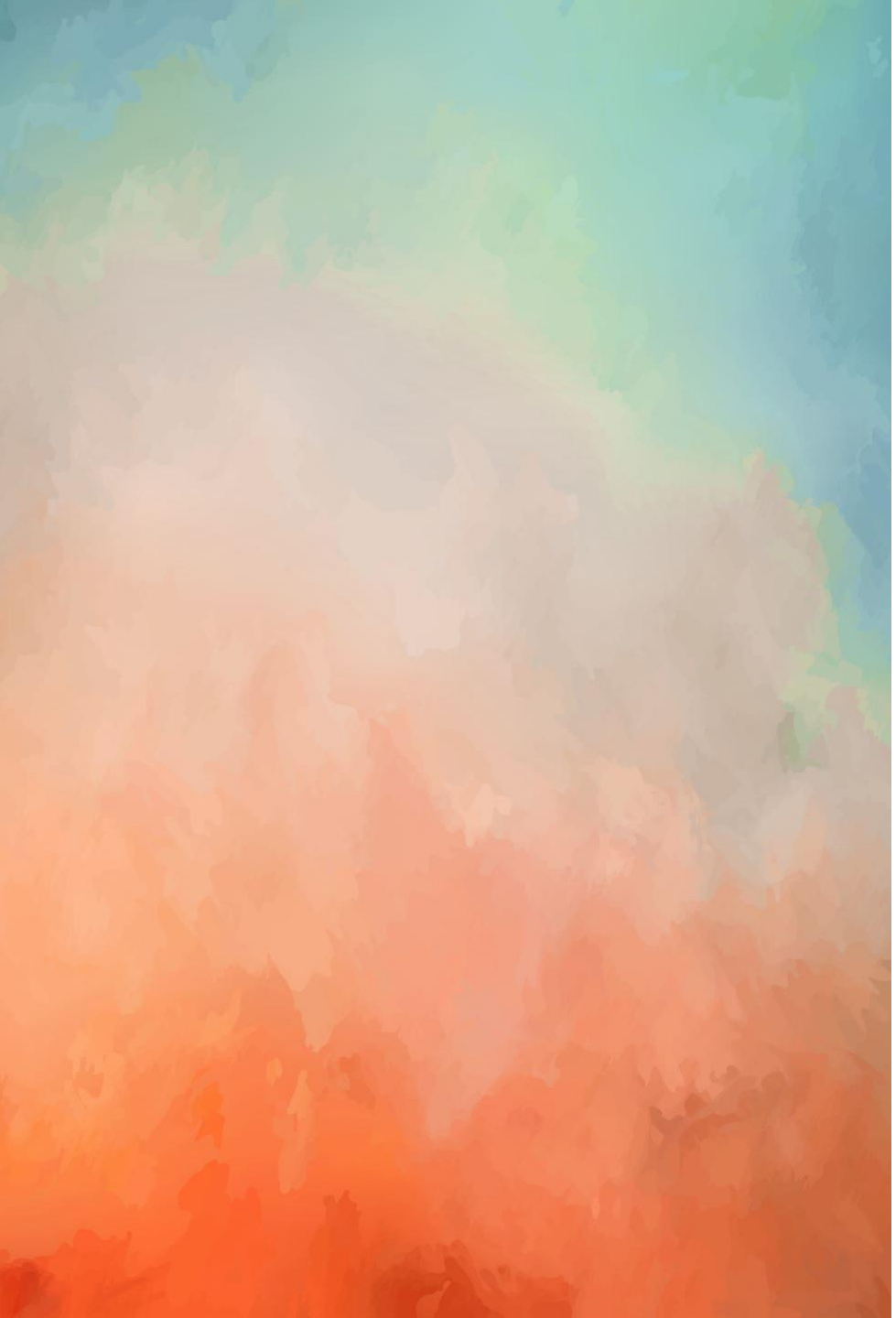


Mitigating Adverse Events of Immunotherapies (Case Studies)

FLASCO FALL SESSION

JEANELLE KING, PA-C

Question 1

Patient CN has stage IV NSCLC and was started on immunotherapy with a 2-drug regimen of ipilimumab and nivolumab. About 4 days after her 3rd cycle of treatment, she began to develop loose stools that evolved into watery diarrhea up to 6 times a day. What should she do?

A. Call her GI so he can get an appointment first available

B. Call her oncology team immediately because this may be related to the immunotherapy

C. Wait it out because this is likely her body "flushing out" toxins of treatment because she didn't have side effects from treatment the first 2 times

Question 2

The side effect profile for patients on checkpoint inhibitors is typically:

A. Severe pancytopenia

B. Inflammatory/Immune mediated adverse events such as rash, arthralgias, pneumonitis, colitis, and endocrinopathies

C. Severe mucositis

Question 3

62-year-old man on adjuvant pembrolizumab for stage IIIC melanoma presented to the office with complaints of fever (Tmax 102.5F), chills, nausea, vomiting, jaundice, and the following labs. In addition to corticosteroids, what other treatment may be given?

A. Infliximab

B. Acetaminophen for fever

C. Mycophenolate

Component Ref Range & Units	8 mo ago (5/6/22)	8 mo ago (5/2/22)
Glucose 65 - 99 mg/dL	134 ^	125 ^
Sodium 135 - 146 mmol/L	133 v	135
Potassium 3.5 - 5.5 mmol/L	3.6	4.1
Chloride 98 - 110 mmol/L	99	100
CO2 19 - 34 mmol/L	27	27
Anion Gap 6 - 22	7	8
BUN 8 - 23 mg/dL	15	12
Osmolality Calculation 275 - 295 mOsm/kg	269 v	271 v
Creatinine 0.40 - 1.10 mg/dL	1.02	0.94
Calcium, Serum 8.6 - 10.3 mg/dL	8.4 v	9.0
Protein, Total 6.1 - 8.1 g/dL	5.6 v	5.6 v
Albumin 3.5 - 5.2 g/dL	3.2 v	3.3 v
Bilirubin, Total 0.0 - 1.2 mg/dL	10.0 ^	7.8 ^
AST (SGOT) 10 - 40 U/L	555 ^	588 ^
ALT (SGPT) 0 - 41 U/L	549 ^	520 ^
Alkaline Phosphatase, S 40 - 130 U/L	649 ^	623 ^
GFR MDRD Non Af Amer >59 mL/min/1.73m2	79	87
GFR MDRD Af Amer >59 mL/min/1.73m2	>90	>90 CM

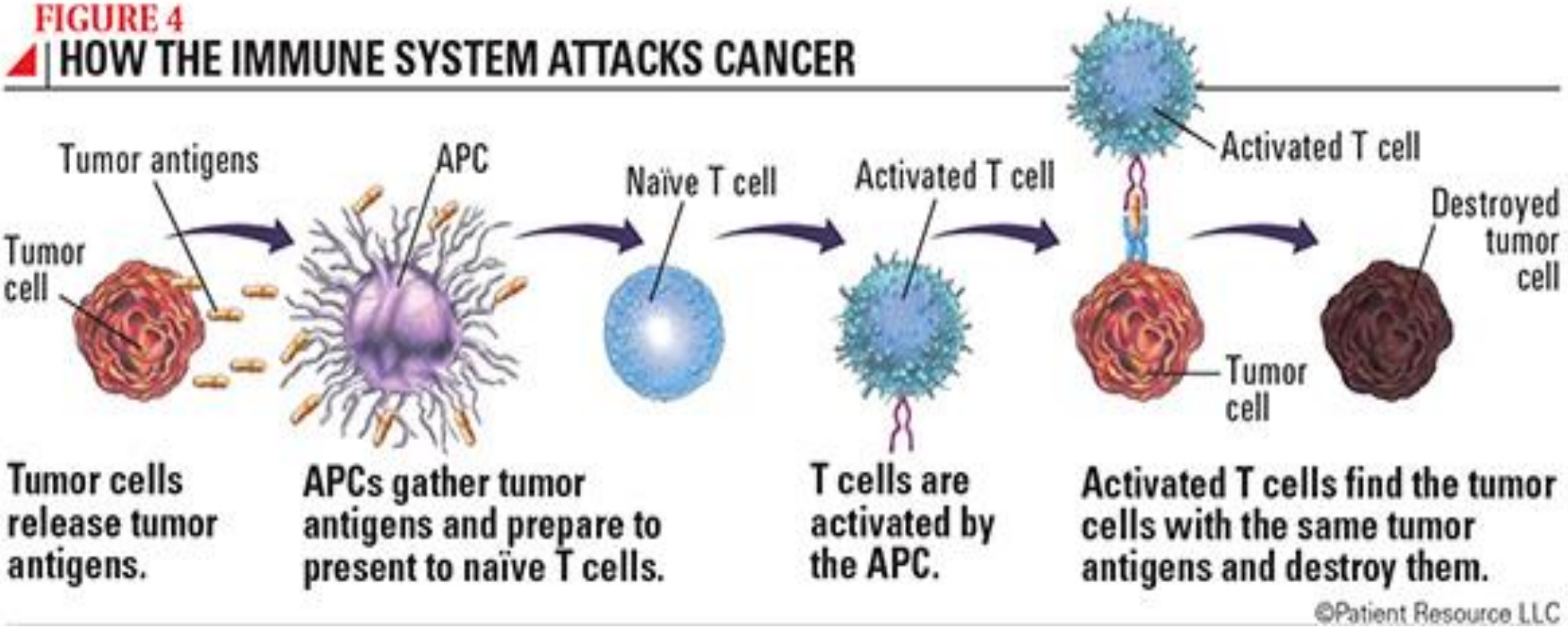


FIGURE 4
HOW THE IMMUNE SYSTEM ATTACKS CANCER
Tumor antigens
APC
Naïve T cell
Activated T cell
Activated T cell
Destroyed tumor cell
Tumor cell
Tumor cell
Tumor cells release tumor antigens.
APCs gather tumor antigens and prepare to present to naïve T cells.
T cells are activated by the APC.
Activated T cells find the tumor cells with the same tumor antigens and destroy them.
©Patient Resource LLC

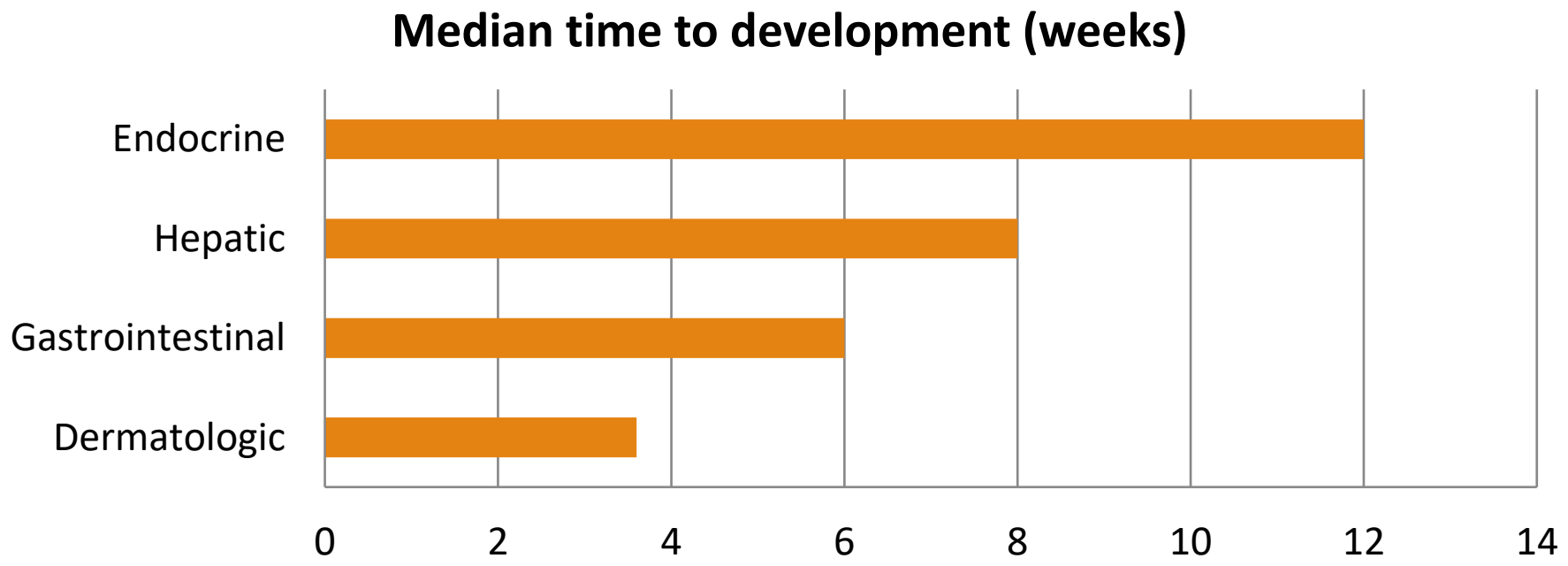
Basic Principles

Adverse events related to the use of immune checkpoint inhibitors are called immune-related adverse events (irAEs)
irAEs are graded according to the Common Terminology Criteria for Adverse Events (CTCAE)
irAEs are usually a result of overstimulating the immune system and are inflammatory in nature
Most treatments for irAEs are geared toward suppressing the immune system
irAEs can affect any organ system but GI, derm, hepatic, endocrine and pulmonary toxicities predominate
Majority of irAEs are mild to moderate
Severity can be asymptomatic to life-threatening; prompt recognition is crucial
Onset is variable; can occur after cessation of therapy

irAEs are Different from AEs of other Cancer Therapies

	Chemotherapy	Immunotherapy
Incidence (moderate/severe AEs)	Almost all patients	Majority without
AE profile	Well-described	Variable
Affected organ systems	Few organs affected	Any organ
Time Course	Well established	Variable
	Predictable	Relatively unpredictable

