Tumori toraco-polmonari: gestione multidisciplinare delle tossicità da immunoterapici

Torino, 2 Novembre 2017

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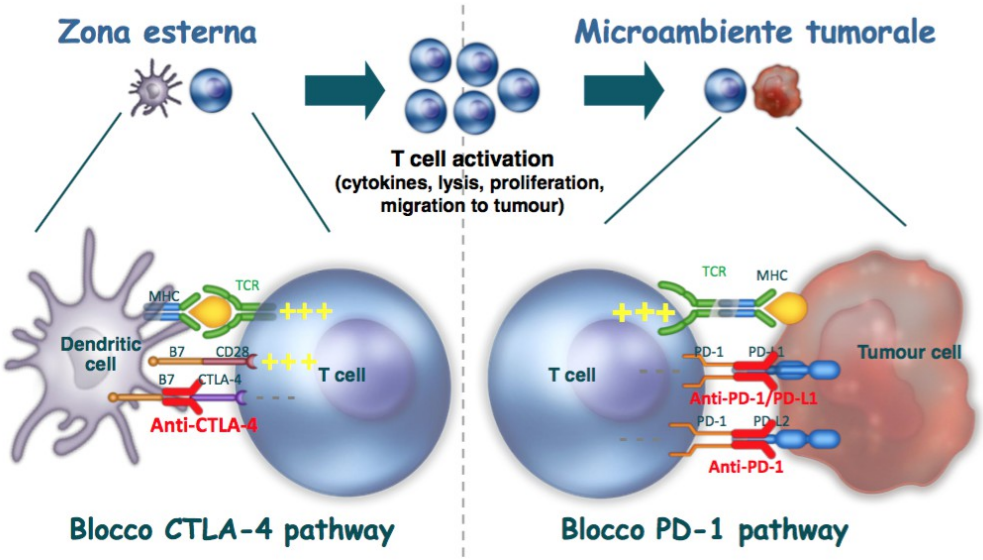
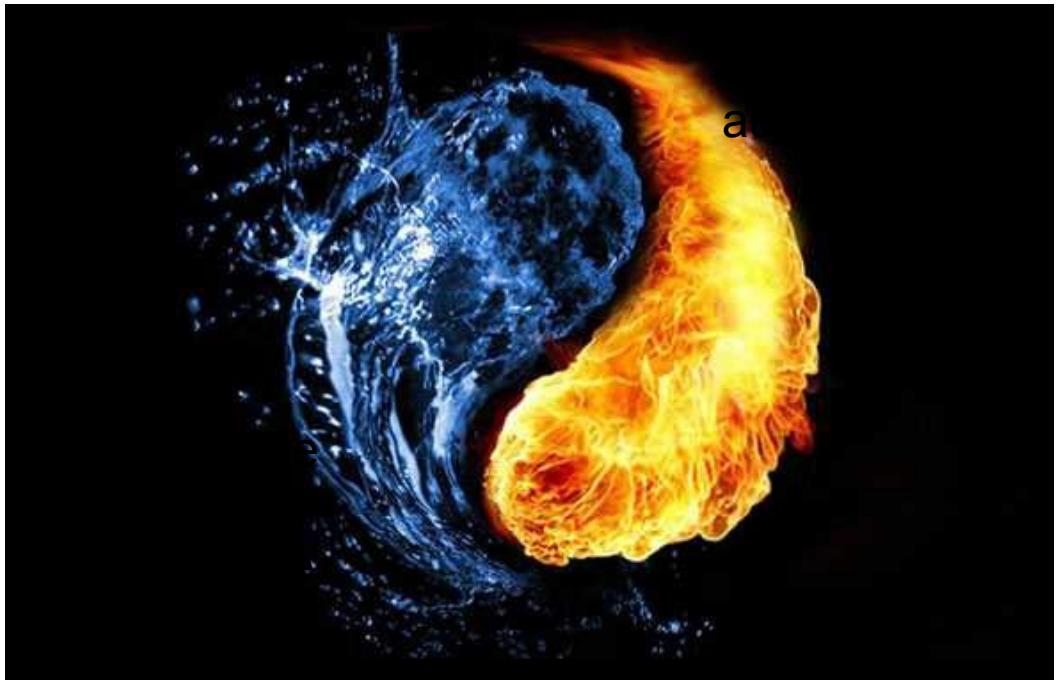
SC Oncologia

A.O. S. Croce e Carle

Cuneo

Meccanismo fisiopatologico



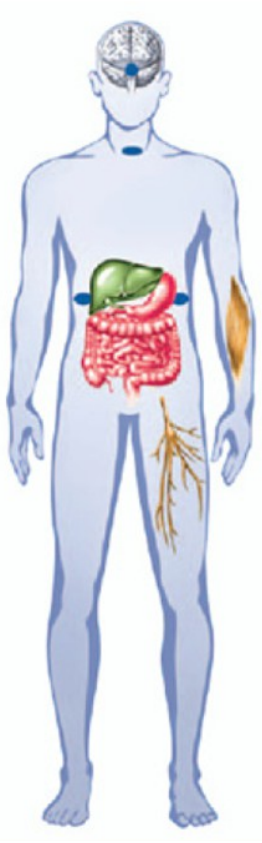


- "Select adverse events" allude to toxicities that have an autoimmune etiology and require careful monitoring and specific management strategies

Eventi avversi immunorelati irAE

Apparato gastrointestinale:
- Diarrea
- Dolore addominale
- Sangue o muco nelle feci
- Perforazione intestinale

Fegato:
- Elevazione degli enzimi di funzionalità epatica (AST, ALT), Bil tot.

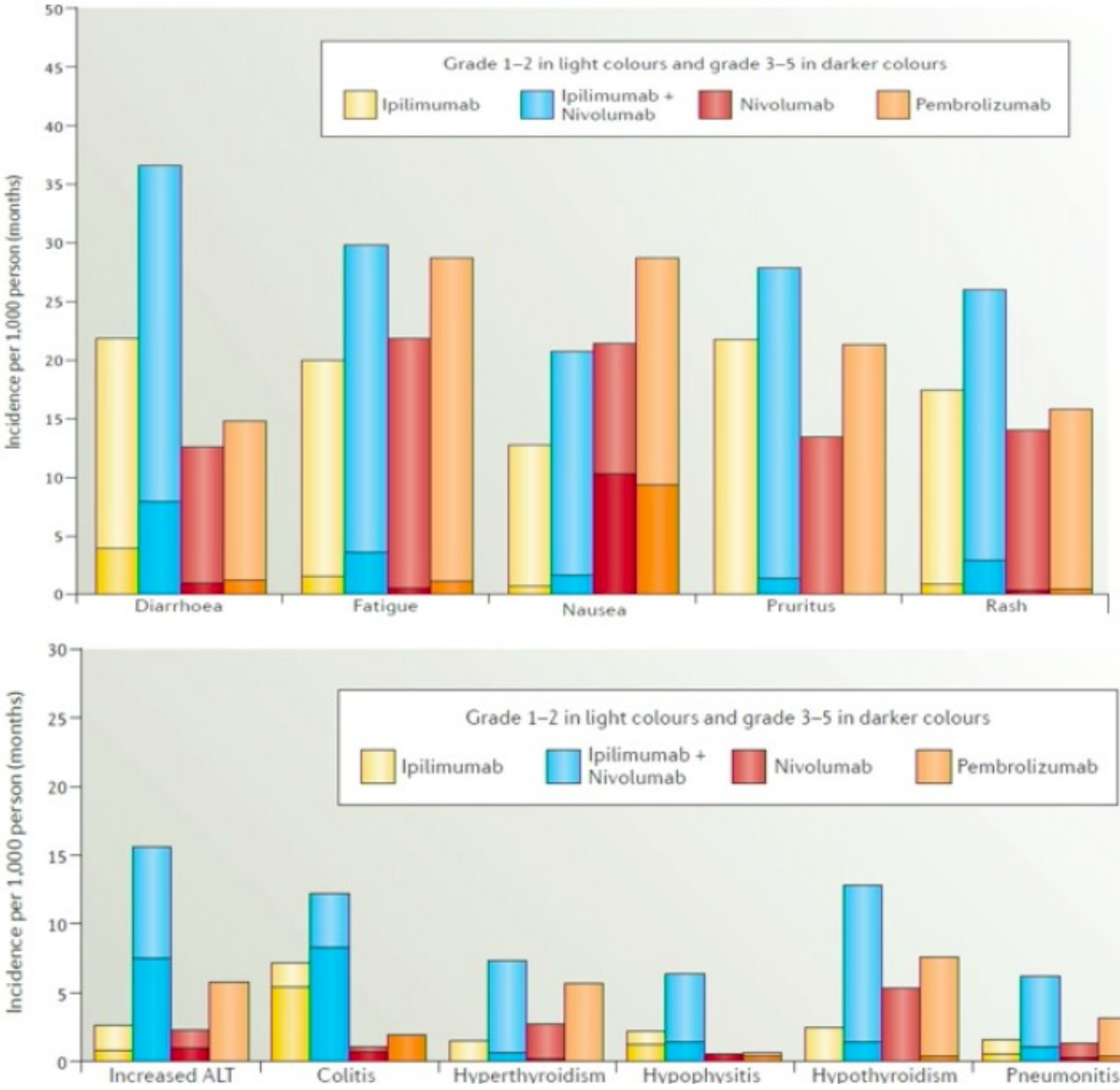


Cute:
- Esantema maculo-papuloso
- Prurito
- Vitiligo-like lesions

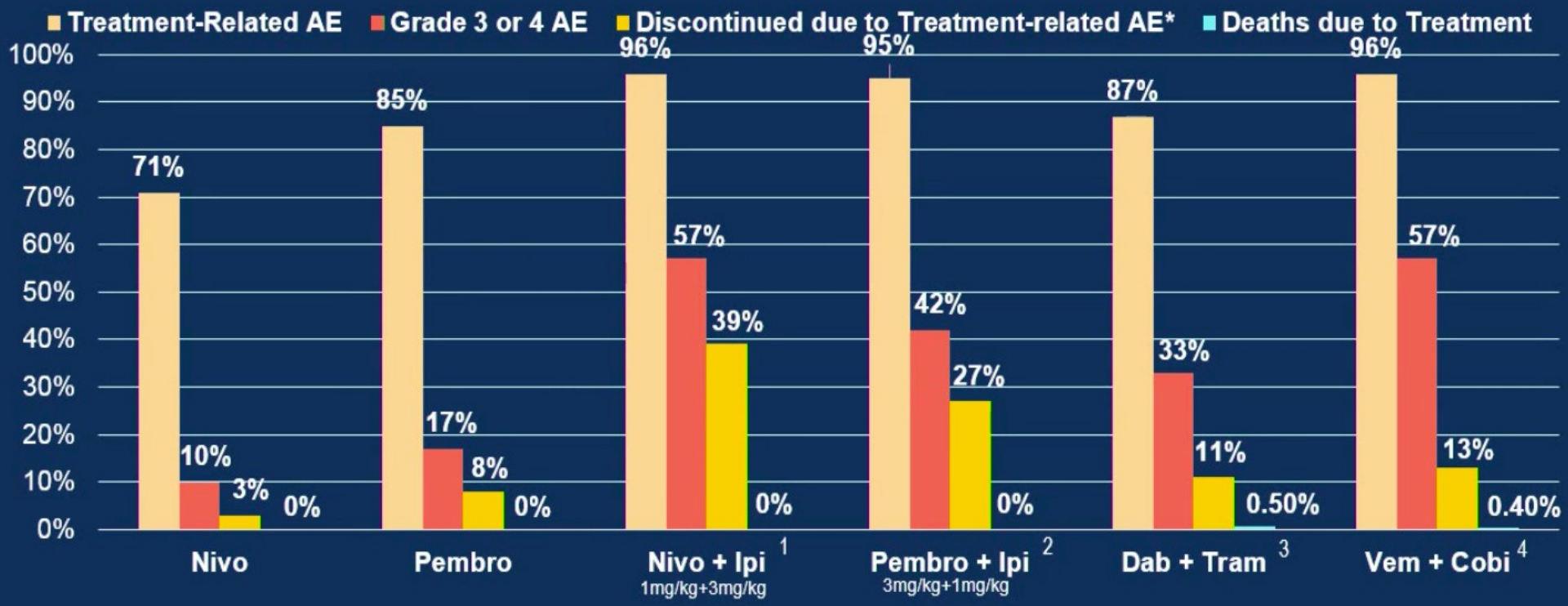
Sistema Endocrino:
- Astenia
- Cefalea
- Alterazioni dello stato mentale
- Alterazioni tiroidee
- Turbe dell'alvo

