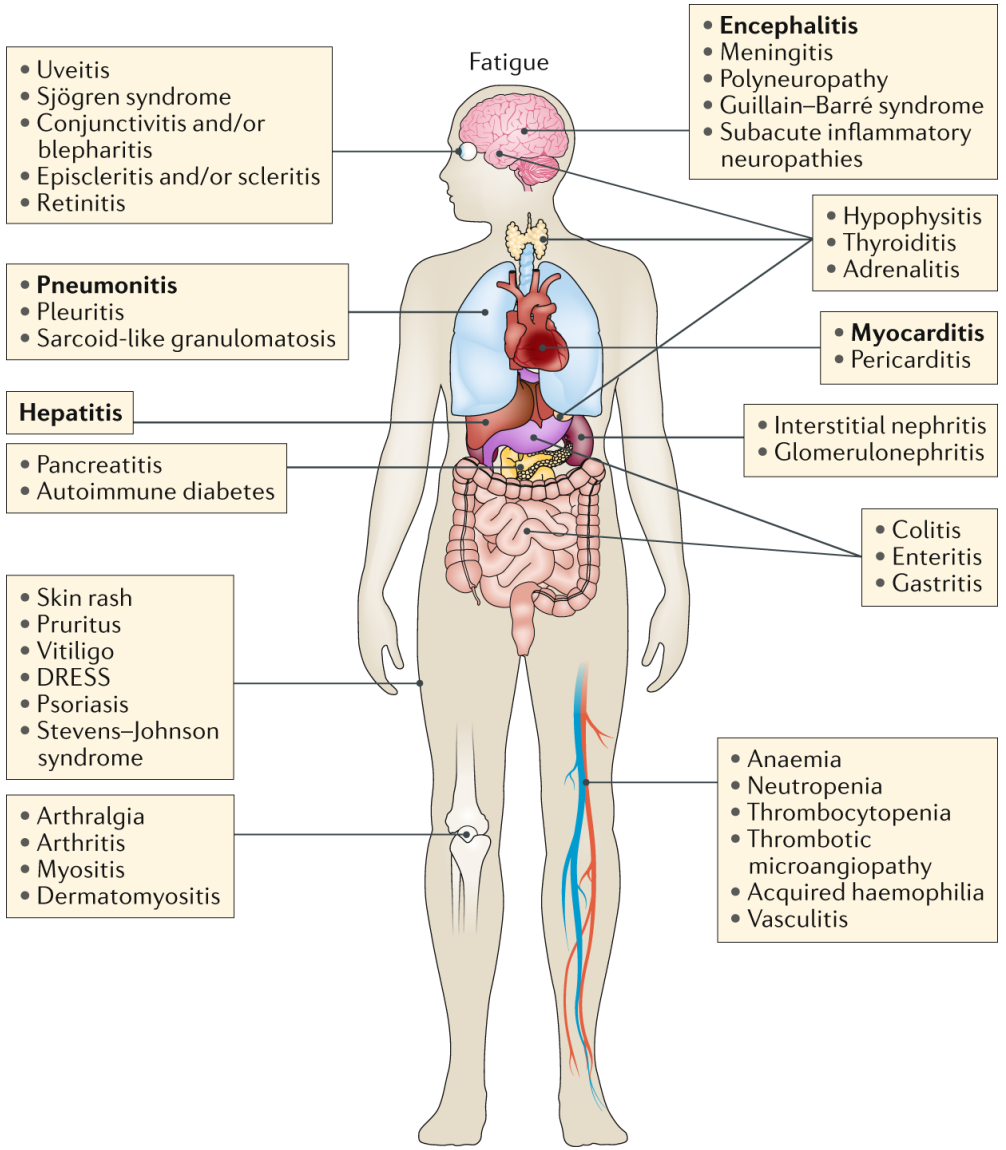
Checkpoint Inhibitors



Mechanism of Action



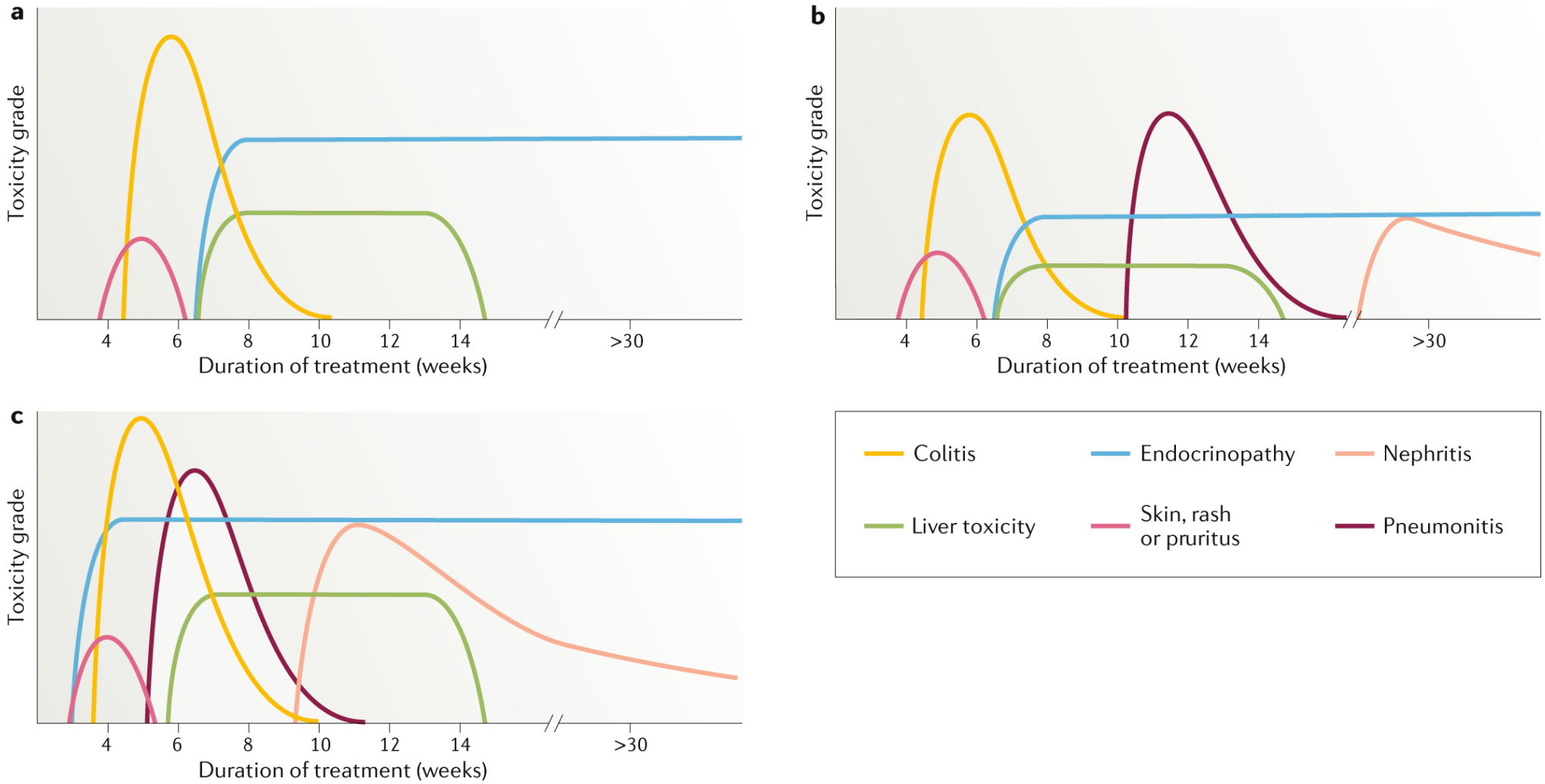
Immune-Mediated Adverse Events



Immune-Mediated Adverse Events

System	Type of irAE	Incidence	Weeks to occurrence
Dermatological	Skin rash/pruritus	40%-60%	2-3
Gastrointestinal	Diarrhea/colitis	2%-7% (severe colitis)	6-7
	Hepatitis	5%-10%	8-12
Endocrine	Hypothyroidism	6%	4-6
	Hypophysitis	0.1%-6%	8-9
Pulmonary	Pneumonitis	5%	12

Immune-Mediated Adverse Events



Management of Toxicities

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Management of Immunotherapy-Related Toxicities