Immune checkpoint inhibitors-irAEs

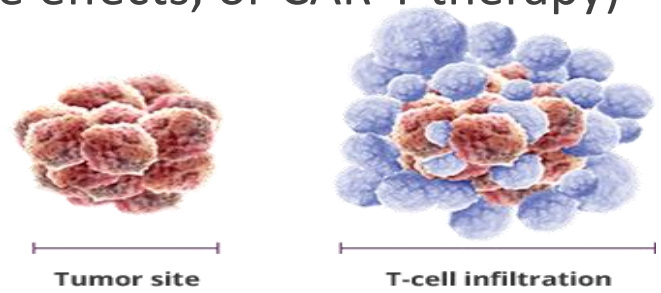


Weber J et al, J Clin Oncol 2012

Management of Immune Related Adverse Events

Basic Principles

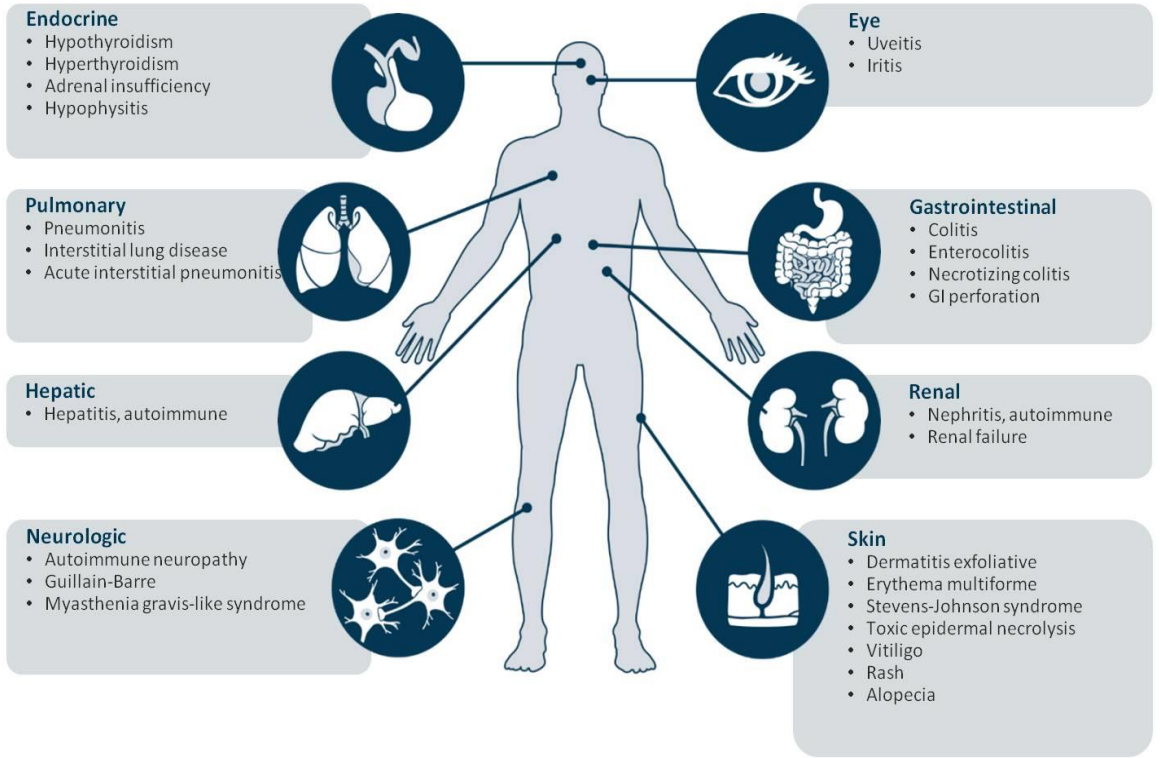
- Three classes of adverse events from immune therapy
    1. Sensitivity reaction to agent
    2. From direct or induced cytokine effects (IL-2, interferon-like effects, or CAR-T therapy)
    3. Inflammatory/autoimmune (MOST COMMON)
- Management of events
    - Supportive care for symptoms
    - Treatment directed at underlying cause (steroids +/-other immune suppressive agents)
- **Prophylactic immune suppression is contra-indicated**
    - Antagonize anti-tumor effects of immune therapy



Sznol, et al. 2013

Immune-Related Adverse Events

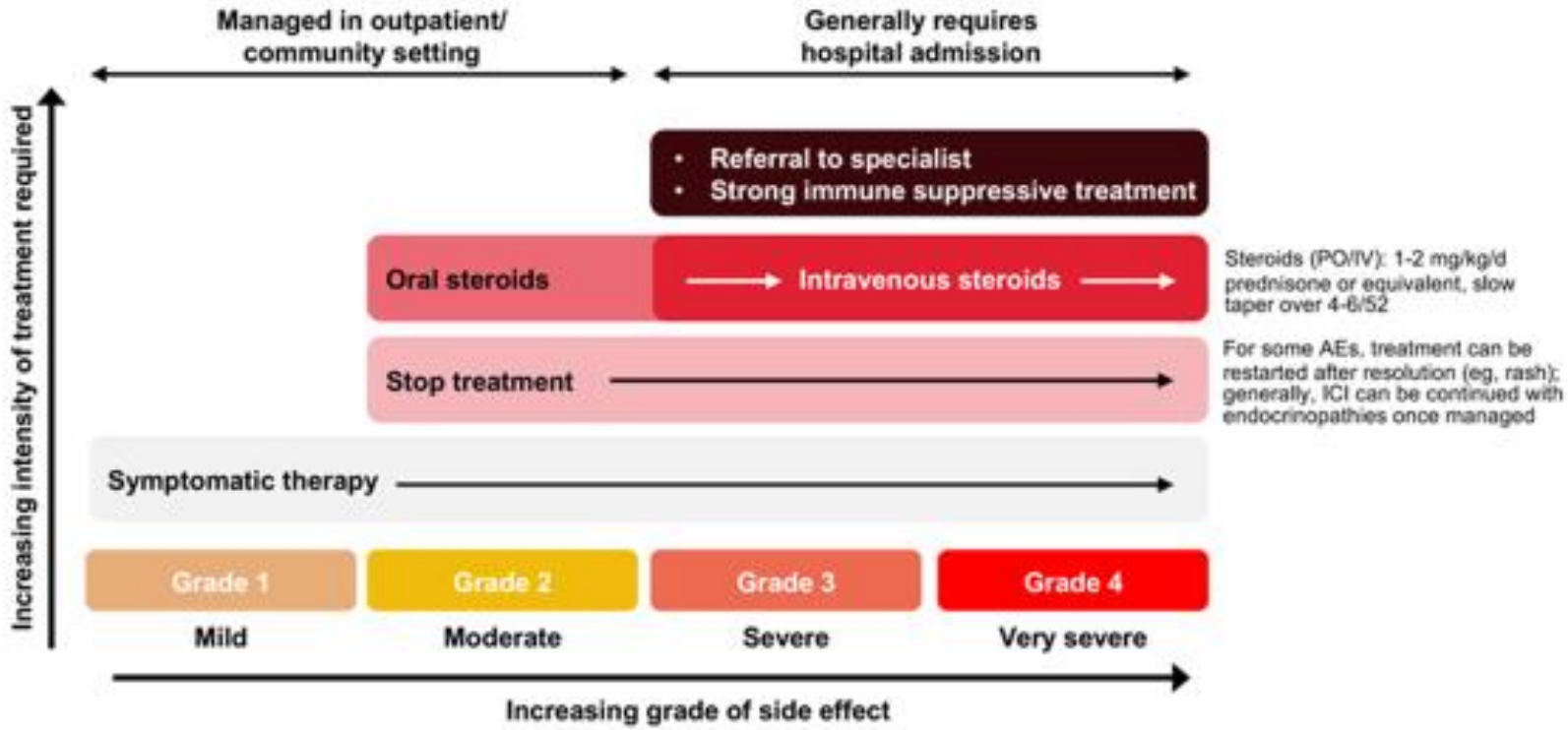
- Result from dysregulation of immunity and tolerance
- Wide spectrum of toxicity



Guidelines

- European Society for Medical Oncology (ESMO)
- American Society of Clinical Oncology (ASCO)
- Society for Immunotherapy of Cancer (SITC)
- National Comprehensive Cancer Network (NCCN)

General Recommendations for Treatment of irAEs[1]



1. Adapted from: Champiat S. European Society for Medical Oncology (ESMO) Patient Guide Series. https://www.esmo.org/content/download/124130/2352601/1/ESMO-Patient-Guide-on-Immunotherapy-Side-Effects.pdf.

PeerView.com

Case 1

59 y/o female with stage IV melanoma treated with combination immunotherapy with ipilimumab 1mg/kg and nivolumab 3 mg/kg on 11/21/2018.

On 12/12/2018 visit, patient presented for cycle 2 of treatment. Complained of grade 2 pruritus and grade 1 dry cough.

Work-up:

-Pulse oximetry (rest and after exertion)→**94% and 92% respectively**

-Preliminary CXR→*no significant findings*

- Treatment:

-Methylprednisolone (to address pruritus and cough).

-Cycle 2 of ipi/nivo.

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Management of Immune Checkpoint Inhibitor-Related Toxicities

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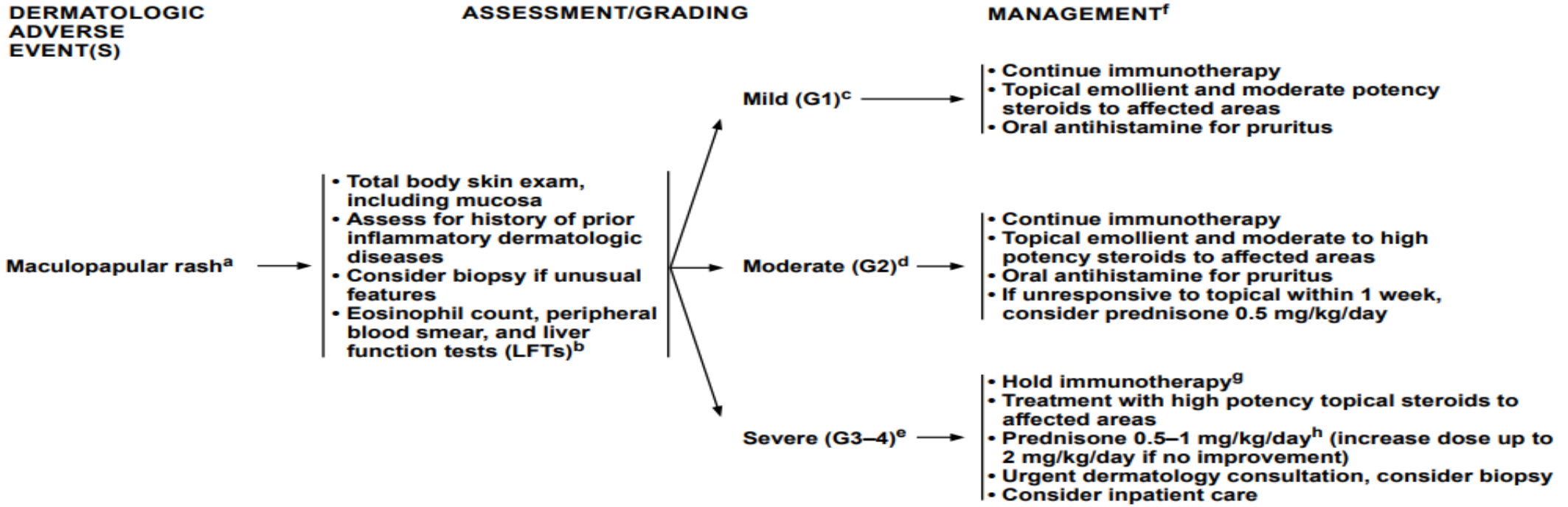

[a] Characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous AEs, frequently affecting the upper trunk, spreading centripetally, and may be associated with pruritus.

[b] These features can be used to assist with the diagnosis of DRESS (drug rash with eosinophilia and systemic symptoms) syndrome. This syndrome is typically characterized by a maculopapular rash that involves the face and ears and typically presents with swelling of the face and hands within 2–8 weeks after drug exposure. Note that certain classes of high-risk medications initiated in the prior few weeks may also cause maculopapular rash, including antiepileptic drugs: carbamazepine, phenytoin, lamotrigine, phenobarbital; antihyperuricemics: allopurinol, febuxostat; sulfonamides and sulphones: trimethoprim sulfamethoxazole, sulfasalazine, dapsone; and other antibiotics: vancomycin, minocycline, other beta-lactams. Kardaun SH, et al. Br J Dermatol 2013;169:1071-1080.

[c] Macules/papules covering <10% BSA with or without symptoms (eg, pruritus, burning, tightness).

[d] Macules/papules covering 10%–30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting iADLs.

[e] Macules/papules covering >30% BSA with or without associated symptoms; limiting self-care activities of daily living (ADLs).

[f] Principles of Immunosuppression (IMMUNO-A).

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

[h] Treat until symptoms improve to Grade ≤1, then taper over 4–6 weeks.