Nervi periferici:
- Ipostenia mono/bilaterale
- Alterazioni sensoriali
- Parestesie

Immunotherapy adverse events



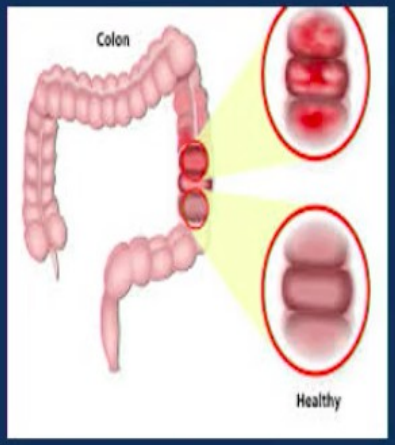
Comparing Treatment Toxicity



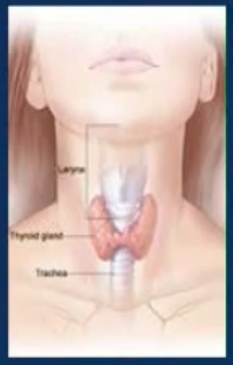
1. Wolchok ASCO 2016. 2. Long GV ASCO 2016. 3. Long GV ASCO 2015. 4. Atkinson SMR 2015

Auto-immune Side Effects: Anti-PD1[1,2]

1. Weber et al JCO 2016 in press; 2. Robert C et al ASCO 2016

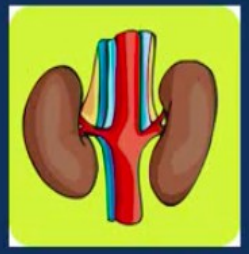


Diarrhea 13%

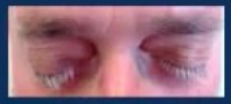


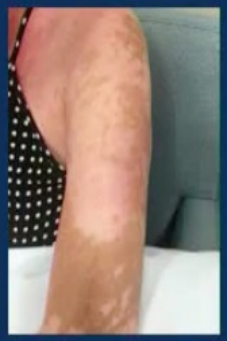
Hypothyroid 5-10%

All Grade = 70-85%
Grade 3/4 = 10-20%
Discontinuation 5-10%

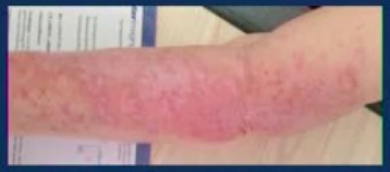


Renal <3%

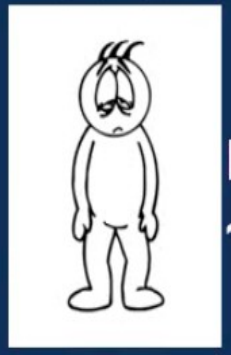




Vitiligo ~10%



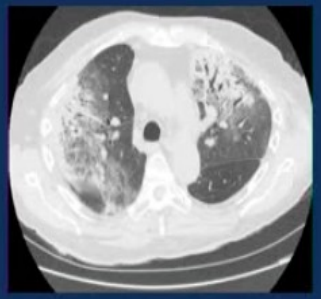
Lichenoid Rash ~15-20%



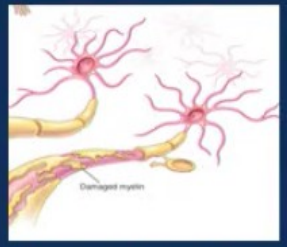
Fatigue ~20-30%

Hepatic 4%

Hypophysitis 0.2%



Pneumonitis 2-4%

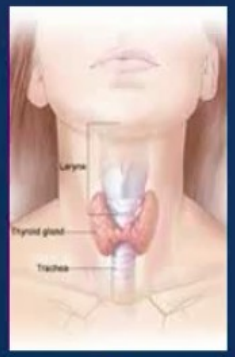


Neurological <1%

Auto-immune Side Effects: Ipi (3mg/kg) + Nivo (1mg/kg)[1,2]

1. Wolchok J et al ASCO 2016; 2. Postow M et al NEJM 2015

Diarrhea 45%



Hypothyroid 16%

↑ Lipase 13%

All Grade = 96%
Grade 3/4 = 57%
Discontinuation = 39%

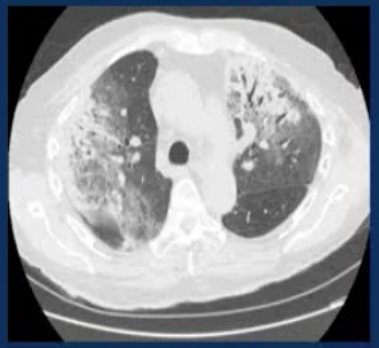
Rash 28%
Pruritus 35%

Renal 6%

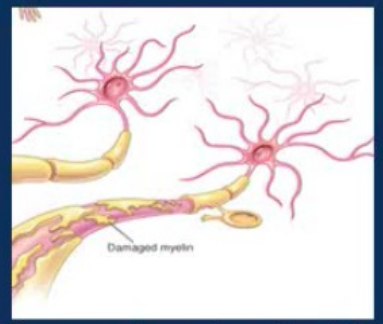
Uveitis <5%

Hepatic 32%

Hypophysitis 8%



Pneumonitis 7%



Neurological <5%

Rare but potentially very severe/life-threatening events

- Systemic
  - Inflammatory syndromes
  - Hematophagocytic lymphohistiocytosis
  - Serositis
- GI –
  - Enteritis/bowel perforations
  - Pancreatitis
- Lung – Severe pneumonitis
- Cardiovascular
  - Myocarditis/CHF
  - Pericarditis
  - Autonomic dysfunction
- Skin- Stevens-Johnson Syndrome
- Endocrine - DKA/IDDM
- Muscular – Rheumatologic
  - Debilitating arthralgias
  - Myositis
- CNS
  - Ascending or multi-focal motor neuropathy
  - Myasthenia Gravis
  - Optic neuritis
  - Uveitis
  - Radiation necrosis of SRS/GKRT-treated brain lesions
- Hematologic (cytopenias)

Learnings from Ipilimumab

- Treatment guidelines for the management of ipilimumab associated irAEs developed in response to safety data obtained from >4,000 study patients
  - Developed in cooperation with external experts and implemented in clinical trials
- Specific to management of irAEs involving skin toxicities, GI toxicities, hepatotoxicities and endocrinopathies
- Non-inflammatory aetiologies (e.g. neoplastic, infectious, metabolic, etc.) ruled out
- irAEs well-characterised, medically manageable, and in most cases reversible by using established algorithms
- Effective management of severe irAEs based on:
  - Early recognition:
    - Educate patient on early reporting
    - Assess patients for appropriate signs/symptoms at baseline and before each dose
  - Frequent monitoring
  - Use of corticosteroids (and/or other immunosuppressive therapies) combined with either delaying or discontinuing ipilimumab

- BMS data on file; Chin K, et al. Poster presented at

Toxicity Profile for Pembro & Nivo (major)

	Pembrolizumab		Nivolumab	
	All grade	Grade3/4	All grade	Grade 3/4
diarroea	8	1	8-10	0-3
colitis	1	1	1	<1
hepatitis	1-3	<1	1-3	<1
pruritus	11	0	6-8	0-1
rash	10	0.2	4-11	0-1
pneumonitis	5	2	3-5	1-3
hypothyroidism	8	<1	4-7	0
hyperthyroidism	2-4	0	1-2	0
hypophysitis	<1	<1	NR	NR
Renal injury	<1	0	0-4	1
Reumatological myalgia arthralgia	 3 9	 0 <1	 2.5 5	 0-1 NR
Fatigue	14	1	16	1-4
Anemia	3	1	2	1

Adapted from Spain L et al, Cancer Treatment ReviewsFeb 2016

Nivo vs PEM

- Nivo
  - Weber JS *et al.* 2015: nivolumab 3 mg/kg every 2 weeks, n=268

- Pem
  - Garon EB *et al.* 2015: all pembrolizumab arms (2 mg/kg or 10 mg/kg every 3 weeks or 10 mg/kg every 2 weeks), n=495

Selected irAEs	All grades, n (%
Dermatologic	
Pruritus	53 (10.7)
Rash	48 (9.7)
Dermatitis acneiform	13 (2.6)
Gastrointestinal	
Diarrhea	40 (8.1)
Hepatic	
Increased ALT	11 (2.2)
Increased AST	15 (3.0)
Respiratory	
Pneumonitis	18 (3.6)
Endocrine	
Hypothyroidism	34 (6.9)
Hyperthyroidism	9 (1.8)
General	
Fatigue	96 (19.4)

Adverse Events are independet from PS

	Nivolumab 3 mg/kg N = 824			Nivolumab 3 mg/kg ECOG PS 0–1 (n = 742)			Nivolumab 3 mg/kg ECOG PS 2 (n = 65)		
	Any Grade n (%)	Grade 3–4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3–4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3–4 n (%)	Grade 5 n (%)
All adverse events	762 (93)	311 (38)	158 (19)	683 (92)	268 (36)	131 (17)	62 (95)	33 (51)	24 (37)
All serious adverse events (SAEs)	309 (38)	223 (27)	158 (19)	257 (35)	185 (25)	131 (17)	42 (65)	29 (45)	24 (37)
All select adverse events	282 (34)	37 (5)	5 (1)	253 (34)	32 (4)	3 (<1)	22 (34)	3 (5)	2 (3)
All treatment-related adverse events	439 (53)	59 (7)	1 (<1)	403 (54)	52 (7)	1 (<1)	27 (42)	4 (6)	0
All treatment-related SAEs	23 (3)	19 (2)	1 (<1)*	18 (2)	14 (2)	1 (<1)	3 (5)	3 (5)	0
All treatment-related select AEs	199 (24)	20 (2)	0	181 (24)	16 (2)	0	14 (22)	2 (3)	0
All AEs leading to discontinuation	87 (11)	53 (6)	34 (4)	69 (9)	42 (6)	27 (4)	16 (25)	9 (14)	7 (11)
All treatment-related SAEs leading to discontinuation	14 (2)	12 (2)	1 (<1)	11 (2)	9 (1)	1 (<1)	2 (3)	2 (3)	0
All treatment-related select AEs leading to discontinuation	12 (2)	11 (1)	0	9 (1)	8 (1)	0	2 (3)	2 (3)	0

Maen Hussein et al, WCLC 2015; ORAL 02

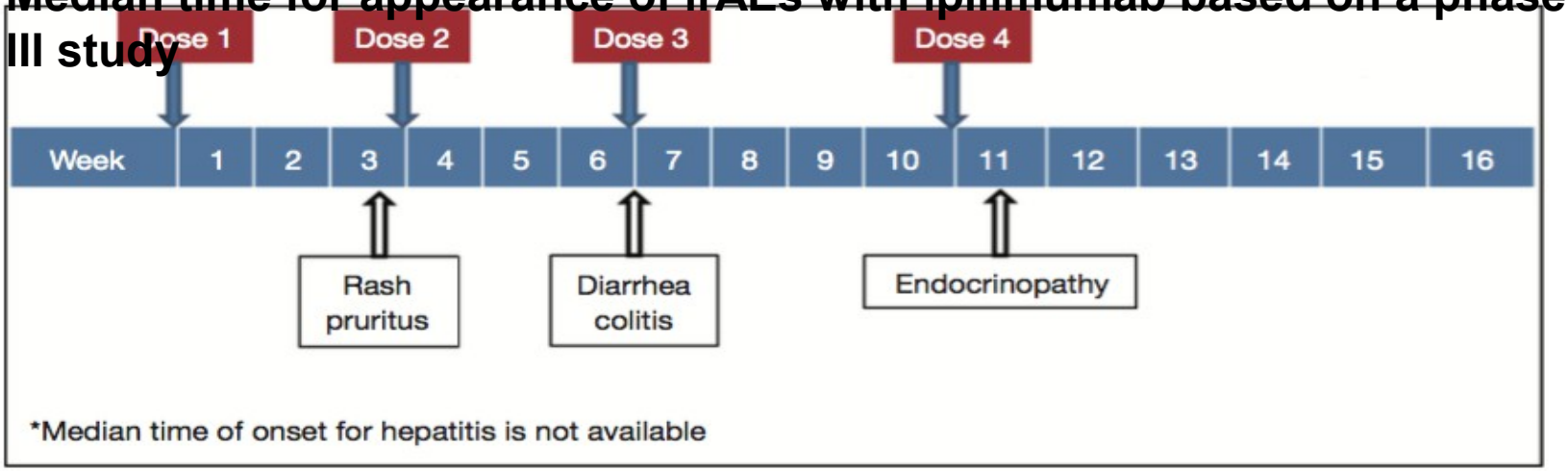
*One fatal event was reported as drug-related respiratory failure, with known comorbidities of lymphangitic spread of tumor, recurrent pulmonary embolism, G-bacteremia, pleural effusion, pneumothorax, or tumor progression. This patient's death was classified as 'Other-Multifactorial' by the investigator.