Version 2.2021 — March 26, 2021

NCCN.org

Continue

Monitoring

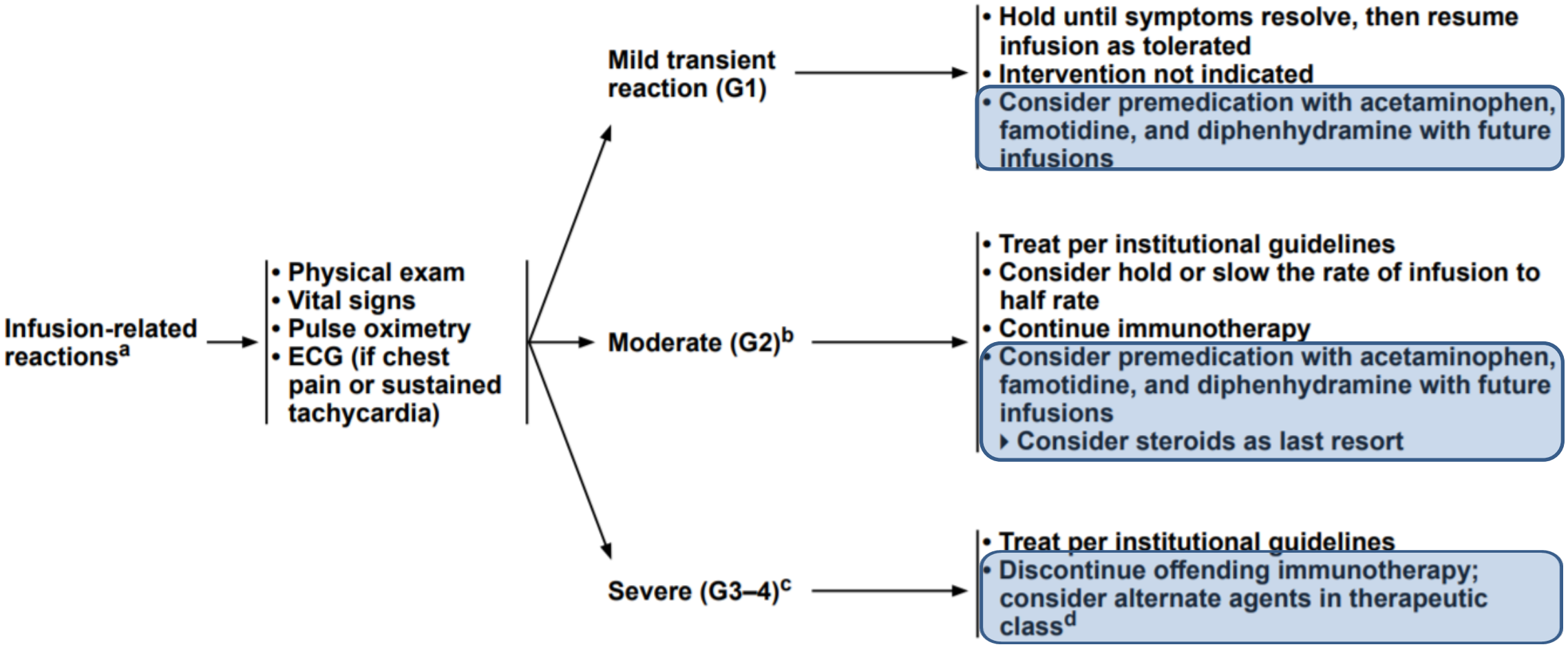
PRINCIPLES OF ROUTINE MONITORING FOR IMMUNE-CHECKPOINT INHIBITORS

Pre-Therapy Assessment[a]	Monitoring Frequency[b]	Evaluation for Abnormal Findings/Symptoms
Clinical • Physical examination • Comprehensive patient history of any autoimmune/organ-specific disease, endocrinopathy, or infectious disease • Neurologic examination • Bowel habits (typical frequency/consistency) • Infectious disease screening (HIV; hepatitis A, B, C) as indicated	Clinical exam at each visit with adverse event (AE) symptom assessment	Follow-up testing based on findings, symptoms
Imaging • Cross-sectional imaging • Brain MRI if indicated	Periodic imaging as indicated	Follow-up testing as indicated based on imaging findings
General bloodwork • CBC (with differential if indicated) • Comprehensive metabolic panel	Repeat prior to each treatment or every 4 weeks during immunotherapy, then in 6–12 weeks or as indicated	HbA1c for elevated glucose
Dermatologic (ICI_DERM-1) • Examination of skin and mucosa if history of immune-related skin disorder	Conduct/repeat as needed based on symptoms	Monitor affected BSA and lesion type; photographic documentation. Skin biopsy if indicated.
Pancreatic (ICI_ENDO-1) • Baseline testing is not required	No routine monitoring needed if asymptomatic	Amylase, lipase, and consider abdominal CT with contrast or MRCP for suspected pancreatitis
Thyroid (ICI_ENDO-2) • Thyroid-stimulating hormone (TSH), free thyroxine (T4)[c]	Every 4–6 weeks during immunotherapy, then follow-up every 12 weeks as indicated	Total T3 and free T4 if abnormal thyroid function suspected.
Pituitary/Adrenal (ICI_ENDO-3) • Consider serum cortisol (morning preferred) and thyroid function as above	Repeat prior to each treatment or every 4 weeks during immunotherapy, then follow-up every 6–12 weeks as indicated	Luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (males), estradiol (females), adrenocorticotropic hormone (ACTH), and serum cortisol
Pulmonary (ICI_PULM-1) • Oxygen saturation (resting and with ambulation) • Consider pulmonary function tests (PFTs) with diffusion capacity for high-risk patients (eg, interstitial lung disease on imaging, COPD, previous suspected treatment-related lung toxicity)	Repeat oxygen saturation tests based on symptoms	Chest CT with contrast to evaluate for pneumonitis, biopsy, or bronchoscopy with bronchoalveolar lavage (BAL) if needed to exclude other causes.
Cardiovascular (ICI_CARDIO-1) • Consider baseline ECG • Individualized assessment in consultation with cardiology as indicated	Consider periodic testing for those with abnormal baseline or symptoms	Individualized follow-up in consultation with cardiology as indicated
Musculoskeletal (ICI_MS-1) • Joint examination/functional assessment as needed for patients with pre-existing disease	No routine monitoring needed if asymptomatic	Consider rheumatology referral. Depending on clinical situation, consider C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or creatine phosphokinase (CPK)

[a] Prior to initiating treatment, counsel patients and caregivers on the warning signs and symptoms of immune-related adverse events (irAEs). See Principles of Immunotherapy Patient Education (IMMUNO-B). For disease-specific COVID-19 recommendations, see the NCCN COVID-19 Resource page.

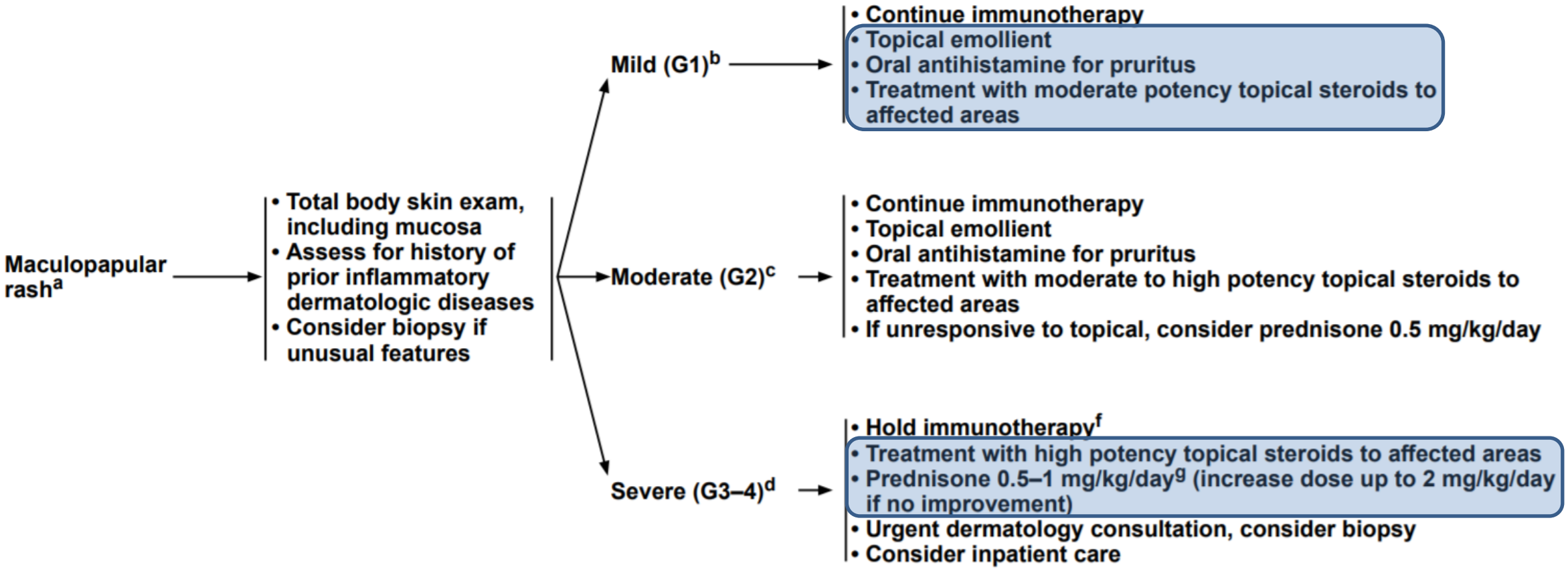
[b] Closer monitoring may be required for patients with combination immunotherapy regimens. Refer to prescribing information for each individual immunotherapy agent for monitoring recommendations.

Infusion-Related Reactions

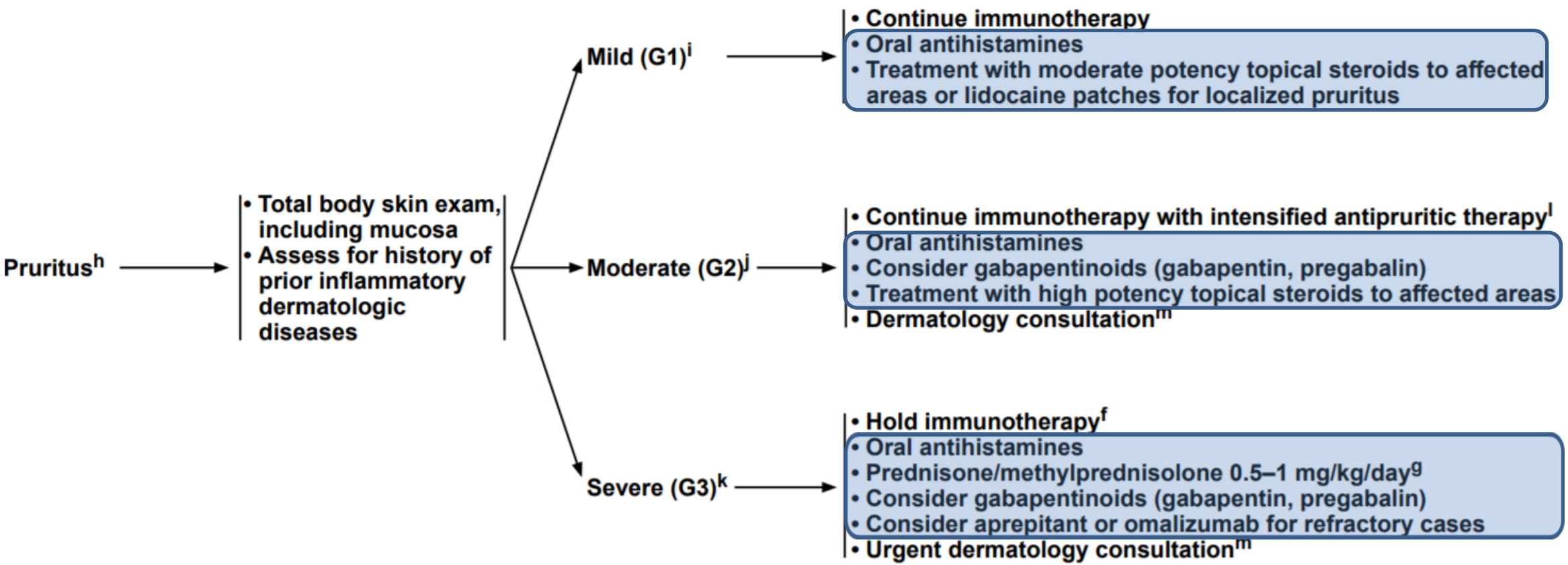


[d] If infusion reactions that are resistant to standard therapy occur in patients receiving PD-L1 inhibitors, consider switching to a PD-1 inhibitor for subsequent treatments. There are no data to guide the use of alternate immune checkpoint inhibitors (ICIs).