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PULMONARY ADVERSE EVENT(S)

Pneumonitis[a]

GRADING	MANAGEMENT[f]
Mild (G1)[b]	• Consider holding immunotherapy[g] • Reassess in 1–2 weeks ▸ H&P ▸ Pulse oximetry (resting and with ambulation) • Consider chest CT with contrast[h,i] ▸ Consider repeat chest CT in 4–6 weeks or as clinically indicated if patient develops symptoms
Moderate (G2)[c,d]	• Hold immunotherapy[g] • Consider pulmonary consultation • Minimally invasive evaluation ▸ Consider infectious workup: ◊ Nasal swab for potential viral pathogens[j] ◊ Sputum culture (including bacterial, fungal, and acid-fast bacilli [AFB]), blood culture, and urine antigen test (pneumococcus, legionella) ▸ Consider chest CT with contrast[h,i] and repeat chest CT in 3–4 weeks • Invasive evaluation ▸ Consider bronchoscopy with BAL (send for institutional immunocompromised panel[k]) and consider transbronchial lung biopsy if clinically feasible • Consider empiric broad-spectrum antibiotics (including coverage for atypical pathogens) if infection has not yet been fully excluded • Prednisone/IV methylprednisolone 1–2 mg/kg/day[l] • Monitor every 3–7 days with[m]: ▸ H&P ▸ Pulse oximetry (resting and with ambulation) • If no improvement after 48–72 hours of steroids, treat as grade 3
Severe (G3–4)[e]	ICI_PULM-2

[a] Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging). Symptoms may include dry cough, shortness of breath, fever, chest pain, and increased oxygen requirement. The imaging features of pneumonitis are known to be variable and may include ground-glass opacities, organizing pneumonia, hypersensitivity, reticulonodular changes, or a mixture of all these appearances.
[b] Asymptomatic; confined to one lobe of the lung or <25% of lung parenchyma.
[c] Presence of new/worsening symptoms.
[d] Consider cardiac etiologies.
[e] G3-severe symptoms involve all lung lobes or >50% of lung parenchyma, limiting self-care ADLs, oxygen indicated; G4–life-threatening respiratory compromise.
[f] Principles of Immunosuppression (IMMUNO-A).
[g] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[h] CT with contrast to rule out other etiologies if not contraindicated.
[i] See Pre-Therapy Assessment: Pulmonary on IMMUNO-1.
[j] Viral pathogen assessment should include COVID-19.
[k] Immunocompromised panel may include CBC with differential, bacterial culture, and Gram stain; AFB culture and stain; fungal immunoassay, culture, and silver stain; CMV, HSV, *Pneumocystis jirovecii* pneumonia (PJP), and respiratory virus PCR.
[l] Treat until symptoms improve to Grade ≤1, then taper over 4–6 weeks.
[m] If clinically indicated and appropriate, monitoring can be done with telemedicine.

ASCO Guidelines

TABLE 3. Lung Toxicities

3.1. Pneumonitis

Workup and evaluation

Should include the following: Pulse oximetry and CT chest[123] preferably with contrast if concerned for other etiologies such as pulmonary embolus.

For G2 or higher, may include the following infectious workup: nasal swab, sputum culture, and sensitivity, blood culture and sensitivity, urine culture, and sensitivity.

COVID-19 evaluation—per institutional guidelines where relevant.

Grading	Management
G1: Asymptomatic; confined to one lobe of the lung or < 25% of lung parenchyma; clinical or diagnostic observations only	Hold ICPi or proceed with close monitoring. Monitor patients weekly with history and physical examination, pulse oximetry; may also offer chest imaging (CXR, CT) if uncertain diagnosis and/or to follow progress. Repeat chest imaging in 3-4 weeks or sooner if patient becomes symptomatic. In patients who have had baseline testing, may offer a repeat spirometry or DLCO in 3-4 weeks. May resume ICPi with radiographic evidence of improvement or resolution if held. If no improvement, should treat as G2.
G2: Symptomatic; Involves more than one lobe of the lung or 25%-50% of lung parenchyma; medical intervention indicated; limiting instrumental ADL	Hold ICPi until clinical improvement to ≤ G1. Prednisone 1-2 mg/kg/d and taper over 4-6 weeks. Consider bronchoscopy with BAL ± transbronchial biopsy. Consider empiric antibiotics if infection remains in the differential diagnosis after workup. Monitor at least once per week with history and physical examination, pulse oximetry, consider radiologic imaging; if no clinical improvement after 48-72 hours of prednisone, treat as grade 3. Pulmonary and infectious disease consults if necessary.
G3: Severe symptoms; Hospitalization required: Involves all lung lobes or > 50% of lung parenchyma; limiting self-care ADL; oxygen indicated. G4: Life-threatening respiratory compromise; urgent intervention indicated (intubation)	Permanently discontinue ICPi. Empiric antibiotics may be considered. Methylprednisolone IV 1-2 mg/kg/d. If no improvement after 48 hours, may add immunosuppressive agent. Options include infliximab or mycophenolate mofetil IV or IVIG or cyclophosphamide (See Table A2 for dosing). Taper corticosteroids over 4-6 weeks[a] Pulmonary and infectious disease consults if necessary. May consider bronchoscopy with BAL ± transbronchial biopsy if patient can tolerate.

Abbreviations: ADL, activity of daily living; BAL, bronchoalveolar lavage; CT, computed tomography; CXR, chest x-ray; DLCO, diffusing capacity of lung for carbon monoxide; ICPi, immune checkpoint inhibitor; IV, intravenous; IVIG, intravenous immune globulin.

[a]Subset of patients may develop chronic pneumonitis and may require longer taper. Chronic pneumonitis is a described phenomenon where the incidence is not known, but < 2%.[111]

SITC Guidelines

Explore the App

The SITC Clinical Practice Guidelines (CPG) Mobile App is the first and only tool of its kind, offering direct, easy, portable access to SITC's CPGs via phone or tablet. Highlighting key information from SITC's published guidelines, the SITC CPG Mobile App features evidence- and expert consensus-based recommendations on important aspects of immunotherapy treatment as well as interactive tools and companion educational resources. Covering a range of topics, from biomarkers and therapy selection to quality of life and management of immune-related adverse events, busy clinicians will find the SITC CPG Mobile App as the go-to resource on when and how to use immunotherapy to help improve outcomes for patients with cancer.

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Case 1

12/17, patient called stating pruritus worse despite methylprednisolone and cough unchanged.

- Treatment:

  -Prednisone increased to 20 mg PO and Doxepin 6mg

- At 12/19 FU, still no relief and cough persists

  -Treatment: Methylprednisolone 40 mg IV in clinic and prednisone 40 mg PO.

- 12/24 CT→ "RIGHT MIDDLE AND LOWER LOBE CHANGES…IMPROVEMENT COMPARED TO 10/27/18 AND 7/25/18, LIKELY REPRESENTING CHRONIC POST RADIATION CHANGES WITH POSSIBLE SUPERIMPOSED COMPONENT OF CHRONIC BRONCHITIS".

  -Treatment: Prednisone increased to 60 mg PO.

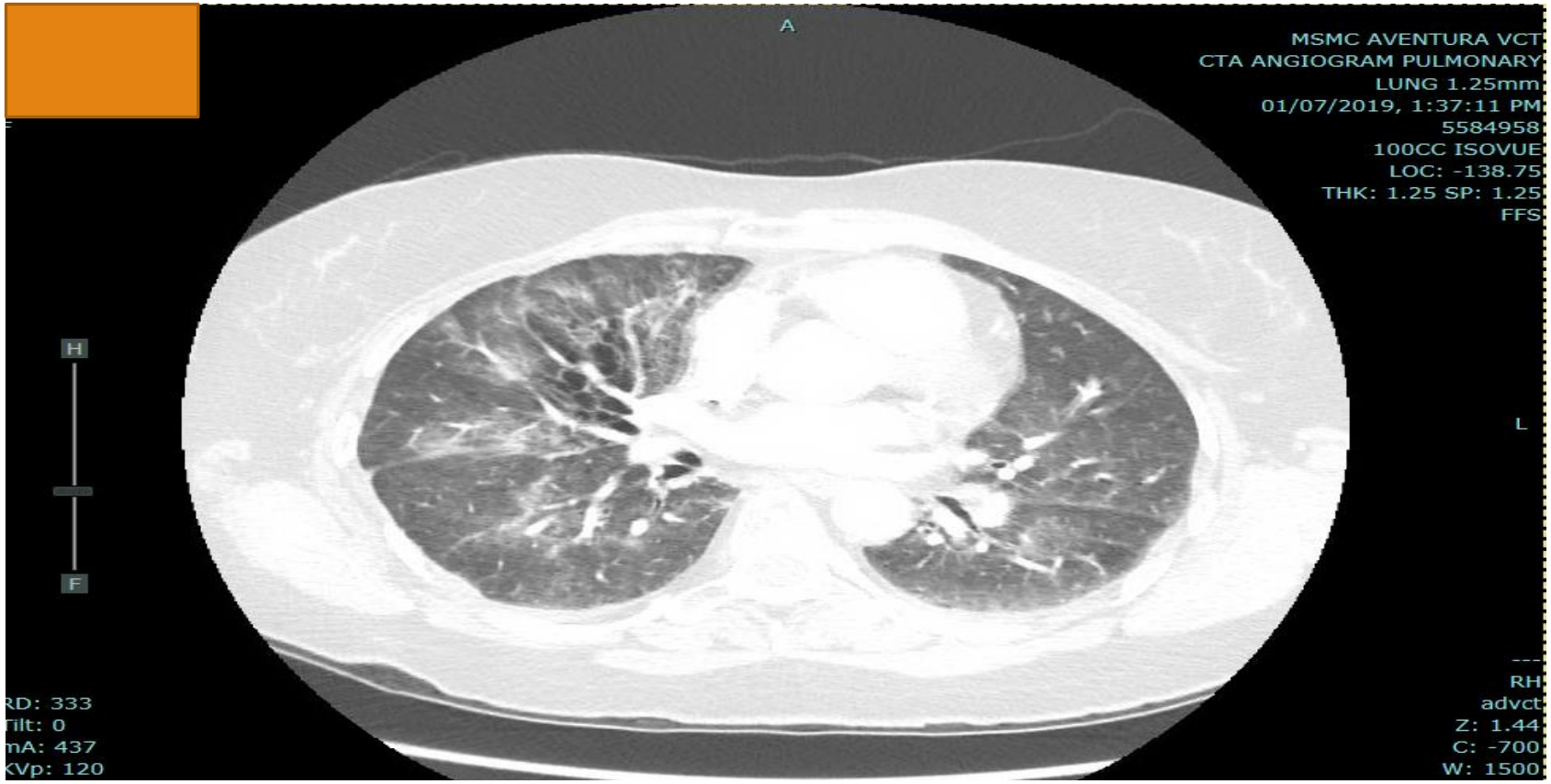
Case 1

Pruritus better with doxepin and prednisone 60 mg, but cough now developed into SOB and chest pain.

While seeing the psychiatrist in clinic on 1/7/2019, she was noted to have obvious SOB and tachypnea.

Taken to the ED and CT angiogram demonstrated

Case 1


A
MSMC AVENTURA VCT
CTA ANGIOGRAM PULMONARY
LUNG 1.25mm
01/07/2019, 1:37:11 PM
5584958
100CC ISOVUE
LOC: -138.75
THK: 1.25 SP: 1.25
FFS
H
F
L
RD: 333
Tilt: 0
mA: 437
KVp: 120
RH
advct
Z: 1.44
C: -700
W: 1500

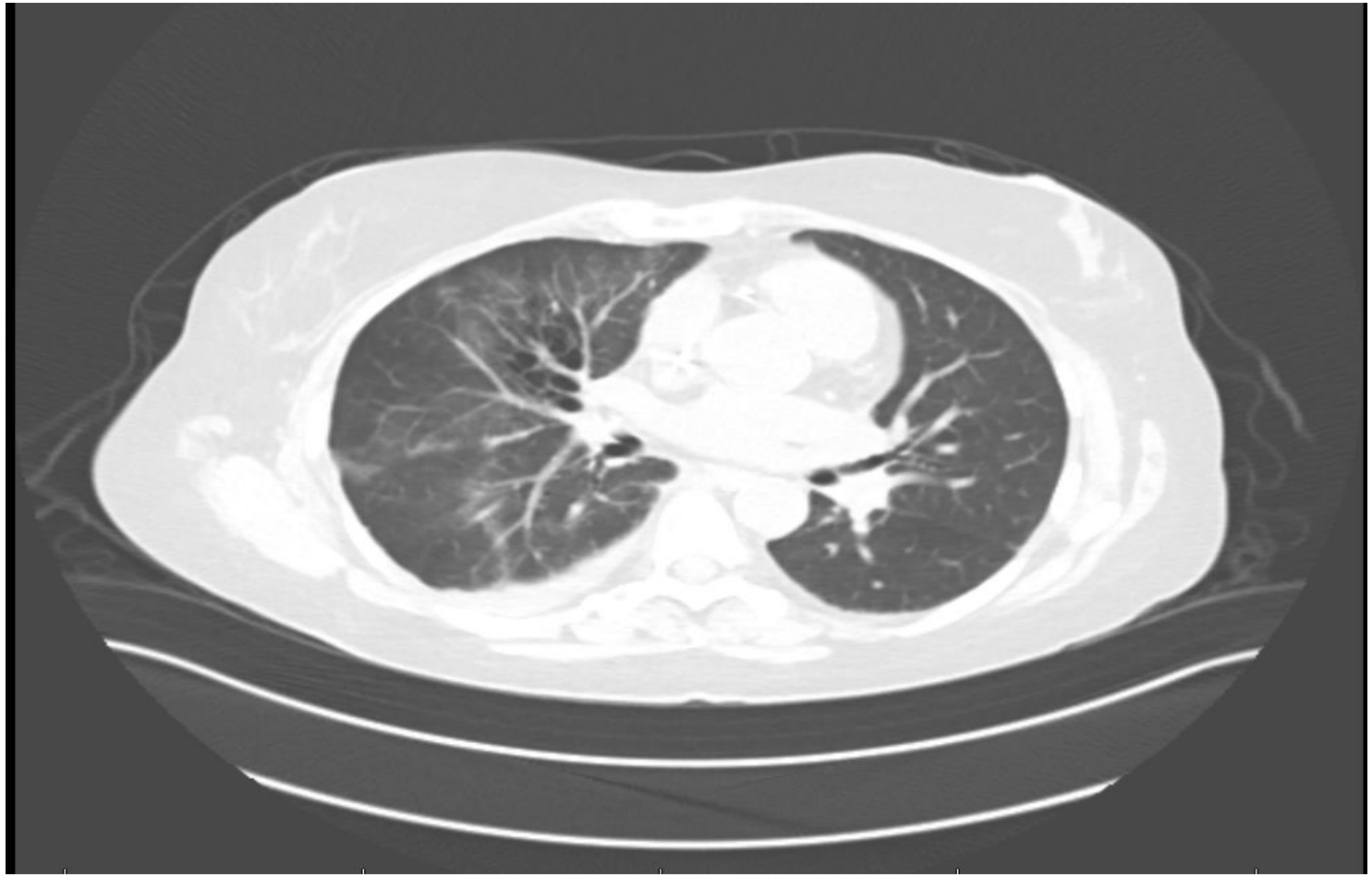
Case 1

Patient admitted from 1/7-1/11 and treated with IV corticosteroids

Patient admitted from 1/7-1/11 followed by 2 week in rehab for steroid myopathy.