IRAEs: average time onset

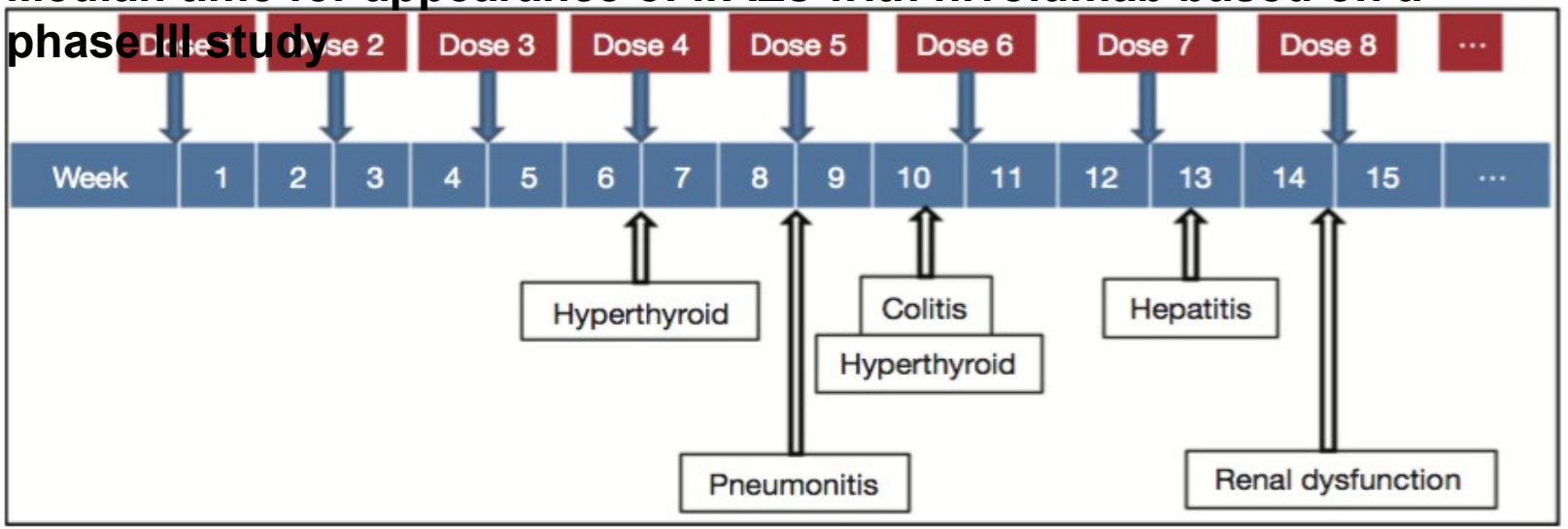
- Average time to onset of irAEs is 6-12 weeks after initiation of therapy
  - Within days of the first dose
  - After several months of treatment
  - After discontinuation of therapy
- Severity: Can be mild and asymptomatic to severe and life threatening

IRAEs: average time onset

Median time for appearance of irAEs with ipilimumab based on a phase III study



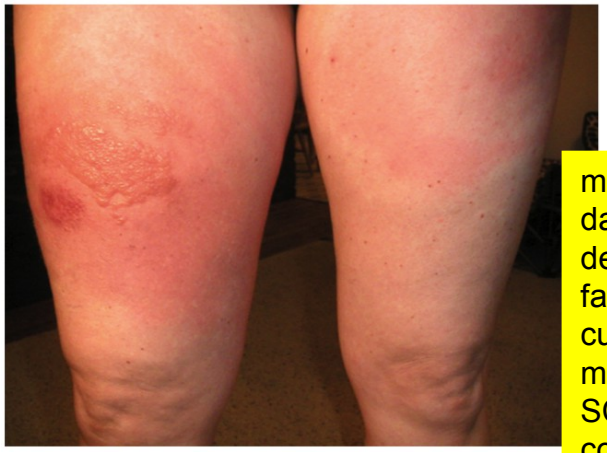
Median time for appearance of irAEs with nivolumab based on a phase III study



- Tossicità dermatologica

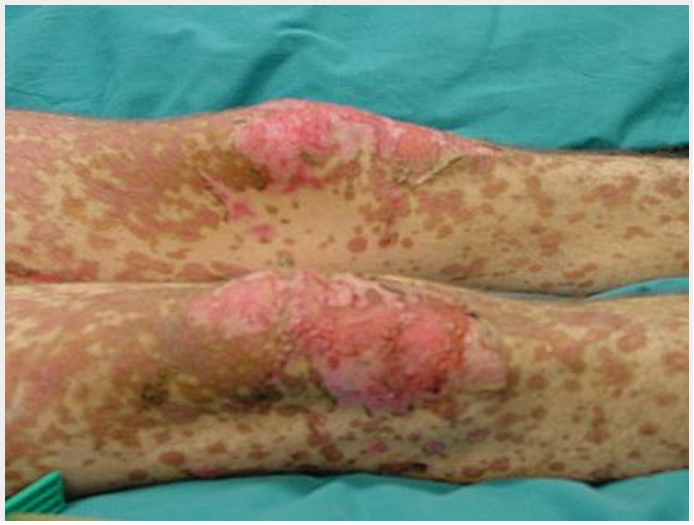
all grades in up to 37.4% of patients

maculopapular rash with or without symptoms (e.g., pruritus, burning, tightness)



Stevens-Johnson syndrome and toxic epidermal necrolys are reported in <1%

malattia dermatologica acuta grave caratterizzata dalla distruzione brutale dello strato superficiale della cute e delle mucose, dovuta a un'allergia farmacologica nel 70% dei casi; la superficie cutanea (SC) coinvolta permette di classificare la malattia in: sindrome di Stevens-Jonhson (<10 % SC) o sindrome di Lyell (≥ 30 % SC) ; le lesioni comprendono eruzioni cutanee, distacchi epidermici ed erosioni mucose, tutte ad insorgenza acuta.



Vitiligo was reported to occur in both CTLA-4 and PD-1 inhibitorclinical trials. Toxicity can be permanent but does not require interruption of immune checkpoint inhibitor therapy or toxicity treatment

- Nota bibliografica

Maculopapular rash in the fourth version of the CTCAE classification:

• Grade 1: macules/papules covering < 10% the body surface area (BSA) with or without symptoms (e.g. pruritus, burning, tightness);

• Grade 2: macules/papules covering 10%–30% BSA with or without symptoms (e.g. pruritus, burning, tightness); limiting instrumental activities of daily living (ADL);

• Grade 3: macules/papules covering > 30% BSA with or without associated symptoms; limiting selfcare ADL;

• Grade 4: papulopustular rash associated with life-threatening superinfection; Stevens-Johnson syndrome, TEN and bullous dermatitis covering > 30% of BSA and requiring intensive care unit (ICU) admission.

ESMO Guidelines 2017

Histopathologically, skin reactions may be categorised into four broad groups:

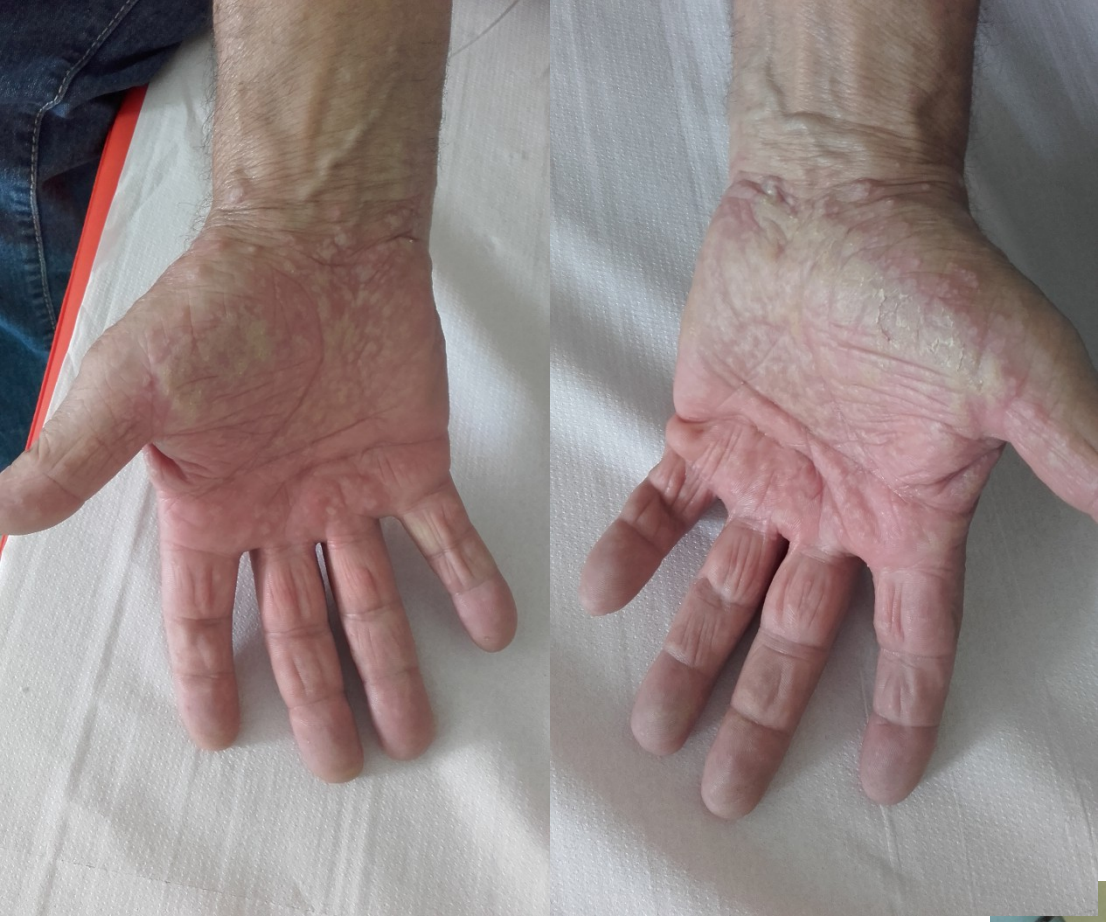
• Inflammatory skin disorders, which comprise a range of changes reflecting acute, subacute or chronic inflammation of various patterns, associated with variable epidermal changes, including psoriasiform or lichenoid reactions. A lichenoid interface chronic dermatitis is a common finding;