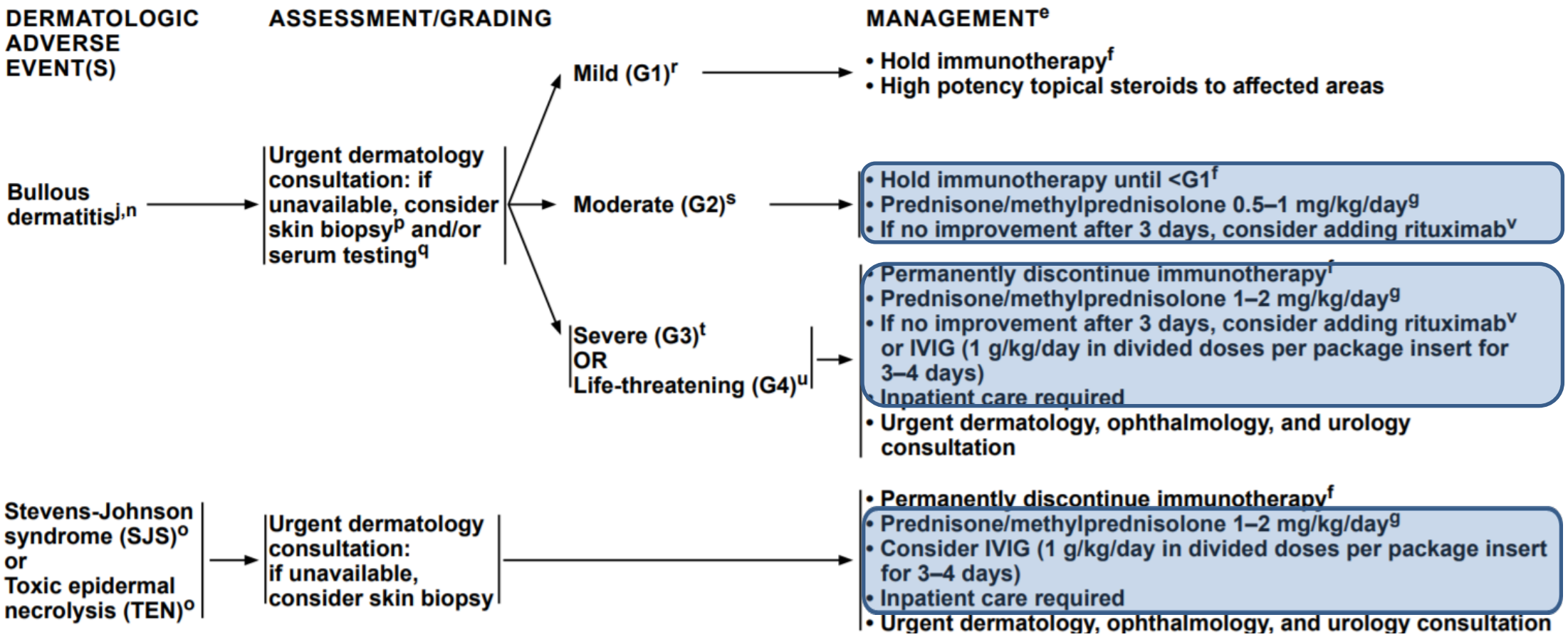
Maculopapular Rash



Pruritus


Pruritus[h]
• Total body skin exam, including mucosa
• Assess for history of prior inflammatory dermatologic diseases
Mild (G1)[i]
• Continue immunotherapy
• Oral antihistamines
• Treatment with moderate potency topical steroids to affected areas or lidocaine patches for localized pruritus
Moderate (G2)[j]
• Continue immunotherapy with intensified antipruritic therapy[l]
• Oral antihistamines
• Consider gabapentinoids (gabapentin, pregabalin)
• Treatment with high potency topical steroids to affected areas
• Dermatology consultation[m]
Severe (G3)[k]
• Hold immunotherapy[f]
• Oral antihistamines
• Prednisone/methylprednisolone 0.5–1 mg/kg/day[g]
• Consider gabapentinoids (gabapentin, pregabalin)
• Consider aprepitant or omalizumab for refractory cases
• Urgent dermatology consultation[m]

Dermatitis and SJS



Gastrointestinal Effects

ADVERSE EVENT(S)

- Diarrhea
- Colitis[a]

→

- Stool evaluation to rule out infectious etiology[b]
  - Nucleic acid amplification tests (NAATs) for GI pathogens/bacterial culture
  - *C. difficile*
  - Ova & parasites; molecular testing for *Giardia* and *Cryptosporidium* spp and *E. histolytica*; consider microsporidia, *Cyclospora/isospora* spp
  - Viral pathogens testing when available
  - Based on institutional availability, consider lactoferrin/calprotectin[c]
- Infectious disease screening (HIV; hepatitis A, B, C) as clinically indicated
- Consider abdominal/pelvic CT with contrast if G2–G4 colitis[a]
- Consider GI consultation if G2–G4
  - Colonoscopy or flexible sigmoidoscopy ± esophagogastroduodenoscopy (EGD) with biopsy[c]

Mild (G1)[d] →

- Consider holding immunotherapy[i]
- Loperamide or diphenoxylate/atropine for 2–3 days
  - If no improvement and not already done, obtain labs for infectious workup
- Hydration
- Close monitoring[j]
- If persistent or progressive symptoms, check lactoferrin/calprotectin[k]
  - If positive, treat as G2 (below)
  - If negative and no infection, continue G1 management and add mesalamine, cholestyramine

Moderate (G2)[e,f] →

- Hold immunotherapy[i]
- Prednisone/methylprednisolone[l] (1–2 mg/kg/day)[m]
- No response in 2–3 days, continue steroids, consider adding infliximab[n,o,p] or vedolizumab[p] within 2 weeks[q]

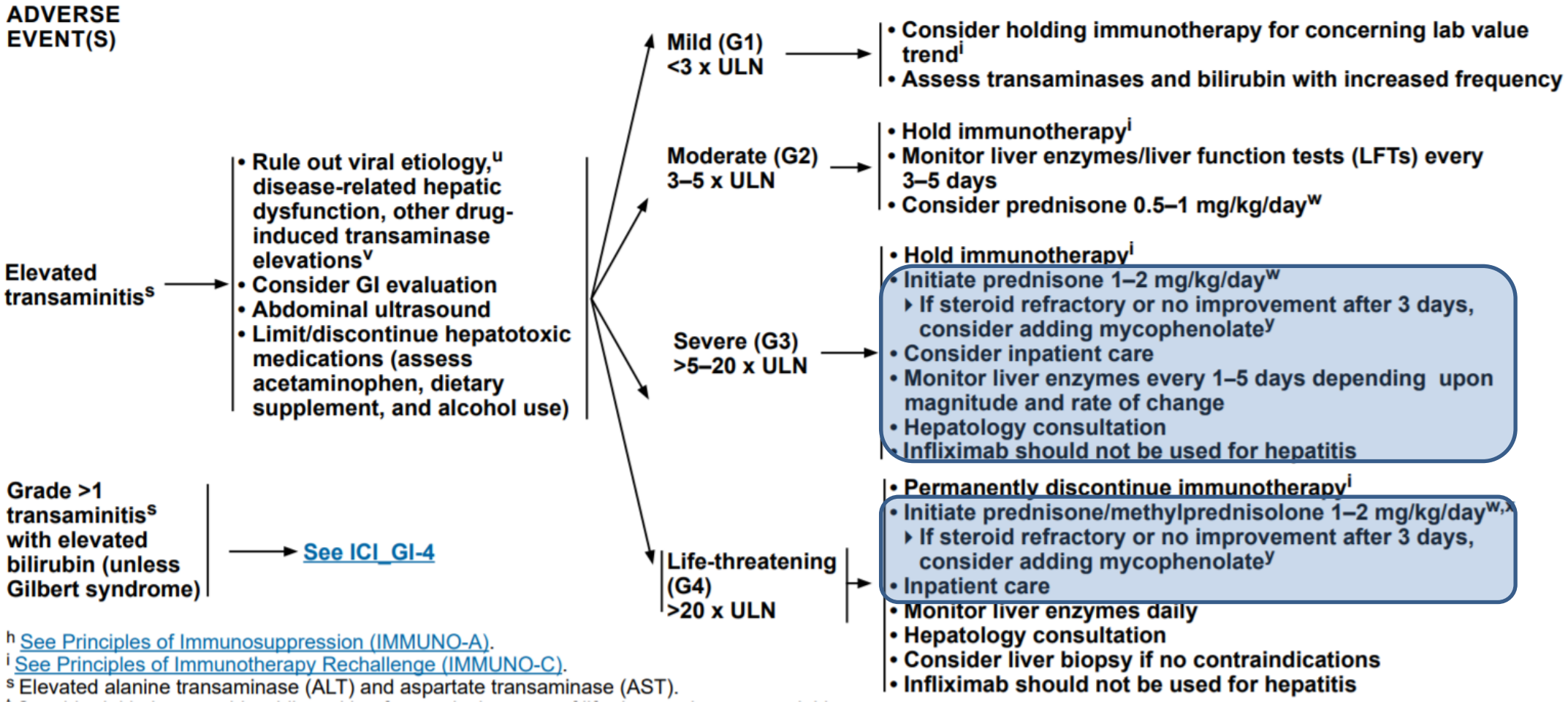
Severe (G3–4)[g] → See ICI_GI-2

Severe (G3–4)[g] diarrhea or colitis →

- G3: Discontinue anti-CTLA-4; consider resuming anti-PD-1/PD-L1 after resolution of toxicity[i]
- G4: Permanently discontinue immunotherapy agent responsible for toxicity[i]
- Consider inpatient care for provision of supportive care
- Intravenous (IV) methylprednisolone[l] (1–2 mg/kg/day)[m]
  - No response in 1–2 days, continue steroids, strongly consider adding infliximab[n,o,p] or vedolizumab[p,q,r]

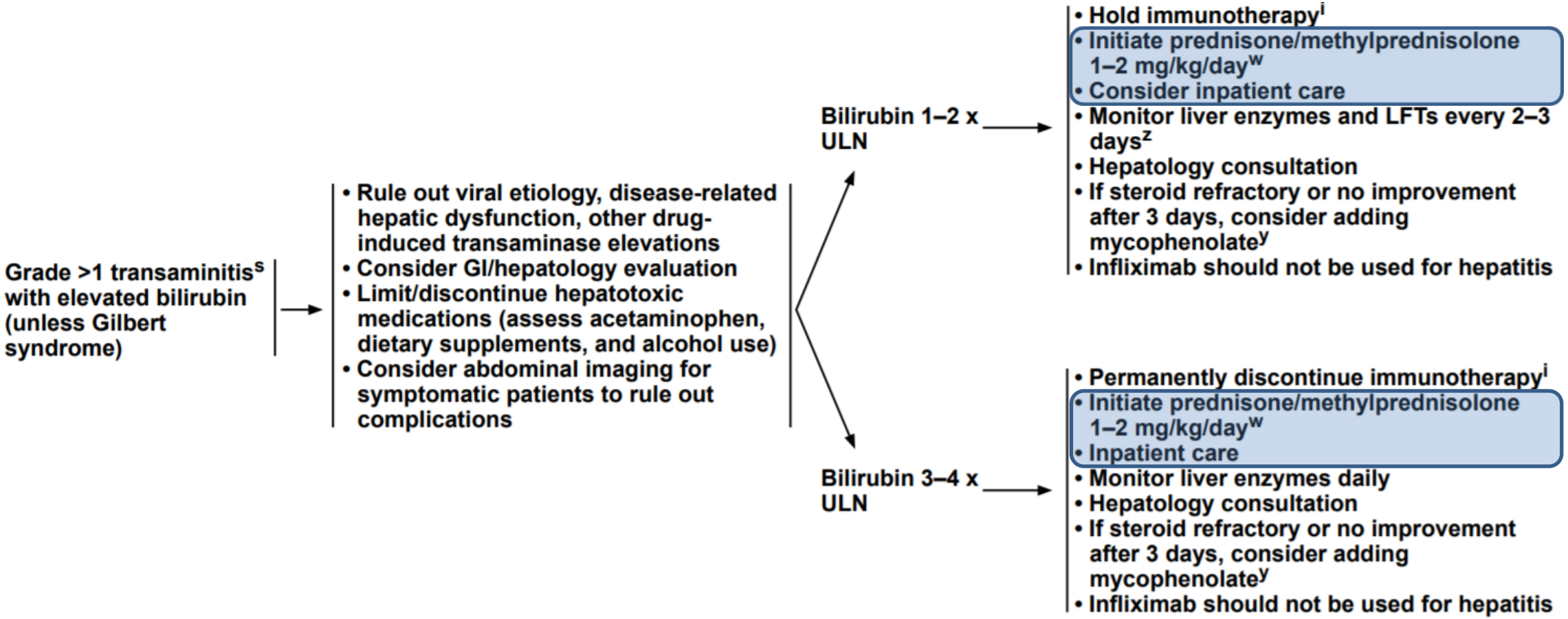
Consider tofacitinib for infliximab/ vedolizumab refractory colitis

