National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)
in partnership with the American Society of Clinical Oncology (ASCO)

Management of Immunotherapy-Related Toxicities

(Immune Checkpoint Inhibitor-Related Toxicities)

Version 1.2018 — February 14, 2018

NCCN.org

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
Management of Immunotherapy-Related Toxicities

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Discussion

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NCCN wishes to acknowledge the contributions of ASCO in supporting advisory committees for the development of the Guidelines.

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NCCN Guidelines Panel Disclosures

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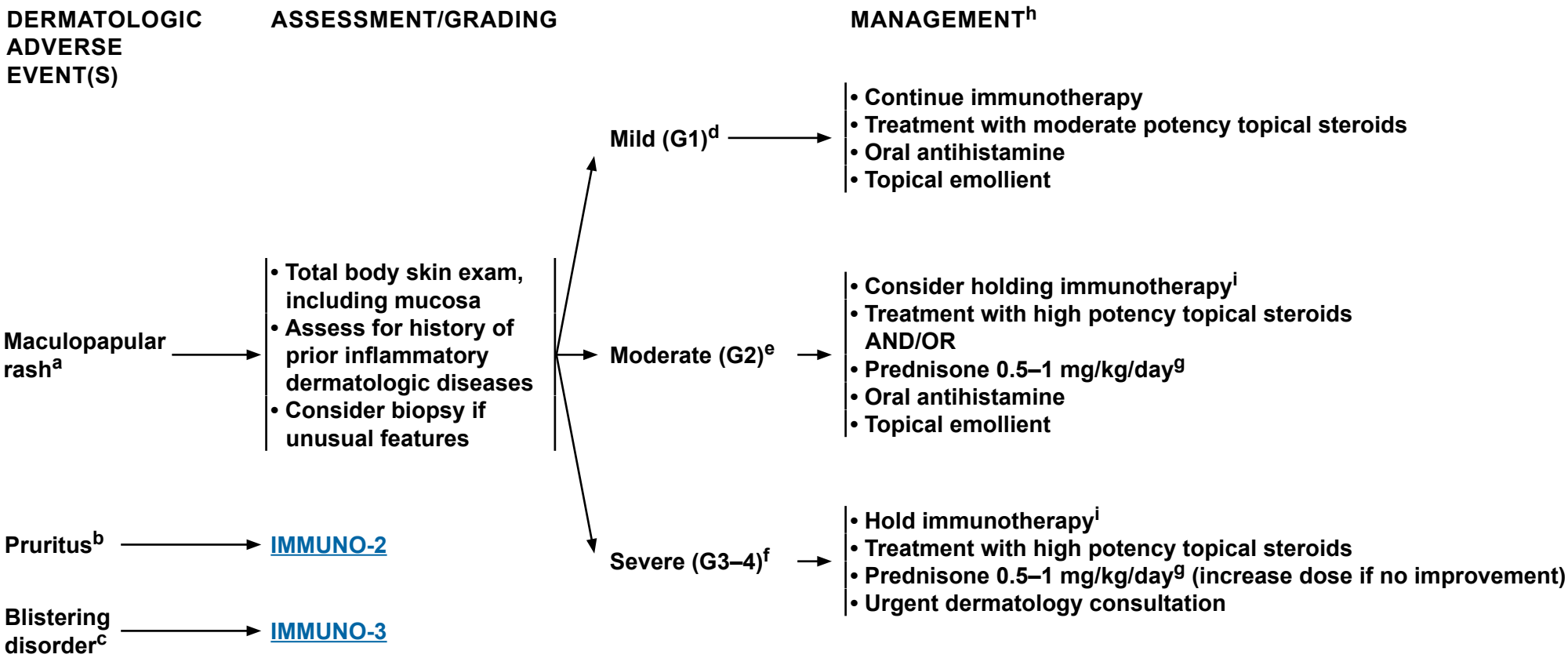
Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/clinicians.aspx.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.



[a]Characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and may be associated with pruritus.
[b]Characterized by an intense itching sensation.
[c]Characterized by inflammation of the skin and the presence of bullae, which are filled with fluid.
[d]Macules/papules covering <10% body surface area (BSA) with or without symptoms (eg, pruritus, burning, tightness).
[e]Macules/papules covering 10%–30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental activities of daily living (ADLs).
[f] Macules/papules covering >30% BSA with or without associated symptoms; limiting self-care ADLs.
[g]Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h]See Principles of Immunosuppression (IMMUNO-A).
[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).

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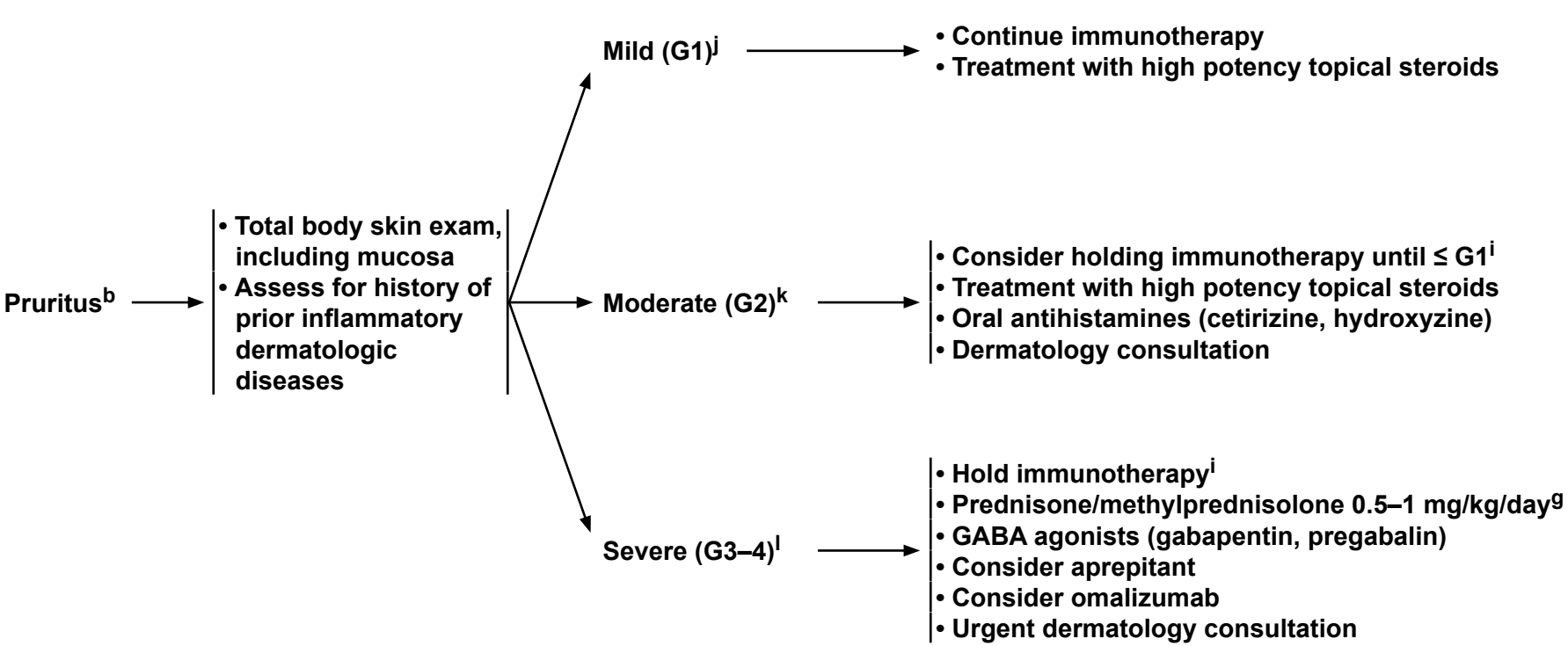

[b]Characterized by an intense itching sensation.
[g]Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h]See Principles of Immunosuppression (IMMUNO-A).
[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[j]Mild or localized.
[k]Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); limiting instrumental ADLs.
[l]Intense or widespread; constant; limiting self-care ADLs or sleep. Assess serum IgE and histamine; consider oral antihistamines for increased histamine and omalizumab for increased IgE.

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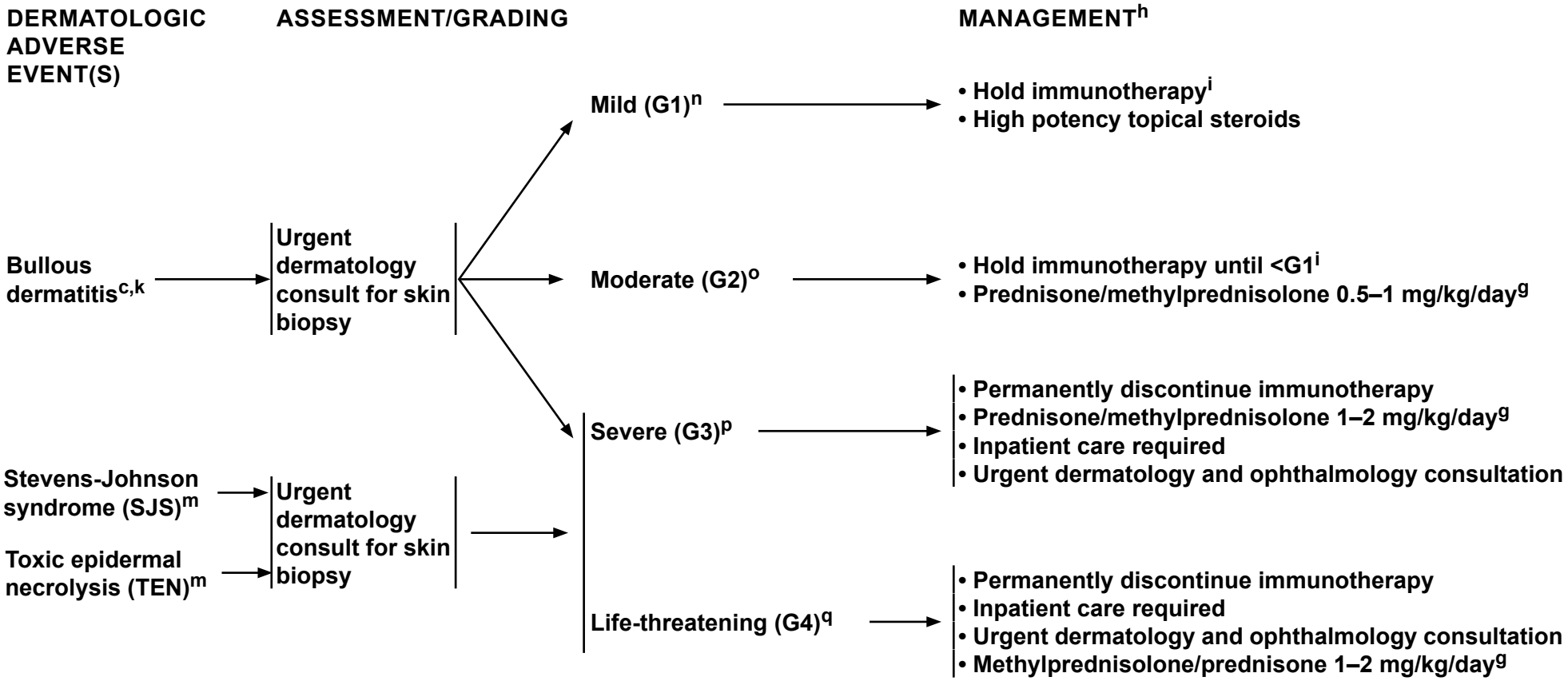

[c]Characterized by inflammation of the skin and the presence of bullae, which are filled with fluid.
[g]Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h]See Principles of Immunosuppression (IMMUNO-A).
[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[k]Intense or widespread; intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); limiting instrumental ADLs.
[m]Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) should be treated as grade 3–4 bullous dermatitis. SJS, overlapping SJS/TEN, and TEN are characterized by separation of the dermis involving <10%, 10%–30%, and >30% BSA, respectively. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.
[n]Asymptomatic; blisters covering <10% BSA.
[o]Blisters covering 10%–30% BSA; painful blisters; limiting instrumental ADLs.
[p]Blisters covering >30% BSA; limiting self-care ADLs.
[q]Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated.