• Immunobullous skin lesions akin to dermatitis herpetiformis or bullous pemphigoid;

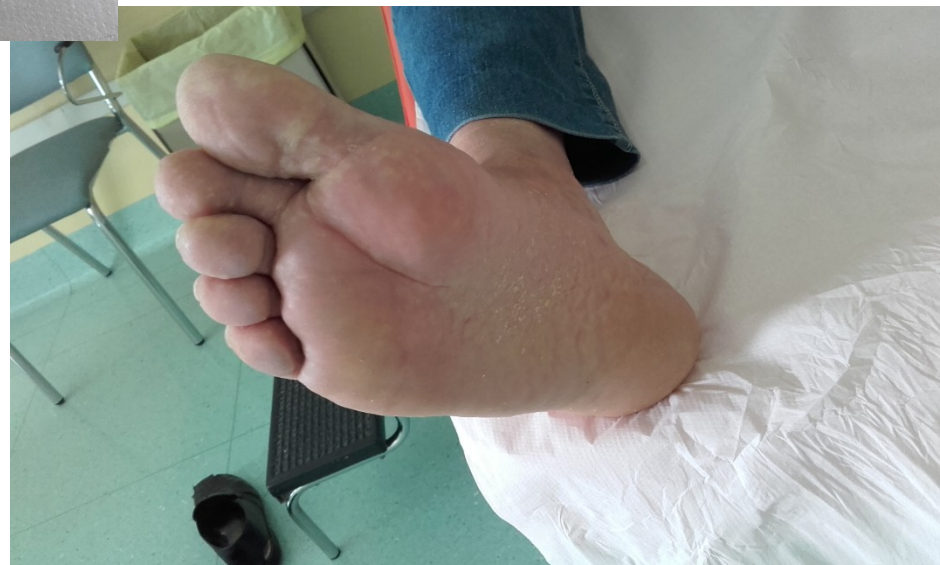
• Keratinocyte alteration—Grover's disease /acantholytic dyskeratosis;

• Immune-reaction mediated by alteration of melanocytes (regression of nevi, prurigo nodularis, tumoural melanosis and vitiligo)

ESMO Guidelines 2017

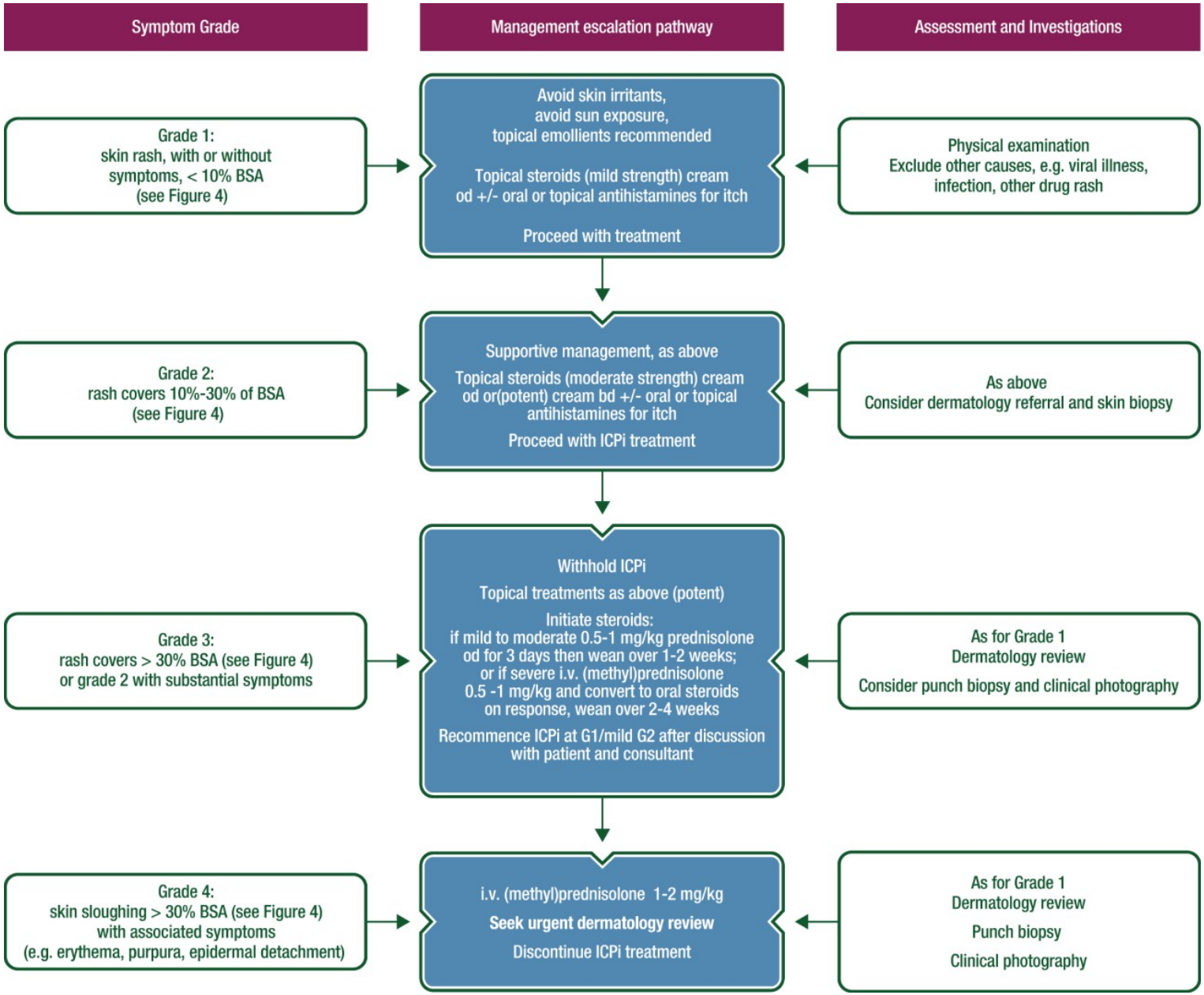


Tossicità cutanea invalidante



8 somministrazioni di Nivolumab
RP alla TAC

SKIN



ESMO Guidelines 2017

- **Immune-related skin toxicity**
- For grade 1–2 skin AEs, continue (at least 1 week) with ICPis. Start topical emollients, antihistamines in the case of pruritus and/or topical (mild strength) corticosteroid creams. Reinitiate ICPi when ≤ grade 1.

- For grade 3 skin AEs, interrupt ICPi and start immediate treatment with topical emollients, antihistamines and high strength corticosteroid creams [II, B].

- For grade 4 skin AEs, discontinue ICPi (permanently), consider admitting patient and always consult dermatologist immediately. Start i.v. corticosteroids [1–2

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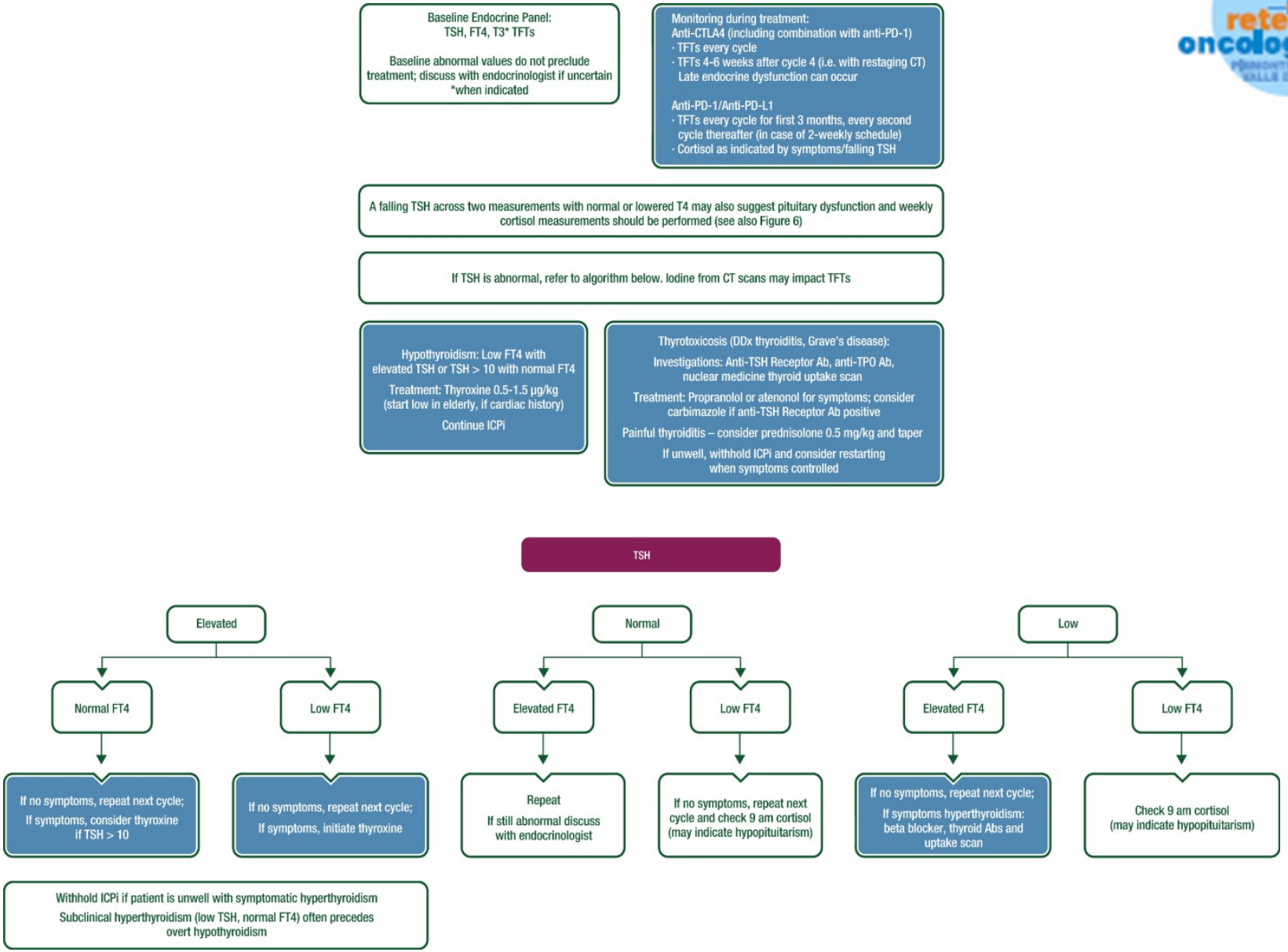
TYROID 2% with ipilimumab and > 8.3% with PD-1 inhibitors



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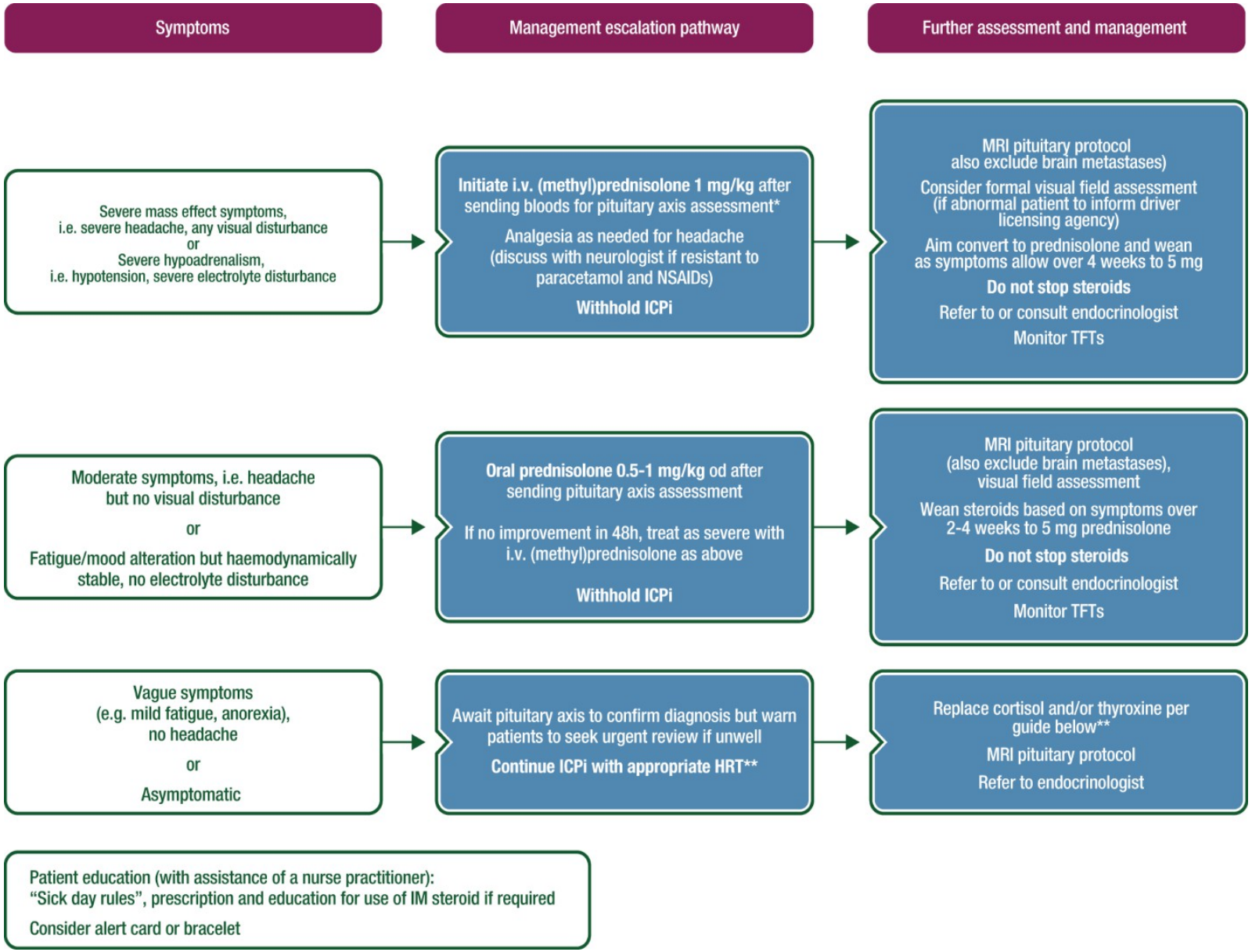
HYPOPHISITIS



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Immune-related endocrinopathies

- In symptomatic hyperthyroism patients, usually grade 1 or 2, interrupt ICPi, start beta-blocker therapy (propranolol or atenolol/metoprolol). Restart ICPi when asymptomatic [IV–V, B].

- In the case of hypothyroidism, rarely > grade 2, start HRT depending on the severity (50–100 µg/day). Increase the dose until TSH is normal. In the case of inflammation of the thyroid gland, start prednisone orally 1 mg/kg. Taper based on recovery of clinical symptoms. Consider interruption of ICPi treatment when symptomatic [IV–V, B].

- In the case of hypophysitis (rarely > grade 2), when headache, diplopia or other neurological symptoms are present, start (methyl)prednisone 1 mg/kg orally and taper over 2–4 weeks. Start HRT depending on the affected hormonal axis (levothyroxine, hydrocortisol, testosterone) [V, B].

- In patients with type I DM grade 3 to 4 [ketoacidotic (sub)coma], admit to hospital immediately and start treatment of newly onset type I DM [I, A]. Role of corticosteroids in

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Hepatotoxicity

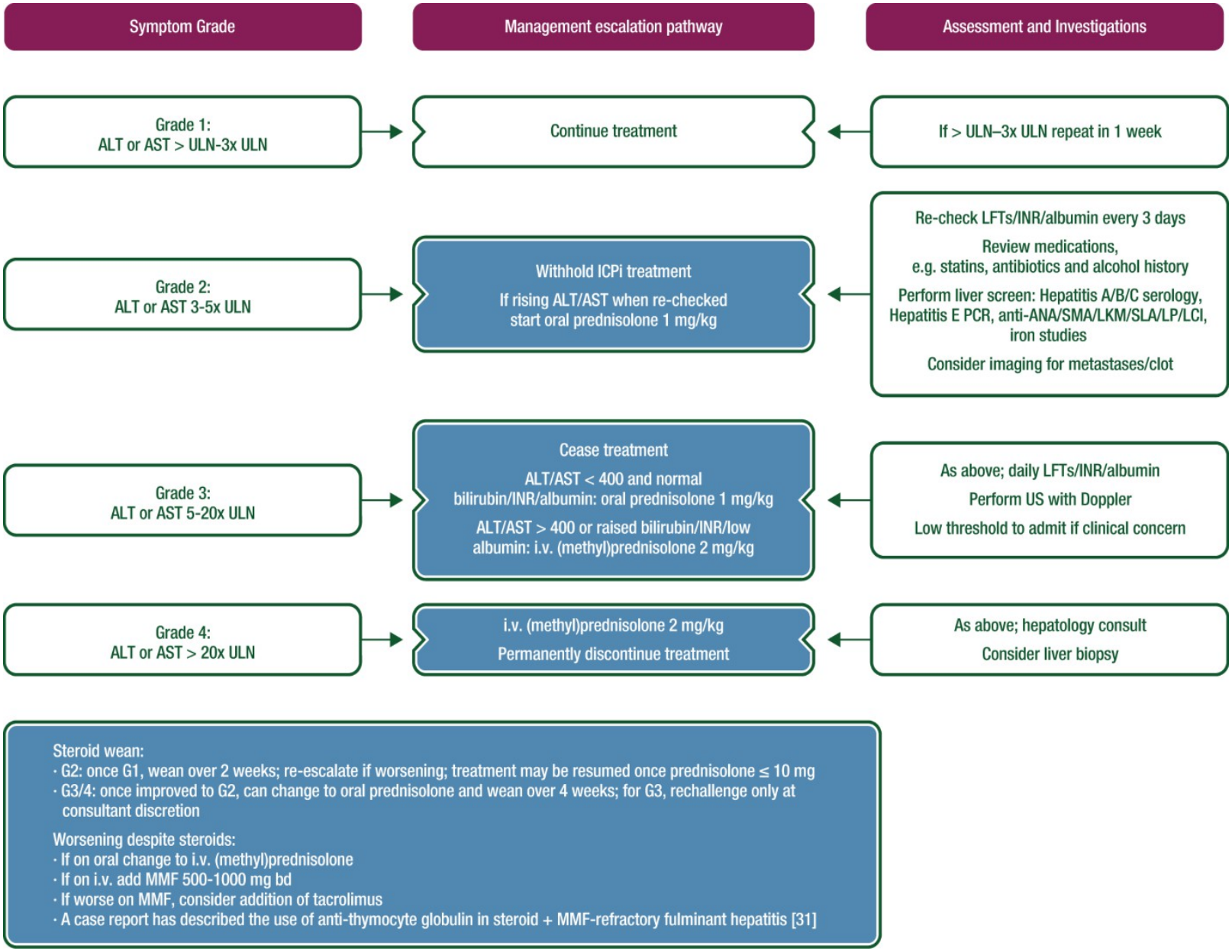
Incidence

- Ipilimumab of grade 2 hepatotoxicity was 2.5% and grade 3-5 events was 2% in a phase III clinical trial.
- PD-1 inhibitor in clinical trials was <5%
- Liver function tests returned to grade 1 within 4-15 days of initiation of corticosteroids, however hepatitis did recur in two of the three patients Of the 411 patients treated with pembrolizumab in a clinical trial database, hepatitis occurred in 0.5% of patients with complete resolution following administration of corticosteroids

Diagnosis

- Hepatic function should be monitored prior to each dose of ipilimumab, nivolumab or pembrolizumab .
- If an increasing trend in liver function tests is noted, evaluation should be carried out to rule out other infectious, non-infectious, and malignant causes such as progression of disease.
- laboratory testing for antinuclear antibodies (ANA), smooth muscle antibody (SMA), CBC with differential, CMP, direct and indirect bilirubin, and gamma- glutamyl transferase (GGT)
- . If hepatotoxicity is suspected, the frequency of liver function test monitoring should increase to every 3 days.
- Computed tomography (CT) scans and liver

HEPATITIS



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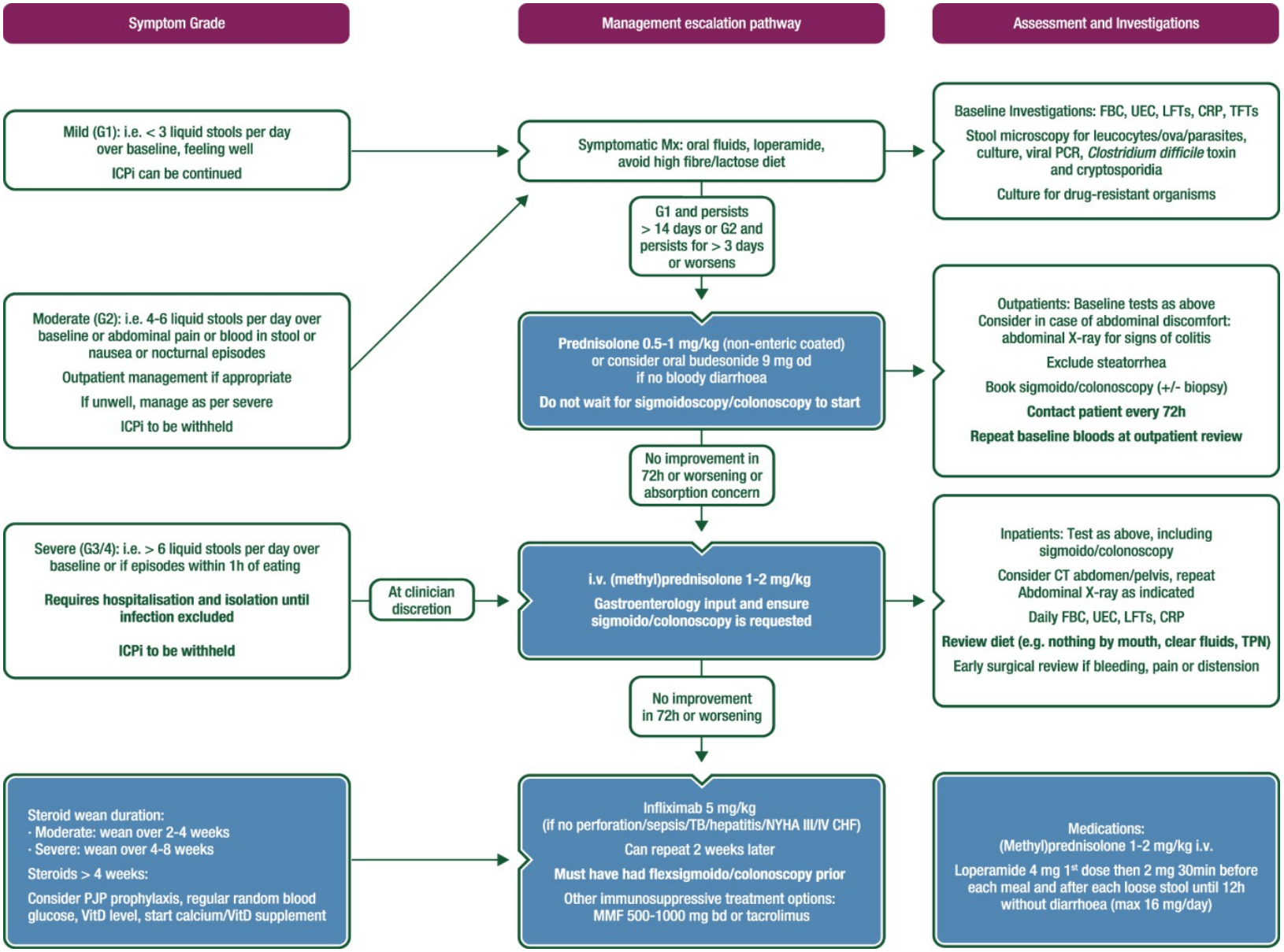
Immune-related hepatotoxicity

- For grade 2 hepatitis, withhold ICPi and monitor AST/ALT levels closely (1–2 times/week). When no improvement over 1 week, start (methyl)prednisone (0.5–1 mg/kg). Taper over several weeks under close monitoring of AST/ALT and bilirubin [IV–V, B].

- For grade 3 hepatitis, discontinue ICPi and immediately start with (methyl)prednisone 1–2 mg/kg. When no improvement in 2–3 days, add MMF (Micofenolato Mofetile1000 mg 3× daily). Taper immunosuppression over 4–6 weeks under close monitoring of AST/ALT and bilirubin [IV–V, B].

- For grade 4 hepatitis, permanently discontinue ICPi, admit patient to the hospital and initiate (methyl)prednisone 2 mg/kg i.v. Add MMF if no improvement is observed within 2–3 days. Consult hepatologist if no improvement under double immunosuppression. Other immunosuppressive drugs to

GASTROINTESTINAL



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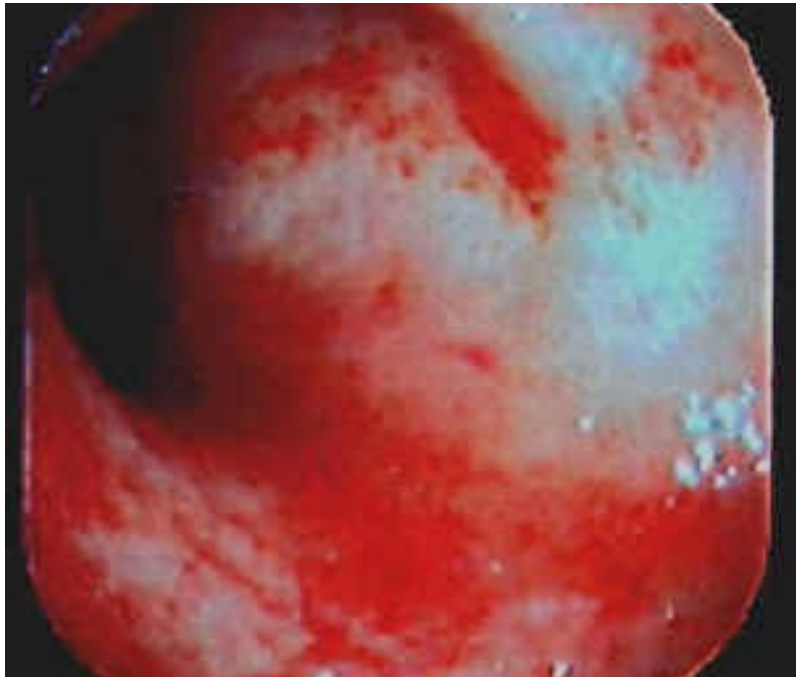
Diarrhoea and colitis



- Immune-mediated Colitis

Diarrhoea and colitis may present approximately 6 weeks into immune checkpoint inhibitor therapy

grade 3 or 4 immune-mediated colitis, occurred in 1-2% of patients .

appears to be dose- dependent with Ipilimumab.
Diarrhoea at any grade was reported in approximately 30%

Patients who had significant diarrhea/colitis during Ipilimumab treatment have subsequently been treated with PD-1 inhibition without developing diarrhoea/colitis

Gastrointestinal toxicity

- In patients with non-severe diarrhoea (grade 1), ICPi can be continued. Treatment with antidiarrhoeal medication (e.g. loperamide) should be prescribed [IV–V, B].

- In grade 2 diarrhoea, ICPi should be interrupted and the patient should start with corticosteroids depending on the severity and other symptoms (either budesonide or oral corticosteroids 1 mg/kg). In the case of no improvement within 3–5 days, colonoscopy should be carried out and, in the case of colitis, infliximab 5 mg/kg should be administered [IV–V, B].

- In patients with severe diarrhoea (grade 3 to 4), permanently discontinue ICPi. Admit patient to the hospital and initiate (methyl)prednisone 2 mg/kg i.v. Add MMF if improvement is observed within 2–3 days. Consult a hepatologist if no improvement under double immunosuppression. Other immunosuppressive drugs to consider are ATG and tacrolimus. Consult or refer patient to an experienced centre. Taper over 6 weeks under close monitoring of liver tests [IV–V, B].

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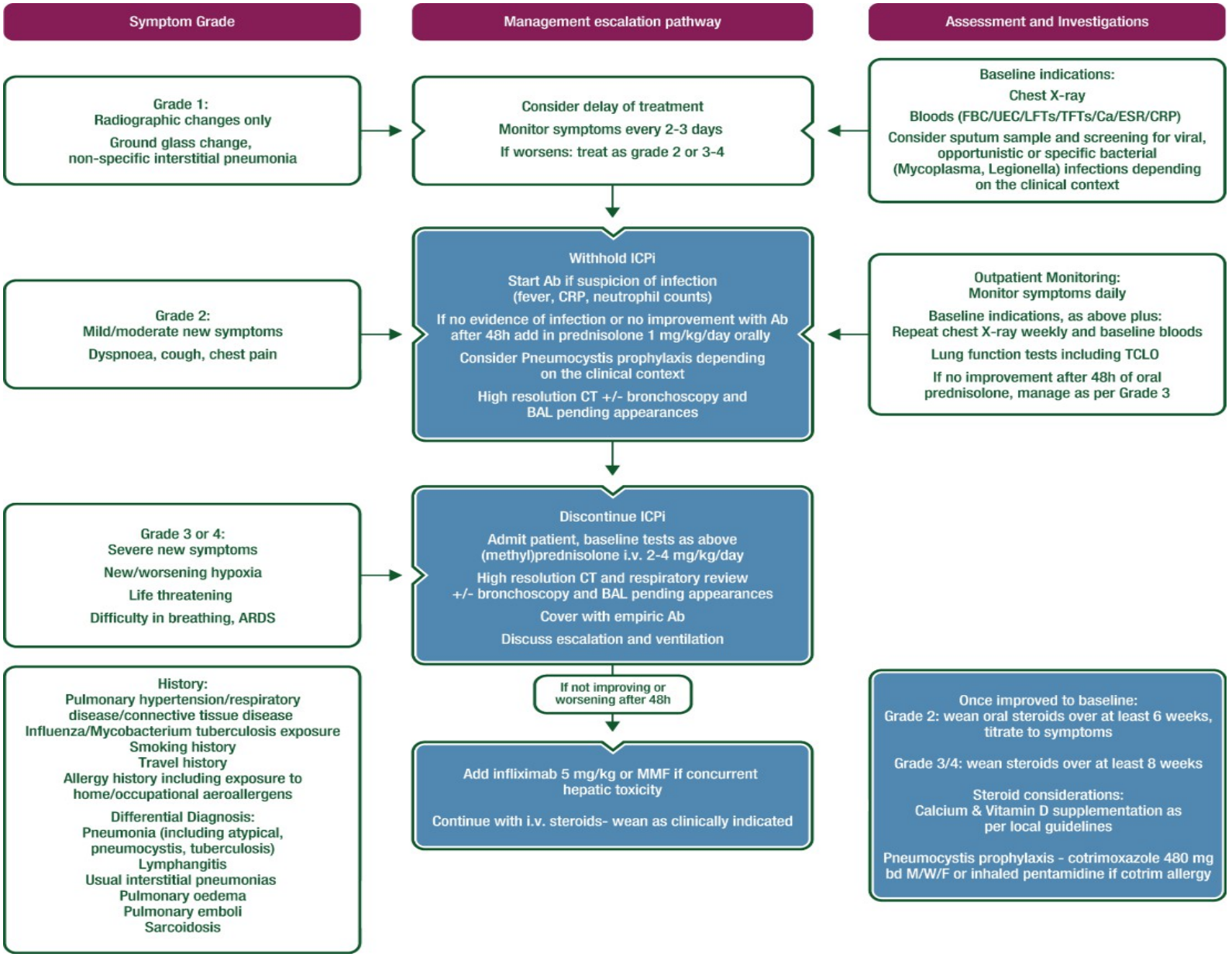
Pneumonitis and NSCLC

- Severe drug-related pneumonitis
  - PD-1 Antibody 2%
  - Erlotinib 1.6-4.5%
  - Gefitinib 3.5%
  - Docetaxel 4.6%
  - Gemcitabine 1-2%
  - Pemetrexed – 2 reports in the literature
- Radiation pneumonitis - 13%
- Treatment: Steroids

Liu et al Chest 132, 1042-4, 2007, Konishi et al Anticancer Res 25:435-41, 2005, Grand C, Clin Transl Oncol 9: 578-81, 2007, Roychowdhury DF, Invest New Drugs 20, 311-5, 2002, Hochstrasser A et al, Chemotherapy 58:84-8, 2012, Inoue et al. Int J Radiat Oncol Biol Phys 49:649-55, 2001

PNEUMONITIS



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Immune-related pneumonitis

- In grade 1 and 2 pneumonitis, interrupt ICPi therapy, try to rule out infection and start with prednisone 1–2 mg/kg orally. Taper over 4–6 weeks [IV–V, B].

- In grade 3 and 4 pneumonitis, discontinue ICPi permanently, admit the patient to the hospital, even ICU if necessary and immediately start high-dose (methyl)prednisone 2–4 mg/kg i.v. Add infliximab, MMF or cyclophosphamide in the case of deterioration under steroids. Taper over a period of 4–6 weeks [IV–V, B].

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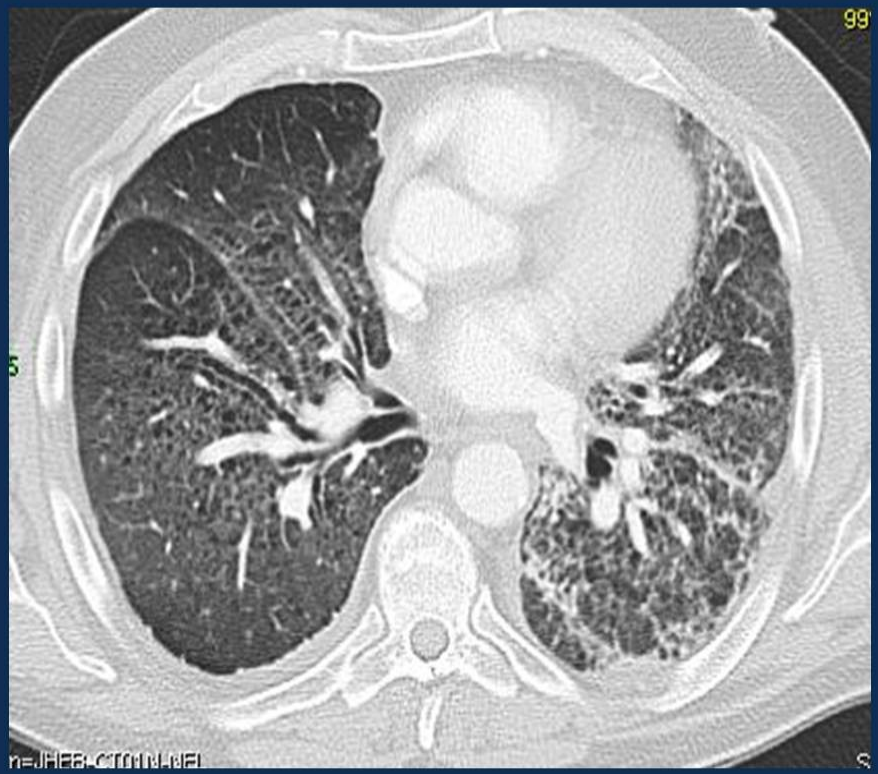
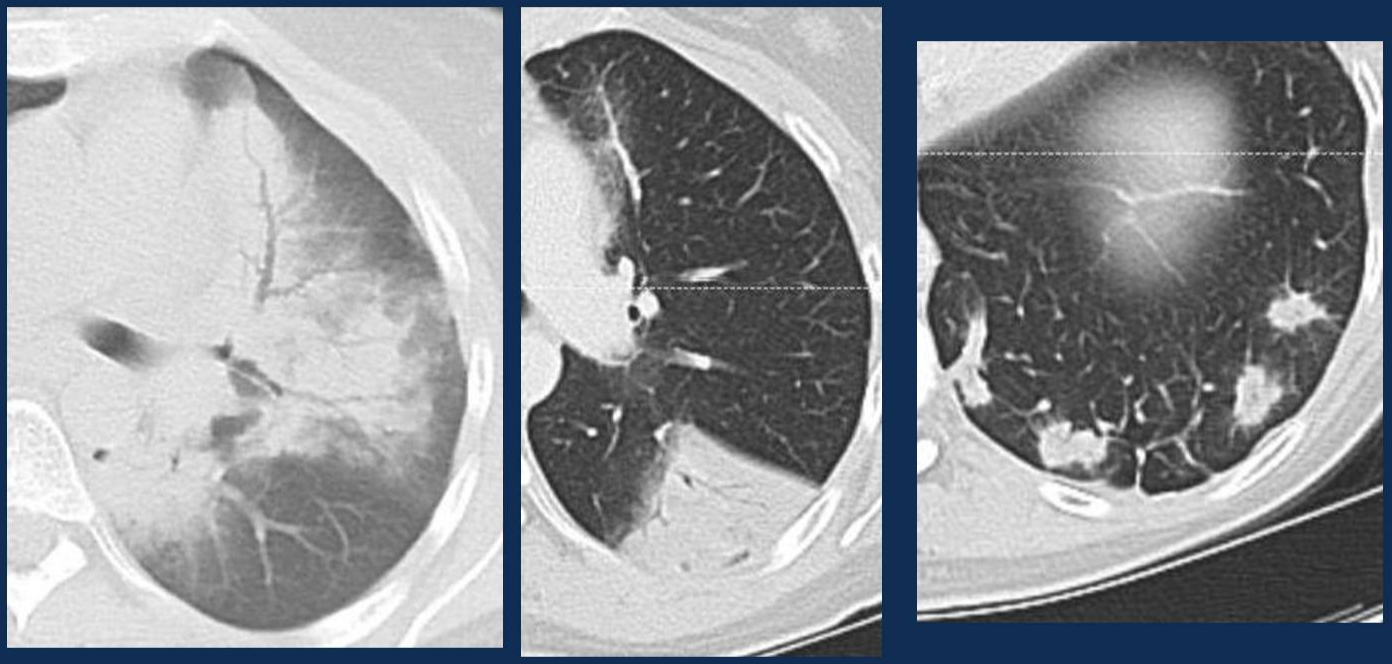
Pneumonitis

- Radiographs –
  - new or changes in ground-glass changes, nodular or interstitial
- Symptoms –
  - new or worsening cough, shortness of breath
- Signs
  - decrease in oxygen saturation



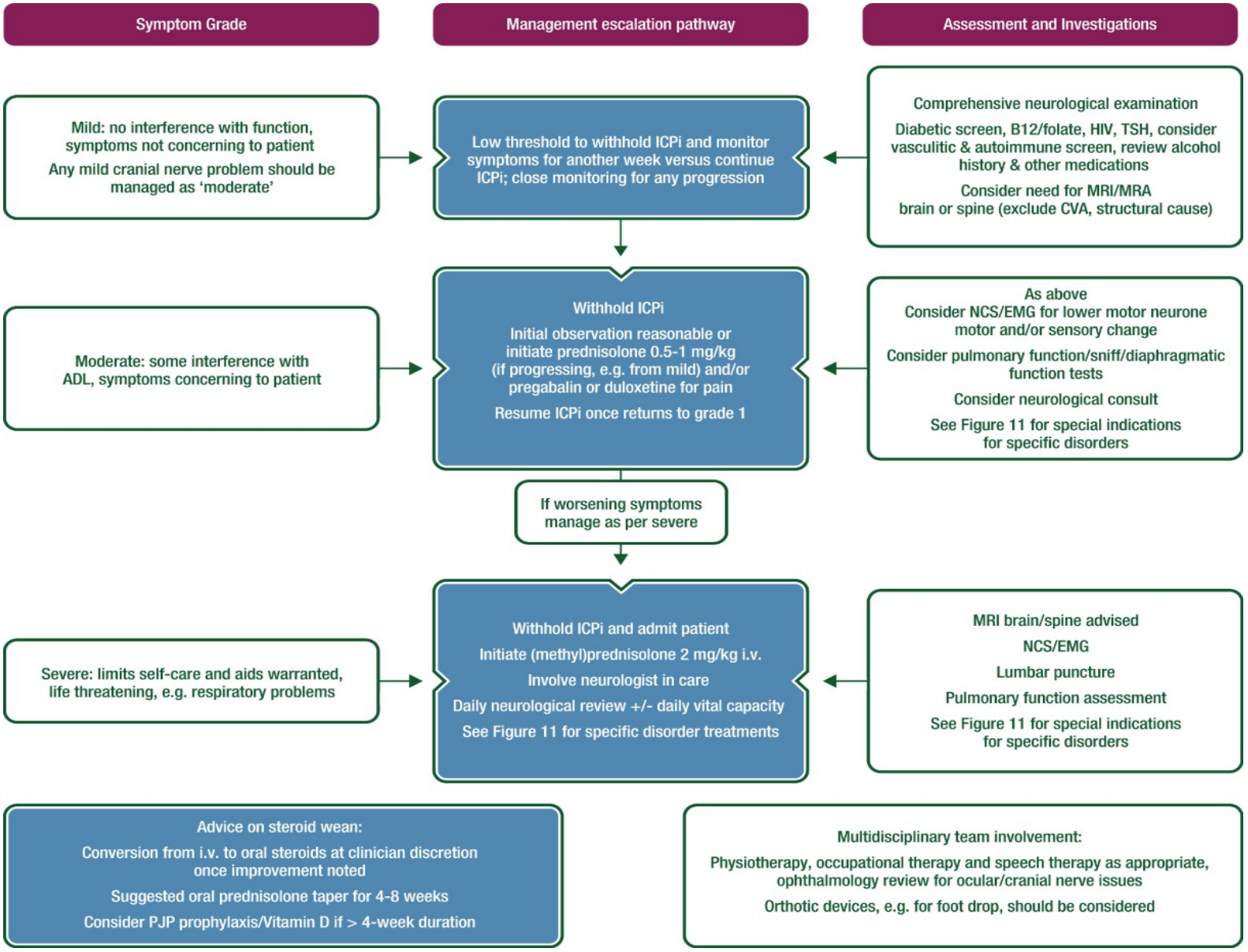
Highly Variable Radiographic Appearance of Pneumonitis



Presented by: Evan J. Lipson, MD

Presented By Julie Brahmer at 2016 ASCO Annual Meeting

PERIPHERAL NEUROLOGICAL TOXICITY



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PERIPHERAL NEUROLOGICAL TOXICITY

Suspected syndrome	Suggested Investigations	Management approach
Guillain-Barré syndrome: Progressive symmetrical muscle weakness with absent or reduced tendon reflexes – involves extremities, facial, respiratory and bulbar and oculomotor muscles; dysregulation of autonomic nerves	Nerve conduction studies (acute polyneuropathy) Lumbar puncture (elevated protein with normal WBC count) Pulmonary function tests with vital capacity and maximum inspiratory/expiratory pressures Antibody testing for GBS variants, e.g. GQ1b in Miller Fisher variant	Use of steroids not recommended in idiopathic GBS; however, trial of (methyl)prednisolone 1-2 mg/kg reasonable Neurological consult If no improvement or worsening, plasmapheresis or IVIG indicated Consider location of care where ventilatory support available (required in 15%-30% idiopathic cases)
Myasthenia Gravis: Fluctuating muscle weakness (proximal limb, trunk, ocular, e.g. ptosis/diplopia or bulbar) with fatigability, respiratory muscles may also be involved	Check for ocular muscle and proximal muscle fatigability AChR and anti-MuSK antibodies Bedside tests, e.g. Tensilon test or ice pack test with neurological input Repetitive nerve stimulation and single fibre EMG	Steroids indicated (oral or i.v. depending on symptoms) Pyridostigmine initial dose 30 mg tds Neurological consult If no improvement or worsening, plasmapheresis or IVIG may be considered Additional immunosuppressants azathioprine, cyclosporine, mycophenolate Avoid certain medications, e.g. ciprofloxacin, beta-blockers, that may precipitate cholinergic crisis

Other syndromes reported:
Motor and sensory peripheral neuropathy, multifocal radicular neuropathy/plexopathy, autonomic neuropathy, phrenic nerve palsy, cranial nerve palsies (e.g. facial nerve, optic nerve, hypoglossal nerve)

Steroids suggested as initial management where indicated with neurology specialist input and close attention to potential for respiratory or visual compromise

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CENTRAL NEUROLOGICAL TOXICITY

Suspected syndrome	Suggested Investigations	Management approach
Aseptic meningitis: Exclusion of infective causes paramount Headache, photophobia, neck stiffness with fever or may be afebrile, vomiting; normal cognition/cerebral function (distinguishes from encephalitis)	Lumbar puncture- M/C/S (normal Gram stain, WBCs < 500/μL, normal glucose), PCR for HSV, cytology CNS imaging to exclude brain metastases and leptomeningeal disease	Exclude bacterial and ideally viral infections prior to high-dose steroids Oral prednisolone 0.5-1 mg/kg or i.v. (methyl)prednisolone 1-2 mg/kg if very unwell Consider concurrent empiric antiviral (i.v. acyclovir) and antibacterial therapy
Encephalitis: Exclusion of infective and metabolic causes paramount Confusion or altered behaviour, headaches, alteration in Glasgow Coma Scale, motor or sensory deficits, speech abnormality, may or may not be febrile	Lumbar puncture- M/C/S (normal Gram stain, WBCs usually < 250/mm^3 with lymphocyte predominance, elevated protein but < 150 mg/dL, usually normal glucose but can be elevated), PCR for HSV & consider viral culture, cytology CNS imaging Consider viral serology	As above for aseptic meningitis Suggest concurrent i.v. acyclovir until PCR result obtained
Transverse myelitis: Acute or subacute neurological signs/symptoms of motor/sensory/autonomic origin; most have sensory level; often bilateral symptoms	MRI brain and spine Lumbar puncture – may be normal but lymphocytosis, elevated protein may be noted, oligoclonal bands not usually present, cytology Serum B12/HIV/syphilis/ANA/anti-Ro and anti-La Abs, TSH, anti-aquaporin-4 IgG	(Methyl)prednisolone 2 mg/kg (or consider 1 g/day) Neurology consultation Plasmapheresis may be required if non-steroid responsive
Other syndromes reported: Neurosarcoidosis, Posterior Reversible Leucoencephalopathy Syndrome (PRES), Vogt-Harada-Koyanagi syndrome, Neurosarcoidosis, demyelination, vasculitic encephalopathy, generalised seizures		

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Neurological toxicity

- In the case of mild neurological AEs, withhold ICPi and perform work-up (MRI scan, lumbar puncture) to define nature of neurotoxicity.

- In the case of deterioration or severe neurological symptoms, admit the patient and start (methyl)prednisone 1–2 mg/kg orally or i.v.

- In the case of Guillain-Barré or myasthenia-like symptoms, consider adding plasmapheresis or i.v. Ig [V, B].