Hepatic Effects

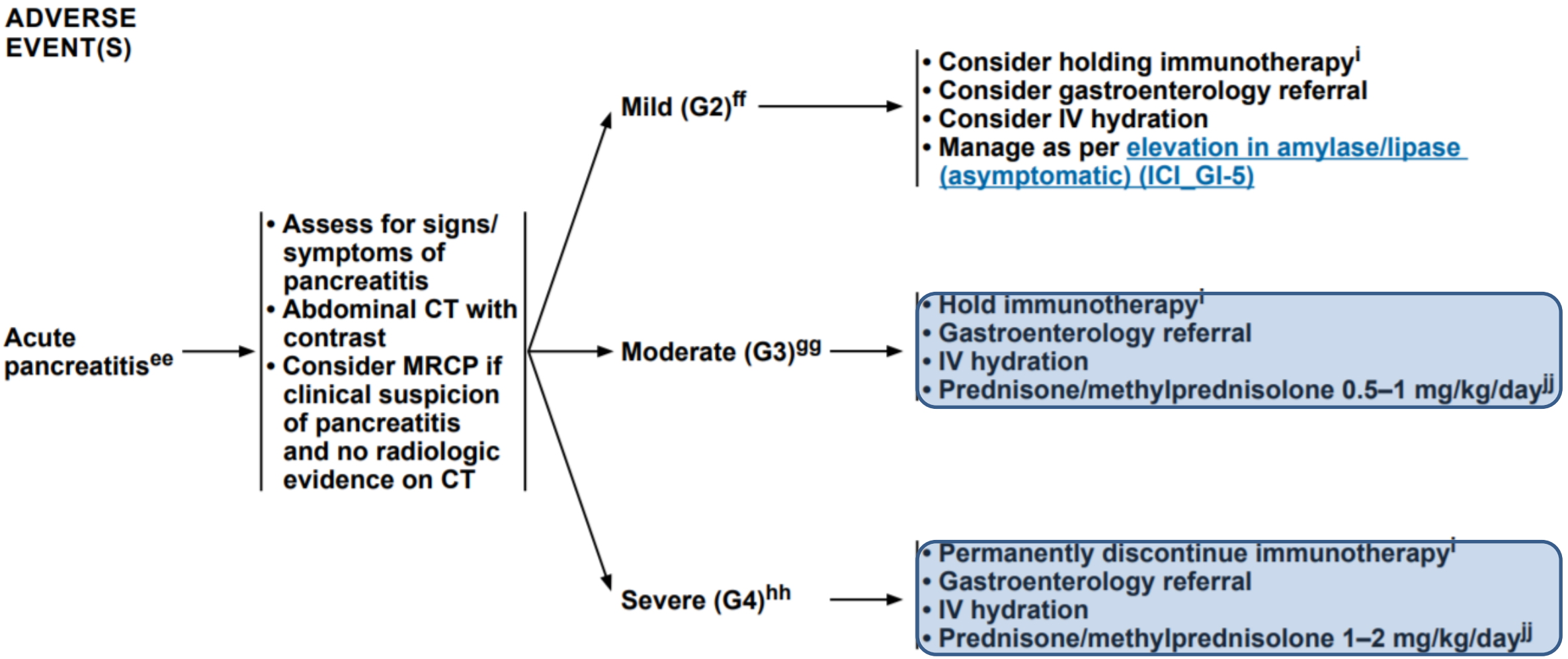


[h] See Principles of Immunosuppression (IMMUNO-A).
[i] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[s] Elevated alanine transaminase (ALT) and aspartate transaminase (AST).

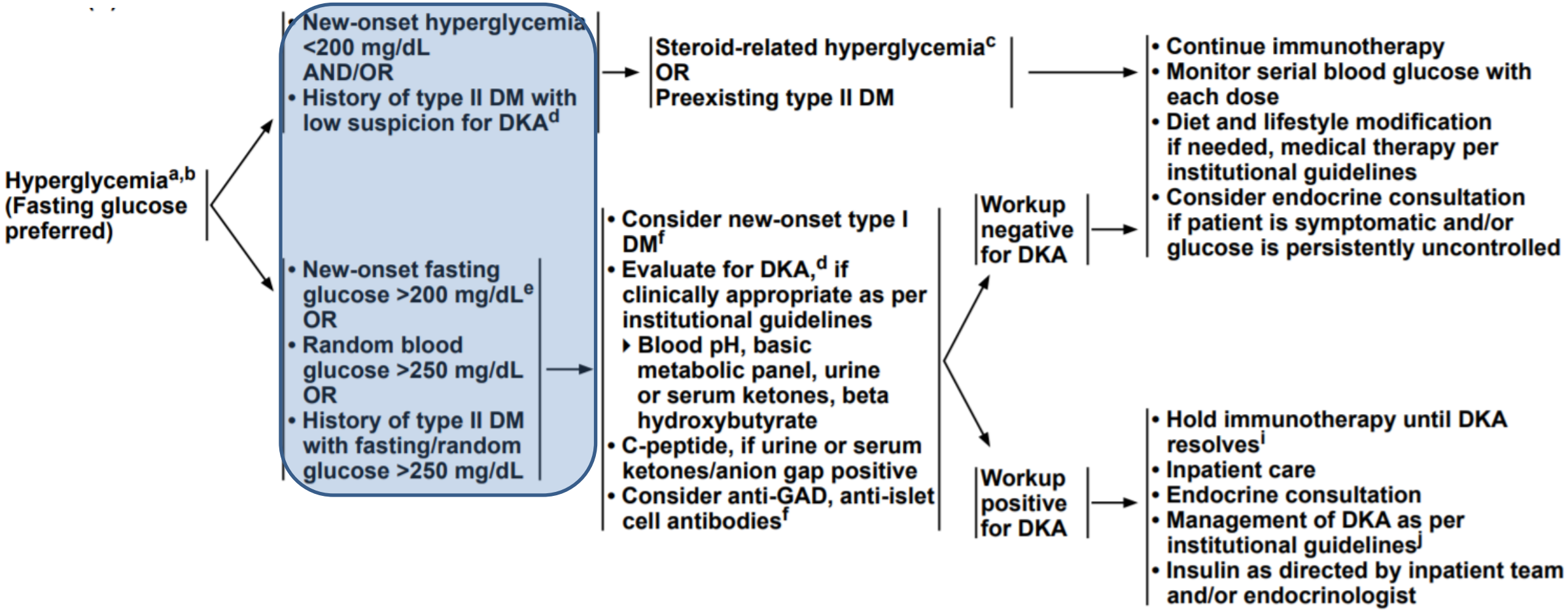
Hepatic Effects



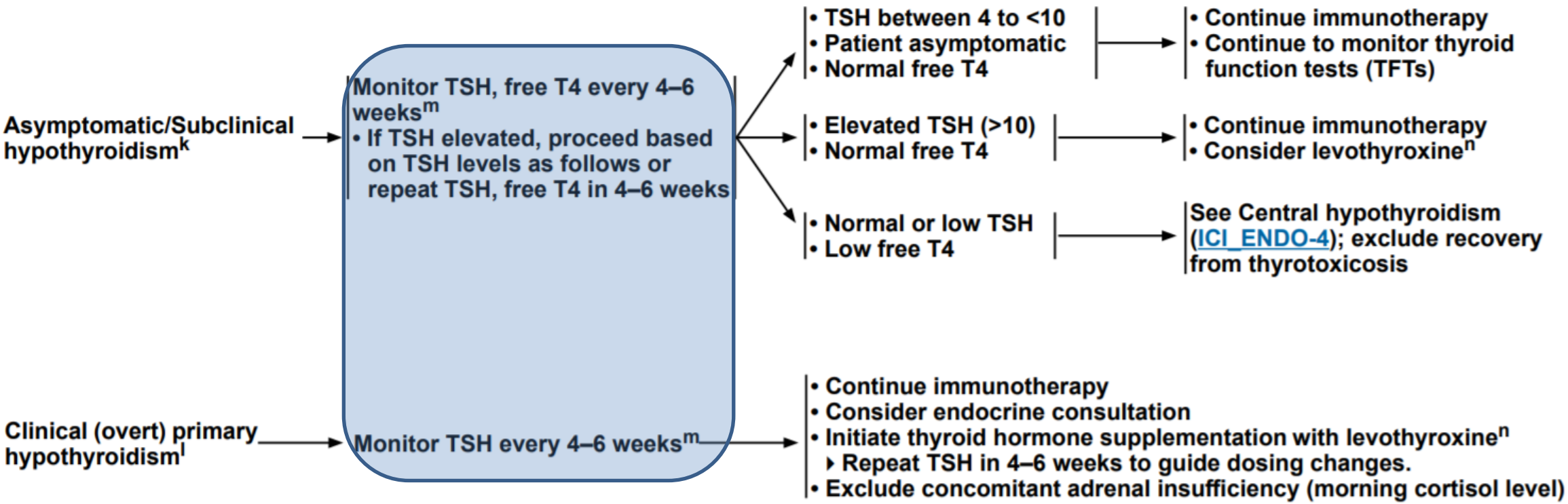
Pancreatic Effects



Endocrine Effects

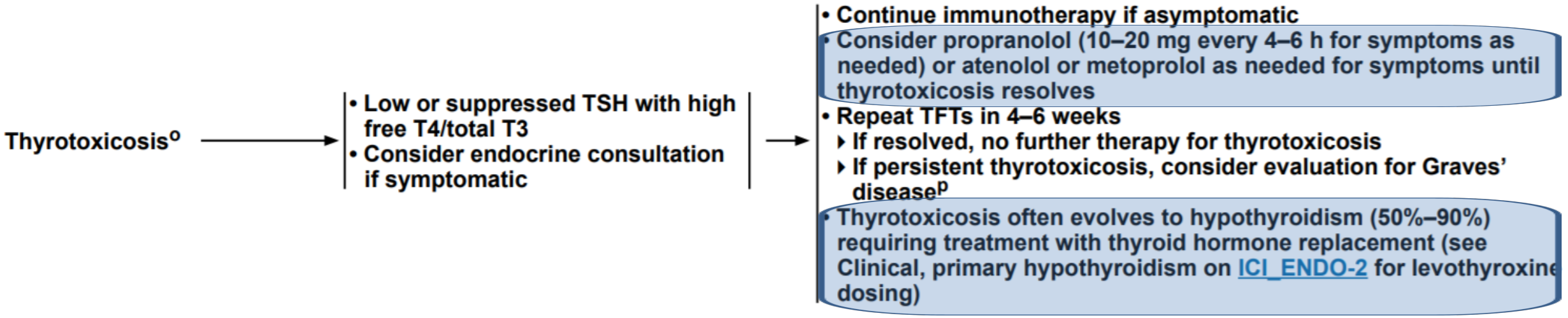


Endocrine Effects



- Patients without baseline abnormalities or asymptomatic can be monitored every 12-18 weeks
- Levothyroxine dosing: 1.6 mcg/kg daily orally
- Reduce dose by 10% in elderly populations or patients w comorbidities (CAD, etc)
- Can also consider starting dose 50 – 100 mcg/day for elderly or sensitive populations