Discharged home on Prednisone 100 mg BID

Case 1 post-treatment scans



Case 1

At office FU on 1/30, patient was still requiring prednisone 80 mg BID.

LFTs demonstrated grade 1 elevation

Component	Value	Ref Range & Units	Status	Collected	Lab
Sodium	138	136 - 145 MMOL/L	Final	01/30/2019 10:30 AM	LCB
Potassium	4.1	3.5 - 5.1 MMOL/L	Final	01/30/2019 10:30 AM	LCB
Chloride	101	98 - 107 MMOL/L	Final	01/30/2019 10:30 AM	LCB
CO2	29.7	21.0 - 32.0 MMOL/L	Final	01/30/2019 10:30 AM	LCB
Glucose	120 ^	74 - 106 MG/DL	Final	01/30/2019 10:30 AM	LCB
BUN	19.0 ^	7.0 - 18.0 MG/DL	Final	01/30/2019 10:30 AM	LCB
Creatinine	0.77	0.55 - 1.02 MG/DL	Final	01/30/2019 10:30 AM	LCB
Calcium	8.7	8.5 - 10.1 MG/DL	Final	01/30/2019 10:30 AM	LCB
AST (SGOT)	40.0 ^	15.0 - 37.0 U/L	Final	01/30/2019 10:30 AM	LCB
ALT (SGPT)	112.0 ^	13.0 - 56.0 U/L	Final	01/30/2019 10:30 AM	LCB
Protein, Total	6.5	6.4 - 8.2 G/DL	Final	01/30/2019 10:30 AM	LCB
Albumin	3.4	3.4 - 5.0 G/DL	Final	01/30/2019 10:30 AM	LCB

Case 1

But on 2/13 FU, while on prednisone 50 mg BID, LFTs markedly increased…

Component Results

Component	Value	Ref Range & Units	Status	Collected
Sodium	137	136 - 145 MMOL/L	Final	02/13/2019 1:43 PM
Potassium	3.7	3.5 - 5.1 MMOL/L	Final	02/13/2019 1:43 PM
Chloride	100	98 - 107 MMOL/L	Final	02/13/2019 1:43 PM
CO2	28.8	21.0 - 32.0 MMOL/L	Final	02/13/2019 1:43 PM
Glucose	147 ^	74 - 106 MG/DL	Final	02/13/2019 1:43 PM
BUN	14.0	7.0 - 18.0 MG/DL	Final	02/13/2019 1:43 PM
Creatinine	0.71	0.55 - 1.02 MG/DL	Final	02/13/2019 1:43 PM
Calcium	9.0	8.5 - 10.1 MG/DL	Final	02/13/2019 1:43 PM
AST (SGOT)	479.0 ^	15.0 - 37.0 U/L	Final	02/13/2019 1:43 PM
ALT (SGPT)	1,631.0 ^^	13.0 - 56.0 U/L	Final	02/13/2019 1:43 PM
NOTIFIED DIEGO BUSTELLO RN ON 02/13/2019 @1448 BY RM				
Protein, Total	7.2	6.4 - 8.2 G/DL	Final	02/13/2019 1:43 PM
Albumin	3.2 v	3.4 - 5.0 G/DL	Final	02/13/2019 1:43 PM
Globulin	4.0 ^	2.3 - 3.5 G/DL	Final	02/13/2019 1:43 PM
Alkaline Phosphatase	259 ^	46 - 116 U/L	Final	02/13/2019 1:43 PM
Bilirubin, Total	1.64 ^	0.20 - 1.00 MG/DL	Final	02/13/2019 1:43 PM
Anion Gap	11.9	10.0 - 20.0 MMOL/L	Final	02/13/2019 1:43 PM
BUN/Creatinine Ratio	19.7	8.0 - 30.0	Final	02/13/2019 1:43 PM
Albumin/Globulin Ratio	0.8 v	1.0 - 2.5	Final	02/13/2019 1:43 PM
Calculated Osmolality	277	275 - 295 MOSM/KG	Final	02/13/2019 1:43 PM
EGFR	>60	>60 mL/min/1.73m2	Final	02/13/2019 1:43 PM
If patient is African American, please multiply this result by 1.212.				

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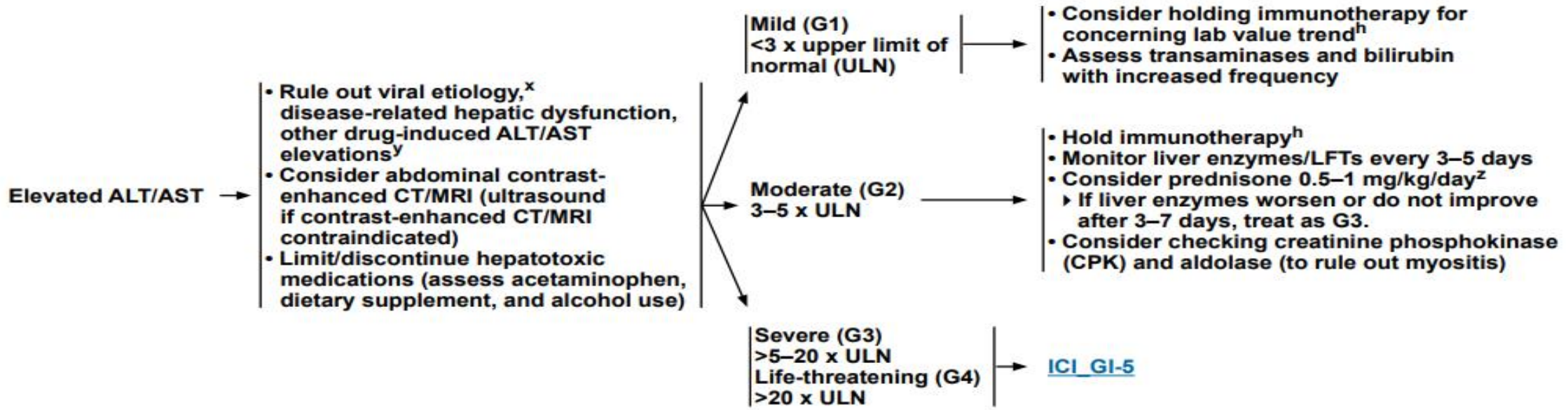
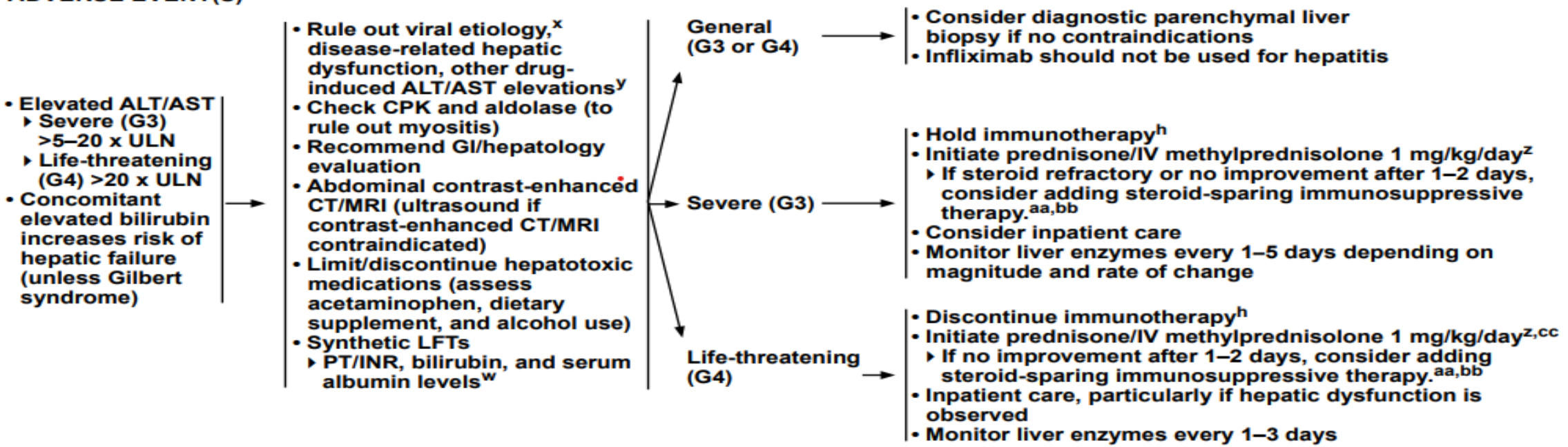


[g] Principles of Immunosuppression (IMMUNO-A).
[h] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[v] Consider initiating steroids while waiting for results in cases of life-threatening ALT/AST elevations.
[w] Hyperbilirubinemia related to hepatic origin should be of conjugated predominance (or conjugated hyperbilirubinemia).
[x] Viral etiology may include hepatitis A/B/C; cytomegalovirus (CMV); Epstein-Barr virus (EBV); HSV; varicella zoster virus (VZV); HIV; anti-HAV IgM; HBsAg; anti-HBc; and hepatitis C virus (HCV) RNA.
[y] Laboratory tests to consider include ceruloplasmin, alpha-1-antitrypsin, ferritin, ANA titer, mitochondrial Ab M2, smooth muscle Ab, liver/kidney microsome type 1 Ab, IgG, IgM, tissue transglutaminase IgA and IgG, TSH, iron, transferrin, HbA1c, and lipid panel (screening for metabolic dysfunction-associated fatty liver disease).
[z] When liver enzymes show sustained improvement or return to ≤ G1, initiate steroid tapering and continue to taper over at least 1 month with frequent follow-up to guide taper duration. Re-escalate as needed.



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[w] Hyperbilirubinemia related to hepatic origin should be of conjugated predominance (or conjugated hyperbilirubinemia).
[x] Viral etiology may include hepatitis A/B/C; CMV; EBV; HSV; VZV; HIV; anti-HAV IgM; HBsAg; anti-HBc; and HCV RNA.
[y] Laboratory tests to consider include ceruloplasmin, alpha-1-antitrypsin, ferritin, ANA titer, mitochondrial Ab M2, smooth muscle Ab, liver/kidney microsome type 1 Ab, IgG, IgM, tissue transglutaminase IgA and IgG, TSH, iron, transferrin, HbA1c, and lipid panel (screening for metabolic dysfunction-associated fatty liver disease).
[z] When liver enzymes show sustained improvement or return to ≤ G1, initiate steroid tapering and continue to taper over at least 1 month with frequent follow-up to guide taper duration. Re-escalate as needed.
[aa] Mycophenolate mofetil treatment (0.5–1 g every 12 hours) can be considered in patients who have persistent severe hepatitis despite high-dose steroids. When LFTs improve to grade 1 or less and after completion of a steroid taper, consider discontinuation of mycophenolate at the same time.
[bb] Maximal efficacy of steroid-sparing immunosuppressive therapy (eg, azathioprine, mycophenolate, tacrolimus, ATG) can be delayed and may require prolonged therapy (≥1 week) in the treatment of irAEs.
[cc] Consider early concomitant use of mycophenolate with the initiation of steroids.

Case 1

The patient was readmitted, steroids continued but at higher doses, mycophenolate started, and viral etiology ruled out.

After a 12-day admission, the patient was discharged home.

As of 3/6, pneumonitis grade 1, LFTS still with grade 3 elevation but markedly decreased with an of ALT and AST of 668 U/L and 153 U/L respectively.

Case 1

Unfortunately, earlier that morning, the patient heard a “crack” in her back followed by severe back pain.

