UNC

SCHOOL OF MEDICINE

Thurston Arthritis Research Center

UNC

LINEBERGER COMPREHENSIVE CANCER CENTER

IMMUNO-ONCOLOGY GROUP

Clinical Algorithms

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Table of Contents

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UNC Thurston Arthritis Research Center & UNC Lineberger Comprehensive Cancer Center

- UNC Health Foundation
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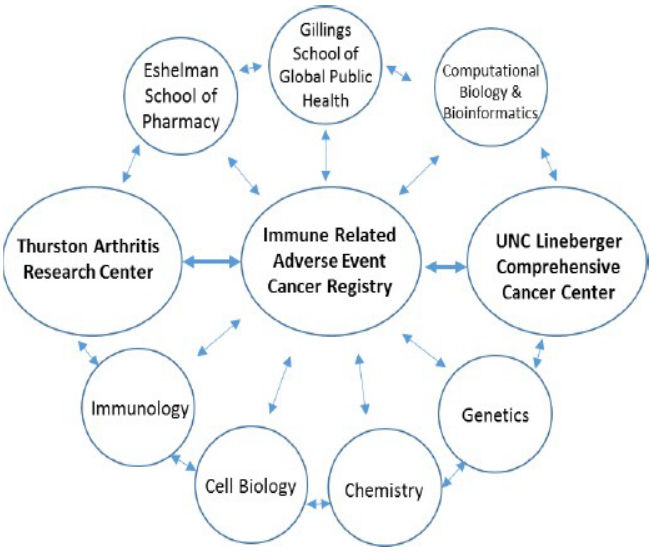


Quick Reference Guide

Inpatient Consult	Outpatient Consult	E-Consult	IOG Liaison	Pager #
CARDIOLOGY				
Request in EPIC and Page @ #216-3764	Refer to UNC Cardiology **AND** Epic msg Dr. Jensen	Dr. Jensen	Brian C. Jensen	2161804
DERMATOLOGY				
Request in EPIC and Page @ #216-1882	For all new patient referrals, please enter Referral to UNC Dermatology in Epic **AND** Epic msg **must** be sent to Dr. Carolyn Ziemer and/or Dr. Edith Bowers to expedite	n/a	Edith Bowers Carolyn Ziemer	2161425 2160100
ENDOCRINOLOGY				
Request in EPIC and Page @ #123-7701	Refer to UNC Endocrinology - Eastowne **AND** Epic msg fellow(s) – Dr. Cater from July 2023 to June 2024	Refer to endocrine e-consult	Taylor Cater	2164126
GASTROENTEROLOGY				
Request in EPIC and Page GI Luminal @ #123-7010	Refer to UNC Gastroenterology with Dr. Herfarth, reason: "suspicion checkpoint inhibitor colitis" **AND** Epic msg Drs. Herfarth	Dr. Herfarth	Hans Herfarth	2164654
HEPATOLOGY				
Request in EPIC and Page @ #123-7020	Refer to UNC Hepatology with Drs. Moon or Shah, reason: "suspicion for checkpoint inhibitor hepatitis" **AND** Epic msg Drs. Moon or Shah	Dr. Shah	Andrew Moon Neil Shah	2165771 3470972
ORAL MEDICINE				
Request in EPIC and Page @ #826-0796	Refer to UNCH Oral Medicine, provider UNCH Oral Medicine Services Chapel Hill	Dr. Hasan	Iquebal Hasan	2164366
NEPHROLOGY				
Request in EPIC and Page @ #393-1866 or @ #393-1865 (after hours)	Refer to UNC Nephrology with Drs. Derebail, Jain, or Taus, **AND** Epic msg Drs. Derebail, Jain, or Taus. Normal Hrs: 5am-7pm M-F, Sun/7am-7pm Sat	Dr. Jain Dr. Derebail Dr. Taus	Koyal Jain Vimal Derebail Patrick Taus	2167086 2163713 3931866
PULMONARY				
Request in EPIC and Page @ #123-7030	<u>For New Pulmonary patient</u>: refer to MTOP reason: "suspicion for ICI pneumonitis" Vickie Dowdy-MTOP patient coordinator. <u>For patients followed in UNC Pulmonary clinic</u>: direct EPIC msg current provider	n/a	Jason Akulian Kunal Patel Jason Lobo	2164549 2163815 2164547
RHEUMATOLOGY				
Request in EPIC and Page @ #123-7017	Contact primary rheumatologist first before seeking referral at UNC Rheum. <u>For New Rheum patient</u>: refer to UNC Rheumatology Eastowne with Dr. Ishizawar, reason "irAE on immunotherapy" **AND** Epic msg Dr. Ishizawar	Refer to Rheum e- consult	Rumey Ishizawar	2163638

Cardiology Clinical Algorithm

Cardiology Consultation

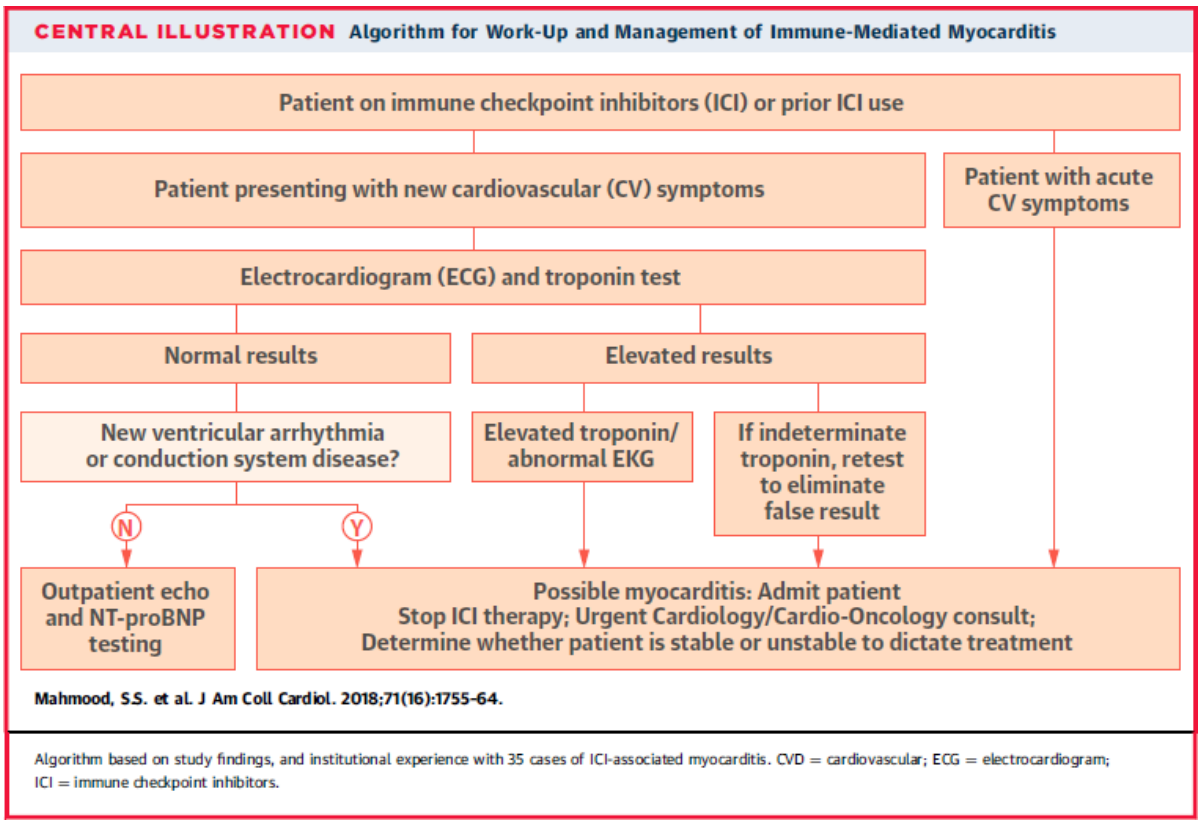
1. **Evaluation and management for potential/suspected Cardiology irAE**
    a. Inpatient consultation –
        i. Place "inpatient consult to cardiology" order in EPIC
        ii. Page cardiology fellow on call #216-3764

    b. Outpatient consultation –
        i. Referral to UNC Cardiology in Epic (specify Cardio-oncology and indicate Dr. Jensen as provider)
        ii. Send Epic message to Dr. Brian Jensen

    c. E-consult – Dr. Jensen

2. **IOG Cardiology physician members/liaisons:** Dr. Brian Jensen

Cardio IRAE Diagnostic Evaluation and Management



Dermatology Clinical Algorithm

Pre-ICI Evaluation Recommendations

1. Recommend dermatologic consult before starting ICI treatment if patient has any of the following:
- Active diagnosis or personal history of lupus
- Psoriasis
- Dermatomyositis
- Autoimmune bullous disorder (e.g. bullous pemphigoid, pemphigus, epidermolysis bullosa, etc.)
- Any chronic skin condition that is poorly controlled at baseline