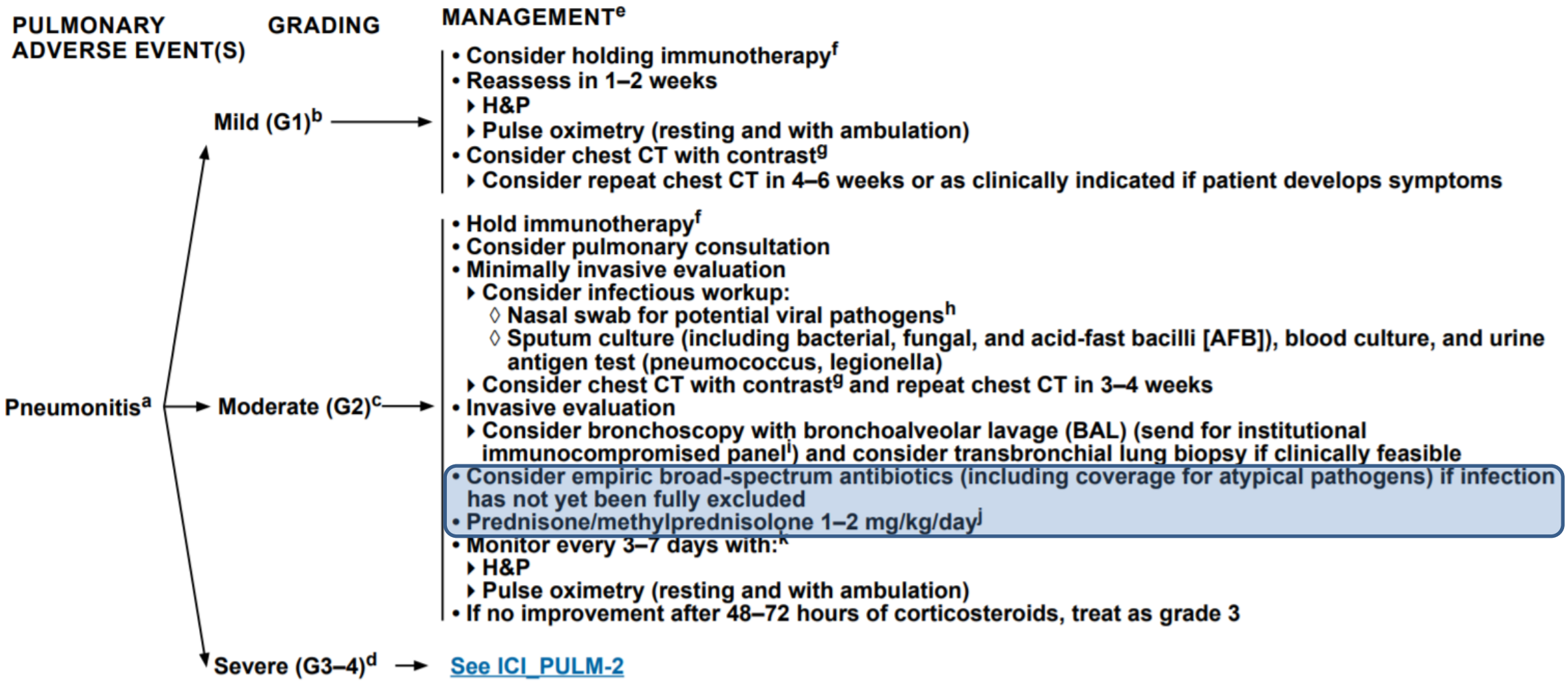
Endocrine Effects



Endocrine Effects

ENDOCRINE ADVERSE EVENT(S)	ASSESSMENT	MANAGEMENT
Hypophysitis[q]	• Evaluate[q,r] ▸ Morning cortisol and ACTH ▸ TSH, free T4 ▸ LH, FSH, testosterone (men), estrogen (premenopausal women) • MRI brain ± contrast with pituitary/ sellar cuts, if symptomatic[s]	• Endocrine consultation • Hold immunotherapy until acute symptoms resolve and hormone replacement initiated[i] • If acute severe symptoms with concern for mass effect, may carefully consider high-dose steroids[t] • Treat with hormone replacement as indicated[u,v,w] ▸ Secondary adrenal insufficiency (low ACTH, low cortisol) ◊ steroid replacement[u] ◊ alert bracelet recommended ◊ patient education for stress dosing with illness, surgery, infection, etc ▸ Central hypothyroidism (low TSH, low FT4) ◊ thyroid hormone replacement[v] ◊ follow free T4 level for thyroid hormone dose titration
Primary adrenal insufficiency (high ACTH with low morning cortisol, abnormal cosyntropin stimulation test)	• Rare diagnosis that is not usually associated with checkpoint immunotherapy • If concern for this diagnosis, recommend endocrine consultation	