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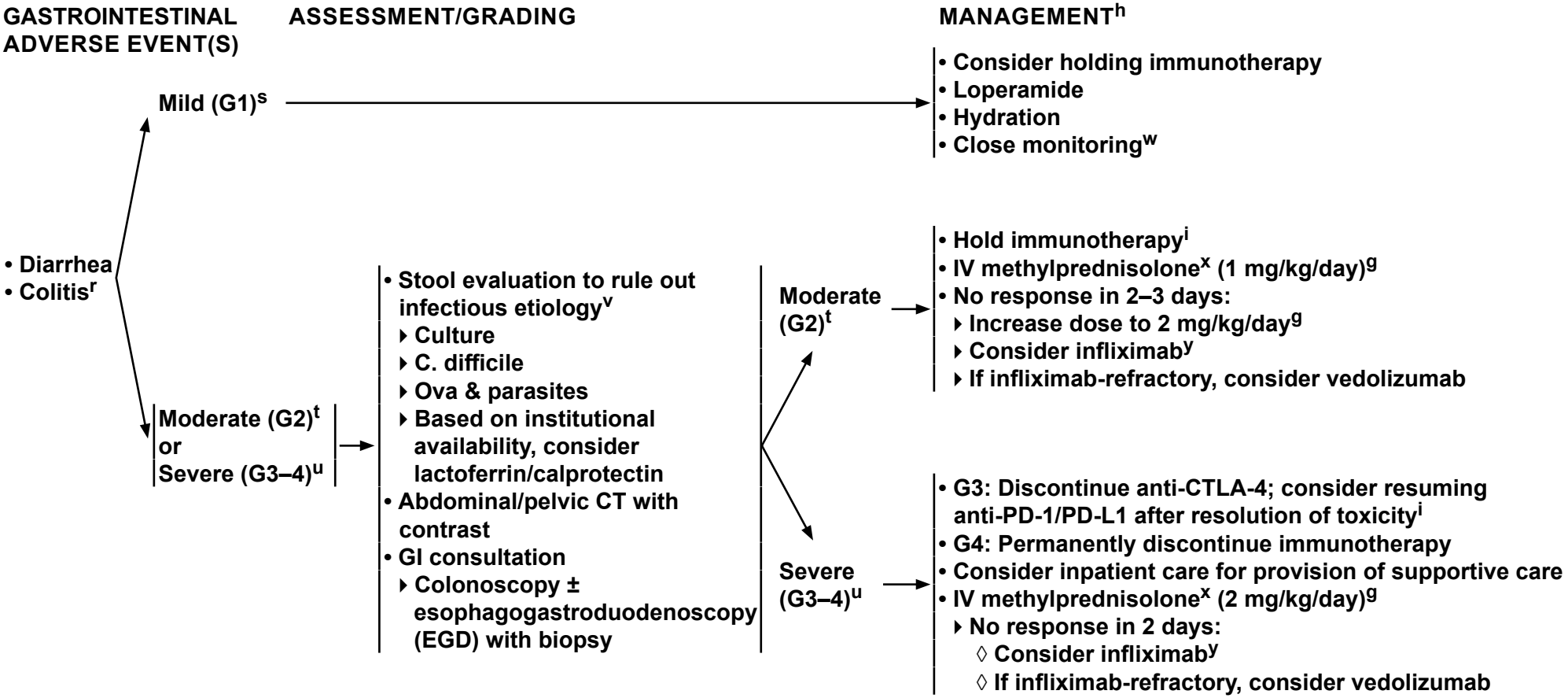

[g]Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h]See Principles of Immunosuppression (IMMUNO-A).
[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[r]Symptoms include: abdominal pain, blood and mucus in the stool, fever.
[s]Fewer than 4 bowel movements above baseline per day and no colitis symptoms.
[t]4–6 bowel movements above baseline per day, colitis symptoms, not interfering with ADLs.
[u]More than 6 bowel movements above baseline per day, colitis symptoms, interfering with ADLs, hemodynamic instability, hospitalization, other serious complications (eg, ischemic bowel, perforation, toxic mega-colon).
[v]It is not necessary to wait for test results before providing therapy to manage irAE.
[w]If progressive, consider stool evaluation to rule out infectious etiology.
[x]Convert to prednisone when appropriate.
[y]Duration of therapy with tumor necrosis factor alpha (TNF-alpha) blockers is not clearly defined, but is usually a single dose. Repeat endoscopy may be helpful, but optional for the guidance of treatment.

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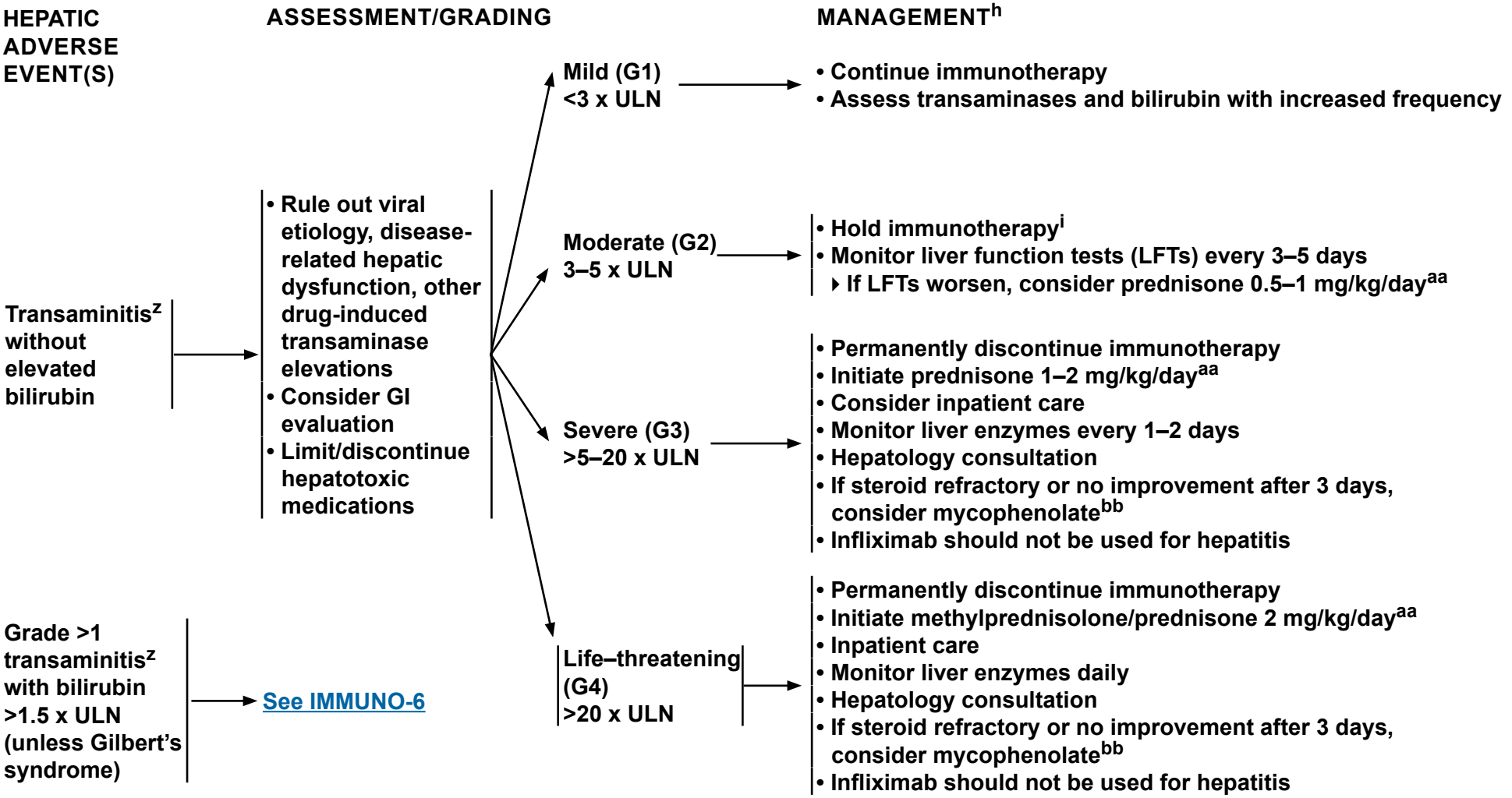

[h]See Principles of Immunosuppression (IMMUNO-A).
[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[z]Elevated alanine transaminase (ALT) and aspartate transaminase (AST).
[aa]When liver enzymes show sustained improvement or return to ≤ G1, initiate steroid tapering and continue to taper over at least 1 month. Re-escalate as needed.
[bb]Mycophenolate mofetil treatment (0.5–1 g every 12 hours) can be considered in patients who have persistent severe hepatitis despite high-dose corticosteroids.

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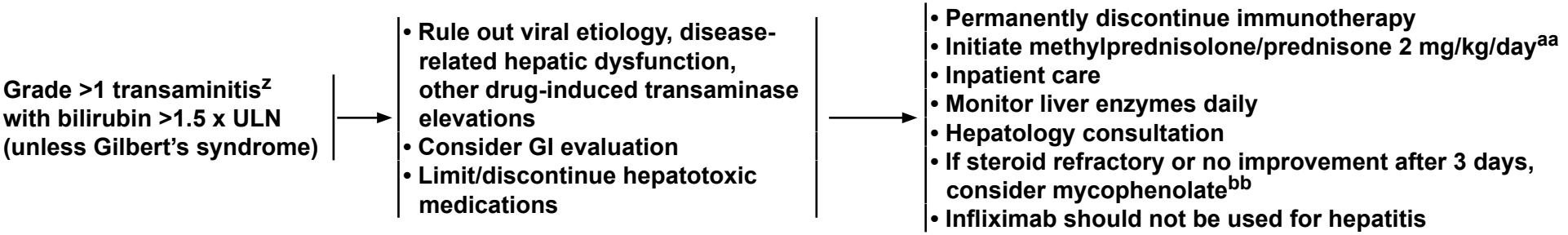

[h]See Principles of Immunosuppression (IMMUNO-A).
[z]Elevated ALT and AST.
[aa]When liver enzymes show sustained improvement or return to ≤ G1, initiate steroid tapering and continue to taper over at least 1 month. Re-escalate as needed.
[bb]Mycophenolate mofetil treatment (0.5–1 g every 12 hours) can be considered in patients who have persistent severe hepatitis despite high-dose corticosteroids.

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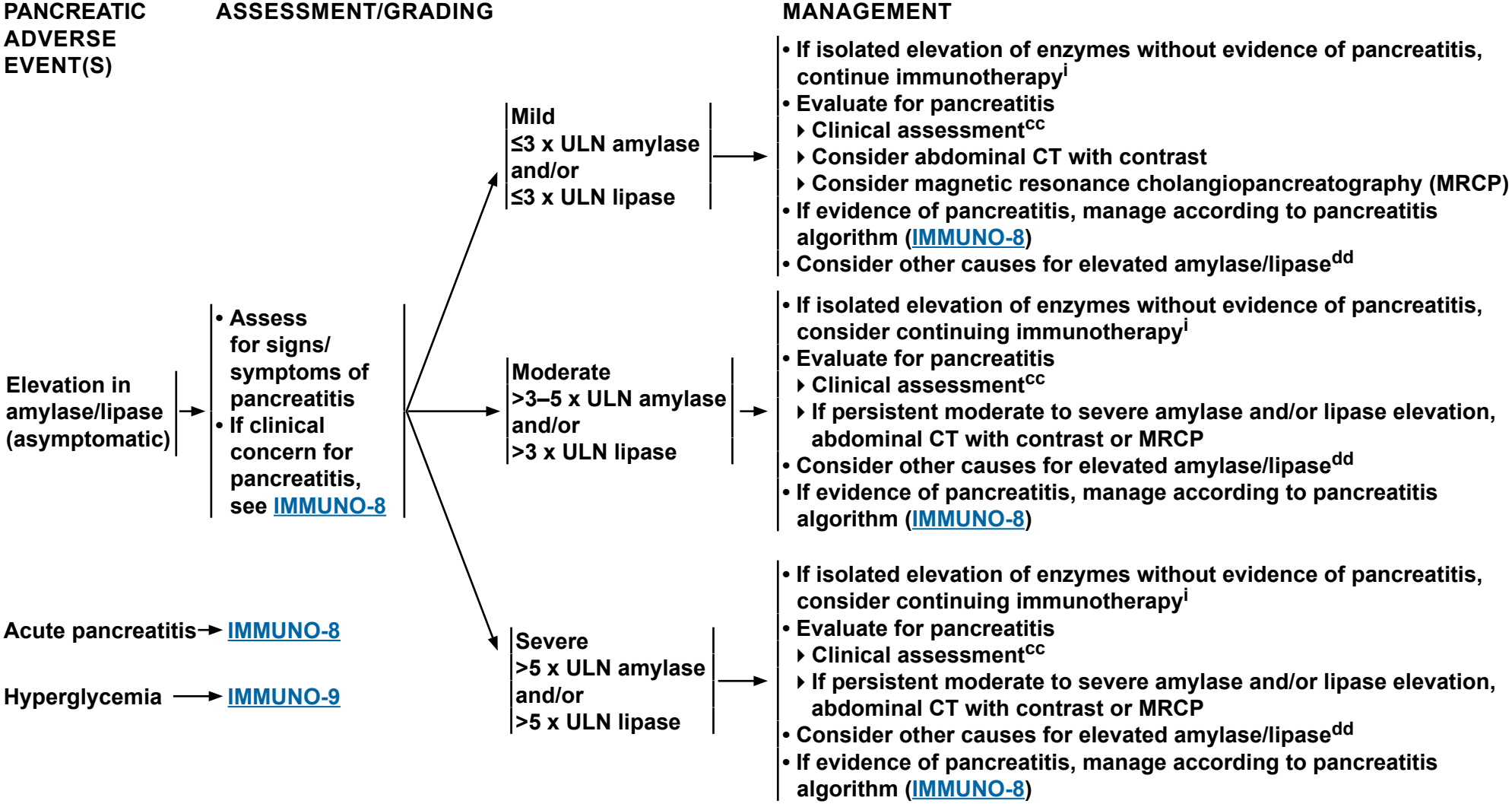

[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[cc]Routine amylase/lipase assessments do not have to be performed outside of clinical suspicion of possible pancreatitis. See Principles of Routine Monitoring (IMMUNO-D).
[dd]Inflammatory bowel disease, irritable bowel syndrome, bowel obstruction, gastroparesis, nausea/vomiting, and/or diabetes mellitus.