2. Grading reactions according to Common Terminology Criteria for Adverse Events (CTCAE) is a challenge for skin. Instead, severity may be based on body surface area, tolerability, morbidity, and duration

Dermatology Consultation

1. **Evaluation and management for potential/suspected Dermatologic irAE**
    a. Inpatient consultation –
        i. Place "inpatient consult to dermatology" order in EPIC
        ii. Page dermatology resident on call #216-1882

    b. Outpatient consultation –
        i. For non-urgent referrals, enter referral to UNC Dermatology in Epic
        ii. For urgent referrals, enter consult order as above and mark urgent
        iii. Send Epic message to James Cook in UNC Dermatology requesting urgent visit with Dr. Ziemer or Dr. Bowers

    c. E-consult – not available

2. **Dermatology physician IOG members/liaisons:** Dr. Carolyn Ziemer, Dr. Edith Bowers

Dermatologic IRAE Management

Rashes/Inflammatory Dermatoses

Grade 1	Grade 2	Grade 3-4
Mild disease not significantly affecting patient's quality of life	Moderate disease affecting patient's quality of life	severe disease or any atypical presentations
- trial of triamcinolone 0.1% ointment to apply to affected areas as needed twice daily (dispense 454g jar if needing to treat a large body surface area) - consider long-acting antihistamine if significant pruritus	- try topical steroid (triamcinolone) - if symptoms do not improve, consider trial of oral prednisone (typically 40-60mg po daily, then taper over 3 weeks) - consider referral to dermatology	- consult dermatology

Bullous (blistering) Dermatoses

For all suspected autoimmune disease patients, please refer to dermatology for likely biopsies for routine histology and direct immunofluorescence

SCARs (Severe Cutaneous Adverse Reactions)

These patients should typically be admitted to the hospital and dermatology consulted for biopsy and management

In addition to skin sloughing, other possible signs of severe drug reactions include:		
DRESS syndrome:	**SJS/TEN:**	**AGEP:**
diffuse rash, facial swelling, new lymphadenopathy, elevated liver enzymes, new renal insufficiency, persistent fevers without infectious cause	new mucositis of mouth, eyes or GU tract, painful rash	diffuse pustules or painful peeling rash of skin folds

ASCO clinical practice guidelines for Dermatologic IRAEs

Grading	Management
Grading according to CTCAE is a challenge for skin. Instead, severity may be based on BSA, tolerability, morbidity, and duration.	
G1: Symptoms do not affect the quality of life or controlled with topical regimen and/or oral antipruritic	Continue ICPi Treat with topical emollients and/or mild-moderate potency topical corticosteroids Counsel patients to avoid skin irritants and sun exposure
G2: Inflammatory reaction that affects quality of life and requires intervention based on diagnosis	Consider holding ICPi and monitor weekly for improvement. If not resolved, interrupt treatment until skin AE has reverted to grade 1 Consider initiating prednisone (or equivalent) at dosing 1 mg/kg, tapering over at least 4 weeks In addition, treat with topical emollients, oral antihistamines, and medium- to high-potency topical corticosteroids
G3: As G2 but with failure to respond to indicated interventions for a G 2 dermatitis	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids Initiate (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks
G4: All severe rashes unmanageable with prior interventions and intolerable	Immediately hold ICPi and consult dermatology to determine appropriateness of resuming ICPi therapy upon resolution of skin toxicity and once corticosteroids are reduced to prednisone (or equivalent) ≤ 10 mg Systemic corticosteroids: IV (methyl)prednisolone (or equivalent) dosed at 1-2 mg/kg with slow tapering when the toxicity resolves Monitor closely for progression to severe cutaneous adverse reaction Should admit patient immediately with direct oncology involvement and with an urgent consult by dermatology Consider alternative antineoplastic therapy over resuming ICPis if the skin irAE does not resolve to G1 or less; if ICPIs are the patient's only option, consider restarting once these adverse effects have resolved to a G1 level

Endocrinology Clinical Algorithm

Pre-ICI Evaluation Recommendations

Recommend pre-treatment labs:

a. TSH
b. Free T4
c. Hemoglobin A1c

Endocrinology Consultation

1. **Evaluation and management for potential/suspected Endocrine irAE**
    a. Inpatient consultation – consult request in EPIC and page endocrinology fellow on call #123-7701

    b. Outpatient consultation –
        i. Place referral to UNC Endocrinology at Eastowne in Epic
        ii. Send Epic inbox message to fellow Dr. Taylor Cate from July 2023 to June 2024.

    c. E-consult – if clinician thinks e-consult is appropriate, send to general endocrine e-consult pool

2. **Endocrinology physician IOG members/liaisons:** Dr. Taylor Cate (Fellow) from July 2023 to June 2024.

Endocrine IRAE Diagnostic Evaluation and Management

Thyroiditis and related Hypo- and Hyper-thyroidism

1. **Definition:** Thyroiditis that progresses from hyperthyroidism to “burnt out” hypothyroidism, Common (5-15%) occurrence.

2. **Monitoring:** Check TSH and free T4 every cycle (max interval 4 weeks) for 6 months, then every 12 weeks while on treatment or if symptoms arise.

3. **Diagnostic Evaluation – Caveats:**
    a. Central hypothyroidism (hypophysitis) has normal or low TSH (<5) and low free T4 (<0.7)

b. Make sure patient is not taking any supplements with biotin (can artificially suppress TSH and elevate FT4)
c. Hyperthyroid phase patients do not need methimazole or PTU.

4. IRAE Management:

Severity	Features		Management
	Hypothyroidism	Hyperthyroidism	
Grade 1	TSH > 5 but < 10 AND asymptomatic	TSH < 0.5 and Free T4 > 1.5 AND asymptomatic	- Monitor thyroid function closely (Q2 weeks) - Continue ICI - Consider Endocrine e-consult
Grade 2	TSH > 10 and Free T4 < 1.5 AND moderate symptoms* but able to perform daily activities *fatigue, weight gain, aches, cold intolerance hair loss, constipation	TSH < 0.5 and Free T4 > 1.5 AND moderate symptoms* but able to perform daily activities *palpitations, sweating, weight loss, tremor, diarrhea	- Consider holding ICI - Consider referral or e-consult Hypothyroidism: - levothyroxine PO 25-50 mcg daily Hyperthyroidism: - Beta blockers only for symptoms (no PTU or Methimazole) - Check Thyroid function every 2 wks and watch for hypothyroid phase - If symptoms > 8 wks consider Graves disease and consult
Grade 3-4	TSH > 10, Free T4 < 0.7 AND severe symptoms* or requiring admission *depressed mental status, bradycardia, CHF, etc.	TSH < 0.5, Free T4 > 1.5 AND severe symptoms* or requiring admission *fever, CHF, liver failure, severe agitation, sustained tachycardia, etc.	- Hold ICI until stabilized - Endocrine consult and admission recommended

Hypophysitis/Hypopituitarism

1. **Definition:** Inflammation of the pituitary gland causing central hormonal deficiencies. Consider when patient has headaches or vision changes along with hypothyroidism symptoms or signs of adrenal insufficiency (hypotension, orthostasis, dehydration, nausea, fatigue, and weight loss), Common (3-10%) occurrence.

2. **Monitoring for suspected Hypophysitis:**
    a. Check pituitary function
        i. Thyroid Axis: TSH, Free T4
        ii. Adrenal Axis: 8 am cortisol with ACTH, BMP
        iii. Gonadal Axis: LH, FSH, Estradiol or Testosterone
    b. Obtain MRI Pituitary

3. **Diagnostic Evaluation - Caveats:**
    a. Patients on steroids for other irAEs or conditions will have secondary adrenal insufficiency
    b. If patient has central hypothyroidism, TSH is not a reliable marker for titration of levothyroxine
    c. If there is high suspicion, start treatment with hydrocortisone immediately after labs collected

Condition	Typical Laboratory Findings
Central Hypothyroidism	TSH < 5 AND Free T4 < 0.7
Secondary Adrenal Insufficiency	8 am cortisol < 10 AND ACTH low (< 20) BMP - may show hyponatremia, hypoglycemia

4. **IRAE Management:**
    a. Recommend endocrine consultation/referral for all these patients
    b. Hold ICI until neurologic/headache symptoms resolved and hormones replaced
    c. If high suspicion, start hydrocortisone immediately after labs are collected

Treatment	Hydrocortisone- Always First	Levothyroxine
Stable- Clinic	Oral 20 mg AM/ 10 mg PM	Oral 25-50 mcg QD
Unstable- ER	IV 50 mg Q6h	Oral 25-50 mcg QD

High dose steroids are no longer considered for all patients:
reserved for severe pituitary edema or neurologic symptoms.

Primary Adrenal Insufficiency

1. **Definition:** Direct destruction of the adrenal glands – consider when patient has symptoms of adrenal insufficiency (hypotension, orthostasis, dehydration, nausea, fatigue, weight loss) *without signs of pituitary hormone deficits*, Rare (< 1%) occurrence.

2. **Monitoring for suspected Primary Adrenal Insufficiency:**
    a. Check pituitary function to rule out secondary AI:
        i. Thyroid Axis: TSH, Free T4
        ii. Gonadal Axis: LH, FSH, Estradiol or Testosterone
    b. Obtain BMP
    c. Perform ACTH stimulation test:
        i. Get baseline ACTH, cortisol,
        ii. IV or IM cosyntropin 250 mcg
        iii. 30- and 60-minute cortisol levels after injection
    d. Consider CT Abdomen/Pelvis for adrenal hemorrhage or metastatic disease

3. **Diagnostic Evaluation - Caveats:**
    a. Patients on steroids for other irAEs or conditions will have secondary adrenal insufficiency
    b. Make sure patient is not taking any supplements with biotin (can artificially suppress TSH and elevate FT4)

Tests	BMP	Baseline cortisol	ACTH	ACTH stimulation test
Typical Findings	Hyponatremia, Hyperkalemia, Metabolic Acidosis, Hypoglycemia	Low (<10)	High (>70)	Low 60-minute cortisol (< 18 if IV, < 16 if IM)

4. **IRAE Management:**
    a. Recommend endocrine consultation/referral for all these patients
    b. Hold ICI until hormones are replaced
    c. If high suspicion, start hydrocortisone immediately after labs are collected

Treatment	Hydrocortisone- Always First	Fludrocortisone
Stable- Clinic	Oral 20 mg AM/ 10 mg PM	Oral 0.1 mg QD
Unstable- ER	IV 50 mg Q6h	Oral 0.1 mg QD

Immunotherapy Induced Diabetes Mellitus

1. **Definition:** Diabetes from ICIs is due to destruction of the endocrine pancreas: functionally Type 1 diabetes. Consider when patient has new rapid onset hyperglycemia, polyuria, dehydration, or presents with signs of DKA (abdominal pain, nausea, confusion). In patients with pre-existing diabetes, consider if rapidly worsening diabetes, Rare (< 1%) occurrence.

2. **Monitoring for suspected ICI related diabetes:**
    a. Rule out DKA, HHS with BMP, VBG
    b. Check c-peptide, GAD 65 antibodies, islet cell antibodies

3. **Diagnostic Evaluation - Caveats:** Steroids may be responsible for hyperglycemia in patients with pre-existing diabetes.

Tests	BMP/VBG	C peptide	Antibodies
Typical Findings	DKA - Hyperglycemia with Anion Gap metabolic acidosis HHS - Hyperglycemia (> 600) without Anion Gap metabolic acidosis	< 1.0	Positive

4. **IRAE Management:**
    a. Default management should be insulin in these patients
    b. Recommend endocrine consultation/referral for all these patients
    c. Hold ICI until insulin is started and acute hyperglycemia or DKA/HHS is resolved
    d. Consider HHS if glucose is > 600 and patient has altered mentation and signs of dehydration

	Criteria	New Diabetes	Pre-Existing DM no insulin	Pre-Existing DM on insulin
Stable - Clinic	Hyperglycemia, No DKA, No HHS	Glargine 0.2U/kg daily	Glargine 0.2U/kg daily, continue oral meds	Increase insulin doses by 10-20% if fasting BG > 200
Unstable - ER	DKA or HHS	Insulin Drip	Insulin Drip	Insulin Drip

Gastroenterology Clinical Algorithm

GI Consultation

1. **Evaluation and management for potential/suspected GI irAE**
    a. Inpatient consultation – request consult in EPIC and page GI Luminal Fellow on call #123-7010

    b. Outpatient consultation –
        i. Enter referral to UNC Gastroenterology
        ii. Select department UNCH GI Medicine Memorial Hospital Chapel Hill
        iii. Select Hans Herfarth as provider
        iv. In the "Comments" section enter reason for consultation as suspicion for checkpoint inhibitor colitis
        v. Message Drs. Herfarth directly through Epic InBasket

    c. E-consult – defining appropriate question to GI and routing to GI eConsult service

2. **GI physician IOG members/liaisons:** Dr. Hans Herfarth

Colitis IRAE Diagnostic Evaluation

1. **Definition:** Abnormal stool frequency, >4/day, abdominal pain, mucus/blood in stool

2. **Diagnostic Evaluation:**

Severity	Features	Diagnostic Criteria
Grade 1	>4 stools/day	- Rule out C difficile infection - Anti-diarrheal medication
Grade 2	>6 stools/day with abdominal pain, mucus/blood in stool	- Additional stool studies, blood work, CT imaging - Consider holding ICI - Consider trial of prednisone - Consider referral to GI
Grade 3	>7 stools/day, severe abdominal pain, peritoneal signs	- Hold ICI - Use steroids, 1 mg/kg - CT imaging - If unresponsive or recurrent, request urgent GI referral for colonoscopy and further management
Grade 4	life threatening clinical picture	- Admit to Hospital - Inpatient GI Luminal consult

Colitis IRAE Management

Consider consulting GI upon failure of initial steroid taper
OR if considering anti-TNF therapy at any point

Recommended management of severe colitis beyond steroid use:

a. Consider empirical anti-diarrhea medication
    i. Negative stool lactoferrin or calprotectin
    ii. Grade 1 diarrhea or colitis

b. Consider endoscopy evaluation
    i. Positive stool lactoferrin or calprotectin
    ii. ≥ Grade 2 diarrhea or colitis

c. In case of steroid failure currently recommended therapy with biologics (either infliximab [1-2 infusions] or vedolizumab [3 infusions])

Hepatology Clinical Algorithm

Hepatology Consultation

1. **Evaluation and management for potential/suspected Hepatitis irAE**
    a. Inpatient consultation – request Inpatient Consult to Hepatology in EPIC and page GI Hepatology Fellow on call #123-7020

    b. Outpatient consultation –
        i. Enter referral to UNC Hepatology
        ii. Select department UNCH GI Medicine Eastowne Chapel Hill
        iii. Select Andrew Moon or Neil Shah as provider
        iv. In the "Comments" section enter reason for consultation as "suspicion for checkpoint inhibitor hepatitis"
        v. Message Drs. Moon or Shah directly through Epic InBasket

    c. E-consult – Dr. Shah

2. **GI physician IOG members/liaisons:**

Hepatitis IRAE Diagnostic Evaluation

1. **Definition:** Elevated transaminases (AST, ALT) +/- hyperbilirubinemia after initiation of immunotherapy

2. **Diagnostic Evaluation:**

    Initial Evaluation:
    - Advice against alcohol consumption
    - Send hepatic function panel, direct bilirubin, and INR to assess degree of liver injury
    - Assess for hepatotoxic medications and dietary supplements
    - Rule out acute viral hepatitis A (HAV IgM), B (HBV surface Ag, HBV core total and IgM, HBV surface Ab) and C (HCV Ab).
    - Consider evaluation for immunocompromised infections such as EBV, CMV, HHV-6 and HSV if clinically appropriate
    - Obtain Ultrasound Liver with Doppler or cross-sectional liver imaging (CT/MRI), particularly when patient has an elevated alkaline phosphatase or total (and direct) bilirubin

Grading Based on NCI CTCAE v5.0:

	Grade 1	Grade 2	Grade 3	Grade 4
AST or ALT Elevation	>ULN–3.0 x ULN if baseline was normal; 1.5–3.0 x baseline if baseline was abnormal	>3.0–5.0 x ULN if baseline was normal; >3.0– 5.0 x baseline if baseline was abnormal	>5.0–20.0 x ULN if baseline was normal; >5.0– 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Bilirubin Elevation	>ULN–1.5 x ULN if baseline was normal; 1.0 – 1.5 x baseline if baseline was abnormal	>1.5–3.0 x ULN if baseline was normal; >1.5– 3.0 x baseline if baseline was abnormal	>3.0–10.0 x ULN if baseline was normal; >3.0– 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Hepatic Failure			Asterixis; mild encephalopathy; DILI, limiting self-care ADL	Life-threatening consequences, moderate to severe encephalopathy; coma

Hepatitis IRAE Management

Severity	Management	When to Refer
Grade 1	- Continue immunotherapy if asymptomatic - Monitor liver tests 1-2 times per week until resolution	- Persistent elevation in enzymes to consider liver biopsy
Grade 2	- Withhold checkpoint inhibitor - Initiate oral prednisone (0.5-1 mg/kg) - Monitor liver tests every 3 days - If improving, taper prednisone over 1 month with liver tests 1-2 times/week - Resume immunotherapy if liver tests return to Grade 1 status or less AND prednisone is ≤ 10mg/day	- Persistent elevation or non-response to steroids to consider liver biopsy
Grade 3-4	- Discontinue checkpoint inhibitor completely - Initiate IV steroids (prednisolone 1-2 mg/kg/day) - Hepatology consultation and liver biopsy - Monitor liver enzymes and INR daily - If improvement, gradually taper prednisone over 1 month or longer with no re-initiation of immunotherapy	- Mandatory referral to Hepatology - For refractory disease, would consider adding MMF 500-1000mg BID

Oral Medicine Clinical Algorithm

Oral Medicine Consultation

1. **Evaluation and management for potential/suspected Oral irAE**
    a. Inpatient consultation –
        i. Consult order for "Oral Medicine/Dental Clearance"
        ii. Page Oral Medicine/Dentistry at 8260796 or 2164366 (Dr. Hasan) and/or Dwayne Moody through epic message

    b. Outpatient consultation –
        i. Enter ambulatory referral to Hospital Oral Medicine (https://www.uncmedicalcenter.org/uncmc/care-treatment/oral-medicine-clinic/)
        ii. Class: internal referral
        iii. Select department UNCH Oral Medicine
        iv. Select provider UNCH Oral Medicine Services Chapel Hill
        v. Priority: routine or urgent
        vi. Select location UNC Hospital Oral Medicine Clinic
        vii. In the "Comments" section enter reason for consultation as suspicion for checkpoint inhibitor oral complications
        viii. Message Dwayne Moody directly through Epic InBasket

    c. E-consult – Dr. Hasan

2. **Oral Specialists IOG members/liaisons:** Dr. Iquebal Hasan (Oral Medicine Specialist);
3. **Other Oral Medicine Specialists:** D'Lana Carroll (Dental Assistant); Chrissy Cheek (Medical Assistant)

Oral IRAE Diagnostic Evaluation

1. **Oral medicine consultation prior to initiating ICI**
    a. Oral vesiculobullous disorders (lichen planus, pemphigus, pemphigoid, lupus, linear IgA)
    b. History of erythema multiforme/ SJS/ TEN
    c. Suspicion or history of autoimmune diseases like Sjogren's Syndrome, rheumatoid arthritis, SLE, impacting oral health (dry mouth, burning mouth)

2. **Diagnostic Evaluation:**
    Patients are evaluated for biopsy and management.
    - Sialometry
    - Schirmer's test
    - Minor salivary gland biopsy for diagnosis of Sjogren's Syndrome

3. **Oral medicine consultation after initiation of ICI**
    a. Oral erythema and ulceration
    b. Dry mouth
    c. Dysgeusia (taste changes)
    d. Dysphagia
    e. Burning mouth
    f. Blistering conditions of the mouth

Oral IRAE Management

1. **Mucosal lesions/ blistering conditions**
    a. For solitary mild lesions (< 1 cm, pain score < 5/10)
    b. Start fluocinonide 0.05% gel, apply to the affected lesion with a guaze x 10 minutes, TID. If no improvement in 7-10 days, refer to oral medicine.
    c. For large or multi-focal lesions
        i. Dexamethasone 0.5 mg/5mL swish for 5 minutes and spit, TID. If no improvement in 7-10 days, refer to oral medicine.

2. **Sudden onset of dry mouth**
    a. Hydration > 40 oz of water per day, minimize caffeine intake.
    b. Consider sugar free lozenges, gum, Biotene gel, and Xylimelts.
    c. Referral to oral medicine for evaluation

3. **Taste changes**
    a. Start dry mouth management
    b. Rule out candidiasis, empirically treat with topical anti-fungals (Mycelex troches 5 times/day x 10 days)
    c. Referral to oral medicine

TABLE 4 Proposed grading criteria and management guidelines for oral mucosal irAEs[a]

Oral mucosal irAEs	
Clinical features: **OLP-like:** white reticulations, erosions, ulcers **MMP/BP:** vesicles, bullae, ulcers, erosions **EM-like:** irregular ulcerations, erosions, hemorrhagic crusting of the lips	
Diagnostic workup: • Pertinent history and physical examination - inquire about skin, ocular, and genital involvement • Rule out any other etiology of the oral lesions • Clinical photos • Biopsy - consider submitting specimen for DIF in addition to H&E	
Grading	**Management**
G1: Asymptomatic or mildly symptomatic	• Treat symptomatic cases with a topical steroid solution (dexamethasone 0.5 mg/5 ml) and/or gel (fluocinonide 0.05%) • Consider tacrolimus 0.1% ointment for lip vermilion involvement
G2: Moderately painful oral lesions that do not interfere with oral intake	• Consider holding ICI in consultation with patient's oncologist • Consider initiating oral prednisone 1 mg/kg or equivalent in addition to topical steroids and/or tacrolimus
G3: Severely painful oral lesions limiting oral intake	• Hold ICI in consultation with patient's oncologist • Treat with super high-potency topical steroid (clobetasol 0.05% solution and/or gel) • Initiate oral prednisone 1–2 mg/kg or equivalent or steroid-sparing systemic medication if control inadequate with topical regimen
G4: Severely painful oral lesions unmanaged with prior interventions and making oral alimentation impossible	• Hold ICI, consider permanently discontinuing in consultation with patient's oncologist • Administer oral or IV (methyl)prednisolone 1–2 mg/kg and/or steroid-sparing systemic treatment • Continue topical regimen

Abbreviations: BP, bullous pemphigoid; DIF, direct immunofluorescence; EM, erythema multiforme; H&E, hematoxylin and eosin; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous; MMP, mucous membrane pemphigoid; OLP, oral lichen planus.
[a]Format of Tables 4 and 5 is adapted from ASCO guidelines; each feature selected content from ASCO, SITC, NCCN and CTCAE grading criteria and management guidelines (Brahmer et al., 2018; National Cancer Institute, 2017; Puzanov et al., 2017; Thompson et al., 2019).

TABLE 5 Proposed grading criteria and treatment guidelines for salivary irAEs

Salivary irAEs	
Clinical features: Xerostomia, hyposalivation, systemic features of Sjögren syndrome (e.g., fatigue, arthralgias)	
Diagnostic workup: • Pertinent history and physical examination • Rule out any other etiology of xerostomia/hyposalivation • Consider whole unstimulated saliva flow (WUSF) • Consider minor salivary gland biopsy • Consider laboratory studies (ANA, anti-Ro, anti-La, RF)	
Grading	**Management**
G1: Xerostomia without significant dietary alteration; WUSF >0.1 ml/min	• OTC dry mouth products • Encourage adequate hydration • Consider sialagogue (pilocarpine 5 mg TID or cevimeline 30 mg TID)
G2: Oral intake alterations (e.g., copious water, diet limited to soft/moist foods); WUSF <0.1 ml/min; mild systemic features of SS	• Consider holding ICI in consultation with patient's oncologist • OTC dry mouth products • Encourage adequate hydration • Topical fluoride supplementation • Initiate sialagogue (pilocarpine 5 mg TID or cevimeline 30 mg TID) • Consider initiating prednisone 1 mg/kg or hydroxychloroquine • Refer to rheumatology
G3: Unable to adequately aliment orally; WUSF <0.1 ml/min; systemic features of SS affecting ADLs	• Hold ICI in consultation with patient's oncologist • OTC dry mouth products • Encourage adequate hydration • Topical fluoride supplementation • Initiate sialagogue (pilocarpine 5 mg TID or cevimeline 30 mg TID) • Initiate systemic treatment with prednisone 1–2 mg/kg or hydroxychloroquine • Co-manage with rheumatologist
G4: -	-

Abbreviations: ADLs, activities of daily living; ANA, antinuclear antibody; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; OTC, over the counter; RF, rheumatoid factor; SS, Sjögren syndrome.

Nephrology Clinical Algorithm

Pre-ICI Evaluation Recommendations

Recommend pre-treatment labs: Creatinine

Nephrology Consultation

1. **Evaluation and management for potential/suspected Renal irAE**
    a. Inpatient consultation – consult request in EPIC and page nephrology fellow on call. To do so please go to UNC intranet then directory -> home -> type "neph" and then floor fellow.

    b. Outpatient consultation –
        i. Enter referral to UNC Nephrology
        ii. Select provider – Dr. Patrick Taus, Dr. Vimal Derebail, or Dr. Koyal Jain
        iii. Message Dr. Patrick Taus, Dr. Vimal Derebail, or Dr. Koyal Jain directly through Epic InBasket

    c. E-consult – defining appropriate question to Renal and routing to appropriate providers (Dr. Patrick Taus, Dr. Vimal Derebail, or Dr. Koyal Jain)

2. **Nephrology physician IOG members/liaisons:** Dr. Koyal Jain, Dr. Patrick Taus

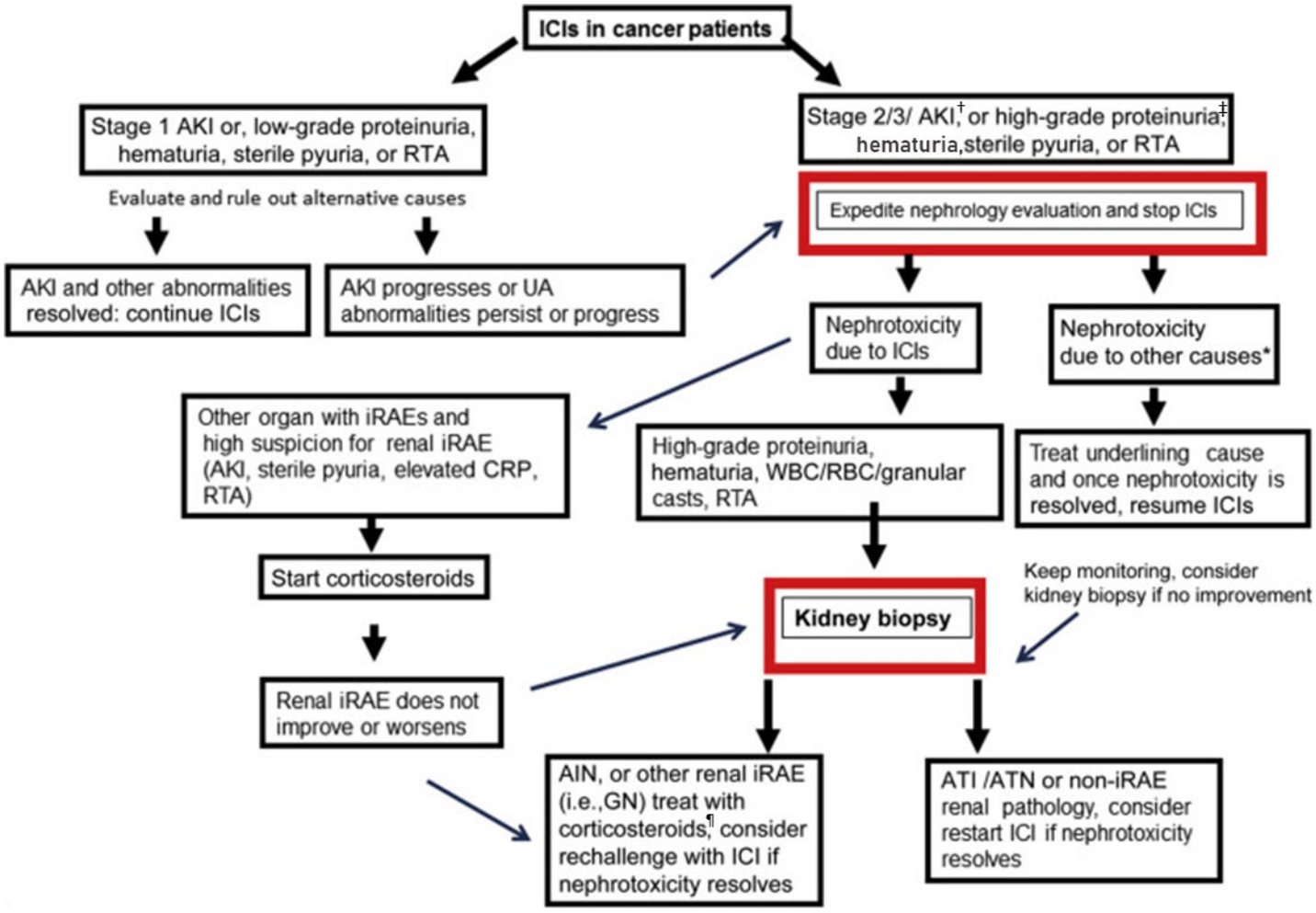
Renal IRAE Diagnostic Evaluation

1. Referral recommended when labs show a creatinine increase of 30% from baseline

2. Essential labs: Basic Metabolic Panel, Urine Protein-Creatinine Ratio, Urinalysis

3. Advised labs: Complements (C3 and C4) if proteinuria (UPC > 0.2 or positive UA) or hematuria, to evaluate for immune complex glomerulonephritis. ANCA testing if hematuria present.

Renal IRAE Management



†: Doubling or greater of baseline creatinine or significant decline in urine output (<0.5ml/kg/hr for 12 hours)
‡: UPC greater than 1.0
*: Obstructive nephropathy, volume depletion, nephrotoxins
¶: +/- other immunosuppression if indicated per nephrology/biopsy

Pulmonary Clinical Algorithm

Pre-ICI Evaluation Recommendations

1. Recommend pulmonary medicine consultation for patients with known or suspected chronic pulmonary disease (e.g., COPD, ILD, sarcoidosis) prior to ICI initiation for risk stratification, diagnostic evaluation and optimization of underlying lung disease management.

2. For patient's receiving Immune checkpoint inhibitor (ICI) who develop new shortness of breath, exercise intolerance, cough, hypoxemia, chest pain, or fever consider ICI-P in differential diagnosis

3. Early consultation recommended when bronchoscopy is being considered to assess for infection

Pulmonary Consultation

1. **Consultation for any suspected or confirmed cases of Immune checkpoint inhibitor-related pneumonitis (ICI-P, Grade 2 or higher) for assistance in diagnostic and management of ICI-P**
    a. Inpatient consultation – Consult the General Pulmonary consultant on call, page #123-7030

    b. Outpatient consultation –
        i. If the patient is already followed in UNC Pulmonary clinic, please direct message to their current provider to request follow up evaluation due to clinical suspicion for ICI-P
        ii. For patients new to UNC pulmonology:
            1. Enter "ambulatory referral to pulmonology" or ambulatory referral to MTOP (Vickie Dowdy- patient intake coordinator)
            2. In the "Comments" section enter reason for consultation as suspicion for checkpoint inhibitor pneumonitis send to MTOP (Vickie Dowdy- patient intake coordinator)
            3. Request one of the following providers for acute pulmonary evaluation: Interventional Pulmonology (Drs. Akulian, Burks and/or MacRosty) in MTOP
            4. Refer to Drs. Lobo and Patel in pulmonology for chronic ILD

2. **Pulmonary physician IOG members/liaisons:** Dr. Jason Lobo, Dr. Jason Akulian, Dr. Kunal Patel

ICI-related pneumonitis (ICI-P) Diagnostic Evaluation

1. **Definition:** – Inflammation of the lungs from non-infectious causes

2. **Diagnostic Evaluation:**

    a. Perform symptom and cardiopulmonary-targeted history and physical examination – ICI-P is a diagnosis of exclusion

    b. Consider acute/chronic co-morbid:
        i. pulmonary disease (*e.g.,* asthma, COPD, interstitial lung disease, sarcoidosis, and alveolar hemorrhage)
        ii. cardiac disease (*e.g.,* heart failure, myocarditis, arrhythmia, and coronary artery disease)
        iii. radiation pneumonitis
        iv. infectious causes (*e.g.,* viral, bacterial, fungal, or mycobacterial respiratory infections)
        v. tumor progression
        vi. tumor pseudo-progression in differential diagnosis.

    c. Recommend non-contrast chest computed tomography (CT) (unless PE in differential then CTA should be done) over simple chest radiography (CXR) when clinical suspicion for ICI-P is high due to the high false negative rate (~25%) of CXR in diagnosing ICI-P1

    d. Chest CT findings are non-specific and can include ground glass opacities (e.g., NSIP pattern), consolidations (e.g., organizing pneumonia), lymphadenopathy (e.g., sarcoidosis-like reactions) with varying distribution and severity.

ICI-related pneumonitis (ICI-P) Management

When clinical and radiographic findings are consistent with ICI-P and alternative diagnoses including an assessment for infection are excluded, ICI-P treatment recommendations are as summarized from the American Society of Clinical Oncology Clinical Practice Guideline[2]:

Severity	Features	Management
Grade 1	Asymptomatic (*Radiographic changes only*), confined to 1 lobe or <25% of parenchyma	- Hold ICI - Repeat CT chest in 3-4 weeks - Can resume if improved imaging - Treated as Grade 2 if no improvement
Grade 2	Symptomatic, limiting ADLs, Involves >1 lobe or 25-50% of parenchyma	- Hold ICI - Consider Bronch/BAL/empiric antibiotics - Pulmonary function tests: flow volume loop, DLCO and six minute walk test - Prednisone 1-2 mg/kg/d (taper 5-10 mg/wk over 4-6 weeks)
Grade 3-4	Severe or life-threatening symptoms, hospitalization required, oxygen required, limiting self-care, Involves ALL lobes or >50% of parenchyma	- PERMANENTLY discontinue ICI - Give antibiotics, Methylpred 1-2 mg/kg - Bronch/BAL +/- TBBx - If no improvement, consider alternative agents: Cellcept, infliximab, IVIG, or cyclophosphamide

Rheumatology Clinical Algorithm

Pre-ICI Evaluation Recommendations

1. Having an underlying autoimmune condition is not a contraindication to starting ICI therapy but some patients may not be an ideal candidate for this treatment if underlying autoimmune process is not well controlled or characterized.

2. Recommend consultation with Rheumatology for patients with known or suspected history of rheumatologic disease (e.g. Rheumatoid arthritis, Psoriatic arthritis, PMR, SLE, MCTD) prior to ICI initiation for diagnostic confirmation and optimization of management. If patient has primary rheumatologist, discuss plan with primary rheumatologist first before considering consulting UNC Rheumatology. Dr. Ishizawar is available for 2nd opinion.

3. Corticosteroids can be used as part of initial therapy in inflammatory arthritis, but due to likely prolonged treatment requirements, physicians should consider referral to Rheum for starting corticosteroid-sparing agents earlier than one would with other categories of irAEs.

4. Patients with rheumatologic IRAEs should be monitored with serial rheumatologic examinations, including inflammatory markers, every 4–8 weeks.

Rheumatology Consultation

1. **Evaluation/management for potential and suspected Rheumatologic/Musculoskeletal irAE**

    a. Inpatient consultation – consult Inpatient Rheumatology Consult Service, page #123-017

    b. Outpatient consultation –
        i. If patient has a primary rheumatologist, discuss/reach out to primary rheumatologist first before seeking referral with Dr. Ishizawar unless 2nd opinion requested/needed
        ii. Select referral “Ambulatory referral to Rheumatology,” and select location in referral “UNC Rheumatology Eastowne”
        iii. Select provider – Rumey Ishizawar
        iv. Under comments - Indicate request for Dr. Ishizawar for “irAE on immunotherapy”
        v. Separately send epic message to Dr. Ishizawar indicating referral request and this will allow us to expedite referral

    c. E-consult – available but is answered by consult attending

2. **IOG Rheumatology physician members/liaisons:** Dr. Rumey Ishizawar

Rheum IRAE Diagnostic Evaluation and Management

Inflammatory arthritis

1. **Definition:** Inflammation of the joints characterized by joint swelling, stiffness, warmth, redness, and pain. Stiffness after inactivity (morning, sitting) > 30 minutes. Responsive to NSAIDs or steroids but not to opioids or other pain medications.

2. **Diagnostic Evaluation:**
    a. History and exam of peripheral joints noting swelling, stiffness, tenderness
        i. follow reports of new joint pain to determine whether inflammatory arthritis is present
        ii. question whether symptom new since receiving ICI
    b. Consider x-ray/imaging to rule out metastatic disease, avascular necrosis
    c. Consider lab tests: ESR sed rate, CRP, ANA, RF, anti-CCP
    d. If there is any joint swelling (synovitis) or if symptoms persist 2 to 4 weeks, refer to Rheumatology for follow-up

3. **Monitoring:** Check ESR, CRP.

4. **IRAE Management:**

Severity	Features	Management
Grade 1	Mild pain with inflammation, erythema, or joint swelling	- Diagnostic evaluation - Continue ICI - Initiate analgesia with acetaminophen and/or NSAIDs - If symptoms > 4 weeks, refer to Rheum
Grade 2	Moderate pain associated with signs of inflammation, erythema, or joint swelling, limiting instrumental activities of daily life (ADL)	- Diagnostic evaluation - Initiate analgesia with acetaminophen and/or NSAIDs – if this fails, initiate prednisone or prednisolone 10-20 mg/d - Hold ICI temporarily – Can resume ICI upon symptom control AND on prednisone ≤ 10 mg/d - If symptoms > 2 weeks, refer to Rheum
Grade 3-4	Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self-care ADL	- Diagnostic evaluation - Hold ICI temporarily - Initiate oral prednisone 0.5–1 mg/kg - Refer to Rheum

Myositis

1. **Definition**: Inflammation of the muscles characterized by weakness, myalgia and elevated muscle enzymes (CK, aldolase).

2. **Diagnostic Evaluation:**
    a. History and exam focused on strength (proximal vs distal), joint tenderness, stiffness, or swelling, as well as muscle group tenderness
    b. Lab tests to assess muscle inflammation: CK, aldolase, TSH, transaminases (AST, ALT), CRP, ESR sed rate, ANA
    c. Consider EMG or MRI STIR imaging of muscle group affected
    d. Consider muscle biopsy

3. **Monitoring:** CK, ESR, and CRP.

4. **IRAE Management:** Refer stable cases to outpatient Rheumatology or Neurology.

Significant weakness on exam (inability to lift head, unable to swallow, having breathing difficulty, inability to ambulate without support) requires inpatient work-up and management with Rheumatology and Neurology Consultation (Rheum can facilitate to Neurology if needed)

Severity	Features	Management
Grade 1	Mild weakness with or without pain	- Diagnostic evaluation with neg CK - Continue ICI - Initiate analgesia with acetaminophen and/or NSAIDs
Grade 2	Moderate weakness with or without pain, limiting age-appropriate instrumental activities of daily life (ADL) * Can resume ICI upon symptom control, normal CK AND on prednisone ≤ 10 mg/d	- Diagnostic evaluation INCLUDES elevated CK - Hold ICI temporarily - Initiate analgesia with acetaminophen and/or NSAIDs OR initiate prednisone or equivalent at <10 mg OR 0.5–1 mg/kg if CK is elevated ≥ 3x - Refer to Rheum or Neuro
Grade 3-4	Severe weakness with or without pain, limiting self-care ADL * Permanently discontinue if any evidence of myocardial involvement	- Diagnostic evaluation - Hold ICI temporarily - Initiate oral prednisone 1 mg/kg or equivalent; Consider 1–2 mg/kg of methylprednisolone IV or higher-dose bolus if severe compromise - Refer to Rheum or Neuro

Polymyalgia Rheumatica

1. **Definition:** – Inflammation characterized by proximal pain and stiffness (shoulders, neck, hip) without evidence of muscle inflammation (weakness, negative CK elevation, negative EMG). No true muscle weakness but range of motion may be limited due to pain.

2. **Diagnostic Evaluation:**
    a. History and exam focused on presence for proximal pain and stiffness vs weakness.
    b. Need to assess for concurrent Giant Cell Arteritis (Fixed Temporal Headache, Jaw Claudication, Visual Disturbances)
    c. Check ANA, RF, anti-CCP, ESR, CRP, CK, Aldolase, Transaminases (AST, ALT)
    d. Recommend referral to Rheumatology early for management (but can start low dose prednisone 10-20 mg daily while awaiting evaluation – 100% improvement within 24-48 hours diagnostic).

3. **Monitoring:** Check ESR, CRP.

4. **IRAE Management:**

Severity	Features	Management
Grade 1	Mild stiffness and pain	- Diagnostic evaluation - Continue ICI - Initiate analgesia with acetaminophen and/or NSAIDs
Grade 2	Moderate stiffness and pain, limiting age-appropriate instrumental activities of daily life (ADL) * Can resume ICI upon symptom control AND on prednisolone ≤ 10 mg/d	- Diagnostic evaluation - Hold ICI temporarily - Initiate prednisone 20 mg/d or equivalent; taper dose after 3-4 weeks if symptoms improve - Refer to Rheum
Grade 3-4	Severe stiffness and pain, limiting self-care ADL	- Diagnostic evaluation - Hold ICI temporarily - Initiate 20 mg/d or equivalent - Refer to Rheum

Sicca Syndrome

1. **Definition:** – Inflammation affecting tear and saliva production

2. **Diagnostic Evaluation:**
    a. Ophthalmologic exam to assess for eye dryness
    b. Assess for parotid swelling and extent of salivary pool on exam
    c. Check ANA, ENA, dsDNA, C3, C4, CBC w/diff, ESR, CRP
    d. Refer to Rheumatology for further assessment and management

3. **IRAE Management:** focus on relieving symptoms until Rheum consult/appointment
    a. For dry eyes: use preservative-free OTC artificial tears
    b. For dry mouth: use good oral hygiene (topical fluoride and antimicrobial mouth rinses), salivary stimulation (sugar-free gum or sour lemon lozenges), use of OTC saliva substitutes
    c. For dry skin: use creams and lotions (like Eucerin or Lubriderm), avoid hot showers, moisturize after bathing
    d. For vaginal dryness: use vaginal lubricants (like Replens)
    e. For severe Sicca symptoms consider prednisone 0.5 to 1 mg/kg per day

Other Rheumatologic IRAEs

EPIC Message Dr. Rumey Ishizawar

Appendix A: Current IOG Team List

Immuno-Oncology Clinical Team				
Provider	Title/Position	Email	Pager ID	Phone
CARDIOLOGY				
Jensen, Brian C.	MD	brian_jensen@med.unc.edu	2161804	919-966-5202
DERMATOLOGY				
Bowers, Edith	MD, PhD	edith_bowers@med.unc.edu	2161425	984-974-3900
Cook, James	Scheduling Assistant	james.cook@unchealth.unc.edu	N/A	984-974-4796
Liu, Zhi	PhD	zhi_liu@med.unc.edu	N/A	919-966-0788
Ziemer, Carolyn	MD, MPH	carolyn_ziemer@med.unc.edu	2160100	984-974-3900
ENDOCRINOLOGY				
Cater, Taylor *July 2023- June 2024	MD (Fellow)	Taylor.Cater@unchealth.unc.edu	2164126	N/A
GASTROENTEROLOGY				
Herfarth, Hans	MD, PhD	hans_herfarth@med.unc.edu	2164654	919-966-6806
Powers, Laurie	RN	laurie_powers@med.unc.edu	2161814	919-966-4318
HEPATOLOGY				
Moon, Andrew	MD	andrew.moon@unchealth.unc.edu	2165771	919-812-0135
Shah, Neil	MD	neil_shah@med.unc.edu	3470972	704-575-8767
NEPHROLOGY				
Derebail, Vimal	MD	vimal_derebail@med.unc.edu	2163713	919-966-2561
Jain, Koyal	MD	koyal_jain@med.unc.edu	2167086	919-966-2561
Taus, Patrick	MD, PhD	patrick_taus@med.unc.edu	3931866	919-445-2718
HEMATOLOGY/ONCOLOGY				
Collichio, Frances	MD	frances_collichio@med.unc.edu	1239869	919-966-6416
Grover, Natalie	MD	natalie_grover@med.unc.edu	2166193	919-368-2782
Landman, Paula	RN, MSN	paula.landman@unchealth.unc.edu	2161515	984-974-8372
MacDonagh, Colleen	Administration	colleen_macdonagh@med.unc.edu	N/A	919-966-5902
Pecot, Chad	MD	pecot@email.unc.edu	2161944	615-305-3955
Rose, Tracy	MD, MPH	tracy_rose@med.unc.edu	2160681	919-962-8561
Somasundaram, Ashwin	MD	ashwin87@email.unc.edu	2160817	919-360-7077
Vincent, Benjamin	MD	benjamin_vincent@med.unc.edu	2164209	919-962-8409
Wehner, Kimberly	DPN	kimberly.wehner@unchealth.unc.edu	2161918	984-974-8349
Weiss, Jared	MD	jared_weiss@med.unc.edu	2164396	919-843-7718
Zeidner, Joshua	MD	joshua_zeidner@med.unc.edu	1239661	919-962-5164
ORAL MEDICINE				
Hasan, Iquebal	DDS	Iquebal.Hasan@unchealth.unc.edu	2164366	704-550-6204
PULMONARY				
Akulian, Jason	MD, MPH, FCCP	jason_akulian@med.unc.edu	2164549	919-216-4549
Burks, Allen Cole	MD	acole_burks@med.unc.edu	2168239	919-843-1960
Lobo, Jason	MD	jason_lobo@med.unc.edu	2164547	919-843-9328
Patel, Kunal	MD	kunal_patel2@med.unc.edu	2163815	919-966-5902
RADIOLOGY				
Lee, Yueh	MD, PhD, FACR	leey@med.unc.edu	2163003	919-537-3730
RHEUMATOLOGY				
Ishizawar, Rumey	MD, PhD	rumey_ishizawar@med.unc.edu	2163638	919-962-4975
Saxena Beem, Shruti	BS, Coordinator, ACRP-CCRC, PM	shruti_saxena@med.unc.edu	2169732	919-966-0545
Surati, Shivani	MS, Coordinator	shivani_surati@med.unc.edu	N/A	919-966-7597

Appendix B: Currently Enrolling Clinical Trials for irAE management

Abatacept Clinical Trial for irAE Myocarditis

ATRIUM
Abatacept for Immune Checkpoint Inhibitor Associated Myocarditis

AbatacepT foR ImmUne checkpoint inhibitor associated Myocarditis (ATRIUM)

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A Phase 3, Investigator-Initiated, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Abatacept Compared to Placebo in Hospitalized Participants with Immune Checkpoint Inhibitor Associated Myocarditis

Study Overview

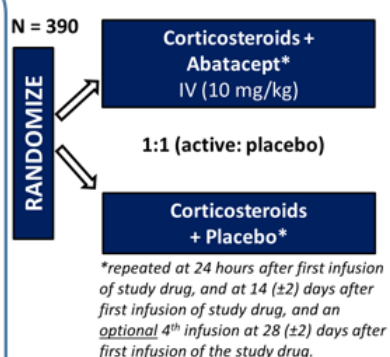
Key Inclusion Criteria

- Age ≥18 years
- Active treatment with an FDA-approved ICI
- Hospitalized
- Diagnosed with ICI Myocarditis

Key Exclusion Criteria

- Prior exposure to abatacept/belatacept
- Active Infection
- Already has a component of the primary endpoint
- Is currently enrolled in another interventional study focused on the management of ICI toxicities.
- Female who is considering becoming pregnant.
- Male who is considering fathering a child or donating sperm during the study or for approximately 30 days after the last dose of study drug.

Study Schema



*repeated at 24 hours after first infusion of study drug, and at 14 (±2) days after first infusion of study drug, and an optional 4th infusion at 28 (±2) days after first infusion of the study drug.

Endpoints

Primary: Major Adverse Cardiac Events, defined as a composite of cardiovascular death, cardiogenic shock, cardiac arrest, significant ventricular tachyarrhythmia, significant bradyarrhythmia and acute decompensated heart failure.

Secondary:

- Individual components of the primary endpoint.
- Change in serum troponin.
- The combination of the composite primary endpoint plus a troponin increase.
- Myocarditis Illness severity using an ordinal scale.
- Clinical status at 90 days and 6 months.
- Rates of fatal and non-fatal DVT and PE.
- Treatment-related adverse events between the two groups.

ATRIUM

Appendix C: IOG Resources for ICI and irAE related research

By promoting cooperative clinical care and research (clinical, translational, and basic science), the IOG hopes to foster a better understanding of ICIs and the development of irAEs; and thereby, improve clinical outcomes for both cancer patients and patients with autoimmune disorders.

IOG Prospective Database and Biorepository

A prospective observational study with the goal of building a patient registry with a biorepository will be a well-characterized cohort of patients with standardized clinical data and biological samples for biomarker analysis, immunophenotyping, microbiome research, and genetic analysis to understand development of autoimmune conditions. We are actively recruiting.

UNC Immuno-Oncology Database and Biorepository – Summary of Study Specimens & Measures.

General Health	Cultural/SES	PROs	Cancer-Related Measures
➢ Height, Weight, Vitals ➢ Physical Exams ➢ Medications ➢ Allergies ➢ Alcohol & Tobacco Use ➢ Comorbidities ➢ Autoimmune Conditions	➢ Demographics ➢ Income ➢ Insurance ➢ Employment ➢ Education ➢ Marital Status	➢ Patient QoL Questionnaire (selected items from the PRO-CTCAE Item Library version 1.0) ➢ Pregnancy Outcome Questionnaire (only for patients who became pregnant while on ICIs)	➢ Cancer Diagnosis & History ➢ Cancer Treatment & History ➢ ICI Treatment & Outcome ➢ Immune-Related Adverse Events (irAEs) ➢ irAE Management & Outcome ➢ Cancer Outcome
Lab Results	**Biomarkers:** *Longitudinal Study Specimens*	**Biomarkers:** *Optional Study Specimens*	**Data from Medical Charts**
➢ CBC w/ diff, CMP ➢ Lipid Panel ➢ Thyroid Studies ➢ Endocrine Labs, HgbA1C ➢ Coagulation ➢ Inflammatory Markers ➢ Auto-Antibodies Panel ➢ Urinalysis ➢ Fecal Markers	➢ DNA from Cheek Swab ➢ Blood Serum ➢ PBMCs ➢ Whole Urine ➢ Urine Supernatant & Pellet ➢ Feces for Microbiome	➢ Body fluids, if available (Synovial Fluid, BAL Fluid, etc.) ➢ Biopsies if available (Skin, GI, Kidney, etc.) ➢ Tissue from surgical waste, if available ➢ FFPE Tissue or Biopsies, if available	➢ Encounter Notes ➢ Imaging reports (X-rays, Ultrasounds, PET scans, MRIs, CT scans, etc.) ➢ Test reports (PFT, 6MWT, EMG, Echo, EKG, etc.) ➢ Procedure reports (Biopsies, Surgeries, BAL, Joint Aspirations, Colonoscopies, Endoscopies, etc.)

Abbreviations:
SES – socioeconomic status; *PRO* – patient reported outcome; *QoL* – quality of life; *PRO-CTCAE* – Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; *ICIs* – immune checkpoint inhibitors; *irAEs* – immune related adverse events; *CBC w/ diff* – complete blood count with differential; *CMP* – complete metabolic panel; *HgbA1C* – hemoglobin A1C; *DNA* – deoxyribonucleic acid; *PBMCs* – peripheral blood mononuclear cells; *BAL* – bronchoalveolar lavage; *GI* – gastroenterology; *FFPE* – formalin fixed paraffin embedded; *PET* – positron emission tomography; *MRI* – magnetic resonance imaging; *CT* – computer tomography; *PFT* – pulmonary function test; *6MWT* – 6-minute walk test; *EMG* – electromyography; *Echo* – echocardiogram; *EKG* – electrocardiogram

IOG Retrospective Study

A longstanding retrospective study examining treatments and outcomes of patients receiving ICI therapy at UNC with the goal of characterizing irAEs at UNC from January 2004 onwards. This study has supported research projects for several trainees. Individual projects stemming from this study are described below:

- Retrospective analysis of cancer patients treated at University of North Carolina between 2004 and 2017 (Project date: December 2016 – November 2018)

- Immune checkpoint inhibitor-related pneumonitis in lung cancer: real-world incidence, risk factors, and management practices across six health care centers in North Carolina (Project date: July 2018 – October 2021. 2nd Project 9/2023-present)

- Neutrophil to Lymphocyte Ratio (NLR) as a predictor of immune-related adverse events in CTLA-4 treated patients (Project date: May 2019 – present)

- Immune-related adverse events in patients with autoimmune rheumatologic disease on immune checkpoint inhibitor therapy (Project date: December 2019 – July 2022)

- Checkpoint inhibitor induced growth hormone deficiency and implications for the treatment of ACTH deficiency (Project date: April 2021 – June 2022)

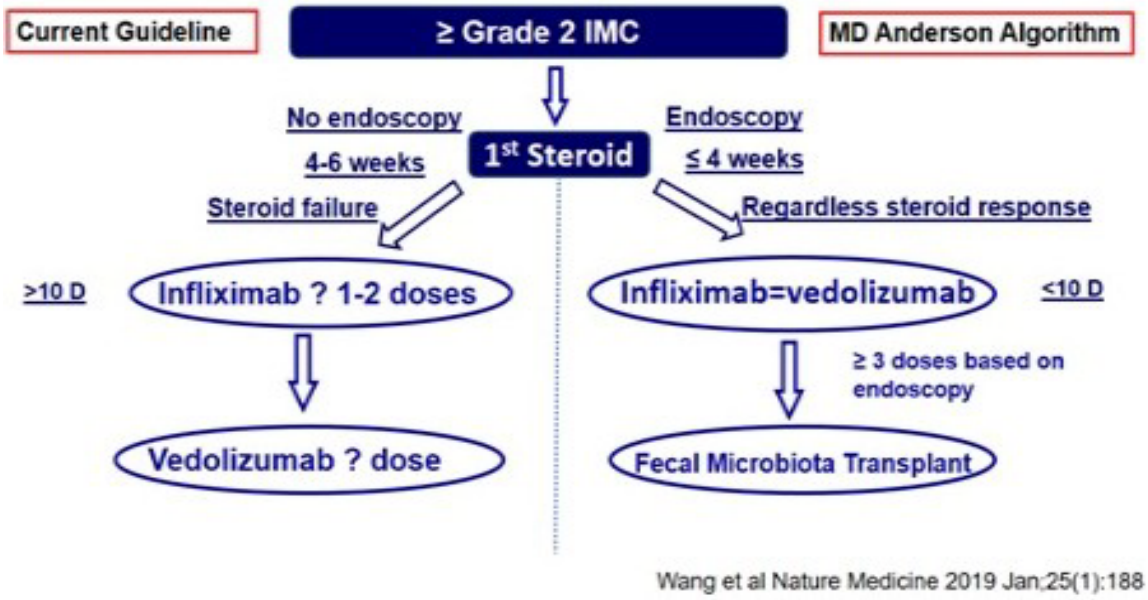
- Correlating RNAseq expression with tumor response and irAEs (Project date: August 2021 – present)

- Neuroimaging analyses in patients experiencing irAEs from ICI therapy (Project date: November 2022 – present)

- GI and Hepatology toxicities in ICI patients with a focus on patients with unresectable HCC (Project date: June 2023 – present)

Appendix D: Clinical Algorithms for Prospective Clinical Research

Gastroenterology Research Algorithm



IMC – Immune mediated colitis
The "MD Anderson Algorithm" is a research algorithm with preliminary data showing promising efficacy.

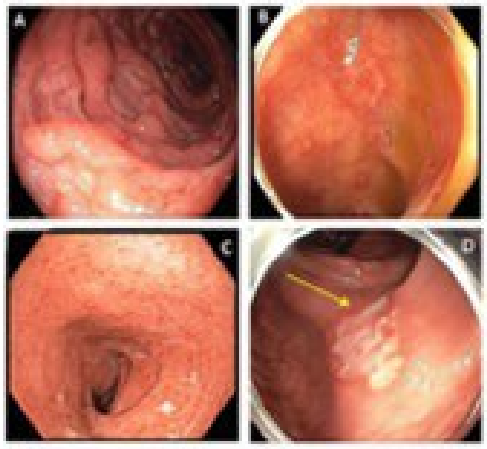
Summarized data comparing efficacy between use of anti-TNF therapy and vedolizumab (aka Entyvio, an integrin inhibitor) presented below. (Abu-Sbeih, Hamzah et al. 2018)

Colitis Outcome by Timing of Endoscopy

Characteristic	> 30 days N = 40	≤ 30 days N = 142	P
IV steroids	23 (57.5)	60 (42.3)	0.05
Days of symptoms	54 (92)	26 (77)	0.06
Days of steroid use	87 (120)	53 (41)	0.02
Days from onset to IFX/vedo	31 (23)	15 (14)	0.03
Outcomes			
ICU admission	4 (10)	3 (2.1)	0.07
Recurrence	20 (50.0)	31 (21.8)	0.01

Clinical Outcome by Endoscopy Features

Characteristic	High-risk N = 71	No high-risk N = 111	P
Duration of symptoms	41 (106)	27 (60)	0.30
IV steroids	41 (66.1)	42 (58.3)	0.38
Infliximab/vedolizumab	30 (46.2)	12 (15.8)	< 0.01
Outcomes			
Hospitalization	58 (81.7)	74 (66.7)	0.03
Duration of hospitalization	9 (8)	6 (5)	0.02



High-risk features

- Deep ulcer ≥ 2mm
- Large ulcer ≥ 1cm
- No. of ulcers ≥ 3
- Proximal to splenic flexure

Conclusions

- Predictors of severe disease
  - High-risk endoscopy features
  - Active histological inflammation
- Early endoscopy reduced
  - Duration of steroid
  - Duration of symptoms
  - Hospitalization
  - Recurrence
- Positive fecal lactoferrin predicts IMC

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2021 ASCO Guidelines for Management of irAEs from ICI therapy

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1. Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol* 2018; 71:1755–64

Dermatology

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