Pulmonary Effects



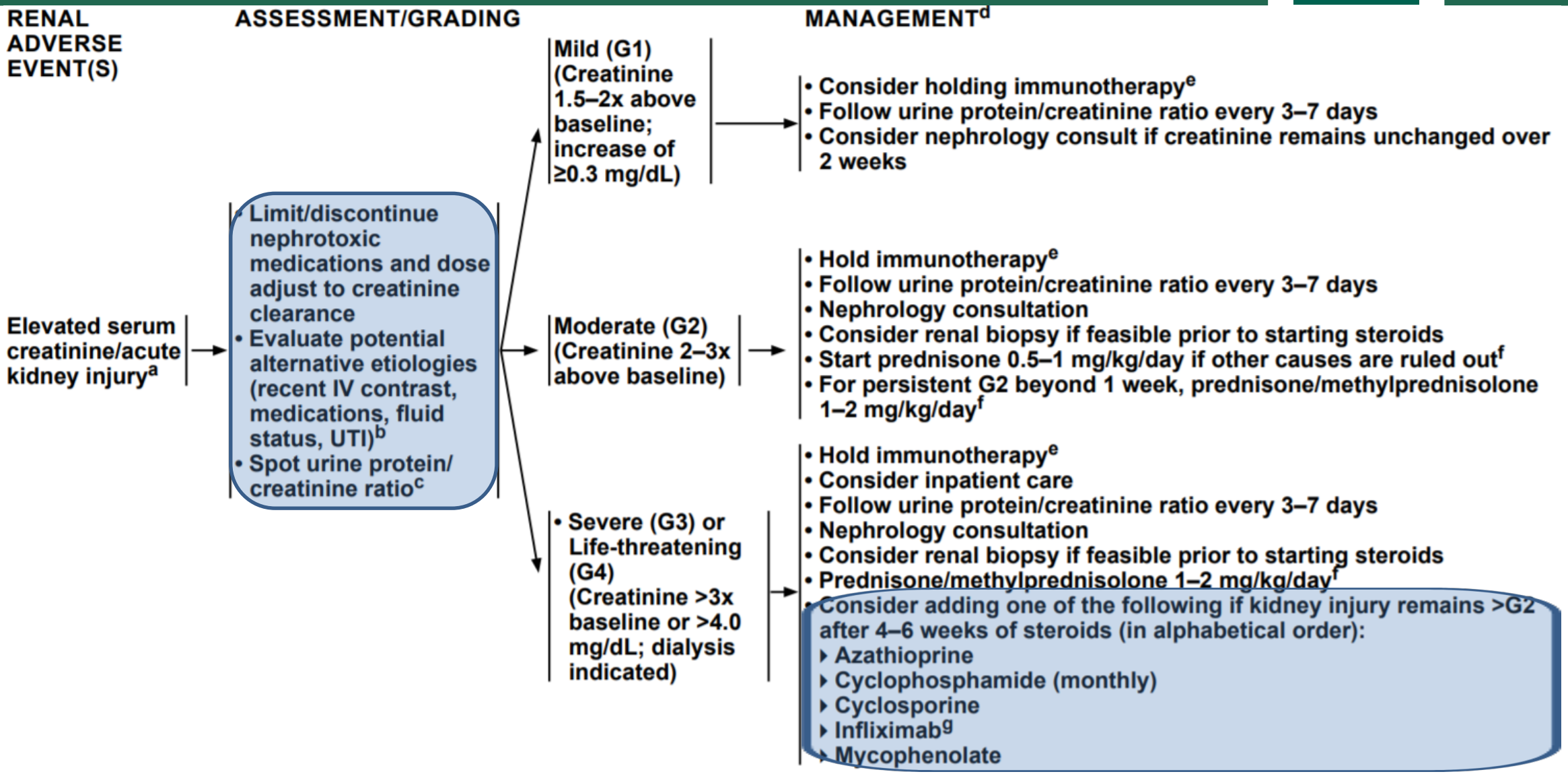
Pulmonary Effects

Severe (G3–4)[d] pneumonitis[a] →

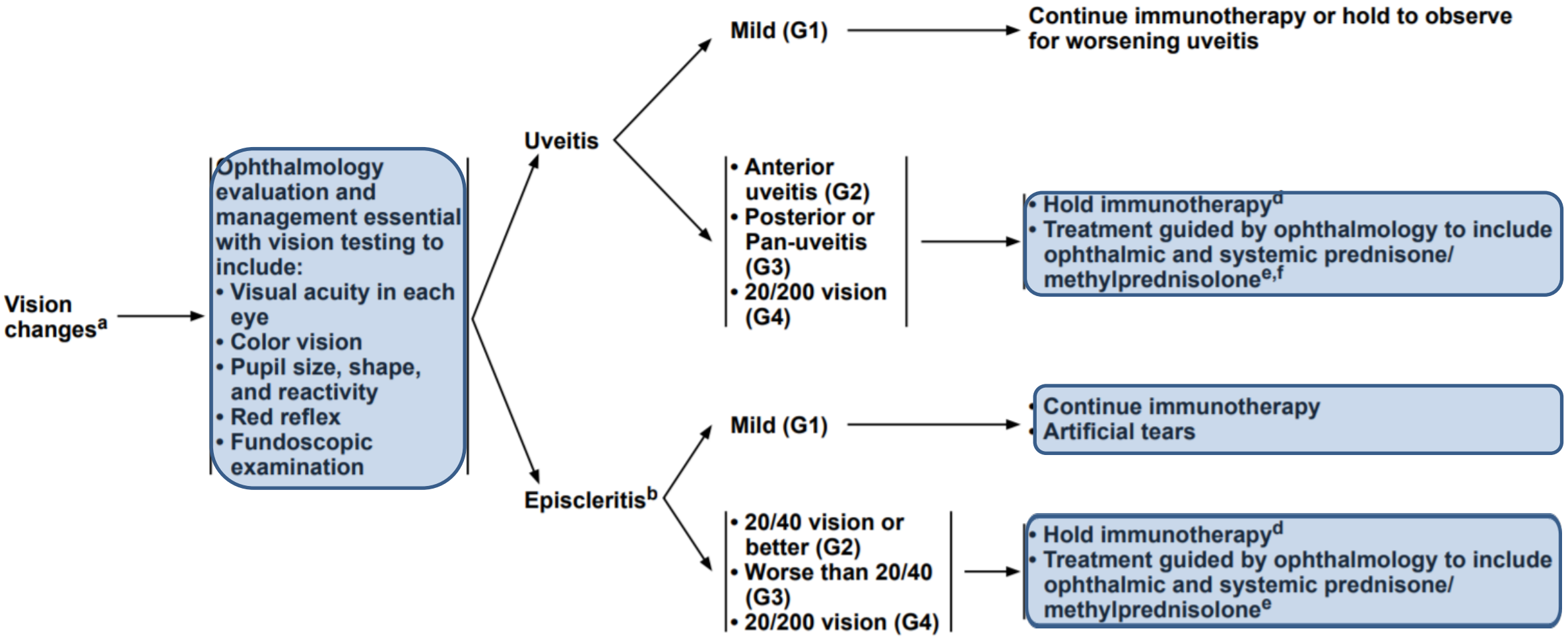
- Permanently discontinue immunotherapy[f]
- Inpatient care
- Pulmonary and infectious disease consultation
- Minimally invasive evaluation
  - Infectious workup:
  - Consider that patient may be immunocompromised
    - ◊ Nasal swab for potential viral pathogens[h]
    - ◊ Sputum culture (including bacterial, fungal, and AFB), blood culture, and urine antigen test (pneumococcus, legionella)
    - ◊ Consider cardiac evaluation to exclude cardiac causes for clinical presentation
- Invasive evaluation
  - Bronchoscopy with BAL (send for institutional immunocompromised panel[i]) if feasible to rule out infection and malignant lung infiltration and consider transbronchial lung biopsy if feasible and clinically indicated
- Consider empiric broad-spectrum antibiotics (including coverage for atypical pathogens) if infection has not yet been fully excluded
- Methylprednisolone 1–2 mg/kg/day. Assess response within 48 hours and plan taper over ≥6 weeks[e]
- Consider adding any of the following if no improvement after 48 hours:[l]
  - Infliximab[m] 5 mg/kg IV, a second dose may be repeated 14 days later at the discretion of the treating provider
  - IVIG[n]
  - Mycophenolate mofetil 1–1.5g BID then taper in consultation with pulmonary service

IVIG Dosing: 2 grams/kg administered in daily divided doses over 2 – 5 days

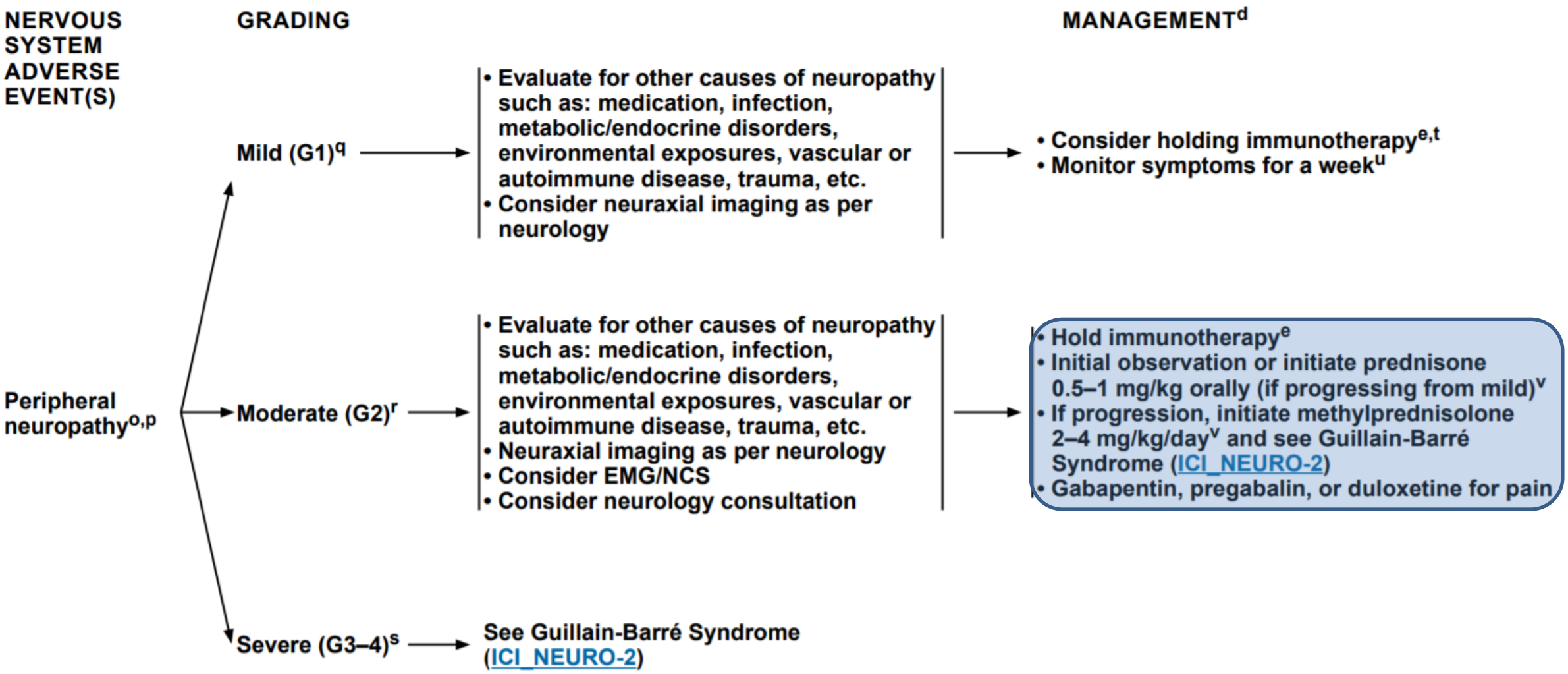
Renal Effects



Ocular Effects



Peripheral Neuropathy



Neurological Effects

Aseptic meningitis[w,x]

- MRI brain with and without contrast + pituitary protocol
- Consider lumbar puncture[z] if feasible
- Consider neurology consultation

→

- Hold immunotherapy[e] if mild/moderate
- Permanently discontinue immunotherapy if severe
- Inpatient care (G3–4[cc])
- Consider IV acyclovir[ee] until polymerase chain reaction (PCR) results obtained
- Rule out bacterial and viral infection, then may closely monitor off steroids or consider prednisone 0.5–1 mg/kg/day or methylprednisolone 1–2 mg/kg/day if moderate/severe symptoms[dd]

Encephalitis[x,y]

- Neurology consultation
- MRI brain with and without contrast[aa]
- Lumbar puncture[bb]
- Electroencephalogram (EEG) to evaluate for subclinical seizures
- CMP, CBC, ESR, CRP, antineutrophil cytoplasmic antibody (ANCA) (if vasculitic process suspected), thyroid panel including TPO and thyroglobulin
- Autoimmune encephalopathy and paraneoplastic panel in CSF and serum

→

- Hold immunotherapy[e] if mild
- Permanently discontinue immunotherapy if moderate/severe
- Inpatient care (G3–4[cc])
- Consider IV acyclovir[ee] until PCR results obtained
- Trial of methylprednisolone 1–2 mg/kg/day[dd]
- If severe or progressing symptoms or oligoclonal bands present, consider pulse steroids methylprednisolone 1 g IV daily for 3–5 days plus IVIG[g] or plasmapheresis
- If positive for autoimmune encephalopathy antibody or limited or no improvement after 7–14 days, consider rituximab[h]

Transverse myelitis[ff]

- Neurology consultation
- MRI of spine and brain
- Lumbar puncture[gg]
- B_{12}, HIV, rapid plasma reagin (RPR), ANA, anti-Ro/La antibodies, TSH, aquaporin-4 IgG, paraneoplastic panel for anti-Hu and anti-CRMP5/CV2
- Evaluation for constipation and urinary retention with bladder scan

→

- Permanently discontinue immunotherapy[e]
- Inpatient care
- Methylprednisolone pulse dosing 1 g/day for 3–5 days
- Strongly consider IVIG[g] or plasmapheresis

Cardiovascular Effects

CARDIOVASCULAR SYMPTOMS/SIGNS ADVERSE EVENT(S)

Suspected myocarditis/ Pericarditis[a] →

- Ventricular arrhythmias/ tachycardia
- Heart failure
- Cardiogenic shock
- Conduction abnormalities
- Myositis/myasthenia gravis[b]
- Pericardial effusion

- Differential
  - Myocardial infarction/acute coronary syndrome
  - Vasculitis
  - COVID-19

→ **ASSESSMENT/GRADING**

- Immediate cardiology consultation (preferably cardio-oncology)
- ECG (at baseline and with any suspected CV adverse event)
- Telemetry monitoring (inpatient)/topical patch monitor (outpatient)
- Echocardiogram
- Cardiac biomarkers (troponin I or T, creatine kinase,[c] BNP or NTproBNP; lipid panel[d])
- Inflammatory biomarkers
  - Consider ESR, CRP, or other inflammatory markers
- Cardiac MRI (if possible)[e]
- Consider cardiac catheterization and/ or myocardial biopsy in a specialized center if myocarditis is suspected
- Consider viral titers (especially COVID-19)