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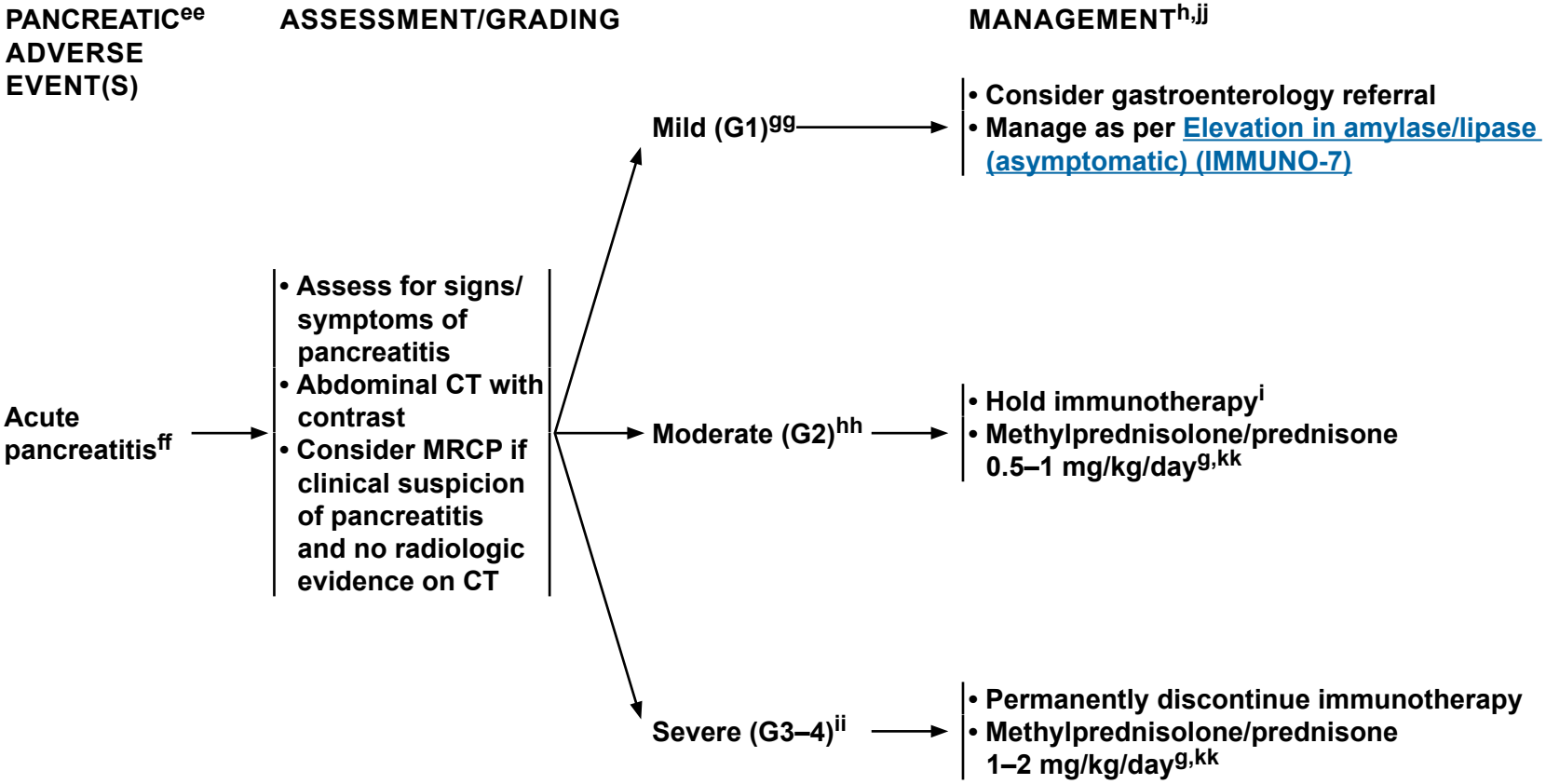

[g]Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h]See Principles of Immunosuppression (IMMUNO-A).
[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[ee]No requirement for routine monitoring of potential pancreatitis with imaging.
[ff]Once pancreatitis is diagnosed, management and monitoring should be directed by gastroenterology/pancreatic subspecialists.
[gg]Any one of the following features present: elevation of amylase/lipase >3 x ULN or radiologic findings on CT or clinical findings concerning for pancreatitis.
[hh]Two of three of the following features present: elevation of amylase/lipase >3 x ULN ± radiologic findings on CT ± clinical findings concerning for pancreatitis.
[ii]Elevation of amylase/lipase ± radiologic findings ± severe abdominal pain or vomiting and hemodynamically unstable.
[jj]Evaluate for signs/symptoms of pancreatic exocrine insufficiency and/or diabetes mellitus, and supplement if needed.
[kk]Additional immunosuppression with mycophenolate mofetil may be considered.

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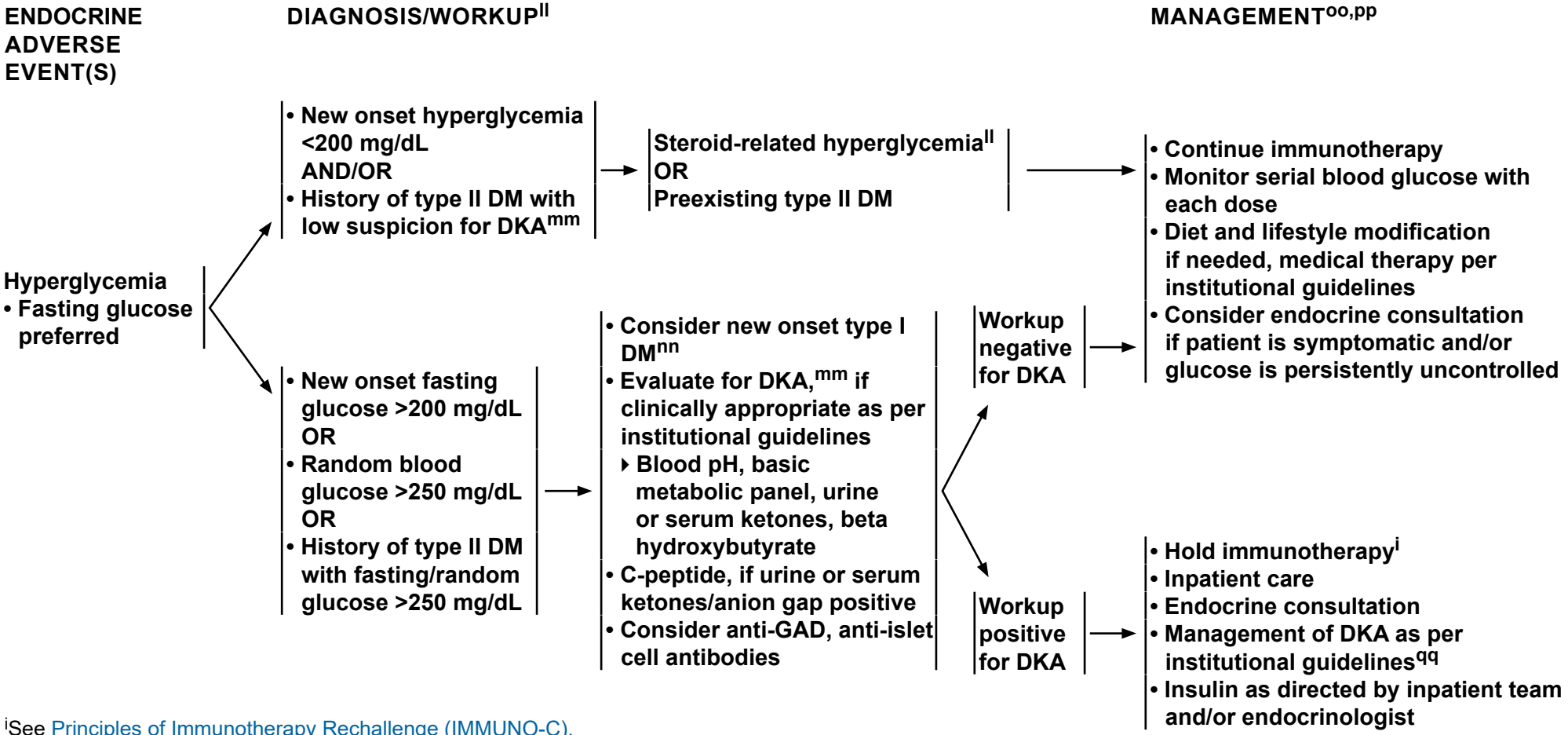

[i] See Principles of Immunotherapy Rechallenge (IMMUNO-C).

[ll] High-dose corticosteroids may induce or exacerbate hyperglycemia. Consider endocrinology referral and appropriate management if symptomatic and/or persistently uncontrolled.

[mm] Symptoms of diabetic ketoacidosis (DKA) may include excessive thirst, frequent urination, general weakness, vomiting, confusion, abdominal pain, dry skin, dry mouth, increased heart rate, and fruity odor on the breath.

[nn] The development of type I diabetes mellitus (DM) is rare (1%–2%) but can be life-threatening if insulin therapy is not provided. Once new type I DM is diagnosed, management and monitoring should be directed by endocrinology team.

[oo] Evaluate for signs/symptoms of pancreatic exocrine insufficiency, and supplement if needed

[pp] Insufficient evidence to suggest corticosteroids may reverse type I DM induced by immunotherapy, and may complicate glycemic control.

[qq] Institutional guidelines may include but are not limited to: intravenous fluids +/– potassium supplementation, intravenous insulin, hourly glucose, serum ketones, blood pH, and anion gap.

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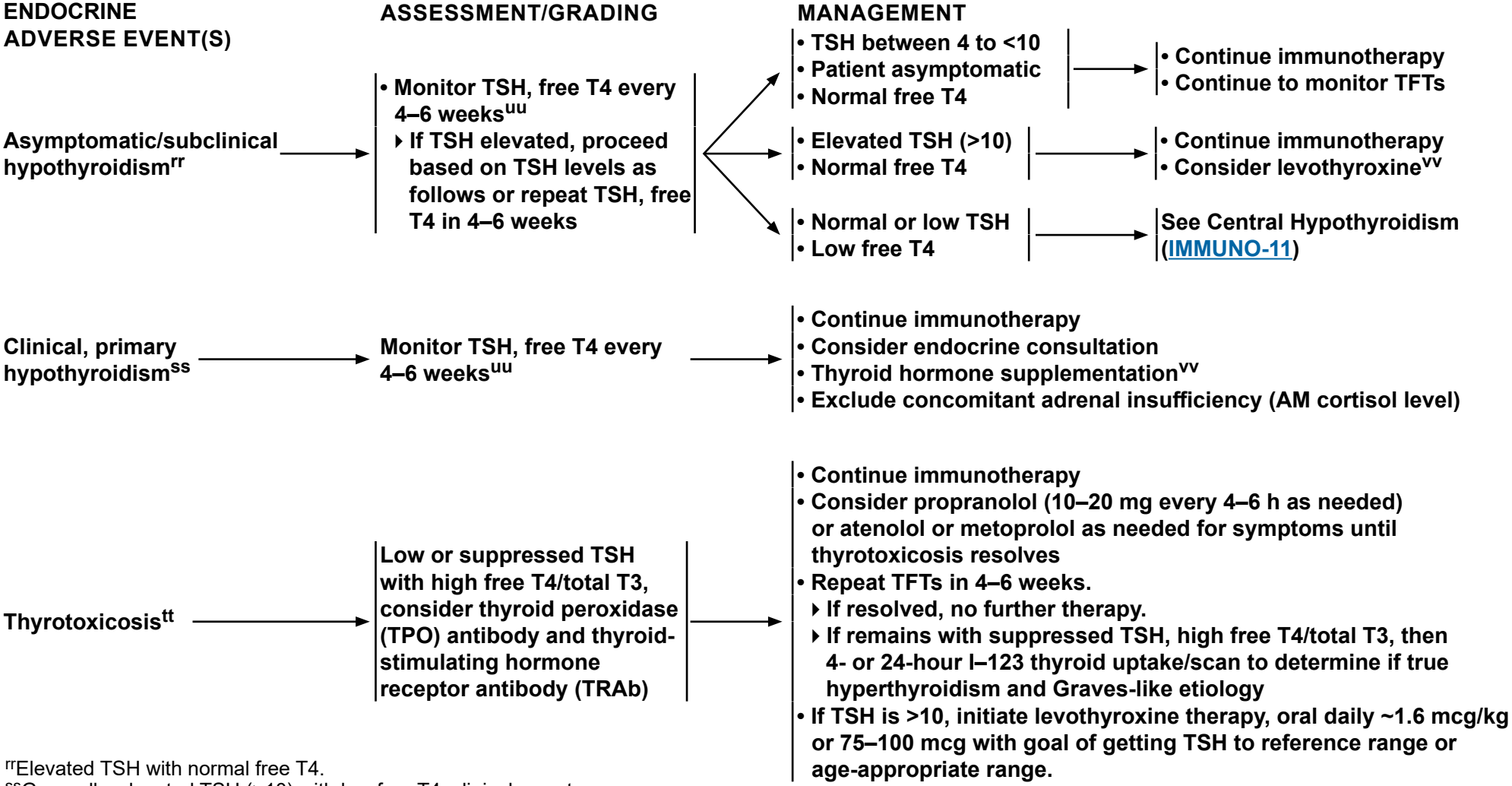

[rr]Elevated TSH with normal free T4.
[ss]Generally, elevated TSH (>10) with low free T4, clinical symptoms.
[tt]Defined as suppressed TSH that may be: a) subclinical if free T4 normal, b) clinical if high free T4. The majority of suppressed TSH (<0.01) are due to transient or progressive painless thyroiditis.
[uu]For patients without baseline thyroid function abnormalities or who are asymptomatic, can increase thyroid function testing interval to every 12–18 weeks as indicated.
[vv]Levothyroxine oral daily ~1.6 mcg/kg with goal of getting TSH to reference range or age-appropriate range; reduce dose by 10% to avoid hyperthyroidism in patient populations that may be sensitive to thyroid supplementation (eg, elderly populations or patients with comorbidities).