And so, the saga continued…

Case 2

56-year-old woman with metastatic melanoma to skin, bones, brain, and peritoneum who was started on ipilimumab + nivolumab on 7/31/2020

On her 12/3/2020 visit, she complained of 2 weeks of worsening BL sensory neuropathy, RLE weakness, and difficulty walking. (“walking on rocks”)

Sent to the ED, admitted and neurology consulted

Neurology exam→multiple abnormalities including facial diplegia (weakness of the bilateral peripheral 7th nerves) with weakness of eye and lip, decreased sensory perception, decreased reflexes in the lower extremities, positive Romberg test, abnormal nerve conduction test suggestive of early demyelinating polyneuropathy.

Treatment: started on IVIG over 5 days, IV methylprednisolone, and FVC monitoring every shift

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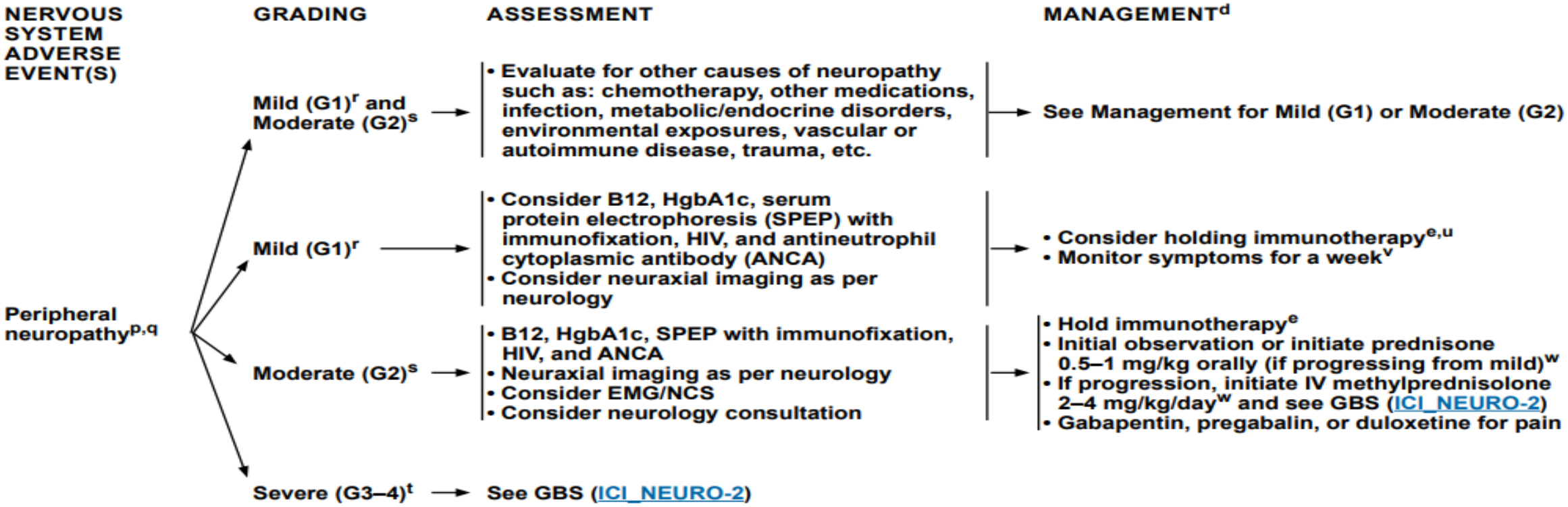
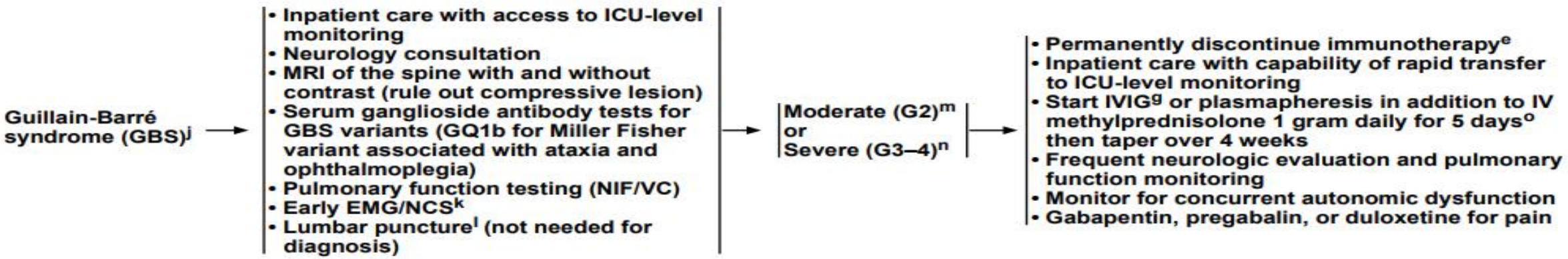


[d] Principles of Immunosuppression (IMMUNO-A).
[e] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[p] The presence of painful, asymmetric sensory/motor deficits should raise concern for mononeuritis multiplex and prompt evaluation for vasculitis or potentially life-threatening autonomic (eg, myenteric plexus) dysfunction. Hypo- or areflexia. Isolated sensory deficit or sensory plus lower motor neuron deficit.
[q] GI tract paresis due to myenteric neuritis is a rare toxicity associated with ICI therapy. The presentation may be fulminant with profound ileus. Early institution of high-dose steroids in concert with multidisciplinary management is recommended.
[r] No interference with function and symptoms not concerning to patient. Note: any cranial nerve problem should be managed as moderate.
[s] Some interference with ADLs, symptoms concerning to the patient (ie, pain but no weakness or gait limitation).
[t] Limiting self-care and aids warranted, weakness limiting walking or respiratory problems (ie, leg weakness, foot drop, rapidly ascending sensory changes). Severe peripheral neuropathy and sensory ganglionopathy are not necessarily GBS but the management can be similar.
[u] There is a low threshold to hold ICIs in mild cases of peripheral neuropathy.
[v] Specifically monitor for new interference with iADLs from either pain or weakness, gait difficulty, ataxia, or autonomic changes.
[w] Treat until symptoms improve to Grade ≤1, then taper over 4–6 weeks.



[d] Principles of Immunosuppression (IMMUNO-A).
[e] Principles of Immunotherapy Rechallenge (IMMUNO-C).
[g] Total dosing should be 2 g/kg, administered in divided doses per package insert.
[j] Progressive, most often symmetrical muscle weakness with absent or reduced deep tendon reflexes. May involve extremities, facial, respiratory, and bulbar and oculomotor nerves. May have dysregulation of autonomic nerves. Often starts with pain in lower back and thighs.
[k] Early EMG/NCS findings may assess potential severity of GBS (Sejvar JJ, et al. Vaccine 2011;29:599-612; Leonhard SE, et al. Nat Rev Neurol 2019;15:671-683) and rule out sensory ganglionopathy, which may have a different prognosis.
[l] Cerebrospinal fluid (CSF) typically has elevated protein and often elevated white blood cell (WBC) count; while cytology is negative in typical GBS, it is important to send given the risk of leptomeningeal carcinomatosis. Consider infectious disease consult. Infectious disease workup: Measure opening pressure and check cell count, protein glucose, Gram stain, culture, PCR for HSV, and other viral PCRs depending on suspicion and cytology. May see normal glucose, normal culture, and Gram stain. May see reactive lymphocytes or histiocytes on cytology.
[m] Some interference with ADLs, symptoms concerning to patient.
[n] Limiting self-care and aids warranted, weakness limiting walking, any dysphagia, facial weakness, respiratory muscle weakness, or rapidly progressive symptoms.
[o] Steroids are not usually recommended for idiopathic GBS; however, in immunotherapy-related forms, a trial is reasonable in addition to IVIG or plasmapheresis.

Case 3

53-year-old woman with metastatic uveal melanoma who was started on nivolumab + relatlimab in the context of a clinical trial on 11/1.

On 4/21, patient reported 5-6 episodes of diarrhea daily.

-Management: Stool cultures drawn, started on prednisone 40 mg PO and infliximab 5 mg/kg.

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Management of Immune Checkpoint Inhibitor-Related Toxicities

GASTROINTESTINAL ADVERSE EVENT(S)	ASSESSMENT/GRADING	MANAGEMENT[g]
• Diarrhea • Colitis[a] Moderate (G2)[e]	• Stool evaluation to rule out infectious etiology[b] ▸ *C. difficile* ▸ NAATs for GI pathogens (other bacteria, viruses) ▸ In appropriate clinical context, consider ova & parasites; molecular testing for *Giardia* and *Cryptosporidium* spp and *E. histolytica*; and microsporidia and Cyclospora/isospora spp • Based on institutional availability, consider fecal lactoferrin/calprotectin[c] • Consider abdominal/pelvic CT with contrast[l] • Consider GI consultation ▸ Colonoscopy or flexible sigmoidoscopy ± esophagogastroduodenoscopy (EGD) with biopsy[c]	• Hold immunotherapy[h] • For pathologically confirmed microscopic colitis, consider budesonide 9 mg daily prior to systemic steroids[m] • Prednisone/IV methylprednisolone[k,n] (1–2 mg/kg/day)[o] • If no response to oral steroids after 3 days, consider IV steroids, consider adding infliximab[p,q,r,s] or vedolizumab[p,r] ▸ Consider tofacitinib or ustekinumab for infliximab- and/or vedolizumab-refractory colitis[t]

[a] Symptoms include: watery diarrhea, cramping, urgency, abdominal pain, blood and mucus in the stool, fever, and nocturnal bowel movements. Blood in the stool and/or fever should prompt a more thorough workup for infection and for other causes of GI bleeding, including PUD and malignant bleeding.

[b] It is not necessary to wait for test results before providing therapy to manage irAEs.

[c] Consider endoscopy exam within 2 weeks if either lactoferrin or calprotectin is positive. Serial monitoring of calprotectin levels while on treatment (every 2 months) may be helpful to guide treatment duration until achieving endoscopic remission.

[e] 4–6 bowel movements above baseline per day, colitis symptoms, not interfering with ADLs.

[g] Principles of Immunosuppression (IMMUNO-A).

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

[k] IV steroid is preferred due to possible absorption impairment.

[l] In cases with high suspicion for complications (eg, toxic megacolon, abscess, or perforation).

[m] Hughes M, et al. J Immunother Cancer 2019;7:292.

[n] Convert to prednisone when appropriate.

[o] Treat until symptoms improve to Grade ≤1, then taper over <4–6 weeks. In cases where infliximab or vedolizumab is used, an attempt to taper steroids in <2–4 weeks should be made to minimize the complication of infection. If strong clinical suspicion for ICI diarrhea, start empiric IV steroids while waiting for EGD/colonoscopy/flexible sigmoidoscopy results.

[p] Duration of therapy with infliximab or vedolizumab is not clearly defined; however, receipt of three or more doses (at weeks 0, 2, and 6) has been associated with favorable overall survival. Repeat endoscopy and/or fecal calprotectin to assess endoscopic healing may be helpful to guide colitis treatment duration, but is optional. Principles of Immunosuppression (IMMUNO-A).

[q] An FDA-approved biosimilar is an appropriate substitute for infliximab.

[r] Perform infectious disease screening (HIV; hepatitis A, B, C) and T-Spot/QuantiFERON TB Gold (depending on facility), preferably before administering first dose of infliximab or vedolizumab. In urgent situations, treatment does not need to be held for results.

[s] Infliximab antibody testing is generally not recommended and should not delay switch of therapy.

[t] Esfahani K, et al. N Engl J Med 2020;382;2374-2375; Thomas A, et al. N Engl J Med 2021;384:581-583; Bishu S, et al. Gastroenterology 2021;160:932-934.

Case 3

- The patient's diarrhea resolved after 10 weeks of corticosteroids
- On 8/4, she was restarted on therapy
- On 8/14 she redeveloped diarrhea, reporting 6-8 episodes daily→restarted on prednisone and retreated with infliximab.
- Diarrhea completely resolved within 3 days of infliximab rechallenge but redeveloped (~10/18) when patient decreased prednisone to 20 mg PO.
- Patient started on vedolizumab for steroid and infliximab-refractory colitis

Case 4

- 44-year-old man with metastatic melanoma to the neck and lung started on combination ipilimumab + nivolumab on 5/26
- During is first infusion, he developed urticaria and “itchiness” of the throat.
- Management

  -Infusion stopped, IV antihistamines given, and treatment completed the next day with premedication

Case 4

- On the morning of 6/13, the patient called the office reporting substernal chest pain x 45 minutes
- Management→ referred to ED for evaluation

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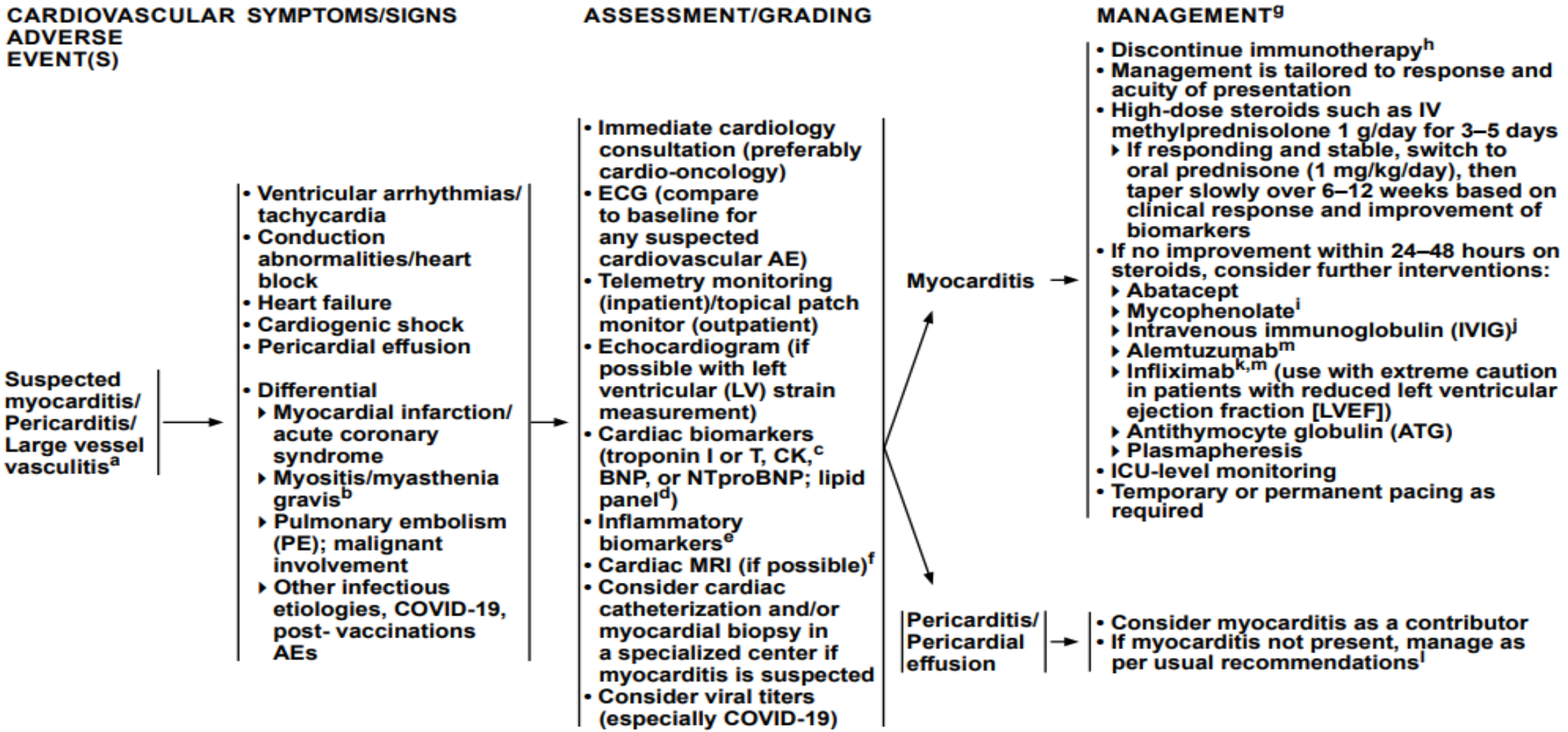


FOOTNOTES

[a] Myocarditis symptoms are nonspecific and may occur as early as days to weeks after 1–2 doses of ICI. Although rare, myocarditis is often severe and associated with myositis/myasthenia gravis (3 M's), and more common with combination therapy. In fatal cases, conduction abnormalities were the cause of death, and ejection fraction was preserved.

[b] This can also be associated with thymoma.

[c] To assess for associated myositis.

[d] Lipid panel would be recommended at baseline to assess cardiovascular risk. Also consider troponin and NTproBNP at baseline for identifying those at increased risk. Also, consider high-sensitivity troponin and NTproBNP at baseline and serially during treatment to detect abnormal blood biomarkers that may precede symptomatic myocarditis induced by ICI.

[e] Consider ESR, CRP, or other inflammatory markers.

[f] Use of multiparameter tissue characterization by MRI, including T1 and T2 mapping and application of modified Lake Louise Criteria provides important diagnostic value for myocarditis. If cardiac MRI is negative or myocarditis is highly suspected, consider endomyocardial biopsy.

[g] Principles of Immunosuppression (IMMUNO-A).

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

[i] Mycophenolate mofetil treatment (0.5–1 g every 12 h).

[j] Total dosing should be 2 g/kg, administered in divided doses per package insert.

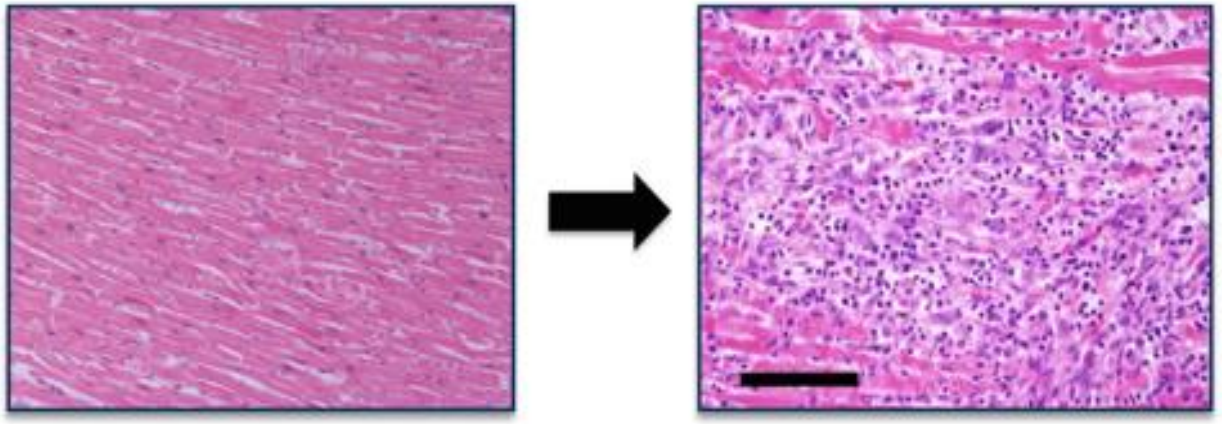
[k] An FDA-approved biosimilar is an appropriate substitute for infliximab.

[l] Adler Y, et al. Eur Heart J 2015;36:2921-2964.

[m] Perform a T-Spot and quantiFERON tuberculosis (TB) gold test (depending on facility) and consider hepatitis testing at time of suspected toxicity to facilitate administration.

LAB	6/14/2022 09:01 EDT	6/14/2022 00:17 EDT	6/13/2022 18:45 EDT	6/13/2022 13:58 EDT	6/13/2022 10:56 EDT	5/14/2022 12:00 EDT
Sodium Lvl	141 mmol/L				141 mmol/L	
Potassium Lvl	4.5 mmol/L				4.4 mmol/L	
Hemolysis	None				None	
Chloride	108 mmol/L (H				105 mmol/L	
CO2	23 mmol/L				27 mmol/L	
Anion Gap	10				9	
Glucose Lvl	125 mg/dL (H)				108 mg/dL (H)	
BUN	19 mg/dL				14 mg/dL	
Creatinine	0.9 mg/dL				1.2 mg/dL	
eGFR (African American)	>60 mL/min/1				>60 mL/min/1	
eGFR(NonAfrican American)	>60 mL/min/1				>60 mL/min/1	
Calcium Lvl	9.8 mg/dL				10.0 mg/dL	
Albumin Lvl					4.0 g/dL	
Total Protein					6.7 g/dL	
A/G Ratio					1.5	
Alk Phos					86 units/L	
AST					41 units/L (H)	
ALT					42 units/L	
Bili Total					0.3 mg/dL	
Troponin I		0.80 nanog/ml	1.66 nanog/ml		3.48 nanog/ml	
Cholesterol	121 mg/dL					
Triglycerides	85 mg/dL					
HDL Cholesterol	26 mg/dL (L)					
LDL Cholesterol	78 mg/dL					
Chol/HDL Ratio	4.65					
LDL/HDL Ratio	3.00 *					
Hgb A1C					5.3 %	
Estimated Average Glucose					105 mg/dL	
COVID -19						
COVID19						
COVID19 Antigen BD				Negative *		

ICI-Associated Myocarditis: Defining a New Clinical Syndrome



ICI-Associated Myocarditis[1]

- T-cell and macrophage infiltration in striated muscle
- ECG abnormalities (arrhythmias)
- 1% incidence with combination therapy

Who and When[2]

- Early and unpredictable
- 50% mortality
- Combination ICI (main RF)
- Concomitant myositis, MG

Bigger Problems[3]

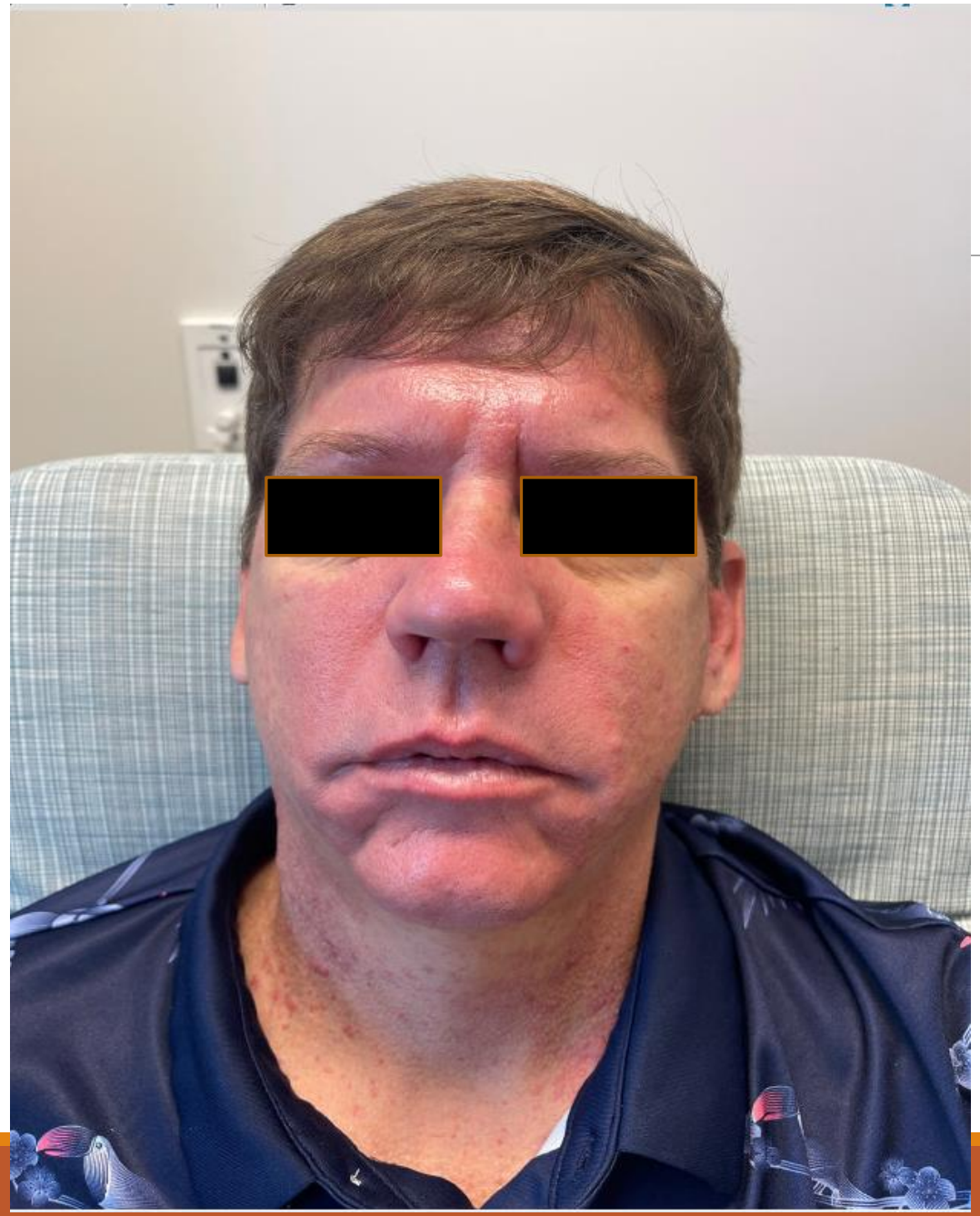
- Other heart and vessel problems (pericarditis, vasculitis, and arrhythmias)
- High mortality

1. Johnson D et al. *N Engl J Med*. 2016;375:1749-1755. 2. Moslehi JJ et al. *Lancet*. 2018;391:933. 3. Salem J-E et al. *Lancet Oncol*. 2018;19:1579-1589.