→ **Myocarditis** →

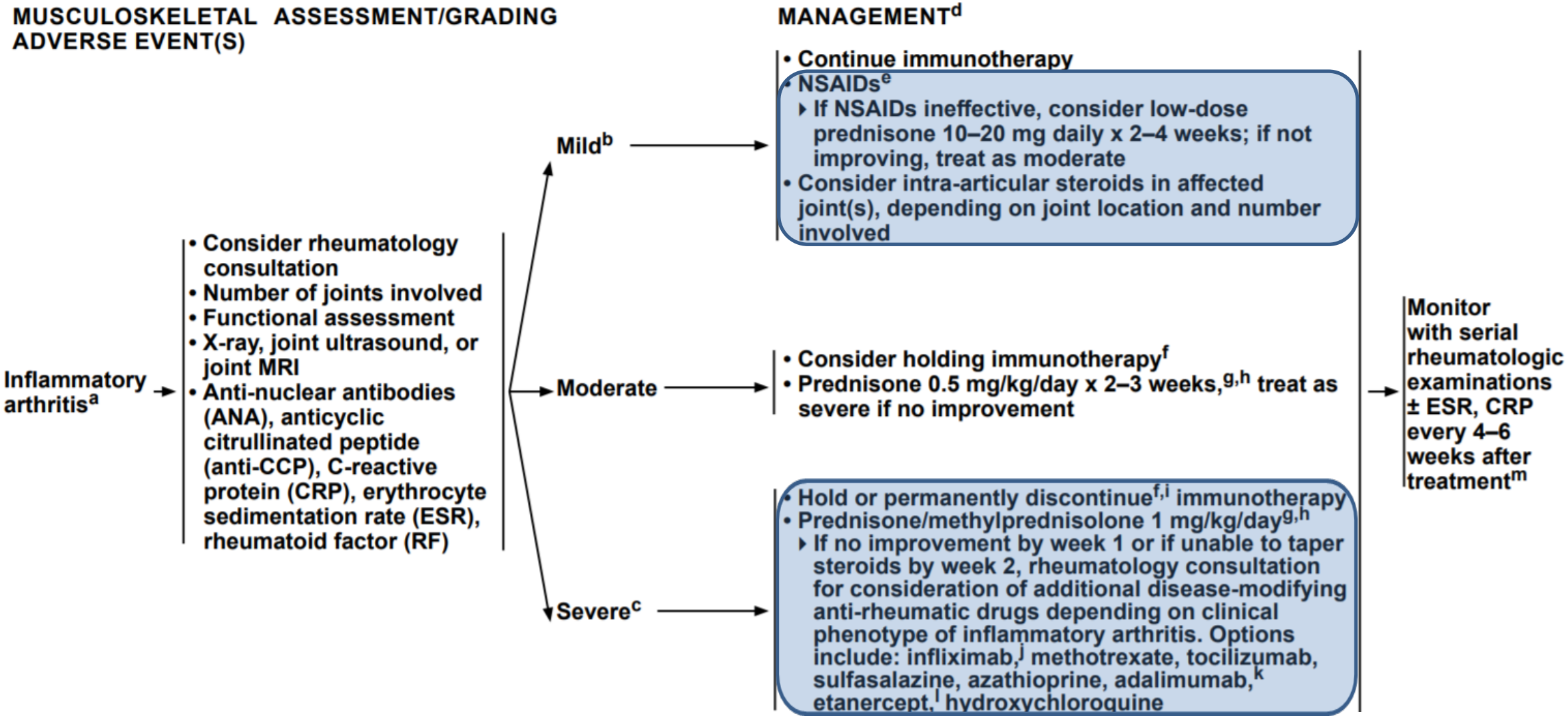
MANAGEMENT[f]

- Permanently discontinue immunotherapy[g]
- Management is tailored to response and acuity of presentation
- High-dose steroids such as methylprednisolone pulse dosing 1 g/day IV for 3–5 days
  - Switch to oral prednisone, then taper slowly over 4–6 weeks based on clinical response and improvement of biomarkers
- If no improvement within 24 hours on steroids, consider adding other potent immunosuppressive agents:
  - Abatacept
  - Mycophenolate[h]
  - Intravenous immunoglobulin (IVIG)[i]
  - Alemtuzumab
  - Infliximab[j] (use with extreme caution in patients with reduced LVEF)
  - Anti-thymocyte globulin (ATG)
- ICU-level monitoring
- Temporary or permanent pacing as required

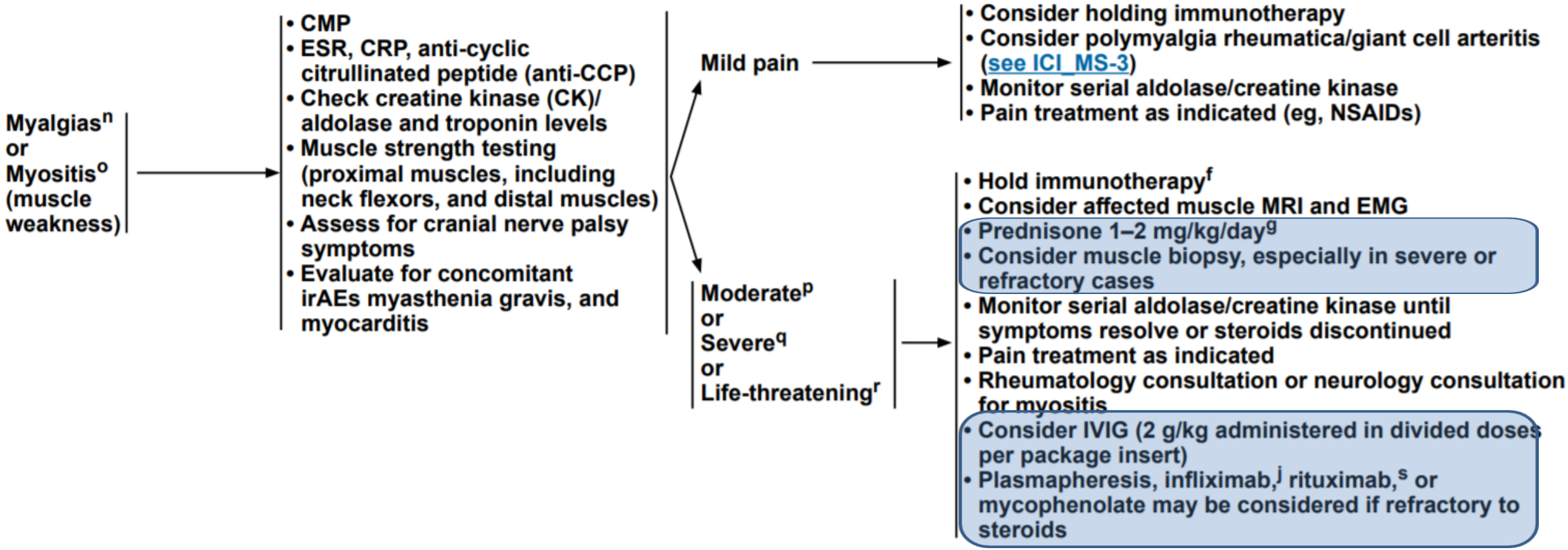
→ **Pericarditis/ Pericardial effusion** →