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ENDOCRINE ADVERSE EVENT(S)	ASSESSMENT/GRADING	MANAGEMENT[h,yy]
Primary Adrenal Insufficiency[ww]	• Evaluate ACTH, cortisol level (AM) • Comprehensive metabolic panel (Na, K, CO_2, glucose), renin level	• Endocrine consultation ▸ Endocrine evaluation prior to surgery or any procedure • Hold immunotherapy[i] • Start corticosteroid first before other hormone replacement to avoid adrenal crisis • Steroid replacement[zz,aaa] ▸ Hydrocortisone 20 mg in AM, 10 mg in PM, then slowly titrating doses down according to symptoms[bbb] OR ▸ Prednisone 7.5- or 10-mg starting dose, then reduce to 5 mg daily as appropriate AND ▸ Fludrocortisone can be started 0.1 mg every other day; then titrated up or down by BPs, symptoms, lower extremity edema, and labs • If hemodynamically unstable, inpatient care and initiate high-dose/stress-dose steroids • Patients with severe symptoms (hypotension) may require additional fluids (eg, normal saline often >2 L required) • Patient education regarding stress doses of hydrocortisone for infection, trauma, etc. ▸ Alert bracelet is recommended
Central Hypothyroidism[xx]	• Evaluate ACTH, cortisol (AM), FSH, LH, TSH, free T4, DHEA-S • Estradiol testing in women • Testosterone testing in men • Consider MRI of pituitary if confirmed central thyroid/ adrenal insufficiency	• Continue immunotherapy • Treat as hypophysitis (IMMUNO-12)

[h]See Principles of Immunosuppression (IMMUNO-A).
[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[ww]Low morning cortisol (<5) with high ACTH (> reference range) with or without abnormal electrolytes and symptoms. Other criteria: 30- or 60-minute cortisol <18 after ACTH stimulation in the setting of low morning cortisol and high ACTH. Other abnormalities: hypotension, orthostatic hypotension, low Na, and high K.
[xx]Low or suppressed TSH with inappropriately low free T4 may represent sequela of hypophysitis; for which other pituitary axes may be affected. Follow free T4 for thyroid replacement in the setting of hypophysitis–induced loss of TSH production.
[yy]If severe acute symptoms (eg, headache/nausea/emesis, fevers), high-dose steroids as indicated until symptoms resolve (1–2 weeks) then rapid taper to physiologic replacement.
[zz]If acutely ill, double or triple these doses for 24–48 hours (ie, sick day rules for fever >101, nausea/emesis, surgeries).
[aaa]Will require physiologic replacement steroids indefinitely.
[bbb]The goal for physiologic steroid replacement is to identify the lowest steroid dose needed to prevent symptoms of adrenal insufficiency. For many patients, this may be, for example, 10 mg in AM and 5 mg in PM, if tolerated.

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ENDOCRINE ADVERSE EVENT(S)	ASSESSMENT	MANAGEMENT[h]
Hypophysitis[ccc]	• Evaluate ACTH, cortisol (AM), FSH, LH, TSH, free T4, testosterone in men, estrogen in premenopausal women • MRI brain ± contrast with pituitary/sellar cuts, if symptomatic	• Consider endocrine consultation • Hold immunotherapy until acute symptoms resolve[i,ccc] • Methylprednisolone/prednisone 1–2 mg/kg/day[yy] • Hormone replacement as indicated[ddd] • Patient education regarding stress doses of hydrocortisone for infection, trauma, etc. ▸ Alert bracelet is recommended

[h]See Principles of Immunosuppression (IMMUNO-A).
[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[yy]If severe acute symptoms (eg, headache/nausea/emesis, fevers), high-dose steroids as indicated until symptoms resolve (1–2 weeks) then rapid taper to physiologic replacement.
[ccc]Hypophysitis may present with acute symptoms such as headache, photophobia, dizziness, nausea/emesis, fevers, or anorexia. Tests may show low ACTH, low AM cortisol, low Na, low K, low testosterone, and DHEA-S. Non-acute symptoms may include fatigue and possible weight loss.
[ddd]Hormone replacement for pituitary damage should include steroid replacement (hydrocortisone 20 mg PO every AM, 10 mg PO every PM); it may also include levothyroxine for central hypothyroidism and testosterone supplementation in males. Patients may require physiologic replacement hormones indefinitely.

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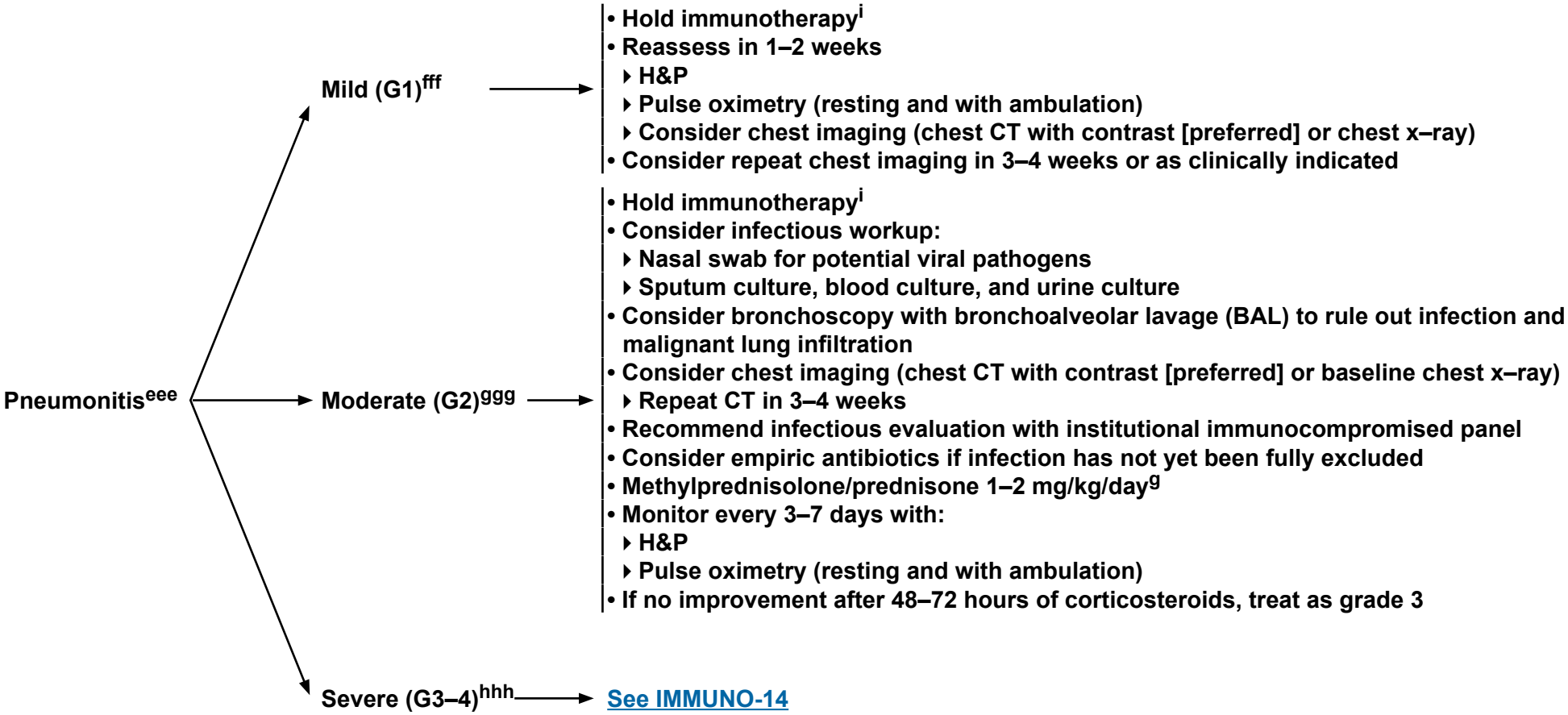

[g]Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h]See Principles of Immunosuppression (IMMUNO-A).
[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[eee]Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging as ground-glass opacities).
[fff]Asymptomatic; confined to one lobe of the lung or <25% of lung parenchyma; clinical or diagnostic observations only.
[ggg]Presence of new/worsening symptoms including: shortness of breath, cough, chest pain, fever, and increased oxygen requirement
[hhh]G3-severe symptoms involve all lung lobes or >50% of lung parenchyma, limiting self-care ADLs; G4–life-threatening respiratory compromise.

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ASSESSMENT/ GRADING	MANAGEMENT[h]

Severe (G3–4)[hhh] Pneumonitis[eee]	• Permanently discontinue immunotherapy
	• Inpatient care
	• Infectious workup:
	  ▸ Consider patient may be immunocompromised
	  ▸ Nasal swab for potential viral pathogens
	  ▸ Sputum culture, blood culture, and urine culture
	• Pulmonary and infectious disease consultation
	• Bronchoscopy with BAL to rule out infection and malignant lung infiltration
	• Consider empiric antibiotics if infection has not yet been fully excluded
	• Methylprednisolone 1–2 mg/kg/day until symptoms improve to Grade ≤1 then taper over ≥6 weeks
	• Any of the following can be considered if no improvement after 48 hours:
	  ▸ Infliximab 5 mg/kg IV, a second dose may be repeated 14 days later at the discretion of the treating provider
	  ▸ Mycophenolate mofetil 1–1.5g BID then taper in consultation with pulmonary service
	  ▸ Intravenous immunoglobulin (IVIG) 0.4 g/kg/day x 5 days

[h]See Principles of Immunosuppression (IMMUNO-A).
[eee]Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging as ground-glass opacities).
[hhh]G3-severe symptoms involve all lung lobes or >50% of lung parenchyma; limiting self-care ADL, G4–life-threatening respiratory compromise.

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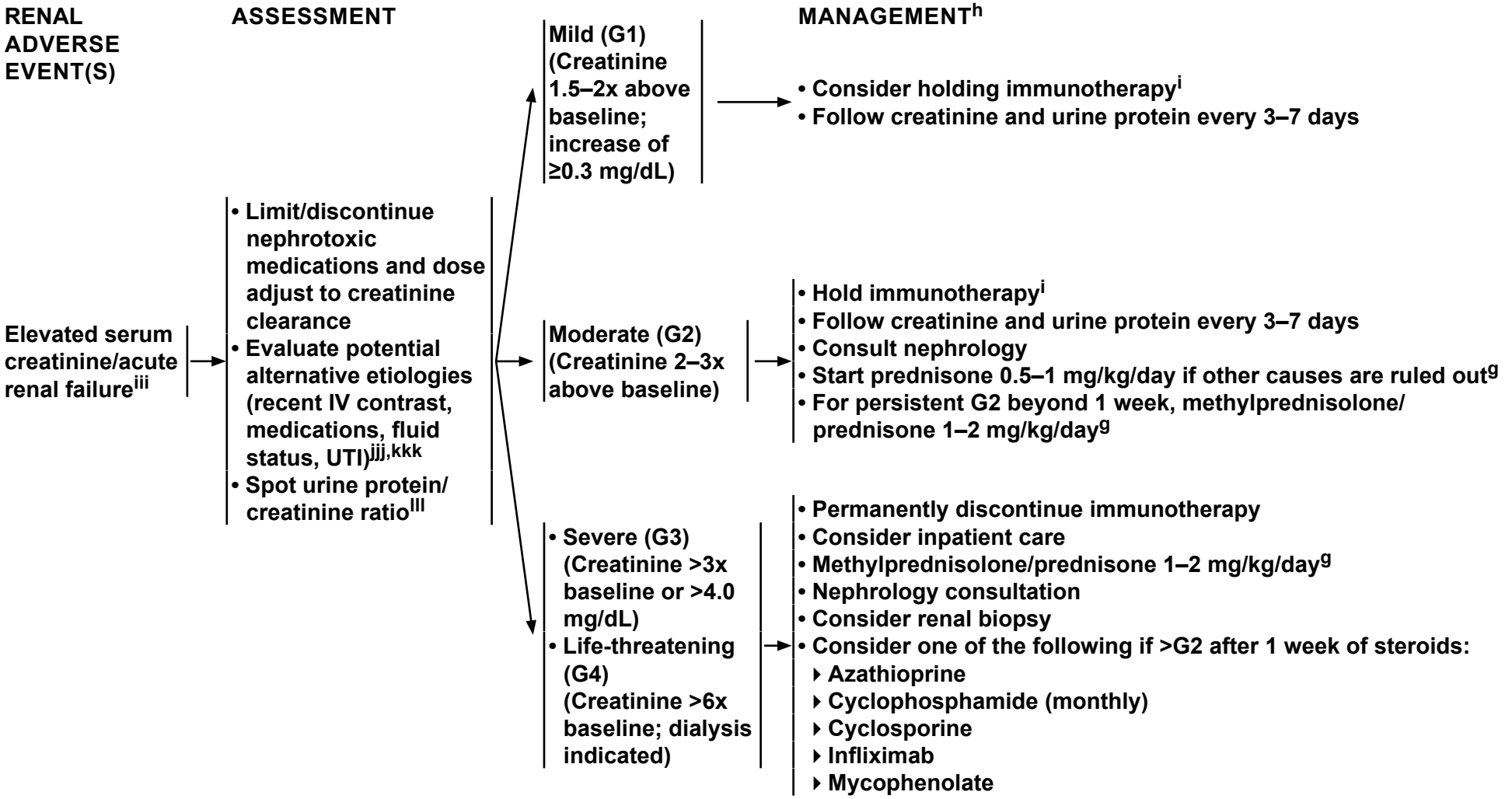

[g]Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h]See Principles of Immunosuppression (IMMUNO-A).
[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[iii]Azotemia, creatinine elevation, inability to maintain acid/base or electrolyte balance, and urine output change.
[jjj]General medical review and testing as warranted for prerenal and postrenal causes. Include medication review for nephrotoxic agents such as NSAIDS, consider obstruction, cardiomyopathy/heart failure, pulmonary hypertension, diuretics, hypovolemia due to primary GI cause, stones, and infection.
[kkk]Distinguish cell infiltrate vs immune-complex mediated renal injury.
[lll]For proteinuria >3 g/24-hour check ANA, RF, ANCA, anti-dsDNA, and serum C3, C4, and CH50.

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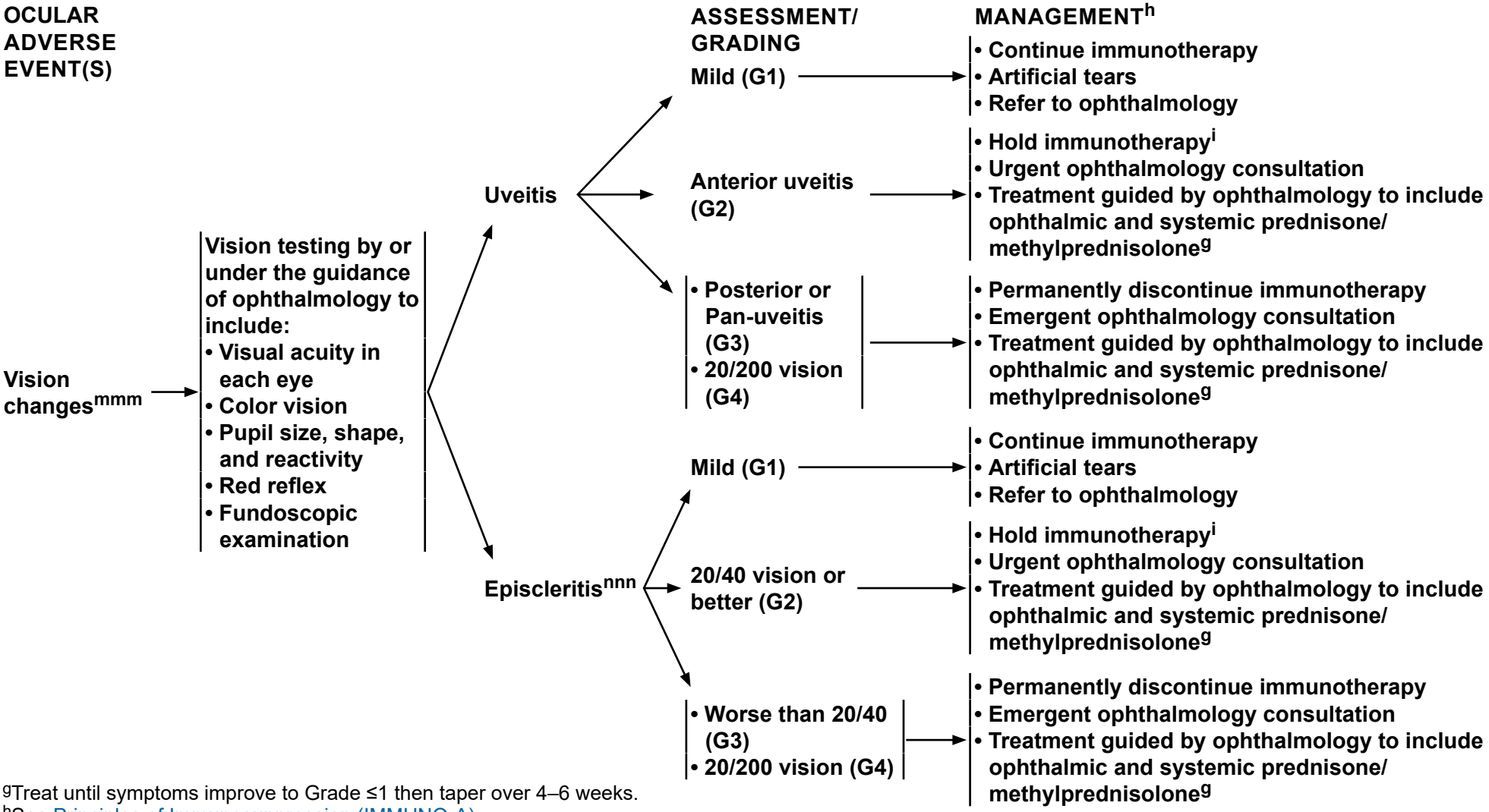

[g]Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h]See Principles of Immunosuppression (IMMUNO-A).
[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[mmm]Patients experiencing ocular AEs may present with any of the following symptoms: blurred/distorted vision, blind spots, change in color vision, photophobia, tenderness/pain, eyelid swelling, proptosis. Episcleritis can be associated with red or purple discoloration of the eye. Uveitis can be associated with eye redness.
[nnn]Treat blepharitis per the episcleritis algorithm.

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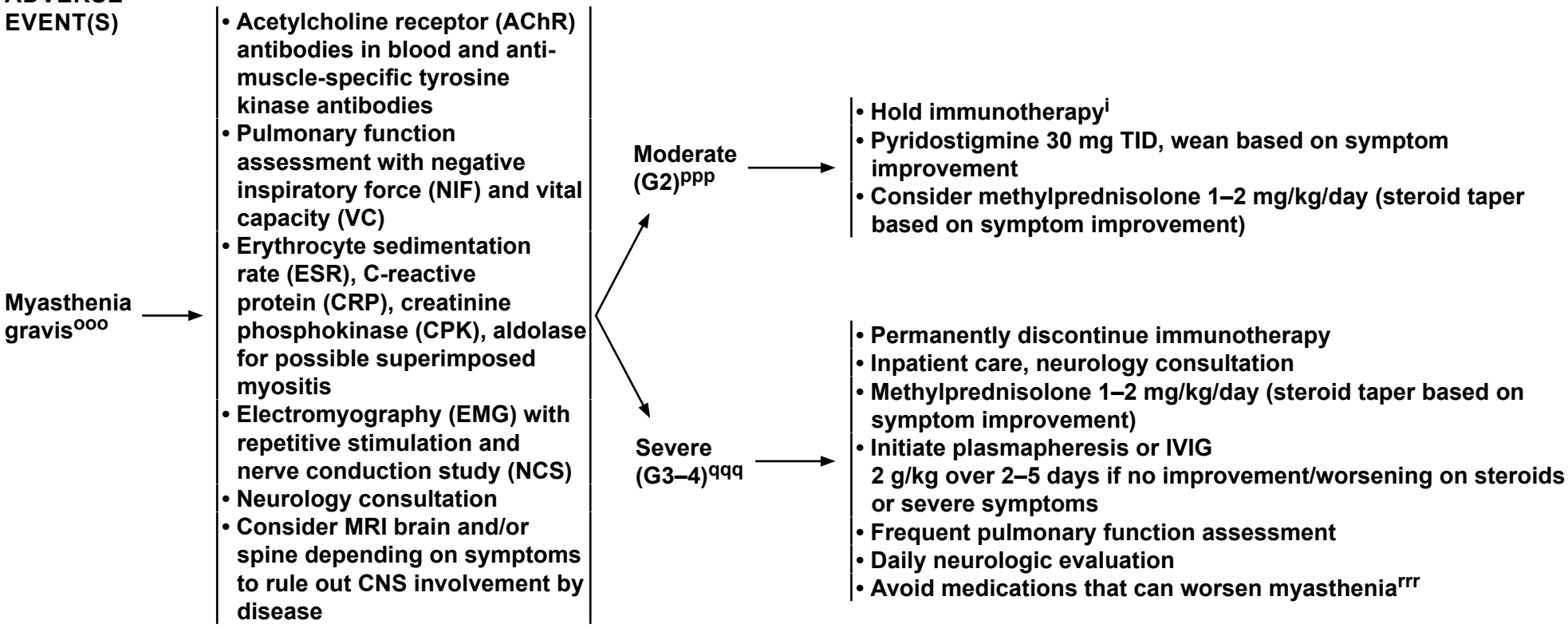

[h]See Principles of Immunosuppression (IMMUNO-A).
[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[ooo]Progressive or fluctuating muscle weakness, generally proximal to distal. May have bulbar involvement (ie, ptosis, extraocular movement abnormalities resulting in double vision, dysphagia, facial muscle weakness) and/or respiratory muscle weakness. May occur with myositis. Respiratory symptoms may require evaluation to rule out pneumonitis. Miller Fisher variant of Guillain-Barre syndrome (GBS) has overlapping symptoms (ophthalmoplegia and ascending weakness).
[ppp]Some symptoms interfering with ADLs.
[qqq]Limiting self-care and aids warranted, weakness limiting walking, any dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms.
[rrr]Beta-blockers, ciprofloxacin, and IV magnesium.

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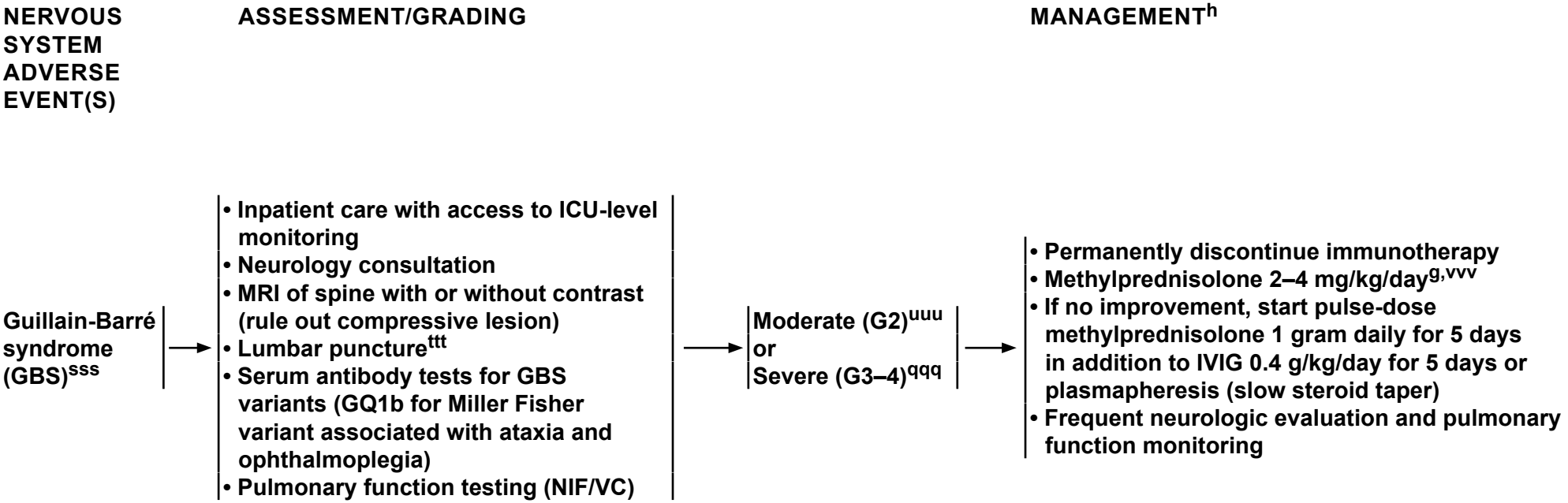

[g]Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h]See Principles of Immunosuppression (IMMUNO-A).
[qqq]Limiting self-care and aids warranted, weakness limiting walking, any dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms.
[sss]Progressive most often symmetrical muscle weakness with absent or reduced deep tendon reflexes. May involve extremities, facial, respiratory, and bulbar & oculomotor nerves. May have dysregulation of autonomic nerves. Often there is lower back pain.
[ttt]Cerebrospinal fluid (CSF) typically has elevated protein and often elevated white blood cell (WBC) count, even though this is not typically seen in classical Guillain-Barre (GBS), cytology should be sent with any CSF sample.
[uuu]Some interference with ADLs, symptoms concerning to patient.
[vvv]Steroids are not usually recommended for idiopathic GBS; however, in immunotherapy-related forms, a trial is reasonable.