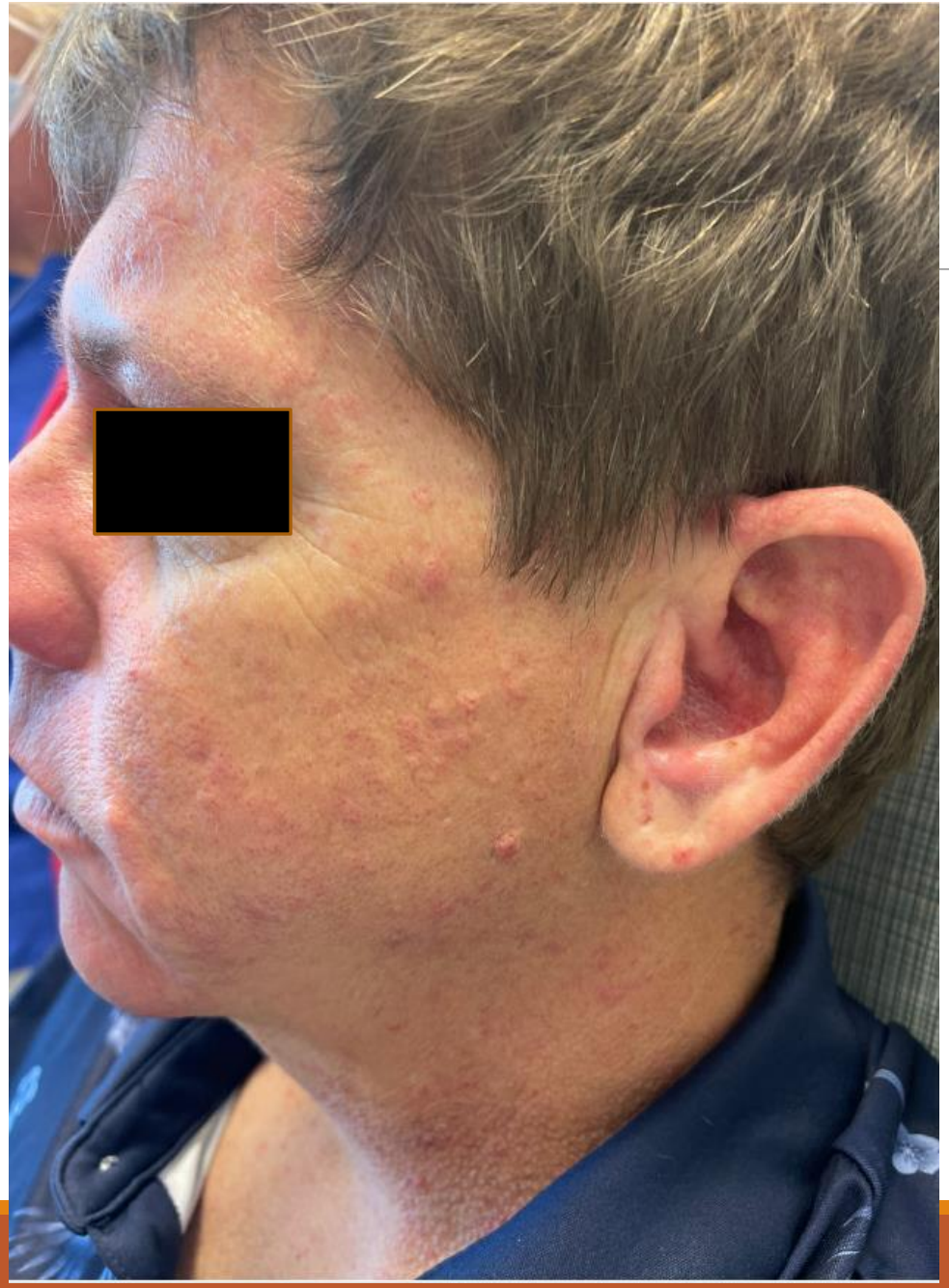
Case 4

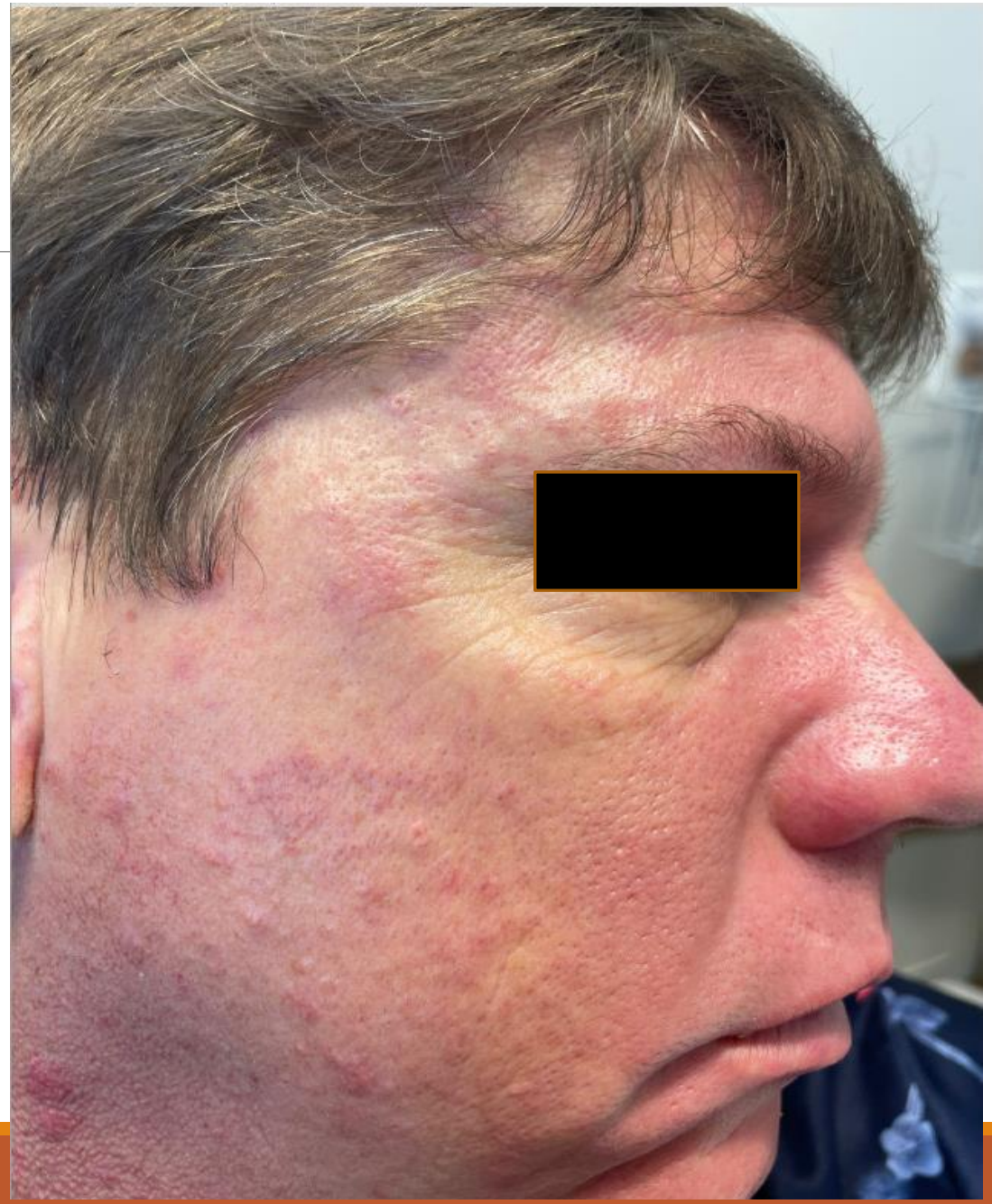
- Case was presented at our tumor board. Consensus was to retreat WITH IPILIMUMAB. He was rechallenged with immunotherapy

- And this is what happened…



Case 4





National Comprehensive Cancer Network®

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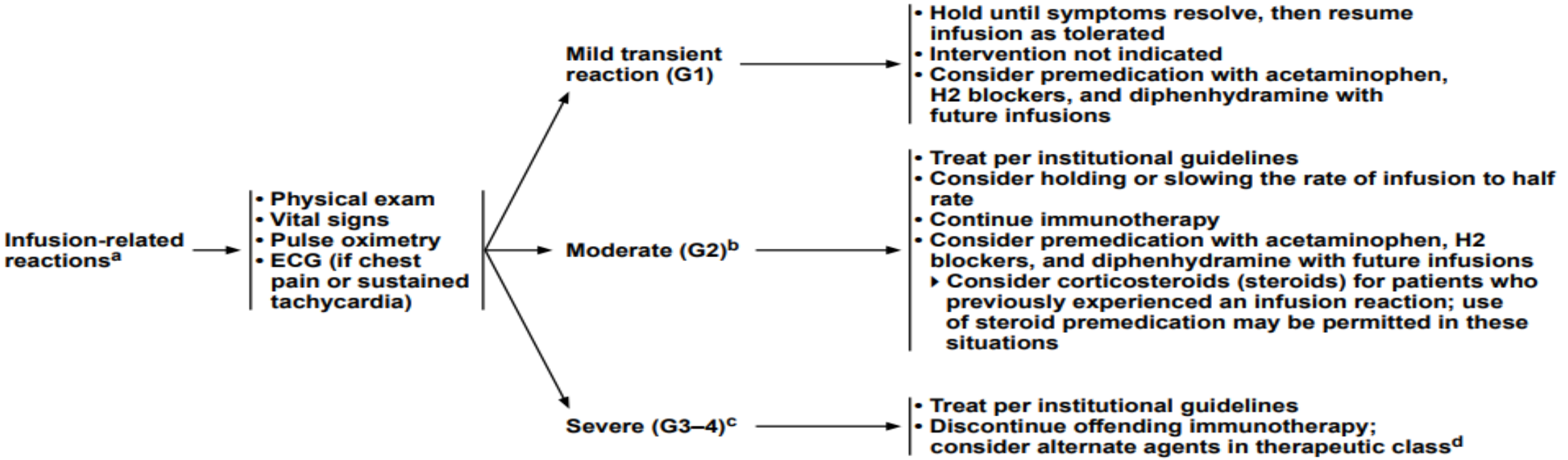


[a] Symptoms include: Fever/chills/rigors, urticaria/pruritus, angioedema, flushing/headache, hypertension, hypotension, shortness of breath, cough/wheezing, hypoxemia, dizziness/syncope, sweating, and arthralgia/myalgia. Refer to prescribing information for each individual immunotherapy agent for recommendations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

[b] Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], narcotics, intravenous [IV] fluids); prophylactic medications indicated for ≤24 hours.

[c] 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.

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

Case 5

- 67-year-old man on single agent pembrolizumab for stage III melanoma initiated on 7/8
- On 11/17, he came to the office earlier than expected with complaints of 4 days grade 2 fatigue, grade 2 headaches despite ibuprofen, abdominal cramping without diarrhea, nausea, and myalgias.
- (Note: Recent MRI and PET/CT brain negative)
- Management: Check TFTs, cortisol, ACTH and MRI of sella to rule out immune-mediated endocrinopathy. Patient treated with IV methylprednisolone in clinic, IV fluids and sent home with hydrocortisone 20 g in AM and 10 mg in PM
- MRI of sella ordered

Case 5

Component Ref Range & Units	1 mo ago (11/17/22)
Glucose 65 - 99 mg/dL	110 ^
Sodium 135 - 146 mmol/L	134 v
Potassium 3.5 - 5.5 mmol/L	4.6
Chloride 98 - 110 mmol/L	99
CO2 19 - 34 mmol/L	30
Anion Gap 6 - 22	5 v
BUN 8 - 23 mg/dL	18
Osmolality Calculation 275 - 295 mOsm/kg	271 v
Creatinine 0.40 - 1.10 mg/dL	1.31 ^
Calcium, Serum 8.6 - 10.3 mg/dL	9.3
Protein, Total 6.1 - 8.1 g/dL	6.5
Albumin 3.5 - 5.2 g/dL	3.8
Bilirubin, Total 0.0 - 1.2 mg/dL	0.3
AST (SGOT) 10 - 40 U/L	24
ALT (SGPT) 0 - 41 U/L	32
Alkaline Phosphatase, S 40 - 130 U/L	85
eGFR FAS-EKFC >60 mL/min/1.73m2	53 v
eGFR CKD-EPI >60 mL/min/1.73m2	60 v

Component Ref Range & Units	1 mo ago (11/17/22)
Acth, Plasma 7.2 - 63.3 pg/mL	<1.5 v

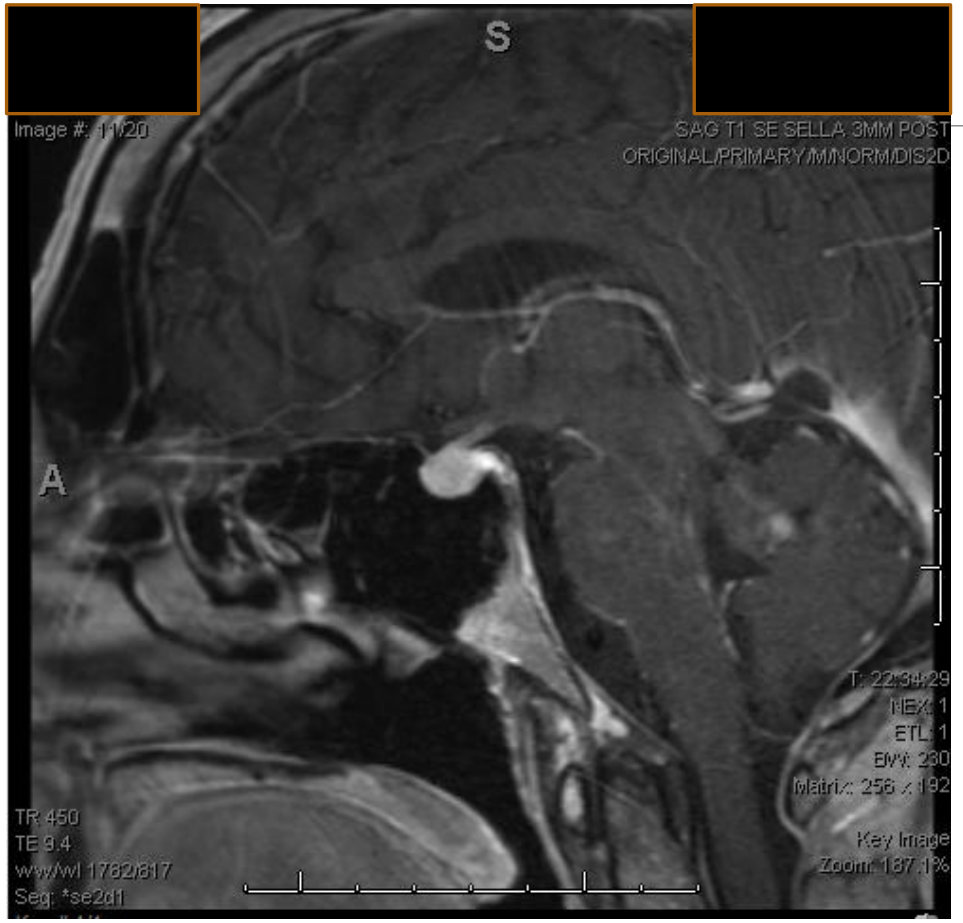
Comment: (NOTE)
ACTH reference interval for samples collected between 7 and 10 AM.