- Manage as per usual recommendations
- Consider myocarditis as a contributor

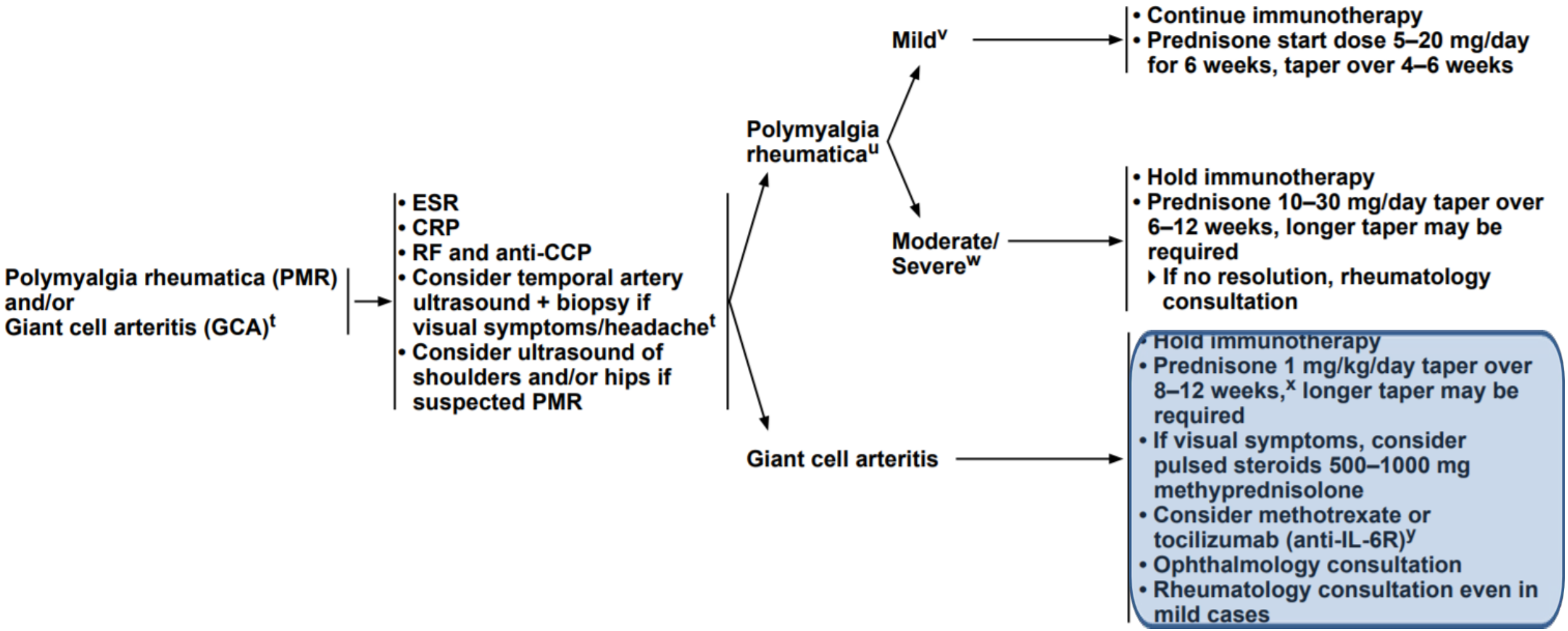
Musculoskeletal Effects



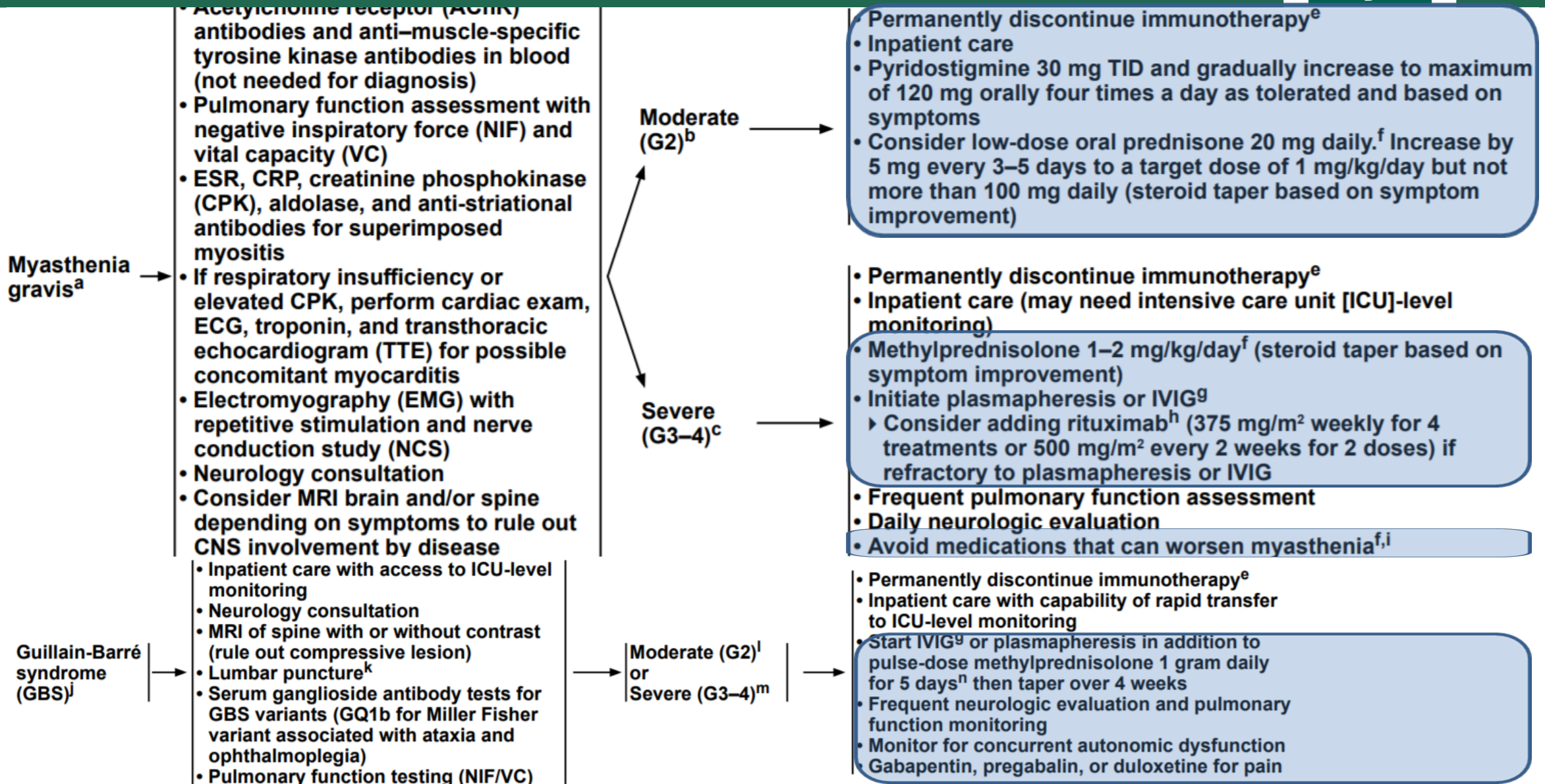
Musculoskeletal Effects



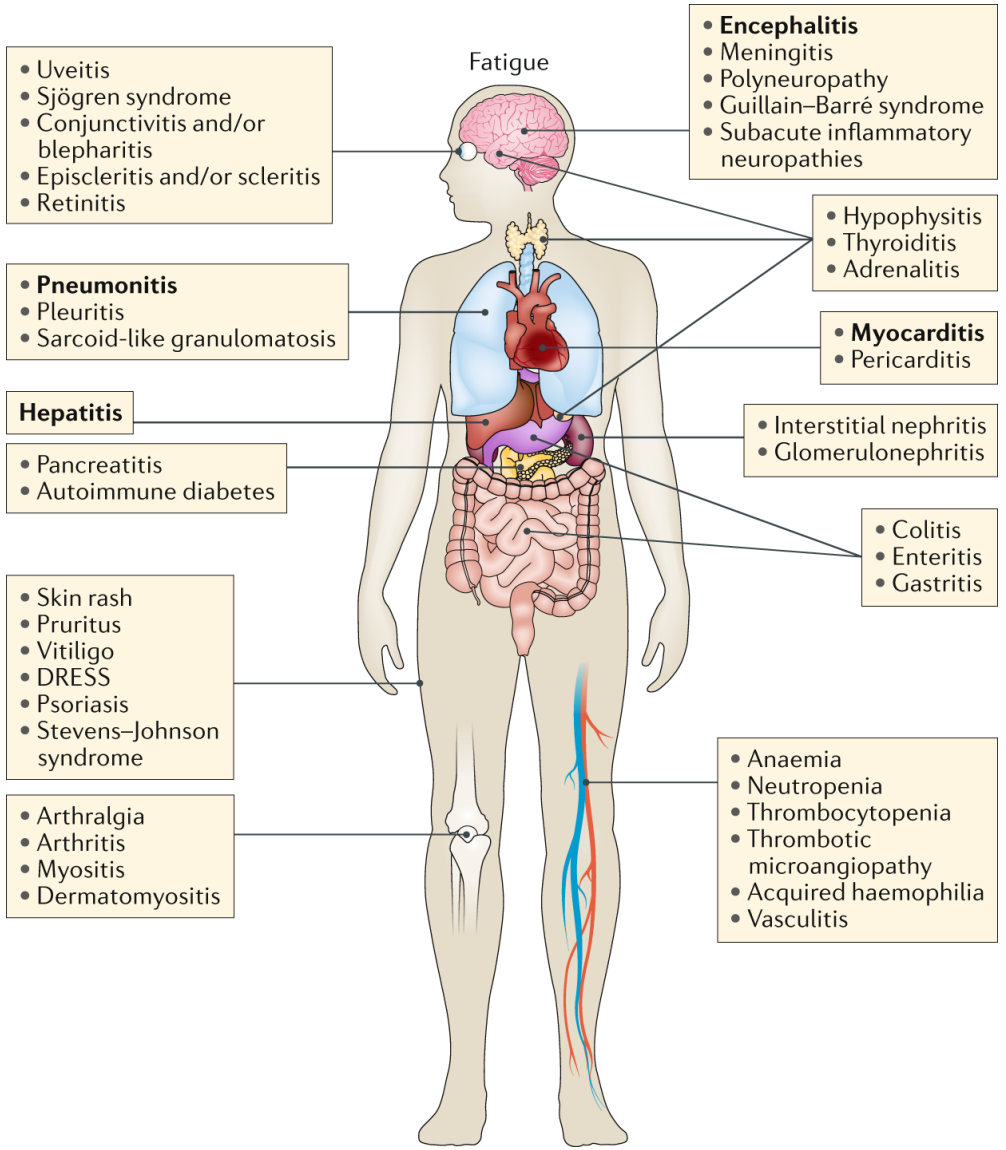
Musculoskeletal Effects



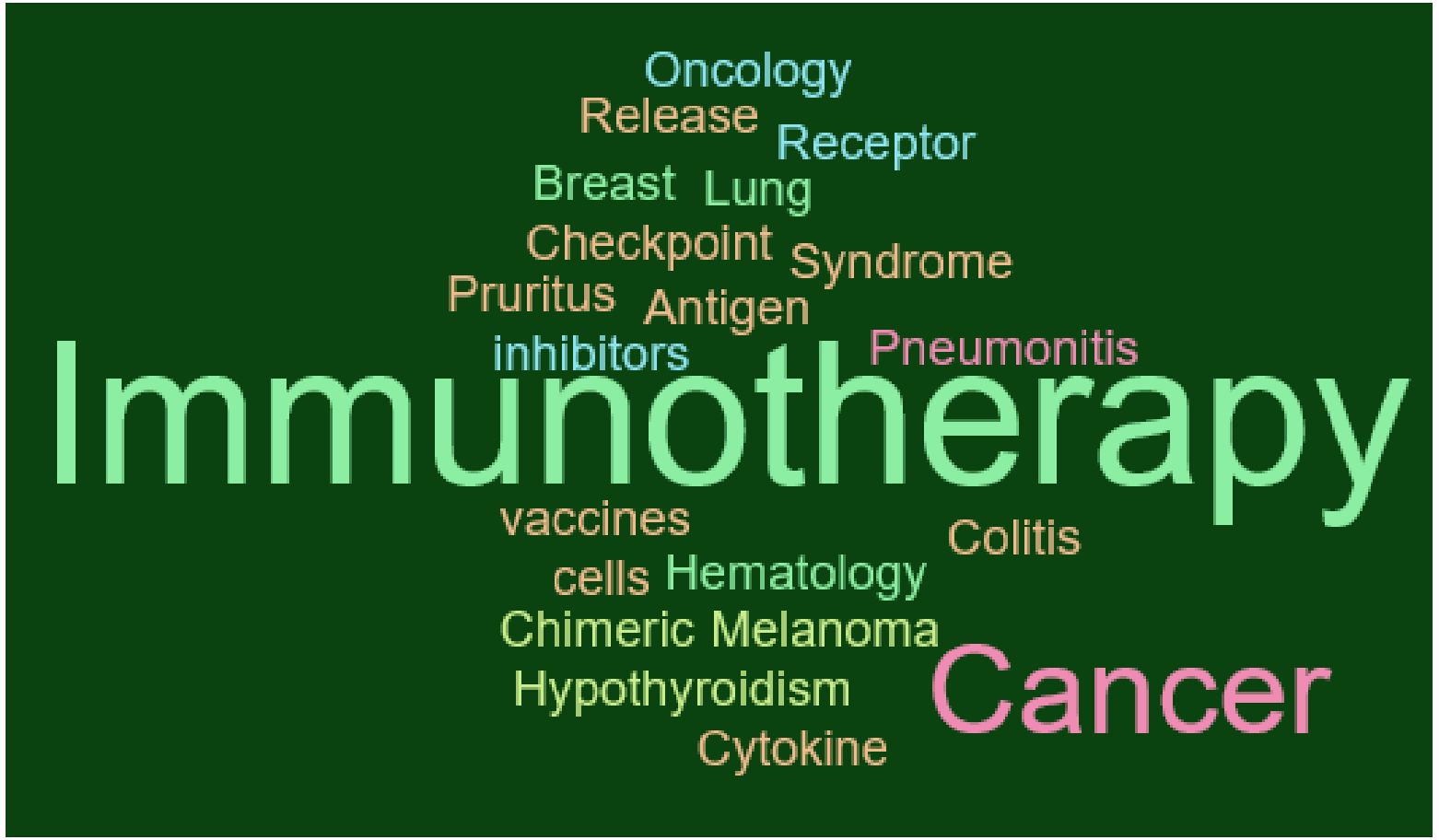
Musculoskeletal Effects



Immune-Mediated Adverse Events



Questions?


Oncology
Release
Receptor
Breast
Lung
Checkpoint
Syndrome
Pruritus
Antigen
inhibitors
Pneumonitis
Immunotherapy
vaccines
Colitis
cells
Hematology
Chimeric
Melanoma
Hypothyroidism
Cancer
Cytokine

References

- Marin-Acevedo, Julian A., et al (2019). Immune Checkpoint Inhibitor Toxicities. Mayo Clinic Proceedings, Volume 94, Issue 7, 1321 – 1329.
- Martins, F., Sofiya, L., Sykiotis, G.P. et al (2019). Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol 16, 563–580 (2019). https://doi.org/10.1038/s41571-019-0218-0
- NCCN (2021). Management of Immune Checkpoint Inhibitor-Related Toxicities. Retrieved from: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf