Management of Immune related adverse events

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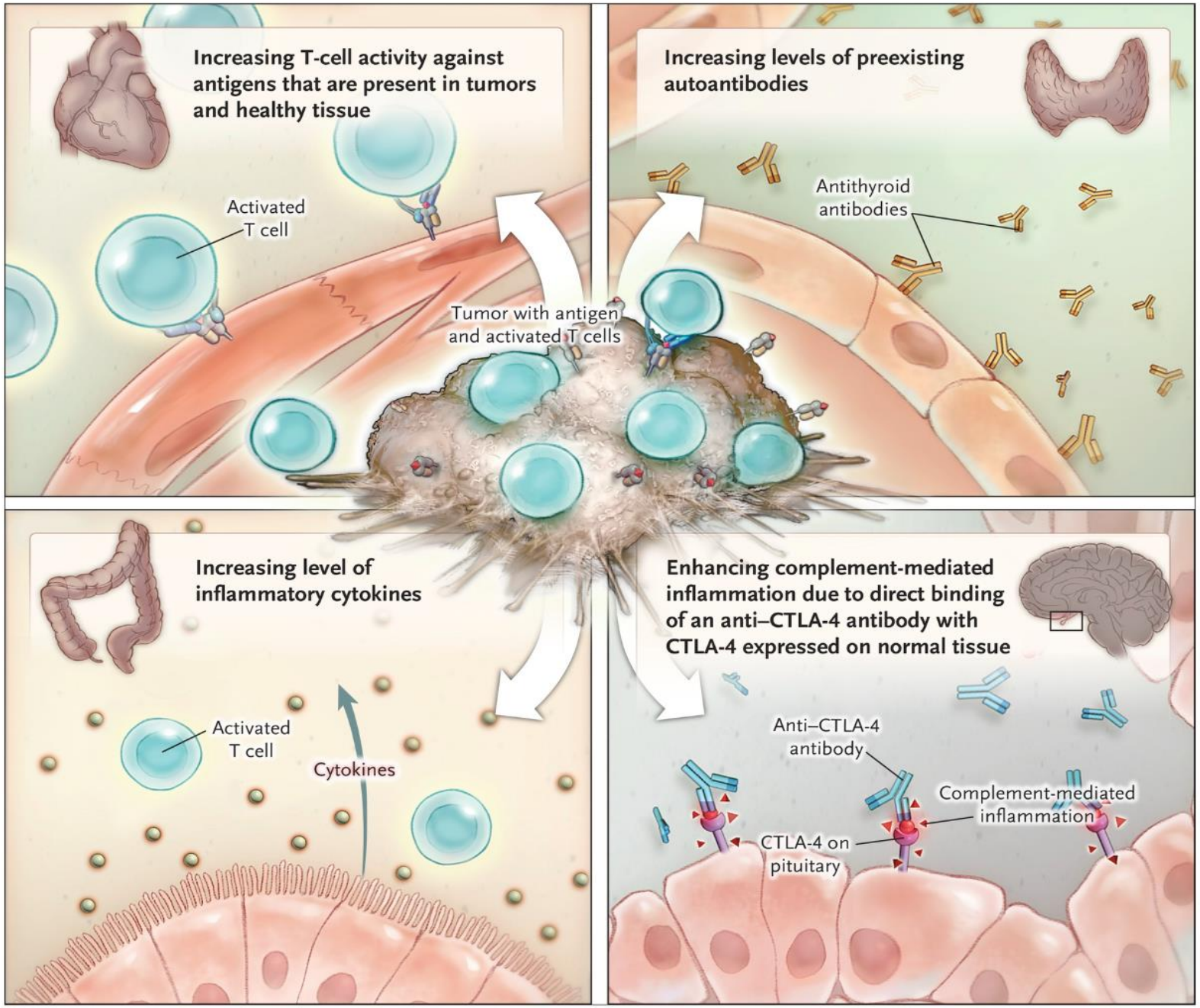
Outline

- irAEs Associated With ICIs
- Identification, Assessment, and Management of irAEs
- Recommended Treatment (Duration) for irAEs
- Retreatment After irAEs

Immune-Related AEs

- ICIs introduce the potential for transformative, durable responses in multiple malignancies
- ICIs also introduce the potential for new toxicity
- Adverse events (AEs) related to the use of immune checkpoint inhibitor (ICI) therapy are defined as immune-related(IR) AEs (ir-AEs).
- Ir-AEs are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5
- Immune-related AEs
  - Activation of immune cells in nontumor compartments
  - Can mimic autoimmune conditions



N Engl J Med 2018;378:158-68

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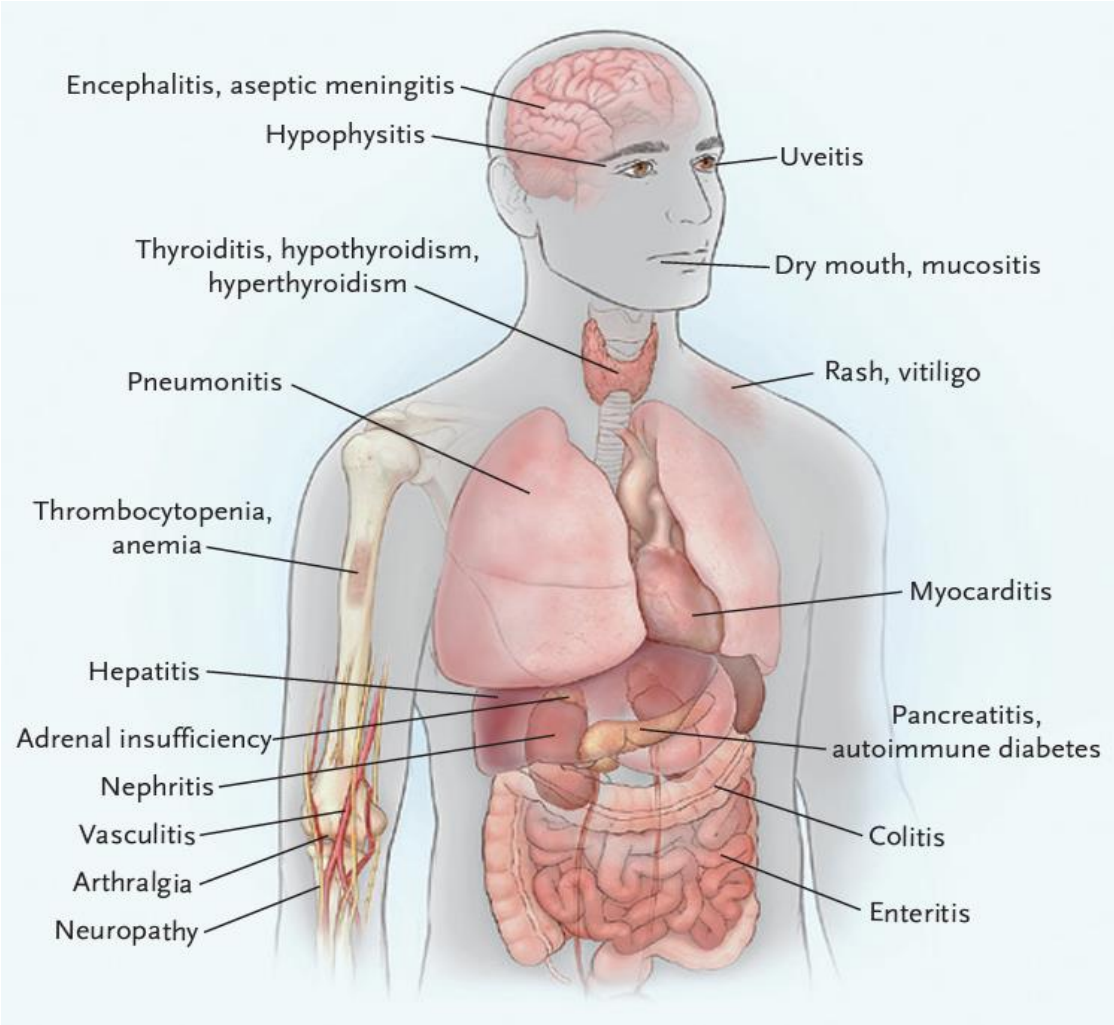
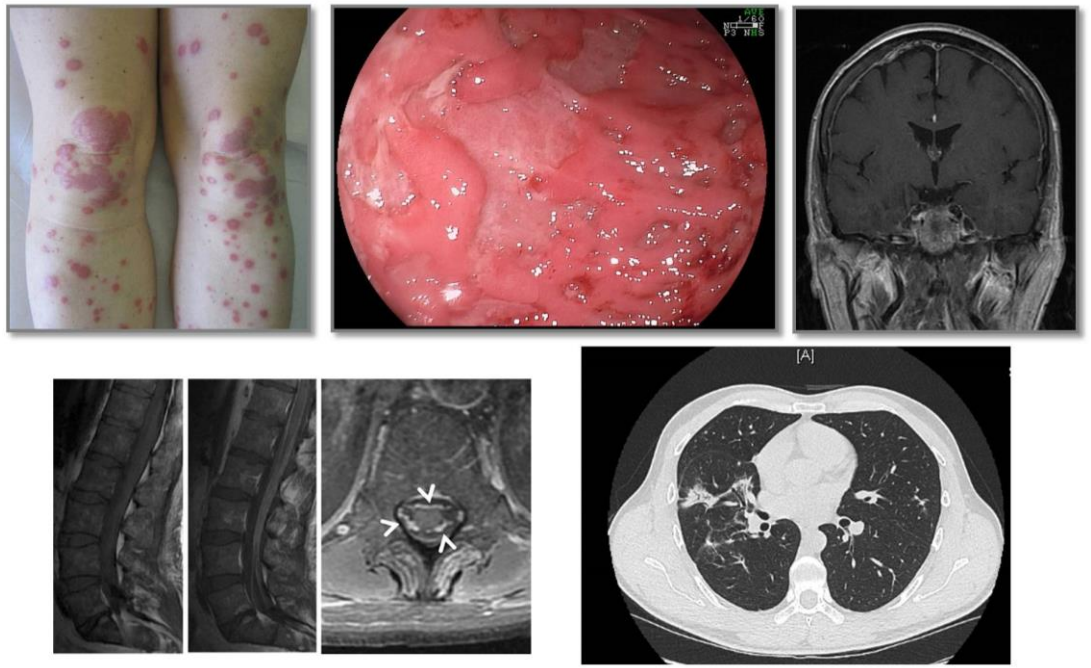
A New Spectrum of Adverse Events