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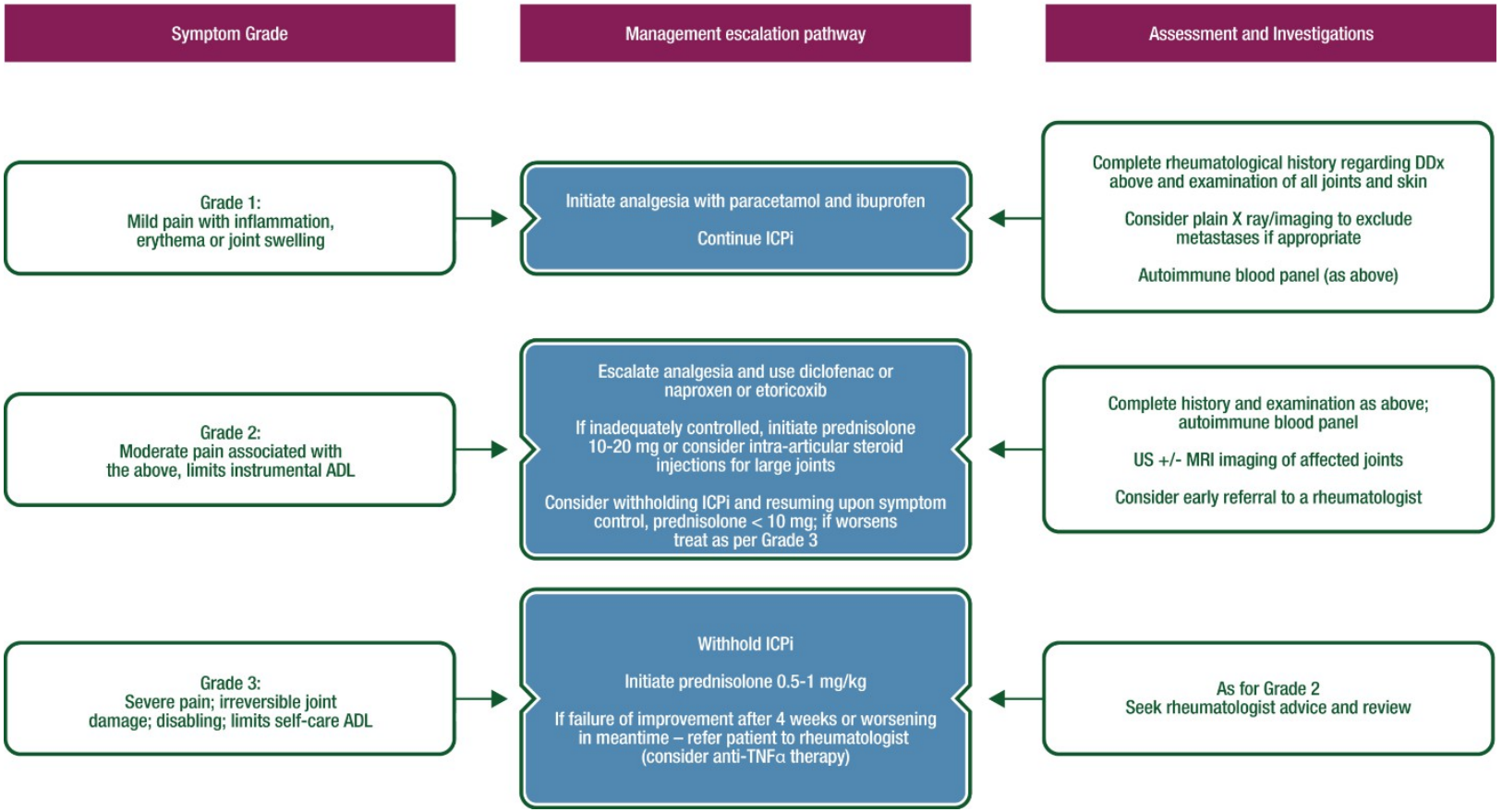
ARTHRALGIA

Arthralgia: Pain in the joints without associated swelling; may be found in conjunction with myalgia (muscle pain), a common AE

DDx to consider:
- Arthritis (see Figure 14 for further tests and management)
- Polymyalgia rheumatica (see arthritis as may present with small joint synovitis)
- Myositis (characterised by tenderness to palpation of muscle)

Due to the paucity of literature on management of this AE, this algorithm serves as a general guide only; seek rheumatology advice if severe symptoms not responding to steroids



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CASE REPORT Open Access

Acute heart failure due to autoimmune myocarditis under pembrolizumab treatment for metastatic melanoma

Heinz Lä

therapy

AT2-receptor blocker (candesartan), a beta-blocker (bisoprolol), aldosterone- antagonist (spironolactone) and diuretics (torasemid) ac cording to ACC/AHA guidelines as well as prednisone 2 mg per kilogram body weight.

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Dispnea ingravescente

DD: TEPA, polmonite

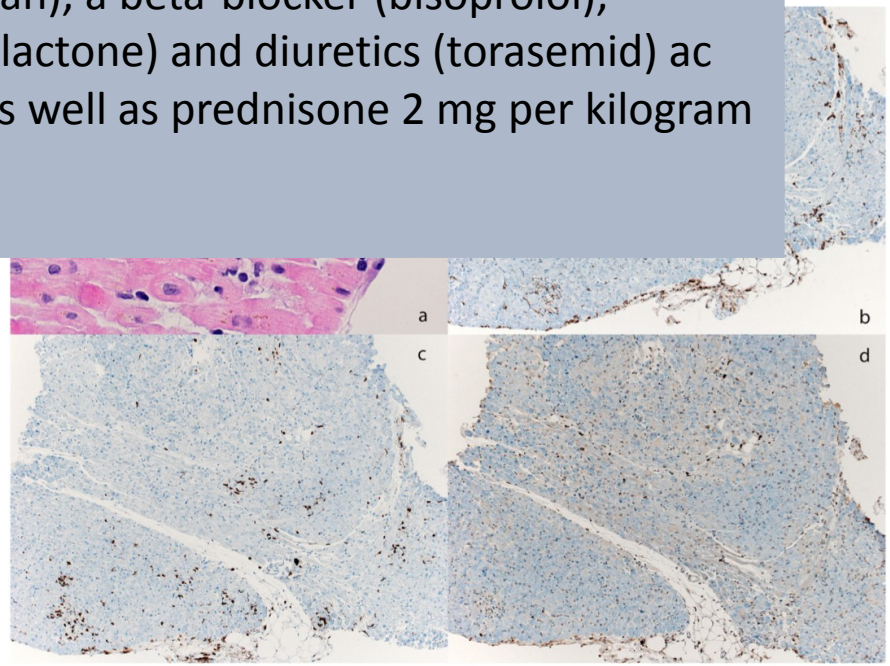

Figure 3 Histological analysis of endomyocardial biopsy. (a) Hematoxylin and eosin staining of the myocardial biopsy with focal mononuclear infiltrates. **(b)** Immunohistochemical analysis of CD68 macrophages. **(c)** Staining for CD8 positive T cells **(d)** and FOXP3 positive cells within the myocardium of the patient.

Cardiac toxicity

- When a myocarditis is suspected, admit the patient and immediately start high-dose (methyl)prednisone (1–2 mg/kg).

- In the case of deterioration, consider adding another immunosuppressive drug (MMF or tacrolimus) [V, B].

Rheumatological toxicity

- For mild arthralgia, start NSAIDs, and in the case of no improvement, consider low dose steroids (10–20 mg prednisone).

- In the case of severe polyarthritis, refer patient to or consult a rheumatologist and start prednisone 1 mg/kg. Sometimes infliximab or another anti-TNFα drug is required for improvement of arthritis [V, B].

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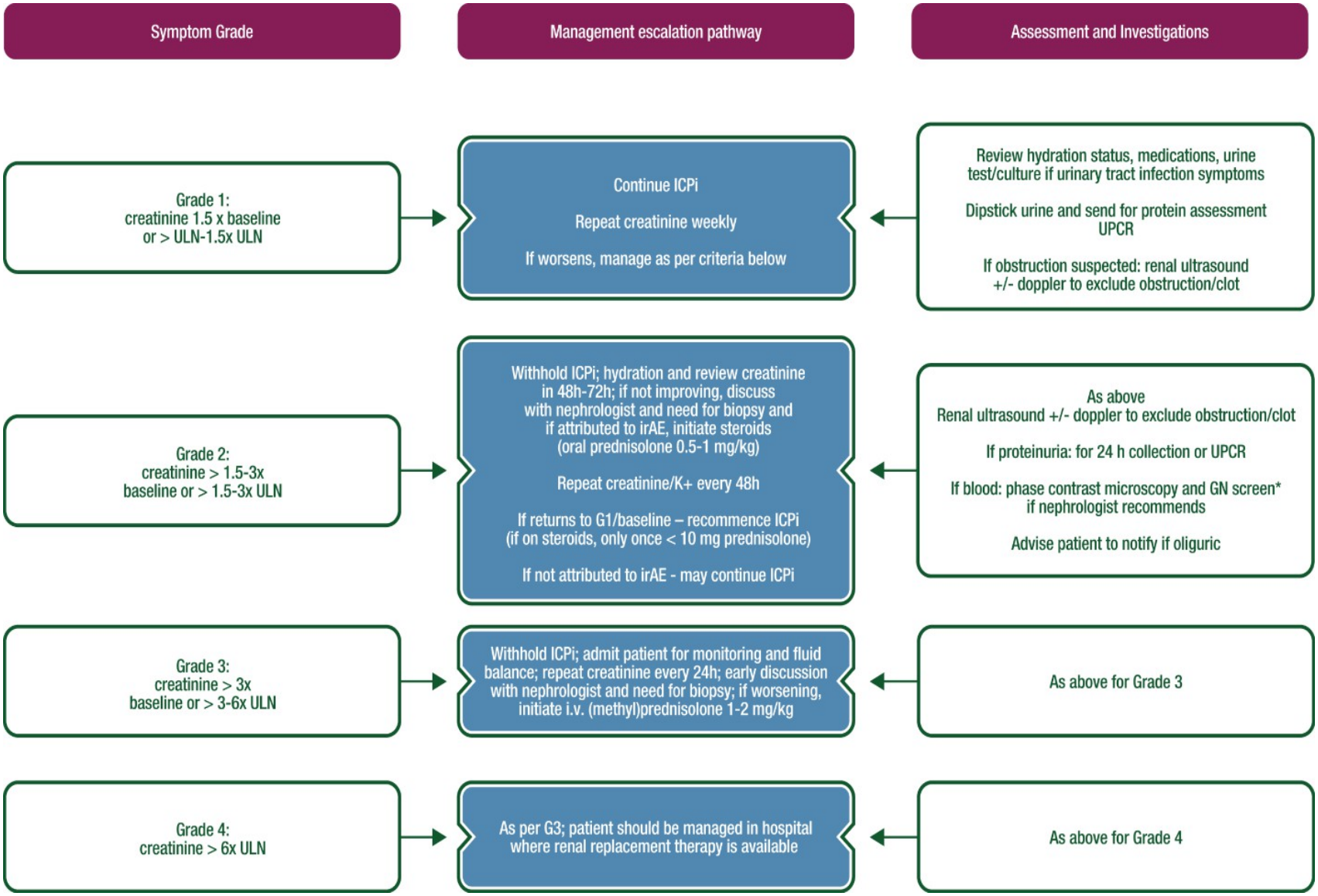
RENAL TOXICITY



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Renal toxicity

- In case of nephritis, rule out other causes of renal failure first. Interrupt or permanently discontinue ICPi depending on the severity of the renal insufficiency. Stop other nephrotoxic drugs.

Start (methyl)prednisone 1–2 mg/kg. Consider renal biopsy to confirm diagnosis [V, B].

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Conclusion

- Although the irAEs profiles of the three approved agents may differ slightly, they share the clinical presentation of symptoms and general principles guiding their management.

- The irAEs can be insidious and unpredictable

- Education: clinical team, as well as the patient, to reported early the potential AE, generate appropriate level of suspicion and prompt investigation.

- If identified early, the irAEs are almost always reversible with the initiation of immunosuppression.

- If they go unrecognized, these events can lead to significant morbidity, organ dysfunction, and even death.

Multidisciplinary Approach