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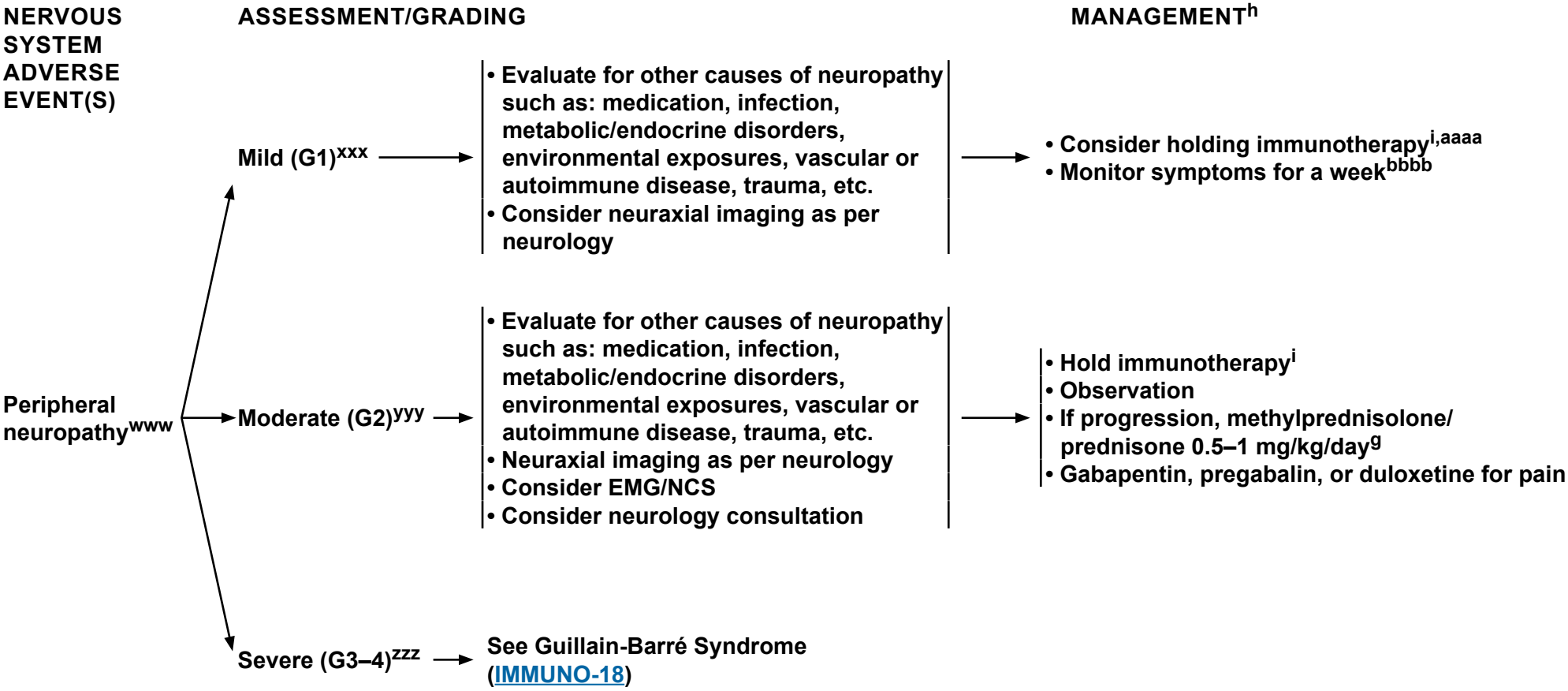

[g]Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h]See Principles of Immunosuppression (IMMUNO-A).
[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[www]Can present as asymmetric or symmetric sensory-motor deficit. Sensory deficit may be painful or painless parasthesias or potentially life-threatening autonomic (eg, myenteric plexus) dysfunction. Hypo- or areflexia. Isolated sensory deficit or sensory plus lower motor neuron deficit.
[xxx]No interference with function and symptoms not concerning to patient. Note: any cranial nerve problem should be managed as moderate.
[yyy]Some interference with ADLs, symptoms concerning to patient (ie, pain but no weakness or gait limitation).
[zzz]Limiting self-care and aids warranted, weakness limiting walking or respiratory problems (ie, leg weakness, foot drop, rapidly ascending sensory changes). May be GBS and should be managed as GBS.
[aaaa]There is a low threshold to hold immune checkpoint inhibitors in mild cases of peripheral neuropathy.
[bbbb]Specifically monitor for new interference with IADLs from either pain or weakness, gait difficulty, ataxia, or autonomic changes.

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NERVOUS SYSTEM ADVERSE EVENT(S)	ASSESSMENT/GRADING	MANAGEMENT[h]
Aseptic meningitis[cccc,dddd]	• MRI brain with and without contrast + pituitary protocol • AM cortisol, ACTH to rule out adrenal insufficiency • Consider lumbar puncture[ffff]	• Hold immunotherapy[i] if mild/moderate • Permanently discontinue immunotherapy if severe • Inpatient care (G3–4[iiii]) • Consider IV acyclovir until CSF results • 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[jjjj]
Encephalitis[dddd,eeee]	• Neurology consultation • MRI brain with and without contrast[gggg] • Lumbar puncture[hhhh] • EEG to evaluate for subclinical seizures • Comprehensive metabolic panel, CBC, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antineutrophil cytoplasmic antibody (ANCA) (if vasculitic process suspected), thyroid panel including TPO and thyroglobulin • Autoimmune encephalopathy and paraneoplastic panel	• Hold immunotherapy[i] if mild • Permanently discontinue immunotherapy if moderate/severe • Inpatient care (G3–4[iiii]) • Consider IV acyclovir until polymerase chain reaction (PCR) results obtained • Trial of methylprednisolone 1–2 mg/kg/day[g] • If severe or progressing symptoms or oligoclonal bands present, consider pulse steroids methylprednisolone 1 g IV daily for 3–5 days plus IVIG 0.4 g/kg/day for 5 days • If positive for autoimmune encephalopathy antibody and limited or no improvement, consider rituximab

[g]Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h]See Principles of Immunosuppression (IMMUNO-A).
[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[cccc]May present with headache, photophobia, and neck stiffness, often afebrile but may be febrile. There may be nausea/vomiting. Mental status should be normal (distinguishes from encephalitis).
[dddd]Exclude infectious causes, especially viral (ie, HSV).
[eeee]Confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, and speech abnormality.
[ffff]Measure opening pressure, check cell count, protein glucose, gram stain, culture, PCR for HSV, and other viral PCRs depending on suspicion, cytology. May see elevated WBC with normal glucose, normal culture, and gram stain. May see reactive lymphocytes or histiocytes on cytology.
[gggg]May reveal T2/FLAIR changes typical of what is seen in autoimmune encephalopathies or limbic encephalitis or may be normal.
[hhhh]Check cell count, protein glucose, gram stain, culture, PCR for HSV, and other viral PCRs depending on suspicion, cytology, oligoclonal bands, and autoimmune encephalopathy panel. May see elevated WBC with lymphocytic predominance and/or elevated protein.
[iiii]Limiting self-care and aids warranted.
[jjjj]Taper steroids rapidly once symptoms resolve.

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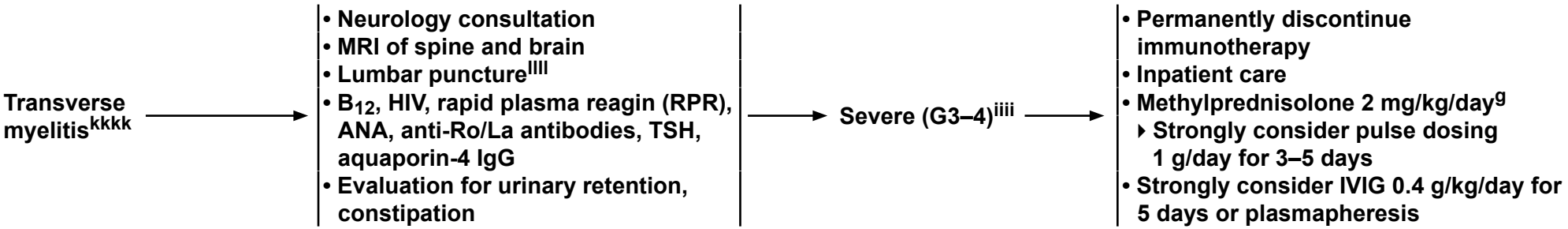

[g]Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h]See Principles of Immunosuppression (IMMUNO-A).
[iiii]Limiting self-care and aids warranted.
[kkkk]Acute or subacute weakness or sensory changes bilaterally, often with increased deep tendon reflexes.
[llll]Cell count, protein, glucose, oligoclonal bands, viral PCRs, cytology, and onconeural antibodies.

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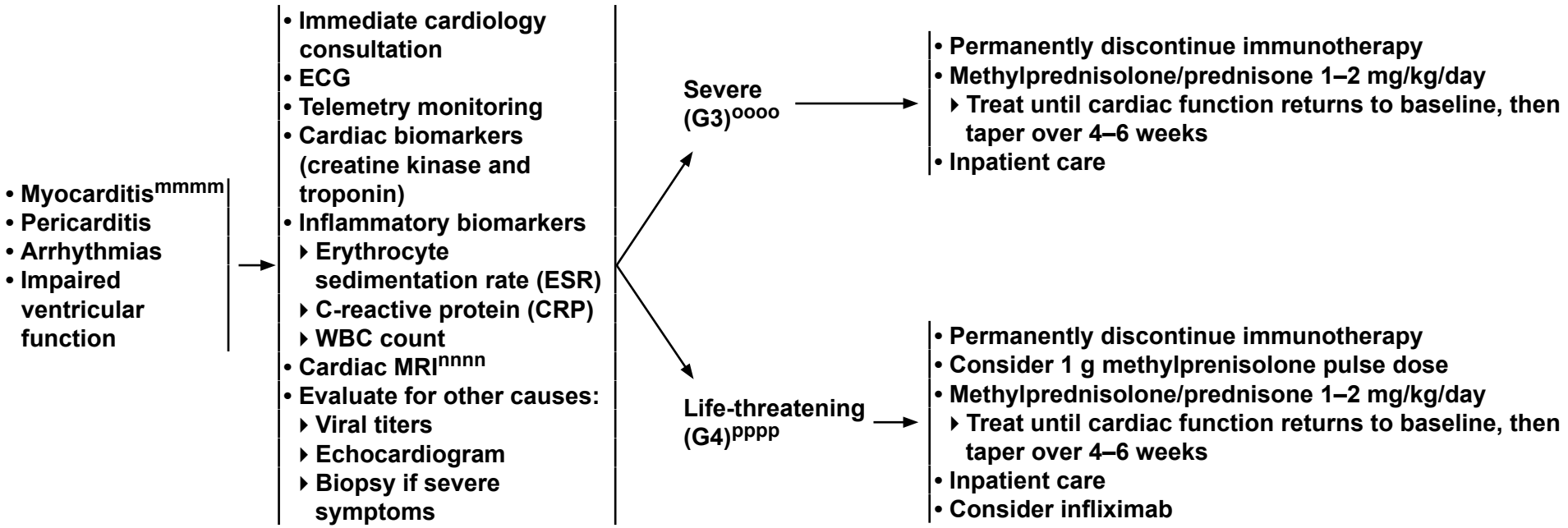

[h]See Principles of Immunosuppression (IMMUNO-A).
[mmmm]Myocarditis symptoms are nonspecific. It is rare, but potentially severe, not viral in etiology, associated with myositis, and is more common in combination therapy. In fatal cases, conduction abnormalities were mode of death and ejection fraction was preserved.
[nnnn]No evidence specific to immunotherapy-related myocarditis, recommendations drawn from other causes of myocarditis.
[oooo]Arrhythmia, significant echo findings without hypotension, cardiac markers >ULN.
[pppp]Arrhythmia, hemodynamic (hypotension/cardiomyopathy) >3xULN.

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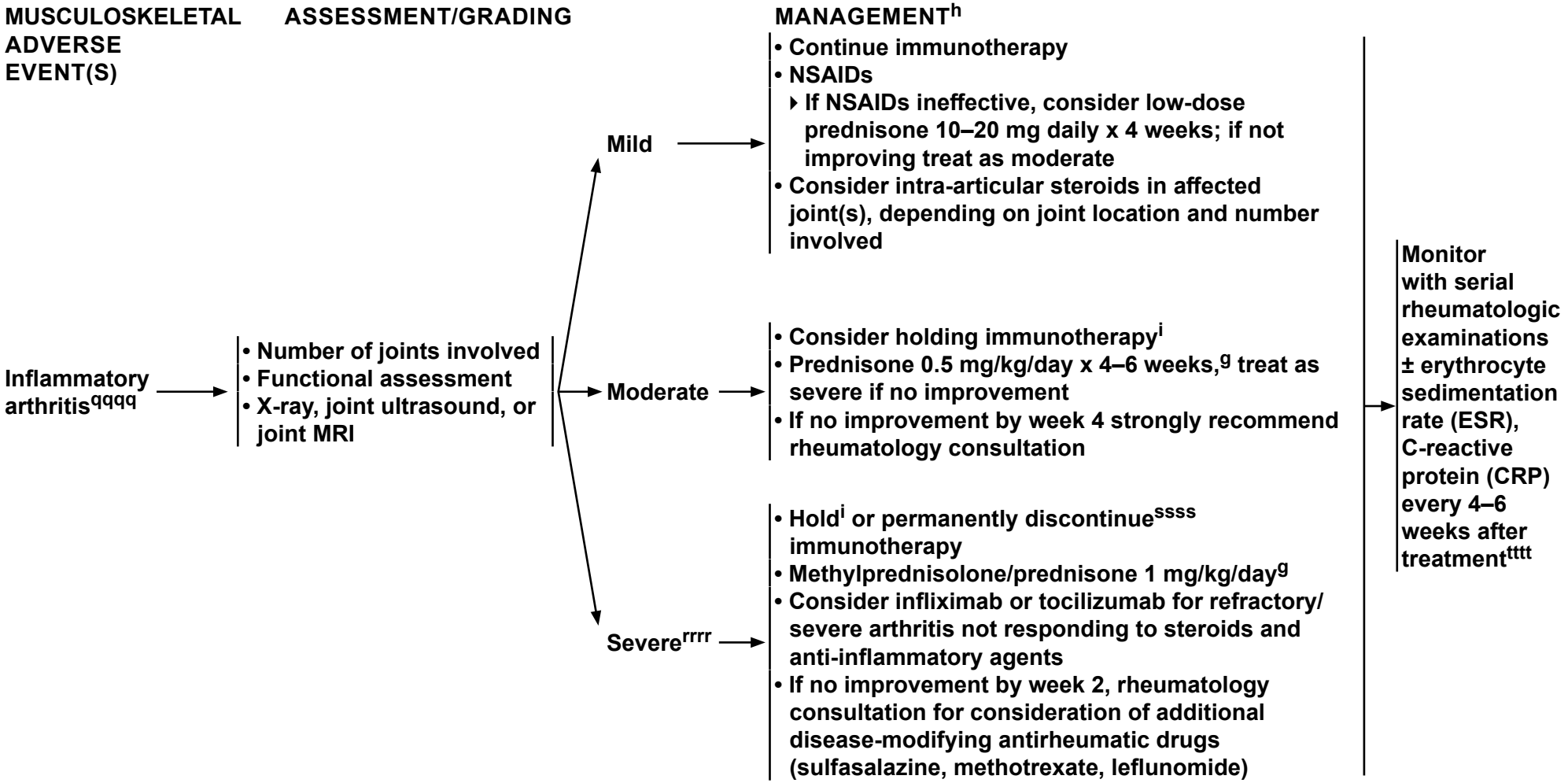

[g]Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h]See Principles of Immunosuppression (IMMUNO-A).
[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[qqqq]Clinical symptoms: joint pain, joint swelling; inflammatory symptoms: stiffness after inactivity, improvement with heat.
[rrrr]Limits instrumental ADLs, with or without irreversible joint damage.
[ssss]Consider discontinuing immunotherapy if arthritis worsens, with repeated dosing, to the point where daily activities are limited or patient's quality of life is severely impaired.
[tttt]Consider ESR, CRP to monitor response.