Michot. Eur J Cancer. 2016;54:139. Robert. ASCO 2017. Education session: Checkpoint inhibitor immunotherapy.
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Common irAEs:Typical Presentations

irAE	Common Presentation
Dermatologic[1,2]	Maculopapular rash with pruritus, predominantly on trunk and to lesser extent the upper limbs, spreading to extremities; eczematous, lichenoid, psoriasiform manifestations; blistering skin reactions
Diarrhea/colitis[3]	Diarrhea, abdominal pain, hematochezia, weight loss, fever, vomiting
Hepatic[3]	Often asymptomatic and diagnosed via routine blood tests
Pancreatic[1]	Asymptomatic elevation in amylase/lipase; CT, clinical findings of pancreatitis; severe abdominal pain, vomiting, and hemodynamically unstable
Endocrine[3]	Headaches, visual disturbances, fatigue, altered consciousness, deranged electrolytes (particularly hyponatremia), anorexia, mood changes

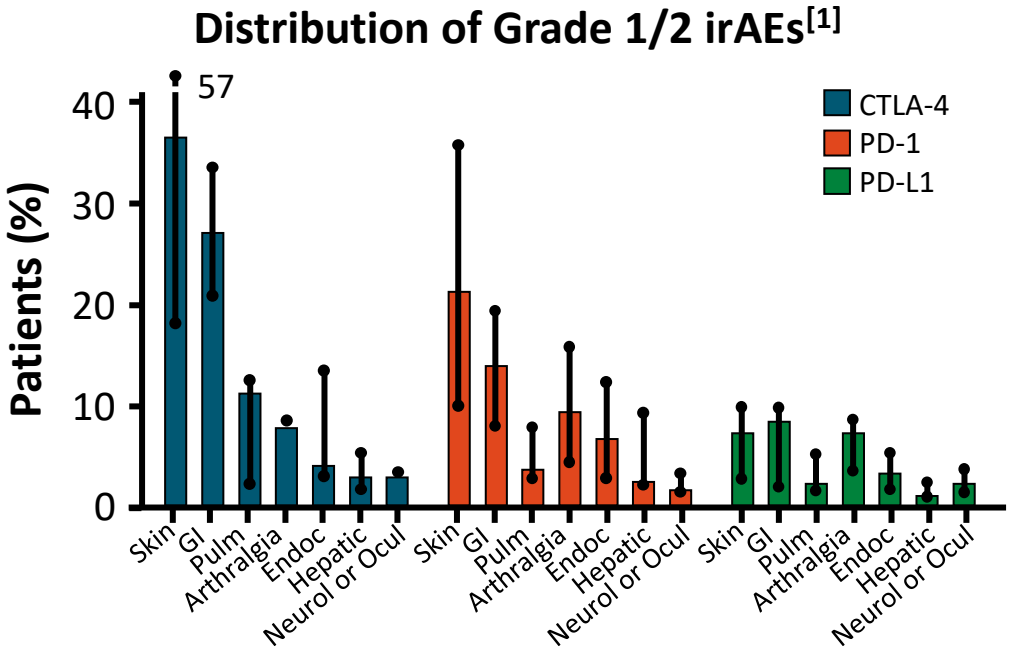
1. NCCN Guidelines for Management of Immunotherapy-Related Toxicities. v1. 2023.
2. Sibaud. Am J Clin Dermatol. 2018;19:345. 3. Pickwell-Smith. Br J Hosp Med (Lond). 2018;79:372.

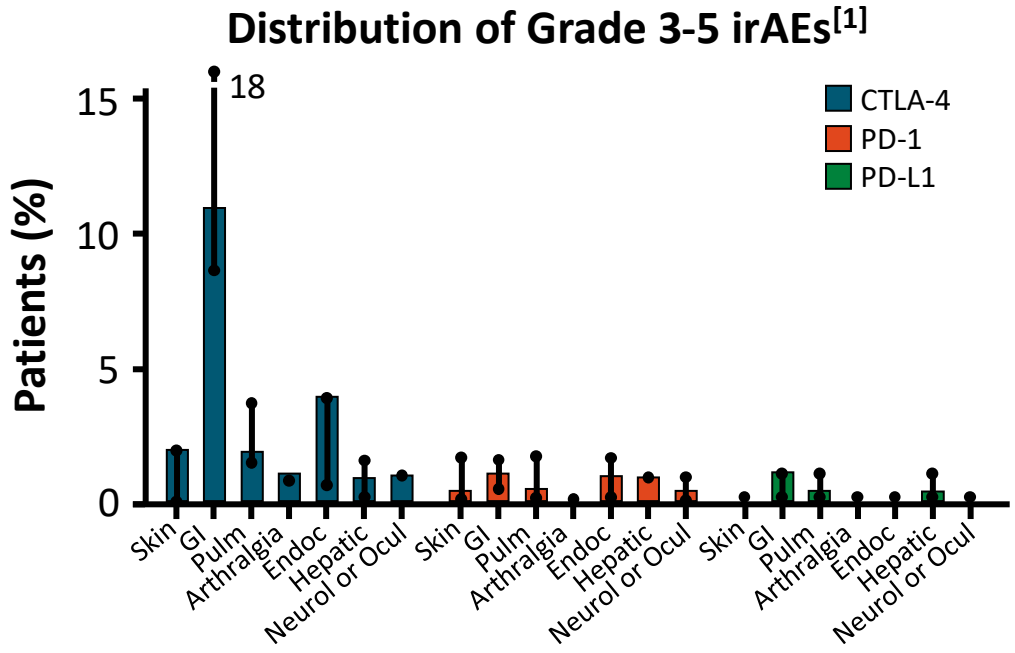
Less Common irAEs: Typical Presentations

Immune-Related AE	Common Presentation
Pneumonitis[1]	Dyspnea, cough, fever, chest pain
Renal[2]	Elevated serum creatinine; azotemia; inability to maintain acid–base or electrolyte balance; urine output change
Ocular[2]	Vision changes; photophobia; tenderness/pain; eyelid swelling; proptosis; red/purple discoloration; eye redness
Neurologic[2]	Progressive or fluctuating muscle weakness, usually proximal to distal; absent/reduced deep tendon reflexes; sensory–motor deficit; headache, photophobia, neck stiffness with nausea/vomiting; confusion, altered behavior, seizures, short-term memory loss, depressed level of consciousness, focal weakness, speech abnormality
Cardiovascular[3]	Generalized malaise and fatigue; dyspnea; edema; decreased ejection fraction on ECG
Musculoskeletal[2]	Joint pain, swelling; inflammatory symptoms; stiffness after inactivity; improvement with heat; myalgias; myositis

1. Pickwell-Smith. Br J Hosp Med (Lond). 2018;79:372. 2. NCCN Guidelines for Management of Immunotherapy-Related Toxicities. v1. 2023. 3. Brumbaugh. Cardiol Rev. 2019;27:97.

Frequency of irAEs With ICI Monotherapy



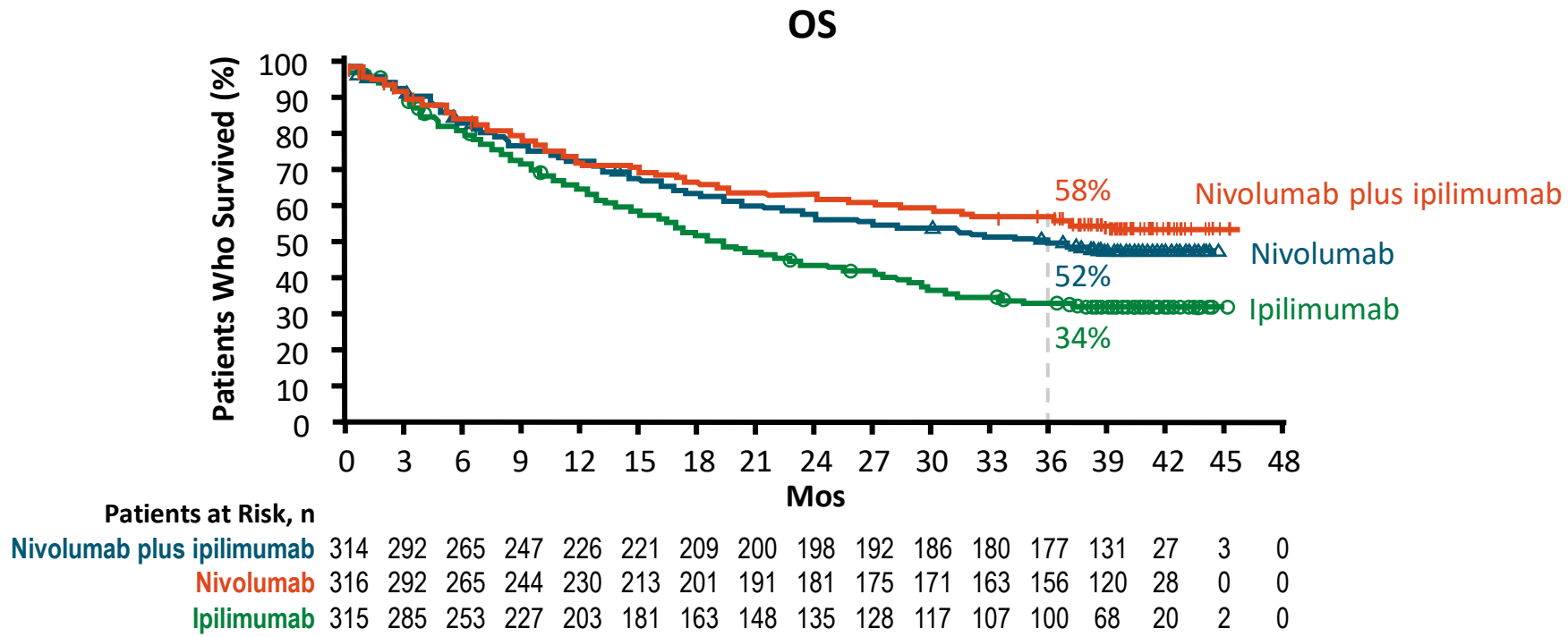


- Incidence of irAEs can vary among malignancies[2]
  - Retrospective review found an overall incidence of colitis in 6% and pneumonitis in 3.84% of patients with multiple cancer types at a single institution
  - Colitis was significantly more common in melanoma (P = .016), pneumonitis significantly more common in NSCLC (P = .004)

1. Michot. Eur J Cancer. 2016;54:139. 2. Owen. ESMO 2018. Abstr 1772P.

Survival Benefit and Rates of AEs -Combination ICI Therapy

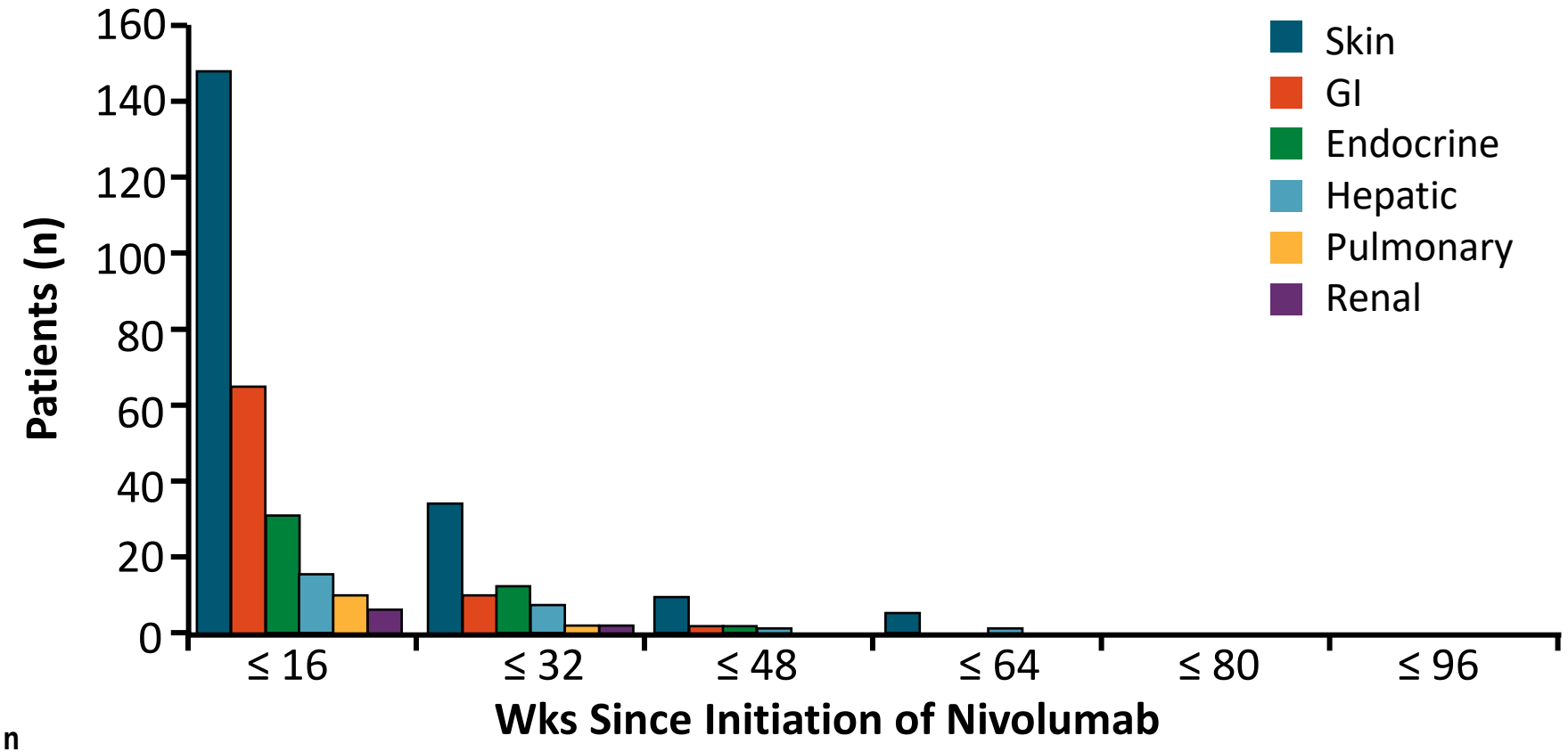
- Phase III CheckMate 067: nivolumab + ipilimumab in previously untreated melanoma



Treatment-Related AEs, %	Nivolumab + Ipilimumab (n = 313)	Nivolumab (n = 313)	Ipilimumab (n = 313)
Grade 3/4	59	21	28

Wolchok. NEJM. 2017;377:1345.

Select Any-Grade, Treatment-Related AEs Over Time



Patients at Risk, n						
Still in study	453	281	138	26	10	9
Still receiving treatment	298	172	76	11	3	0
Total with new event	239	34	4	5	0	0
Still in study with new event, %	53	12	3	19	0	0

Weber. JCO. 2017;35:785.

ED Visit-Most Common irAEs in Patients With Cancer

- Retrospective review of 628 patients receiving ICIs who visited ED at MD Anderson Cancer Center (March 2011 to February 2016)
  - Of 1026 visits, 257 (25.0%) related to irAEs, with 210 (81.7%) of irAE-related visits leading to admission

irAE, %	Ipilimumab (n = 186)	Nivolumab (n = 154)	Pembrolizumab (n = 109)	> 1 Agent (n = 179)
Diarrhea	14.5	8.4	6.4	18.4
Colitis	7.0	2.6	1.8	7.3
Pneumonitis	3.2	7.1	4.6	4.5
Dermatitis	4.3	4.5	4.6	7.8
Hypophysitis	4.3	0.6	0	5.0
Hepatitis	1.1	6.1	1.3	0.9
Thyroiditis	1.6	0.6	0	5.0
Pancreatitis	1.1	1.9	0.9	5.0
Adrenalitis	0.5	1.3	0	1.1

Least common irAEs (all ≤ 1.1%): nephritis, hematologic effects, myocarditis, vasculitis, eye effects.

Majzoub. Ann Emerg Med. 2019;73:79.

irAEs Can Occur After Discontinuation of ICIs

- Retrospective review of 64 patients with advanced/unresectable melanoma treated with nivolumab + ipilimumab at a single center (Dec 2014 to Jan 2016)
  - 31 patients stopped nivolumab + ipilimumab early due to toxicity
    - 4/31 (13%) experienced a clinically significant irAE > 16 wks after discontinuation (range: 22-33 wks post dose)

Shoushtari. JAMA Oncol. 2018;4:98.

Outline

- irAEs Associated With ICIs
- Identification, Assessment, and Management of irAEs
- Recommended Treatment (Duration) for irAEs
- Retreatment After irAEs

Management

(i) Diagnosis and grading of IR-AEs,

(ii) Ruling out differential diagnoses and pre-immunosuppression work-up

(iii) Selecting the appropriate immunosuppression strategy for grade ≥2 events

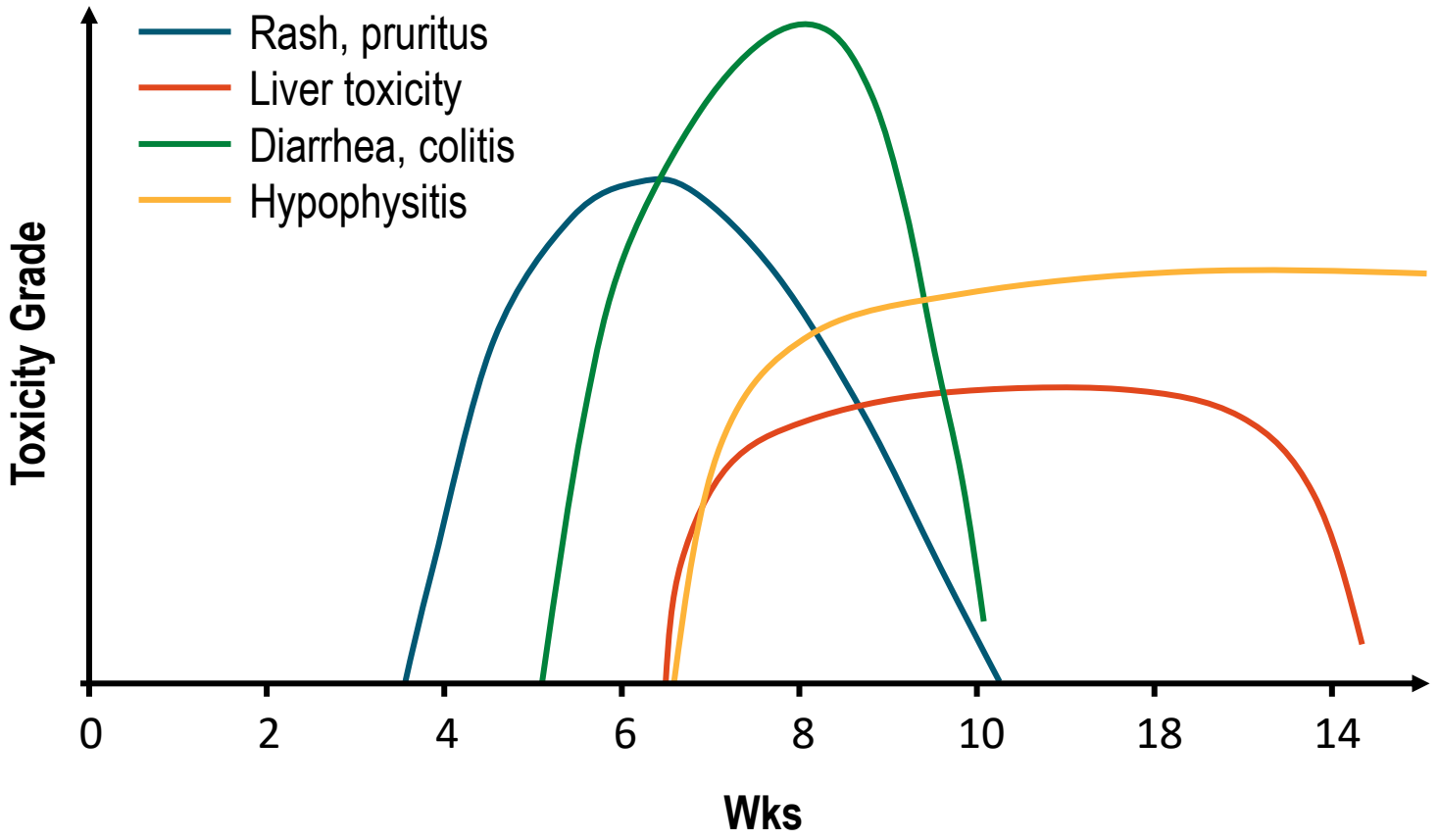
(iv) Active evaluation at 72 h to adapt treatment

General Principles for Managing irAEs

- Consult promptly with relevant specialists for affected organ systems (eg, gastroenterology, dermatology)
- Management generally based on severity of symptoms
  - Mild (grade 1): supportive care, consider holding drug
  - Moderate (grade 2): hold drug, redose if toxicity improves, consider low-dose steroids (prednisone 0.5-1 mg/kg/day)
  - Severe (grade 3): discontinue drug, monitor closely (likely inpatient), start high-dose steroids (prednisone 1-2 mg/kg/day) with a slow taper (≥ 1 mo)
    - If not improving in 1-3 days, increase immunosuppression
- Dose reduction is not a recommended strategy
- Avoid delays in recognition and intervention

Brahmer. JCO. 2018;36:1714.

Most irAEs Are Reversible With Steroids



Weber. JCO. 2012;30:2691.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

SPECIAL ARTICLE

Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

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CHECK FOR UPDATES

Available online 18 October 2022

ASCO special articles

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update

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Management of Immunotherapy-Related Toxicities

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NCCN.org

NCCN Guidelines Version 2.2023
Management of Immune Checkpoint Inhibitor-Related Toxicities

NCCN Guidelines Index
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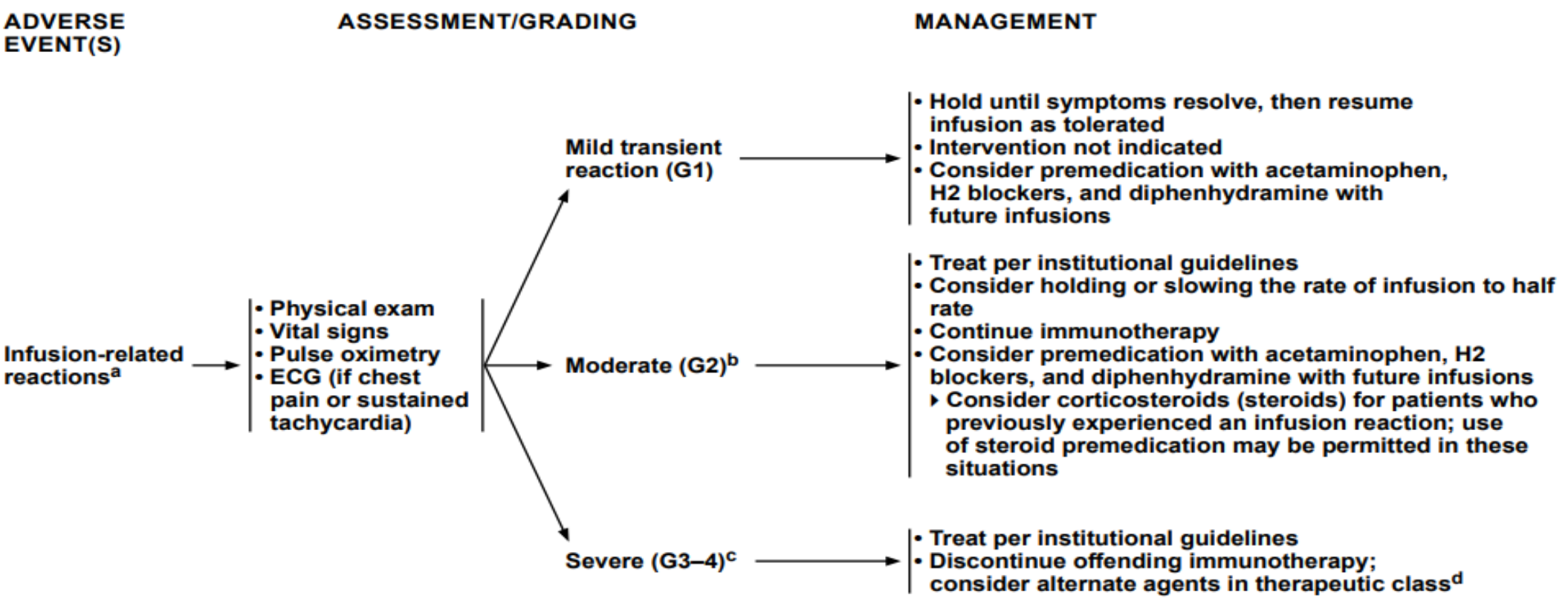
Discussion



[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.

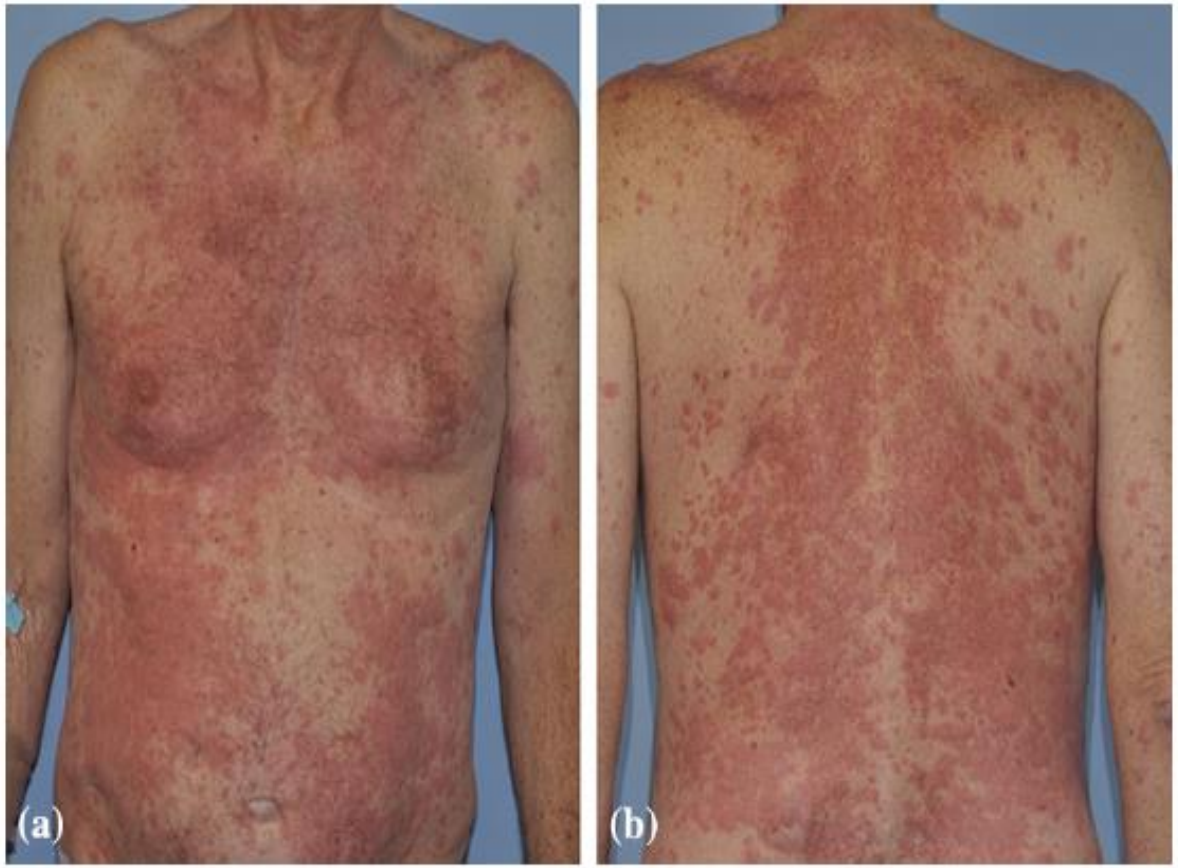
[b] Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], narcotics, intravenous [IV] fluids); prophylactic medications indicated for ≤24 hours.

[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.

Dermatologic Reactions in Patients Treated With ICI

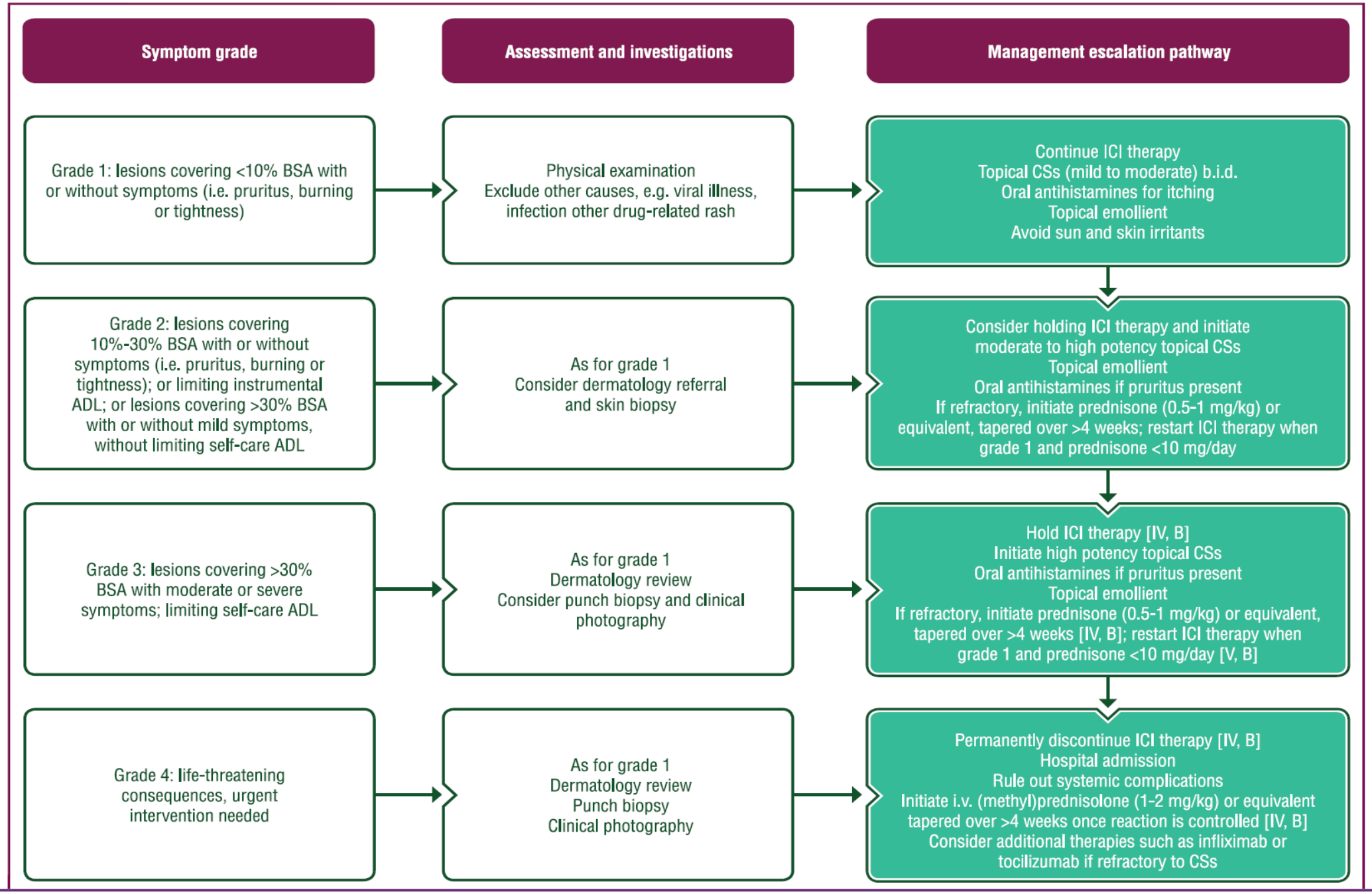
Grade 3 Maculopapular Rash



Non-specific maculopapular rash -first 6 weeks of therapy.
These rashes can be preceded by or associated with pruritus.
Pruritus -sole manifestation of a skin AE

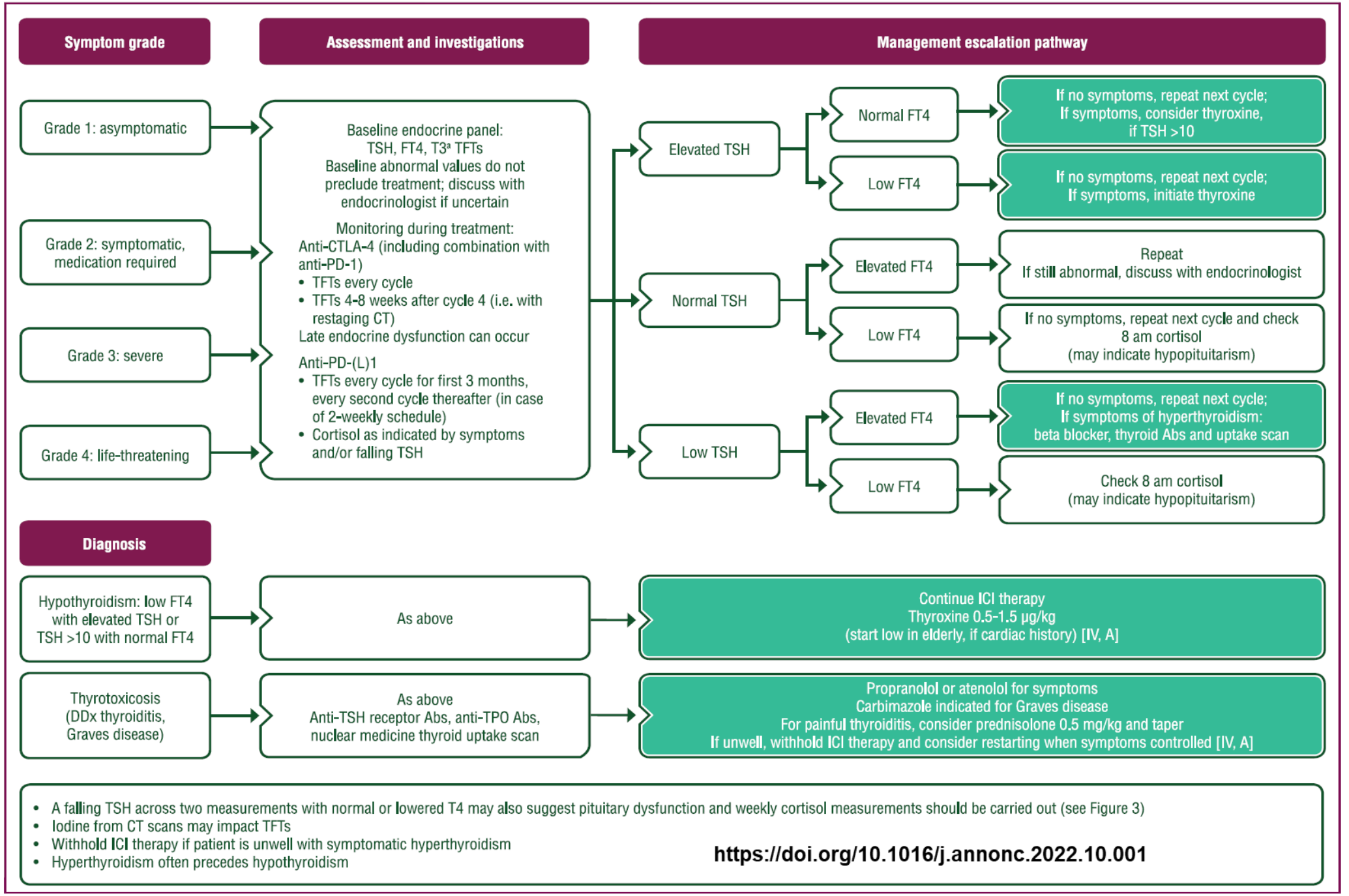
Rare lesions

Bullous pemphigoid
Lichenoid reactions
Psoriasis

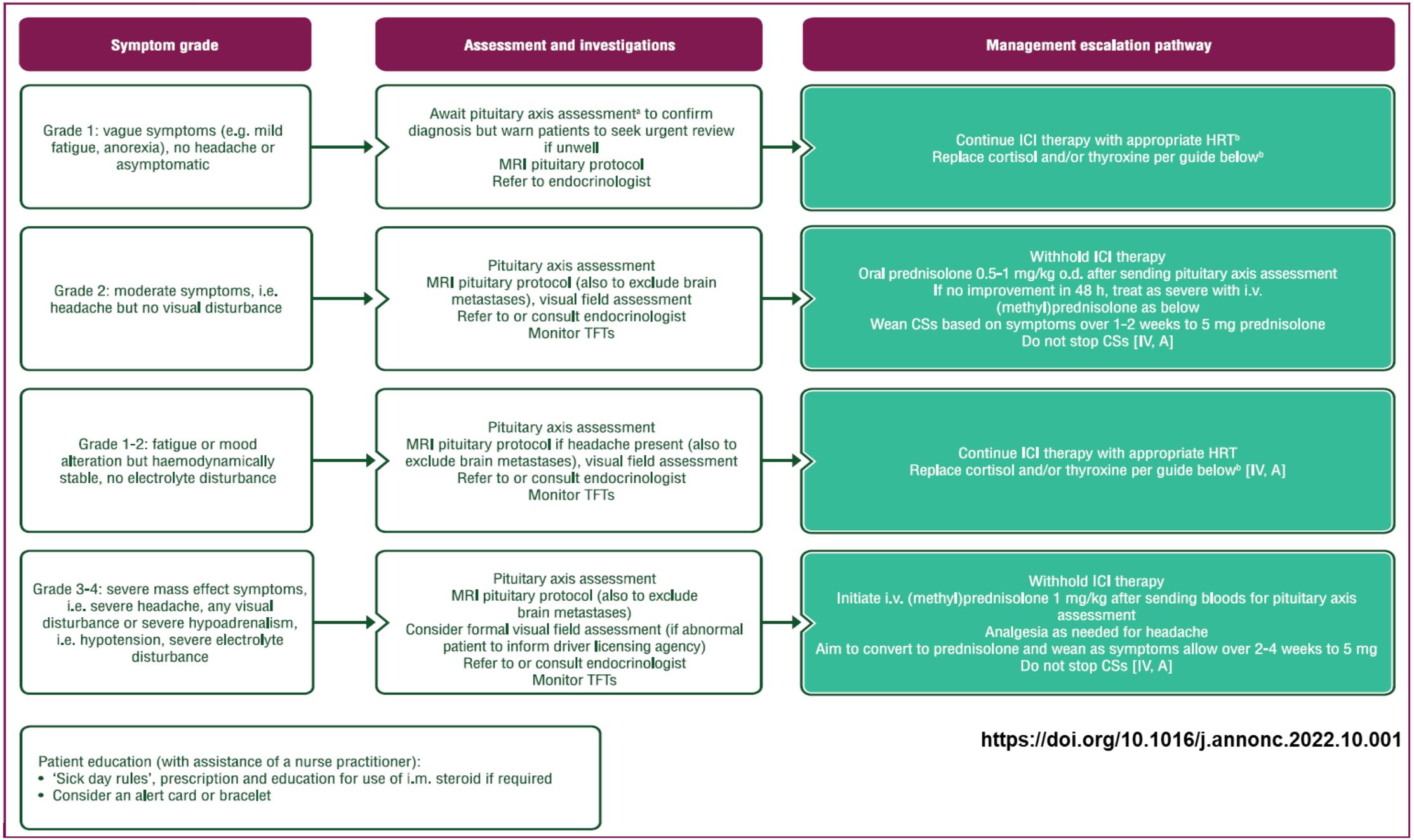

Symptom grade
Assessment and investigations
Management escalation pathway
Grade 1: lesions covering <10% BSA with or without symptoms (i.e. pruritus, burning or tightness)
Physical examination
Exclude other causes, e.g. viral illness, infection other drug-related rash
Continue ICI therapy
Topical CSs (mild to moderate) b.i.d.
Oral antihistamines for itching
Topical emollient
Avoid sun and skin irritants
Grade 2: lesions covering 10%-30% BSA with or without symptoms (i.e. pruritus, burning or tightness); or limiting instrumental ADL; or lesions covering >30% BSA with or without mild symptoms, without limiting self-care ADL
As for grade 1
Consider dermatology referral and skin biopsy
Consider holding ICI therapy and initiate moderate to high potency topical CSs
Topical emollient
Oral antihistamines if pruritus present
If refractory, initiate prednisone (0.5-1 mg/kg) or equivalent, tapered over >4 weeks; restart ICI therapy when grade 1 and prednisone <10 mg/day
Grade 3: lesions covering >30% BSA with moderate or severe symptoms; limiting self-care ADL
As for grade 1
Dermatology review
Consider punch biopsy and clinical photography
Hold ICI therapy [IV, B]
Initiate high potency topical CSs
Oral antihistamines if pruritus present
Topical emollient
If refractory, initiate prednisone (0.5-1 mg/kg) or equivalent, tapered over >4 weeks [IV, B]; restart ICI therapy when grade 1 and prednisone <10 mg/day [V, B]
Grade 4: life-threatening consequences, urgent intervention needed
As for grade 1
Dermatology review
Punch biopsy
Clinical photography
Permanently discontinue ICI therapy [IV, B]
Hospital admission
Rule out systemic complications
Initiate i.v. (methyl)prednisolone (1-2 mg/kg) or equivalent tapered over >4 weeks once reaction is controlled [IV, B]
Consider additional therapies such as infliximab or tocilizumab if refractory to CSs

IR- endocrinopathies

- Relatively frequent
- ICI can be continued in most cases
- High doses of steroids are rarely required
- Endocrine deficiency usually persist
- Life long replacement is required
- Hypothyroidism is more common than hyperthyroidism



https://doi.org/10.1016/j.annonc.2022.10.001



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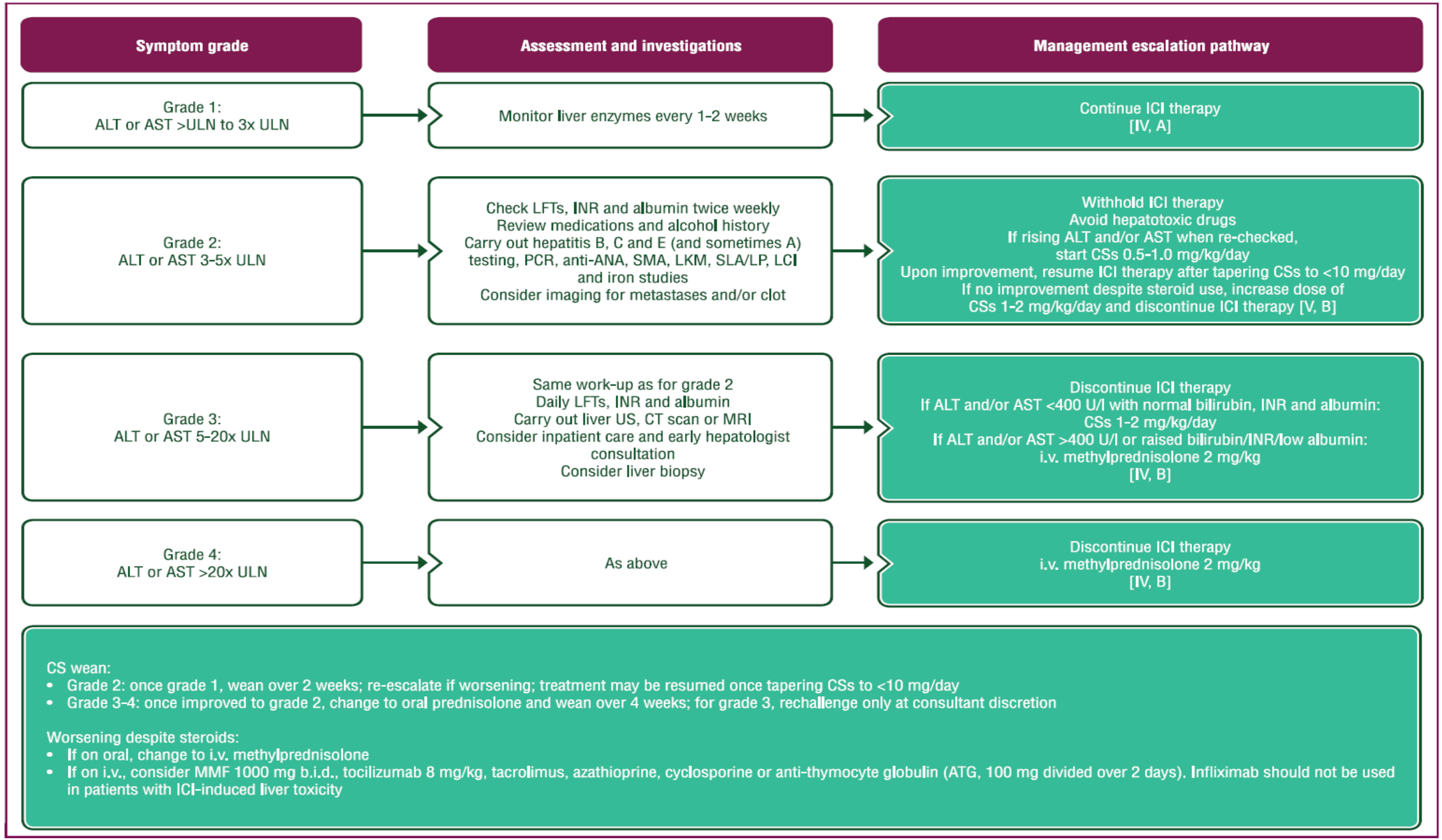
Hepatotoxicity

- Hepatitis occurs in 5%-10% (1%-2% grade 3) of patients during ICI monotherapy
- 25%-30% (15% grade 3) during anti-PD(L)1eanti-CTLA-4 combination therapy.
- All patients undergoing ICI therapy should be routinely assessed with serum transaminases, alkaline phosphatase (ALP) and bilirubin before every treatment cycle
- Hepatitis can be asymptomatic or present with fever, malaise, abdominal discomfort, jaundice and anorexia.
- Exclude other causes of liver toxicity
- Liver biopsy may help solve the other causes
- IR-hepatitis usually resolves within 4-6 weeks with appropriate treatment.



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Colitis

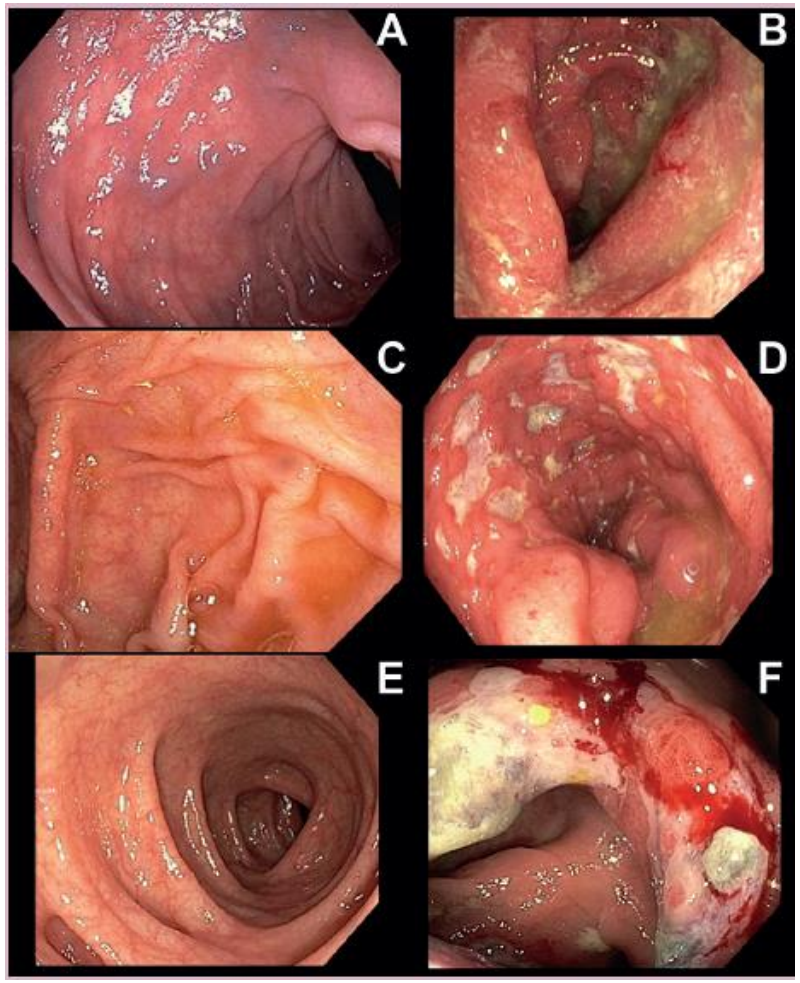
- IR-enterocolitis is the most common form of IR(GI) toxicity.
- Develops after weeks or months of ICI treatment
- anti-CTLA-4 (1 month after first infusion)
- anti-PD-1 (2-4 months after first infusion).
- 40% of patients with IBD- flare up during ICI therapy
- Diarrhoea and abdominal pain- More common
- Haematochezia and fever are less frequent
- Severe acute colitis -dehydration, toxic megacolon, colonic perforation

Colitis in Patients Treated With ICIs

Grade 2 diarrhea with no abnormalities on colonoscopy

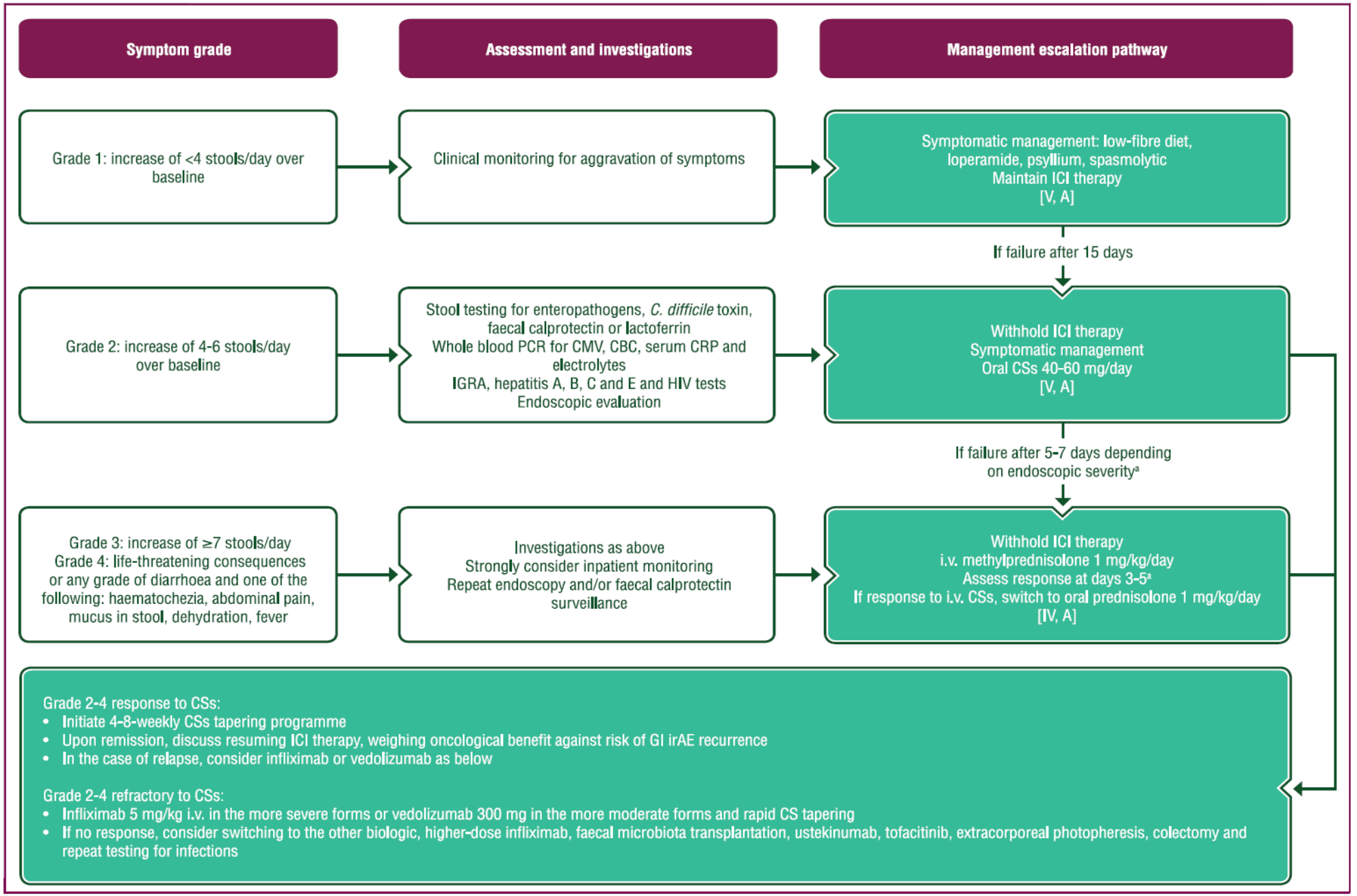
Grade 3 diarrhea with no abnormalities on colonoscopy

Grade 1 diarrhea with no abnormalities in descending colon (E) and swollen, severely friable mucosa with deep ulcers in ascending colon (F)



Grade 2 diarrhea with swollen, erosive, and friable mucosa

Grade 3 diarrhea with deeply red colon where vascular pattern partially absent, mucosa severely friable, multiple ulcers



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IR-Pulmonary toxicity

- IR-interstitial lung disease (IR-ILD)or IR-pneumonitis

  - IR-pneumonitis is relatively rare
  - IR-pneumonitis, combination therapy versus monotherapy (10% versus 1%-5%)
  - Serious and potentially life threatening AE.

- IR-bronchiolitis or IR-lung sarcoidosis.

Symptomatic patient – Exclude common problems

- Infectious pneumonia
- Tumour progression
- Pulmonary embolism
- Cardiac events(CHF, myocarditis, acute MI and arrhythmias)
- Pleural carcinomatosis or effusion

Factors that trigger toxicity

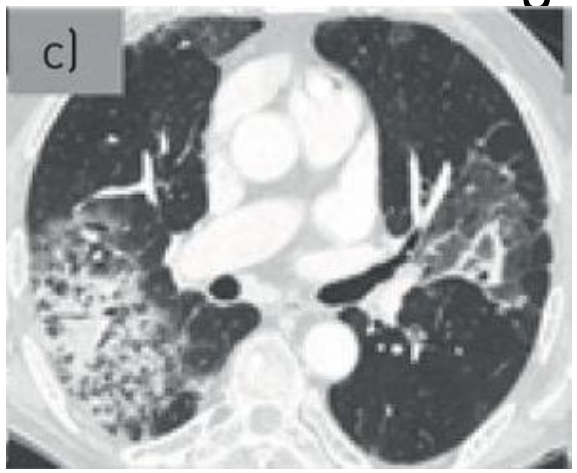
- Tobacco exposure
- COPD in patients with lung cancer
- Previous RT
- Ca lung -squamous histology

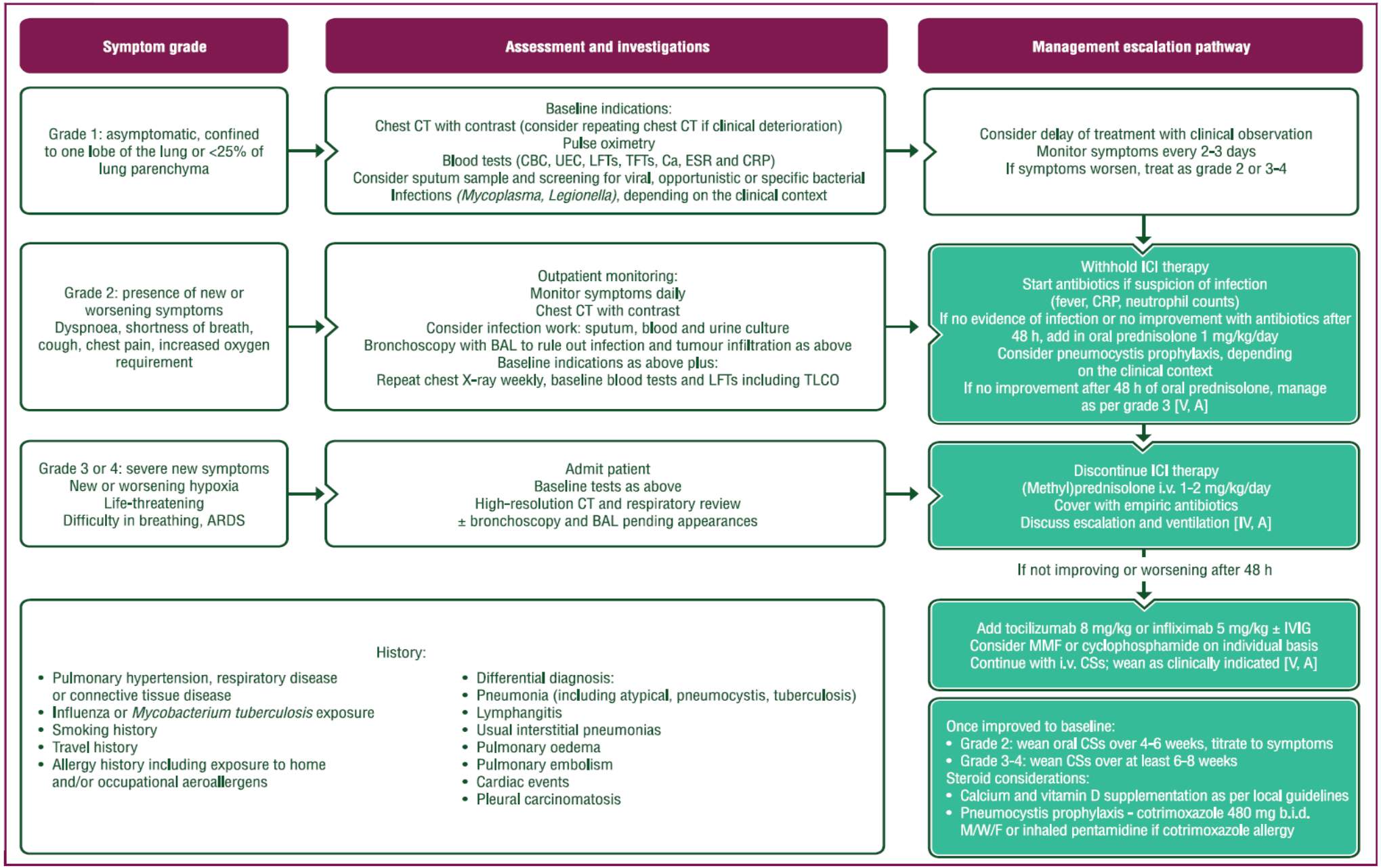
Radiological patterns-IR-ILD

- Cryptogenic organizing pneumonia-like,
- Ground glass opacities
- Interstitial
- Hypersensitivity
- Pneumonitis not otherwise specified.

Patient With Metastatic Melanoma and Acute Dyspnea

- An 82-yr-old man presents to the emergency department with acute dyspnea, cough, and sputum production with bilateral basal crackles
  - His daughter reports that he is receiving pembrolizumab for pulmonary metastatic melanoma, which was diagnosed 2 yrs ago
- CT shows bilateral areas of consolidations and ground-glass infiltrates





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Thank you

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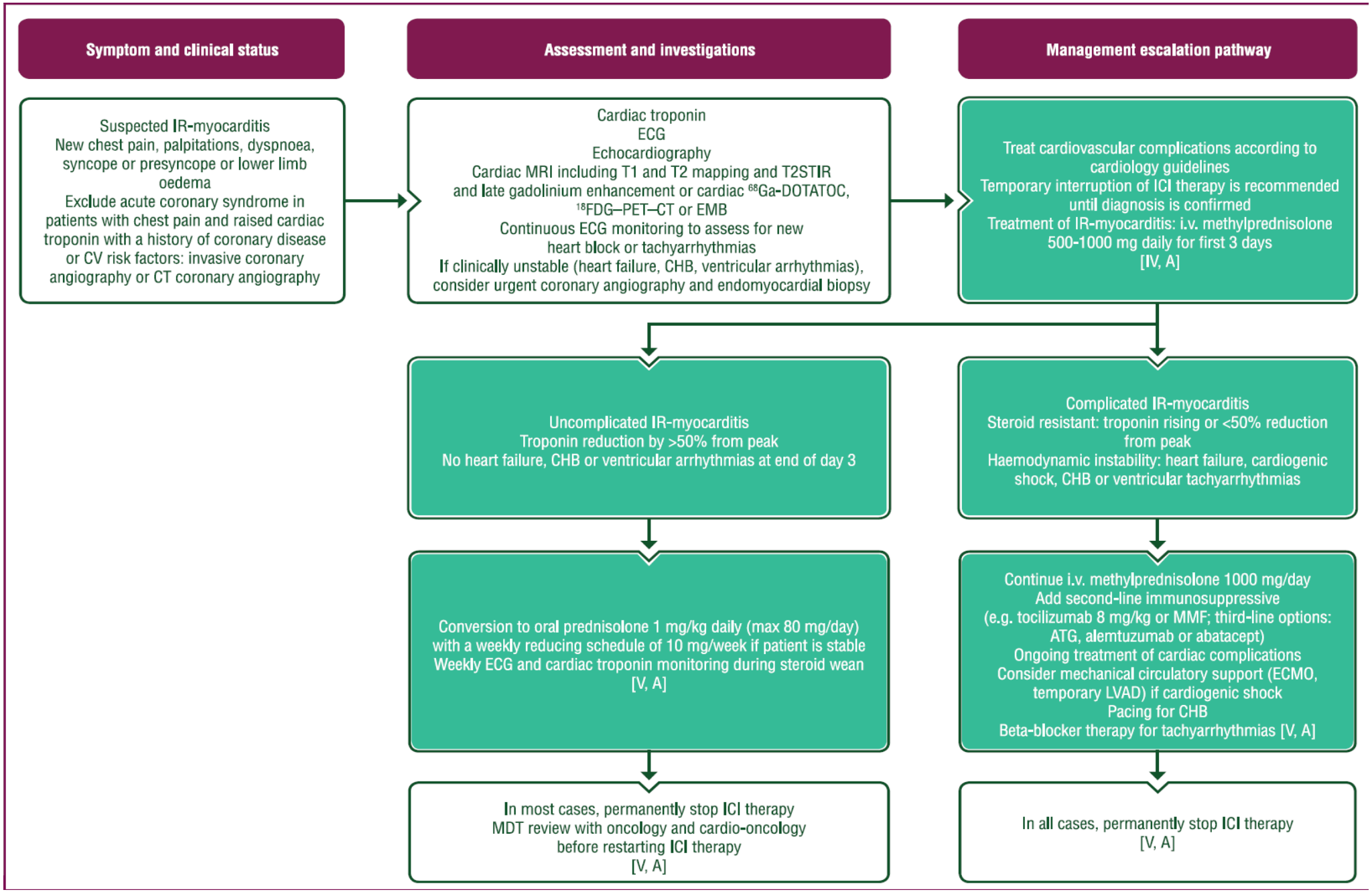

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