Component Ref Range & Units	1 mo ago
Cortisol, Plasma mcg/dL	0.8

Comment: (NOTE)
REFERENCE RANGES:
MORNING COLLECTIONS(HOURS 7-10 a.m.): 6.2-19.4 UG/DL
AFTERNOON COLLECTIONS(HOURS 4-8 p.m.): 2.3-11.9 UG/DL

Component Ref Range & Units	1 mo ago (11/17/22)
TSH 0.270 - 4.200 mcIU/mL	5.440 ^
Resulting Agency	UM SYLVESTER HOSP.& CLINICS

Component Ref Range & Units	1 mo ago (11/17/22)
T4, Free 0.93 - 1.70 ng/dL	0.77 v
Resulting Agency	UM SYLVESTER HOSP.& CLINICS LAB

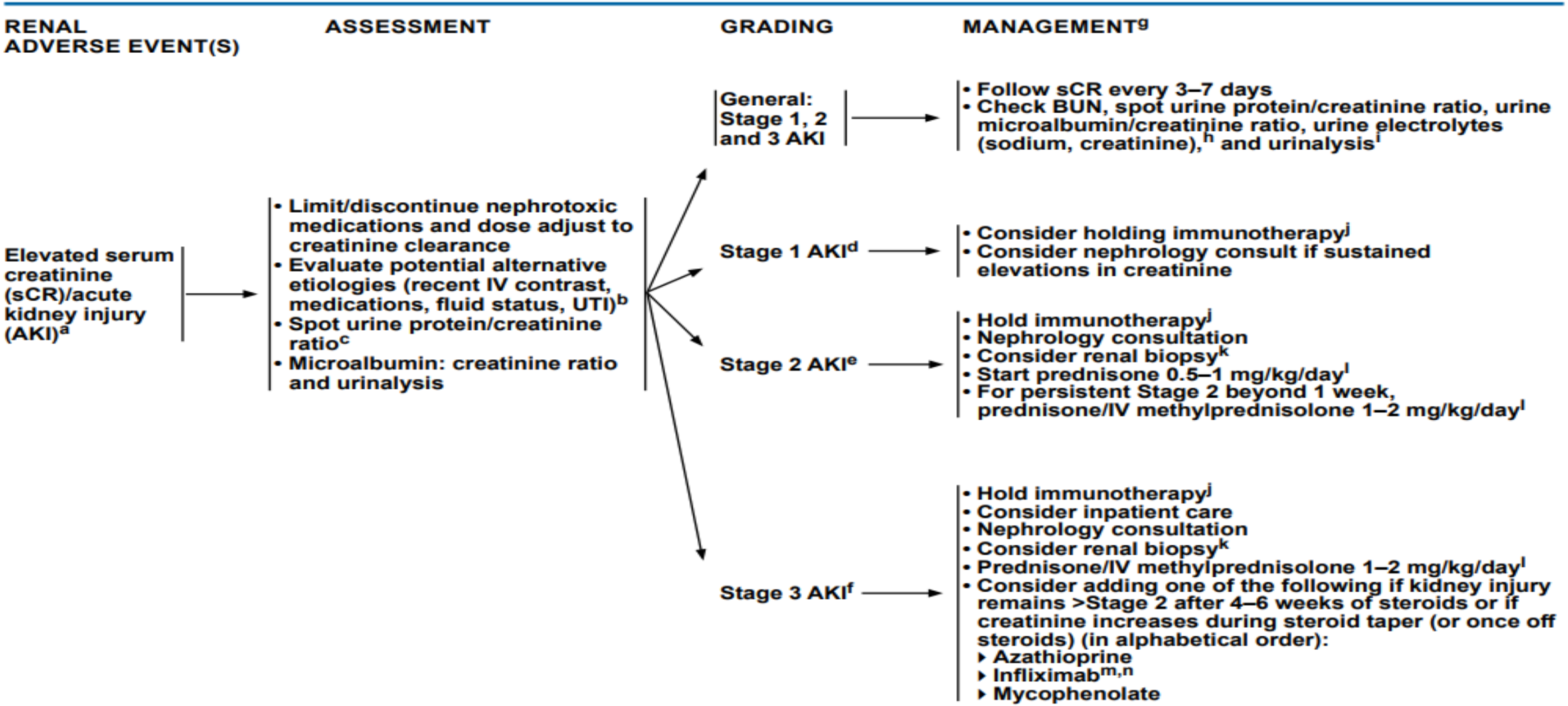

S
A
SAG T1 SE SELLA 3MM POST
ORIGINAL/PRIMARY/M/NORM/DIS2D
TR 450
TE 9.4
ww/wl 1782/817
Seq: *se2d1
NEX: 1
ETL: 1
Key Image

Case 5

Case 5

- He was rechallenged with immunotherapy, and all was going well until a few weeks later, he presented to the ED with complaints of marked fatigued, anorexia, increased urination, nausea, and vomiting

Component Ref Range & Units	04:20	1 d ago	2 d ago	3 d ago
Glucose 65 - 99 mg/dL	124 ^	137 ^	109 ^	87
Sodium 135 - 146 mmol/L	137	137	135	133 v
Potassium 3.5 - 5.5 mmol/L	4.2	4.4	4.4	3.8
Chloride 98 - 110 mmol/L	105	101	100	95 v
CO2 19 - 34 mmol/L	21	22	24	23
Anion Gap 6 - 22	11	14	11	15
BUN 8 - 23 mg/dL	37 ^	29 ^	27 ^	24 ^
Osmolality Calculation 275 - 295 mOsm/kg	284	282	276	270 v
Creatinine 0.40 - 1.10 mg/dL	2.33 ^	2.62 ^	2.76 ^	2.53 ^
Calcium, Serum 8.6 - 10.3 mg/dL	9.0	9.4	8.9	8.6
Protein, Total 6.1 - 8.1 g/dL	6.4	6.8	6.5	6.9
Albumin 3.5 - 5.2 g/dL	3.6	4.1	3.7	3.9
Bilirubin, Total 0.0 - 1.2 mg/dL	0.3	0.5	1.0	1.0
AST (SGOT) 10 - 40 U/L	16	16	19	25 CM
ALT (SGPT) 0 - 41 U/L	18	18	18	17
Alkaline Phosphatase, S 40 - 130 U/L	52	58	54	55
eGFR FAS-EKFC >60 mL/min/1.73m2	28 v	24 v	23 v	25 v
eGFR CKD-EPI >60 mL/min/1.73m2	30 v	26 v CM	24 v CM	27 v CM


RENAL ADVERSE EVENT(S)
ASSESSMENT
GRADING
MANAGEMENT[g]
Elevated serum creatinine (sCR)/acute kidney injury (AKI)[a]
• Limit/discontinue nephrotoxic medications and dose adjust to creatinine clearance
• Evaluate potential alternative etiologies (recent IV contrast, medications, fluid status, UTI)[b]
• Spot urine protein/creatinine ratio[c]
• Microalbumin: creatinine ratio and urinalysis
General: Stage 1, 2 and 3 AKI
• Follow sCR every 3–7 days
• Check BUN, spot urine protein/creatinine ratio, urine microalbumin/creatinine ratio, urine electrolytes (sodium, creatinine),[h] and urinalysis[i]
Stage 1 AKI[d]
• Consider holding immunotherapy[j]
• Consider nephrology consult if sustained elevations in creatinine
Stage 2 AKI[e]
• Hold immunotherapy[j]
• Nephrology consultation
• Consider renal biopsy[k]
• Start prednisone 0.5–1 mg/kg/day[l]
• For persistent Stage 2 beyond 1 week, prednisone/IV methylprednisolone 1–2 mg/kg/day[l]
Stage 3 AKI[f]
• Hold immunotherapy[j]
• Consider inpatient care
• Nephrology consultation
• Consider renal biopsy[k]
• Prednisone/IV methylprednisolone 1–2 mg/kg/day[l]
• Consider adding one of the following if kidney injury remains >Stage 2 after 4–6 weeks of steroids or if creatinine increases during steroid taper (or once off steroids) (in alphabetical order):
▸ Azathioprine
▸ Infliximab[m,n]
▸ Mycophenolate

Footnotes

FOOTNOTES

[a] Azotemia, creatinine elevation, and inability to maintain acid/base or electrolyte balance.
[b] General medical review and testing as warranted for prerenal and postrenal causes. Include medication review for nephrotoxic agents such as NSAIDs and PPIs, and consider obstruction, cardiomyopathy/heart failure, pulmonary hypertension, diuretics, hypovolemia due to primary GI cause, stones, and infection.
[c] For proteinuria >1 g/24-hour with no other etiology for proteinuria present such as diabetes or hypertension and/or gross or microscopic hematuria, check ANA, RF, ANCA, anti-dsDNA, and serum C3, C4, CH50, hepatitis B & C reflexive panels, SPEP, and urine protein electrophoresis (UPEP). For ICI-induced etiologies such as vasculitis and glomerulonephritis, check the following serologies, in addition to obtaining a kidney biopsy: ANA, double-stranded DNA, RF, C3, C4, ANCA, anti-glomerular basement membrane (GBM), hepatitis B and C, HIV, RPR, SPEP, UPEP, and immunofixation electrophoresis (IFE). Consider 24-hour urine collection.
[d] 1.5–<2x baseline or increase of ≥0.3 mg/dL over 48 hours
[e] 2– <3x baseline
[f] ≥3.0x baseline; 4.0 mg/dL or need for renal replacement therapy (RRT); dialysis as indicated
[g] See Principles of Immunosuppression (IMMUNO-A).
[h] Rule out pre-renal volume depletion and/or acute tubular necrosis.
[i] Frequency and additional lab tests to be determined in consultation with nephrology to inform treatment.
[j] See Principles of Immunotherapy Rechallenge (IMMUNO-C).
[k] Renal biopsy will help distinguish between ICI versus non-ICI–related toxicities; however, initiation of steroids should not be delayed while waiting for biopsy.
[l] Treat until symptoms improve to Grade ≤1, then taper over 4–6 weeks.
[m] An FDA-approved biosimilar is an appropriate substitute for infliximab.
[n] Lin JS, et al. Oncoimmunology 2021;10:1877415.

Highlights from these cases…

- One can develop more than one toxicity sequentially or concomitantly
- Many toxicities develop weeks and even months into treatment.
- Don’t be afraid to give high doses of corticosteroids but taper slowly.
- If corticosteroids don’t work quickly, add another immunosuppressant.
- Hospital admission may be necessary if outpatient management not sufficient.
- Consult specialists if needed
- Always consider the complications of long steroids (myopathy, osteoporosis, secondary adrenal insufficiency, chronic immunosuppression)

Thank you

Question 1

Patient CN has stage IV NSCLC and was started on immunotherapy with a 2-drug regimen of ipilimumab and nivolumab. About 4 days after her 3rd cycle of treatment, she began to develop loose stools that evolved into watery diarrhea up to 6 times a day. What should she do?

A. Call her GI so he can get an appointment first available

B. Call her oncology team immediately because this may be related to the immunotherapy

C. Wait it out because this is likely her body "flushing out" toxins of treatment because she didn't have side effects from treatment the first 2 times

Question 2

The side effect profile for patients on checkpoint inhibitors is typically:

A. Severe pancytopenia

B. Inflammatory/Immune mediated adverse events such as rash, arthralgias, pneumonitis, colitis, and endocrinopathies

C. Severe mucositis

Question 3

62-year-old man on adjuvant pembrolizumab for stage IIIC melanoma presented to the office with complaints of fever (Tmax 102.5F) chills, nausea, vomiting, jaundice, and the following labs. In addition to corticosteroids, what other treatment may be given?

A. Infliximab

B. Acetaminophen for fever

C. Mycophenolate

Component Ref Range & Units	8 mo ago (5/6/22)	8 mo ago (5/2/22)
Glucose 65 - 99 mg/dL	134 ^	125 ^
Sodium 135 - 146 mmol/L	133 v	135
Potassium 3.5 - 5.5 mmol/L	3.6	4.1
Chloride 98 - 110 mmol/L	99	100
CO2 19 - 34 mmol/L	27	27
Anion Gap 6 - 22	7	8
BUN 8 - 23 mg/dL	15	12
Osmolality Calculation 275 - 295 mOsm/kg	269 v	271 v
Creatinine 0.40 - 1.10 mg/dL	1.02	0.94
Calcium, Serum 8.6 - 10.3 mg/dL	8.4 v	9.0
Protein, Total 6.1 - 8.1 g/dL	5.6 v	5.6 v
Albumin 3.5 - 5.2 g/dL	3.2 v	3.3 v
Bilirubin, Total 0.0 - 1.2 mg/dL	10.0 ^	7.8 ^
AST (SGOT) 10 - 40 U/L	555 ^	588 ^
ALT (SGPT) 0 - 41 U/L	549 ^	520 ^
Alkaline Phosphatase, S 40 - 130 U/L	649 ^	623 ^
GFR MDRD Non Af Amer >59 mL/min/1.73m2	79	87
GFR MDRD Af Amer >59 mL/min/1.73m2	>90	>90 CM