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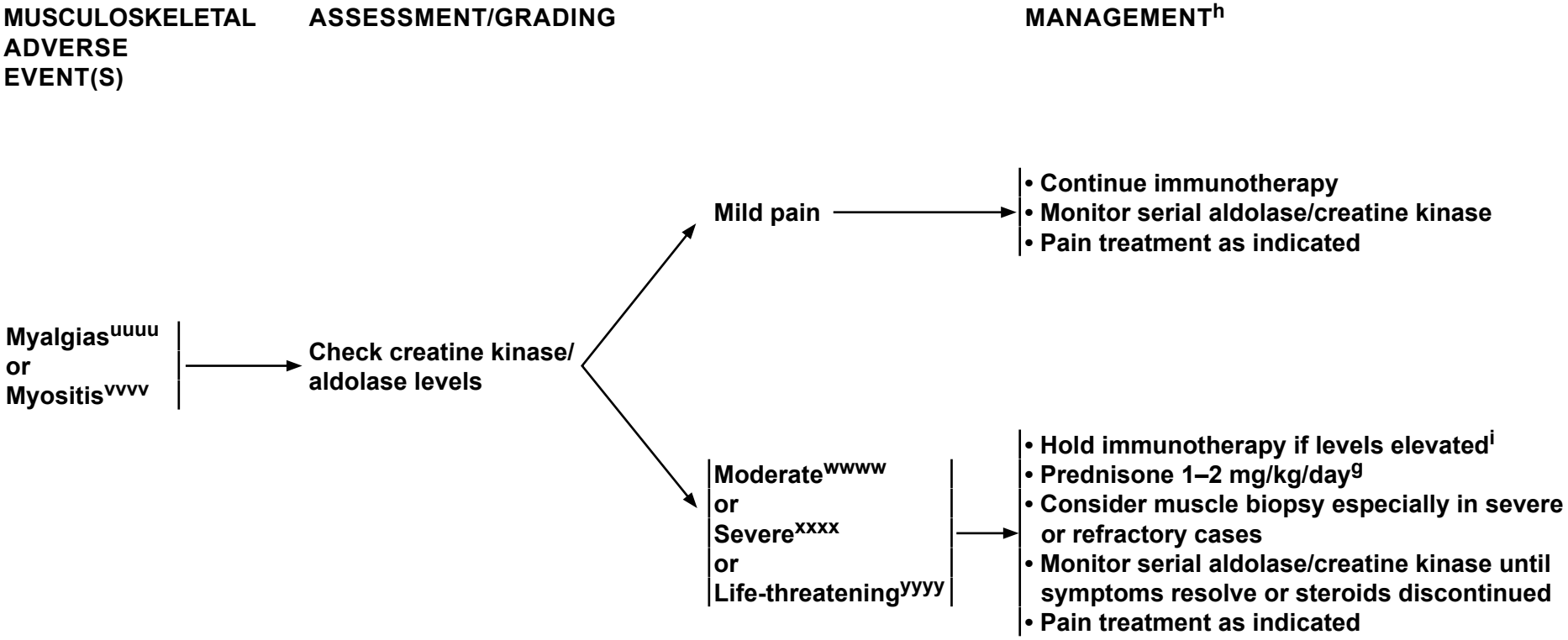

[g]Treat until symptoms improve to Grade ≤1 then taper over 4–6 weeks.
[h]See Principles of Immunosuppression (IMMUNO-A).
[i]See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[uuuu]Myalgia is a disorder characterized by marked discomfort sensation originating from a muscle or group of muscles.
[vvvv]Myositis is a disorder characterized by inflammation involving the skeletal muscles.
[wwww]Moderate pain associated with weakness; limiting self-care ADLs.
[xxxx]For myalgias, moderate pain associated with weakness; pain limiting instrumental ADLs. In myositis, pain associated with severe weakness; limiting self-care ADLs.
[yyyy]Only applies to myositis; urgent intervention indicated.

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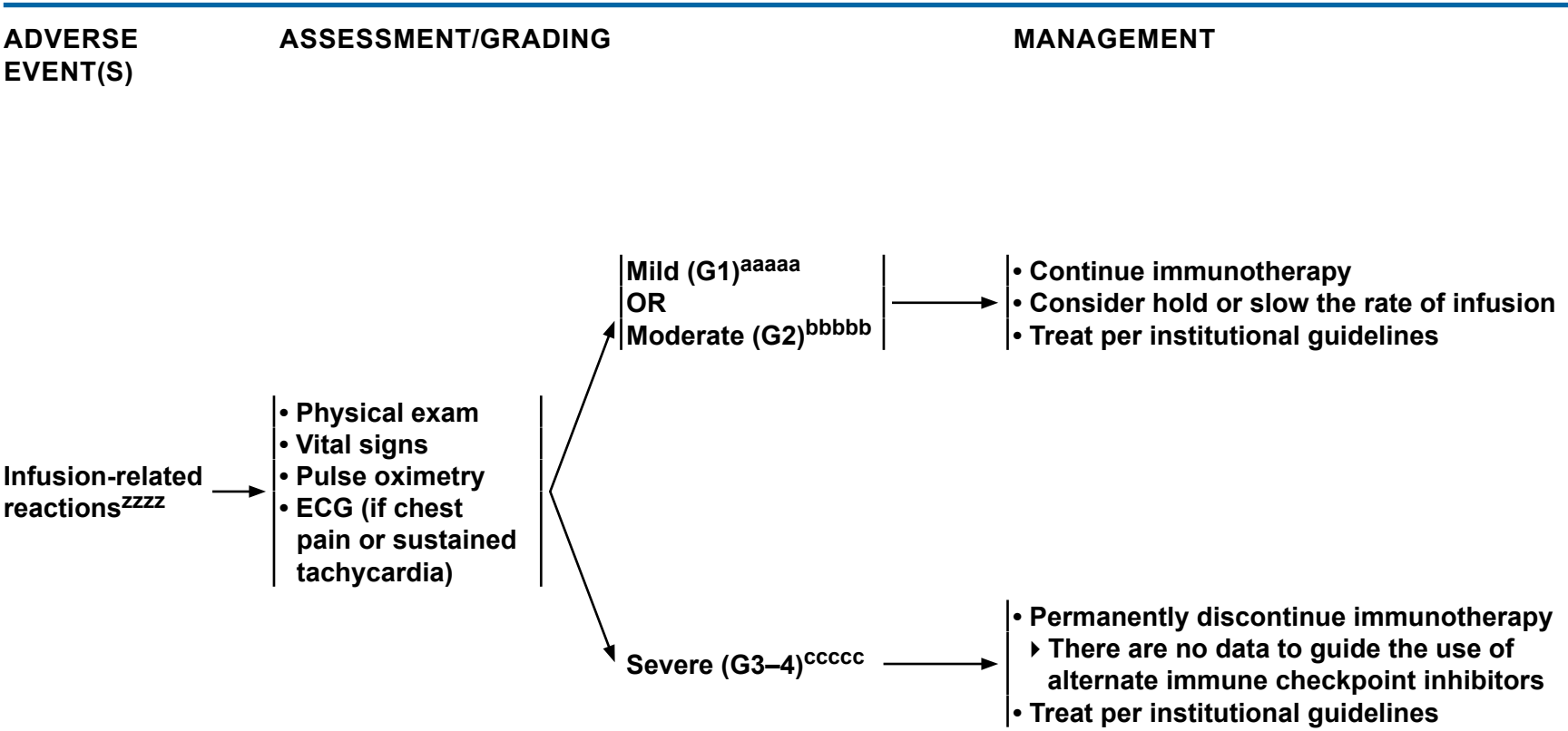

[zzzz]Symptoms include: Fever/chills/rigors, urticaria/pruritus, angioedema, flushing/headache, hypertension, hypotension, shortness of breath, cough/wheezing, hypoxemia, dizziness/syncope, sweating, and arthralgia/myalgia. Refer to prescribing information for each individual immunotherapy agent for recommendations for premedication to prevent infusion reactions.

[aaaaa]Mild transient reaction; infusion interruption not indicated. Intervention not indicated.

[bbbbb]Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for less than or equal to 24 hours.

[ccccc]Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement. Hospitalization indicated; life-threatening consequences; urgent intervention.

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PRINCIPLES OF IMMUNOSUPPRESSION

- These immunosuppression recommendations are for patients receiving immunotherapy defined as immune checkpoint inhibitors.
- Close consultation with disease-specific subspecialties is encouraged.
  - Referral to a tertiary care center may be required for management of complex cases or multi-system immune-related adverse events (irAEs).
- Corticosteroids are the mainstay of treatment of most irAEs related to immunotherapy.
  - Early intervention with corticosteroids is a key goal in general management of immune-related toxicity.
  - Use of corticosteroids to treat irAEs has NOT been shown to reduce anti-tumor efficacy.
    - ◊ Routine premedication with corticosteroids for nausea and infusion reactions is not recommended unless otherwise indicated, given the potential mitigation of immunotherapeutic effectiveness in the prophylactic setting.
  - Longer steroid tapers (>4 weeks, sometimes 6–8 weeks or longer) may be required to prevent recurrent irAE events, particularly pneumonitis and hepatitis.
  - See individual toxicity pages for specific recommendations on steroid dose by grade. Where immunotherapy rechallenge is indicated, see the Principles of Immunotherapy Rechallenge (IMMUNO-C) for guidance by organ site.
  - Prophylaxis against pneumocystis jiroveci pneumonia (PJP) can be considered in patients receiving a prednisone equivalent of 20 mg or more daily for 4 or more weeks.
  - Prophylaxis against fungal infections (eg, fluconazole) can be considered in patients receiving a prednisone equivalent of 20 mg or more daily for 6–8 or more weeks.
  - Proton pump inhibitor therapy or H2 blockers can be considered for patients at higher risk of gastritis (eg, NSAID use, anticoagulation) for the duration of corticosteroid therapy.
  - Higher potency (eg, Class 2 or 3) topical corticosteroids are preferred for short-term use for immune-related dermatitis, compared to longer term use of lower potency steroids.
  - For neurologic, or grade 3 or 4 irAEs, higher dose steroids (eg, methylprednisolone or prednisone 1–2 mg/kg/day) should be given.
  - If patients need to be on long-term steroids, they are at risk for developing osteoporosis. Vitamin D and calcium supplementation should be provided to prevent osteoporosis.
- Selected irAEs including hypothyroidism and other endocrine irAEs may be treated with hormonal supplementation, without the need for corticosteroid therapy. See Endocrine Toxicities section.

Continued

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PRINCIPLES OF IMMUNOSUPPRESSION

- **Anti-TNFα agents (eg, infliximab) are particularly effective in management of immune-related colitis and inflammatory arthritis.**
  - **There is a risk for hepatitis B virus reactivation with infliximab. Test for viral hepatitis B and hepatitis C prior to TNF inhibition and monitor HBV/HCV carriers during and for several months after therapy.**
  - **There is a risk for tuberculosis (TB) activation. Test for latent/active TB prior to TNF inhibition. TB testing should not delay initiation of anti-TNFα agents for the management of irAEs.**
    - ◊ **Results of TB testing need not be finalized prior to dosing anti-TNFα agents in the acute setting.**
    - ◊ **Interferon-gamma release assays for TB testing are preferred.**
  - **For patients with severe irAEs not responsive to steroids within 48–72 hours, early (~72 h) initiation of anti-TNFα therapy (eg, infliximab 5 mg/kg) may be warranted in consultation with the relevant medical specialist.**
    - ◊ **A second dose of anti-TNFα therapy may be required, and can be administered 2 weeks after initial dose of infliximab.**
  - **Anti-TNFα agents should be avoided in patients with immune-related hepatitis.**
    - ◊ **Alpha-4 beta-7 integrin inhibitors (eg, vedolizumab) may be considered in these cases for management of concomitant hepatitis and immune-related colitis.**
    - ◊ **Other anti-TNFα agents may be of use in certain irAEs; see individual toxicity pages.**
- **Patients with pre-existing autoimmune conditions or organ transplant recipients may be candidates for immune checkpoint blockade.**
  - **Anti-CTLA-4–based therapy has a higher incidence of exacerbating baseline autoimmune conditions relative to anti-PD-1/PD-L1–based approaches.**
  - **Optimization of immunosuppression for pre-existing autoimmune conditions, with close follow-up with pertinent subspecialists, is recommended.**
    - ◊ **Goal of immunosuppressive regimen allowing for dose of prednisone <10 mg daily or equivalent prior to initiating cancer immunotherapy.**
  - **Patients with solid organ transplantation may be candidates for immunotherapy, particularly if no prior evidence of graft rejection and if on maintenance immunosuppression.**
    - ◊ **Graft failure while on cancer immunotherapy has been reported, and potential transplant organ loss may be an outcome of treatment with cancer immunotherapy and should be discussed with patient and organ transplant team.**
  - **Patients with autoimmune neurologic conditions or life-threatening autoimmune disorders, particularly if not controlled with immunosuppressive medications or requiring high doses of immunosuppression, are unlikely to be suitable candidates for cancer immunotherapy.**
  - **Patients with prior allogeneic stem cell transplant may be candidates for immunotherapy.**
    - ◊ **There is an increased risk of transplant-related complications, including potentially fatal graft vs. host disease (GVHD).**
    - ◊ **Careful discussion with patient and stem cell transplant physicians should precede initiation of immunotherapy.**
- **Patients with history of HIV or viral hepatitis may be candidates for immunotherapy.**
- **Vaccines that are inactivated or killed preparations are permissible during a course of immunotherapy. There is less clarity regarding live vaccine use and there should be an educated discussion with the patient prior to the administration of live vaccines.**

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PRINCIPLES OF IMMUNOTHERAPY PATIENT EDUCATION

Health Care Provider (HCP) Information

Prior to starting immunotherapy:

- Document any underlying medical conditions affecting any organ system (eg, pulmonary, cardiac, neurologic, musculoskeletal).
- It is important to take a history of any autoimmune diseases.
- Record all medications, including over-the-counter medications and herbal supplements.
- Patients of reproductive age should be advised to use effective birth control during and for at least 5 months after the final dose of immunotherapy.
- Breastfeeding is contraindicated during and for at least 5 months after the final dose of immunotherapy.
- Provide patients with and instruct them to carry a wallet card that outlines the type of immunotherapy they are receiving, potential irAEs, and contact numbers for the oncology health care team.

Instruct patients to notify the oncology health care team if:

- Any new signs or symptoms develop, including severe fatigue, headache, rash, cough, shortness of breath, chest pain, abdominal bloating, change in bowel pattern, weight loss, vision changes or eye pain, severe muscle weakness, severe muscle or joint pains, and/or mood changes.
  - irAEs can occur after completion of therapy. Patients should monitor symptoms for at least 1 year following the conclusion of immunotherapy.
- Patient is evaluated by other health care providers or admitted to the hospital.
- Any new medications are prescribed, or prior to receiving any immunizations or vaccinations.
  - Vaccines that are inactivated or killed preparations are permissible during a course of immunotherapy. There is less clarity regarding live vaccines and patients should have an educated discussion with their HCP before receiving a live vaccine.

Toxicity management:

- Mild to moderate adverse events
  - Provide symptomatic management.
  - Delay in immunotherapy may be required until adverse events resolve to grade 1 or pre-treatment baseline.
  - Corticosteroids may be required if adverse event does not improve. If hormone replacement is required, it is usually for lifetime and may continue beyond the completion of therapy with immune checkpoint inhibitors.
- Severe adverse events
  - Discontinue immunotherapy
  - Initiate corticosteroid therapy immediately. IV methylprednisolone should be considered until there is evidence of improvement in toxicity.
  - Additional immunosuppressant therapy may be required for steroid–refractory adverse events.
  - Inpatient care and additional supportive care may be required.
- Supportive care during immunosuppressant therapy may include the following:
  - Monitor blood glucose levels
  - Proton pump inhibitors or H2 blockers to prevent gastritis
  - Antimicrobial and antifungal prophylaxis to prevent opportunistic infections
  - Vitamin D and calcium supplementation to prevent osteoporosis

Continued

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PRINCIPLES OF IMMUNOTHERAPY PATIENT EDUCATION

Patient Education Concepts

Immunotherapy background:
- One of the functions of the immune system is to distinguish healthy cells from abnormal cells. Tumor cells have proteins on their surface that bind to immune cells, blocking the ability of the immune cell to recognize them as foreign.
- Immunotherapy is a type of therapy that works to boost the body's natural defenses to fight cancer. Immune checkpoint inhibitors are a class of medications that prevent tumors from "hiding" or "evading" the body's natural immune system.

Side effects (adverse events):
- Adverse events from immunotherapy differ from those of other types of cancer treatment and can affect one or several different organ systems.
- Amplifying the immune system can cause T cells to attack healthy cells in the body, causing inflammatory conditions that mimic a range of autoimmune conditions, some of which can be serious. These are known as immune-related adverse events (irAEs).
- irAEs can occur at any time during treatment or after treatment is completed.
- The severity of adverse events can range from asymptomatic to severe or life-threatening. They may be cumulative over the course of therapy.
- Combination therapy may increase the severity of adverse events. This can occur when immunotherapy is combined with chemotherapy, targeted agents, radiation therapy, or other types of immunotherapy.

Monitoring and treatment response:
- Therapy with immune checkpoint inhibitor requires close communications between patient/family and the treating center. Symptoms that patients may think are unrelated (for instance, diarrhea or nausea) are often signs of immune checkpoint inhibitor toxicity.
- Regular monitoring will be conducted to detect any potential irAEs and to assess treatment response.
- Laboratory tests will be obtained at regular intervals.
- Physical exams will include monitoring of organ function and weight.
- Treatment response time differs from standard cancer therapy; it may take longer to see a response than with other types of cancer therapy.
- Most irAEs can be managed effectively if detected and treated early.

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PRINCIPLES OF IMMUNOTHERAPY RECHALLENGE

General Principles

- **Exercise caution when considering resumption of immunotherapy after significant irAEs. Close follow-up should be performed when resuming immunotherapy to monitor for recurrent symptoms.**
  - **If re-challenged and toxicity returns, permanently discontinue class of immunotherapy.**
- **Permanent discontinuation of a given class of immunotherapy is typically warranted in the setting of severe irAEs induced by that class of immunotherapy and may be warranted in the setting of moderate irAEs. For example, if a patient experiences grade 3 or 4 toxicity from an ipilimumab-containing regimen, consideration may be given to later therapy with a PD-1 or PD-L1 monotherapy after resolution of the earlier toxicity.**
- **With some exceptions, resumption of immunotherapy following grade 2 irAEs can be considered upon resolution to ≤ grade 1.**
- **Consult with organ-specific specialists prior to resumption of immunotherapy as appropriate following an immunotherapy hold due to irAEs.**

Organ-Specific Considerations for Immunotherapy Rechallenge After a Hold

Skin	• Maculopapular rash and/or pruritus: consider resuming after symptoms have resolved to ≤ grade 1 (ie, once skin condition is mild/localized with only topical intervention indicated). • Permanent discontinuation of immunotherapy in the setting of severe or life-threatening bullous disease (grade 3–4), including all cases of SJS and TEN.
GI	• PD-1/PD-L1 agents: After grade 2–3 colitis, consider resumption of immunotherapy after symptoms have resolved to ≤ grade 1. In rare circumstances in which the patient cannot completely taper off steroids, immunotherapy may be resumed while patient is still on ≤10 mg steroid daily. • CTLA-4 agents: permanently discontinue if irAE is grade 2 or above.
Liver	• Transaminitis without elevated bilirubin: following a grade 2 irAE, consider resumption of immunotherapy after ALT/AST return to baseline and steroids, if used, have been tapered to ≤10 mg daily. • Permanent discontinuation is warranted in the setting of severe or life-threatening (grade 3–4) hepatitis.
Pancreas	• Grade 2 pancreatitis: consider resumption of immunotherapy if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase. Consider consultation with relevant pancreas specialist regarding resumption. • Permanent discontinuation is warranted for severe (grade 3–4) pancreatitis.

Continued

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PRINCIPLES OF IMMUNOTHERAPY RECHALLENGE

Organ-Specific Considerations for Immunotherapy Rechallenge After a Hold

Endocrine	• Thyroid: no discontinuation required for hypothyroidism. For symptomatic hyperthyroidism resembling Graves-like disease, consider holding immunotherapy and resuming after workup is complete and there is evidence for improvement in symptoms and TFTs. • Primary adrenal insufficiency: after appropriate replacement endocrine therapy is instituted, immunotherapy may continue. • Hypophysitis manifested by deficiency of TSH/ACTH and/or gonad-stimulating hormones, but without symptomatic pituitary swelling: immunotherapy may continue while replacement endocrine therapy is regulated. • Hypophysitis accompanied by symptoms of pituitary swelling (eg, headache, vision disturbance, and/or neurologic dysfunction): hold immunotherapy until resolution of symptoms after steroid therapy; consider resumption of immunotherapy after symptoms are controlled on <10-mg daily steroid dose. • T1DM with DKA: consider resuming once DKA has been corrected and glucose level has stabilized.
Lung	• Progressive grade 1 pneumonitis requiring a hold: consider resuming upon radiographic evidence of improvement. • Grade 2: resume once pneumonitis has resolved to ≤ grade 1. • Permanent discontinuation is warranted in the setting of severe (grade 3–4) pneumonitis.
Kidney	• Grade 1–2 renal irAE: hold immunotherapy per guidelines; upon resolution to ≤ grade 1, consider resuming concomitant with steroid if creatinine is stable. • Permanent discontinuation is warranted in the setting of severe (grade 3–4) proteinuria.
Eye	• Grade 2 irAE: hold immunotherapy per guideline; consider resumption of immunotherapy in consultation with ophthalmology upon resolution to ≤ grade 1. • Permanent discontinuation of immunotherapy is warranted in the setting of severe (grade 3–4) uveitis or episcleritis.
Nervous System	• Myasthenia gravis: consider resuming immunotherapy after moderate (grade 2) AE based on steroid responsiveness. Permanently discontinue immunotherapy after grade 3–4 AE. • GBS: permanently discontinue immunotherapy for any grade GBS. • Peripheral neuropathy: following hold for grade 1–2 AE, consider resuming if symptoms resolve to ≤ grade 1 or if patient has well-controlled isolated painful sensory neuropathy. • Aseptic meningitis: consider resuming following mild to moderate AE if symptoms resolve to grade 0. • Encephalitis: permanent discontinuation is warranted in the setting of moderate to severe encephalitis (grade 2–4). • Transverse myelitis: discontinuation of immunotherapy following any-grade transverse myelitis.
Cardiovascular	• Grade 1 myocarditis: consider resuming upon resolution of symptoms. • Permanent discontinuation is warranted in the setting of grade 2–4 myocarditis.
Musculoskeletal	• Inflammatory arthritis (moderate to severe irAE requiring hold): resume upon stabilization or adequate management of symptoms. Permanent discontinuation may be warranted for severe inflammatory arthritis that significantly impairs ADLs and quality of life.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
Management of Immunotherapy-Related Toxicities

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PRINCIPLES OF ROUTINE MONITORING

Baseline 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)	Clinical exam at each visit with AE symptom assessment	Follow-up testing based on findings, symptoms
Imaging: • CT imaging • Brain MRI if indicated	Periodic imaging as indicated	Follow-up testing as indicated based on imaging findings
General bloodwork: • CBC with differential • Comprehensive metabolic panel • Infectious disease screening as indicated	Repeat every 2–3 weeks during immunotherapy, then in 6–12 weeks or as indicated	HbA1c for elevated glucose
Dermatologic • 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.
Thyroid • Thyroid-stimulating hormone (TSH), free thyroxine (T4)	Every 4–6 weeks during immunotherapy, then follow-up every 12 weeks as indicated	Total T3 if abnormal thyroid function suspected. TPO antibodies if TSH is high, TRAbs if TSH is low.
Adrenal/Pituitary • Adrenal: Morning adrenocorticotropic hormone (ACTH) and cortisol • Pituitary: TSH, free T4, and total T3	Every 2–3 weeks during immunotherapy, then follow-up every 6–12 weeks	Luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone
Pulmonary • Oxygen saturation (resting and with ambulation) • Pulmonary function tests (PFTs)	Repeat oxygen saturation tests based on symptoms	Chest CT to evaluate for pneumonitis, biopsy if needed to exclude other causes
Cardiovascular • ECG and total CK • Cardiac biomarkers (ie, troponin I or T) if risk factors present	Consider periodic testing for those with abnormal baseline or symptoms	Brain natriuretic peptide (BNP) or N-terminal pro B-type natriuretic peptide (NT pro-BNP)
Pancreatic • Baseline amylase/lipase	No routine monitoring needed if asymptomatic	Amylase, lipase, and consider abdominal imaging for suspected pancreatitis
Musculoskeletal • Joint examination/functional assessment as needed for patients with pre–existing disease	No routine monitoring needed if asymptomatic	N/A

[a]Prior to initiating treatment, counsel patients on the warning signs and symptoms of immune-related adverse events.
[b]Closer monitoring may be required for patients with combination immunotherapy regimens. Refer to prescribing information for each individual immuntherapy agent for monitoring recommendations.

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Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

A discussion of the evidence to accompany and support the NCCN Guidelines recommendations is currently under development. A current review of the evidence for managing immune-related adverse events, published by our collaborators at the American Society of Clinical Oncology, can be found here.

Reference

Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. Journal of Clinical Oncology 2018 Feb 14. Available at: http://ascopubs.org/doi/abs/10.1200/JCO.2017.77.6385.