CLINICAL PRACTICE GUIDELINES

An ESMO Product

Management of toxicities from immunotherapy

ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

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on behalf of the ESMO Guidelines Committee

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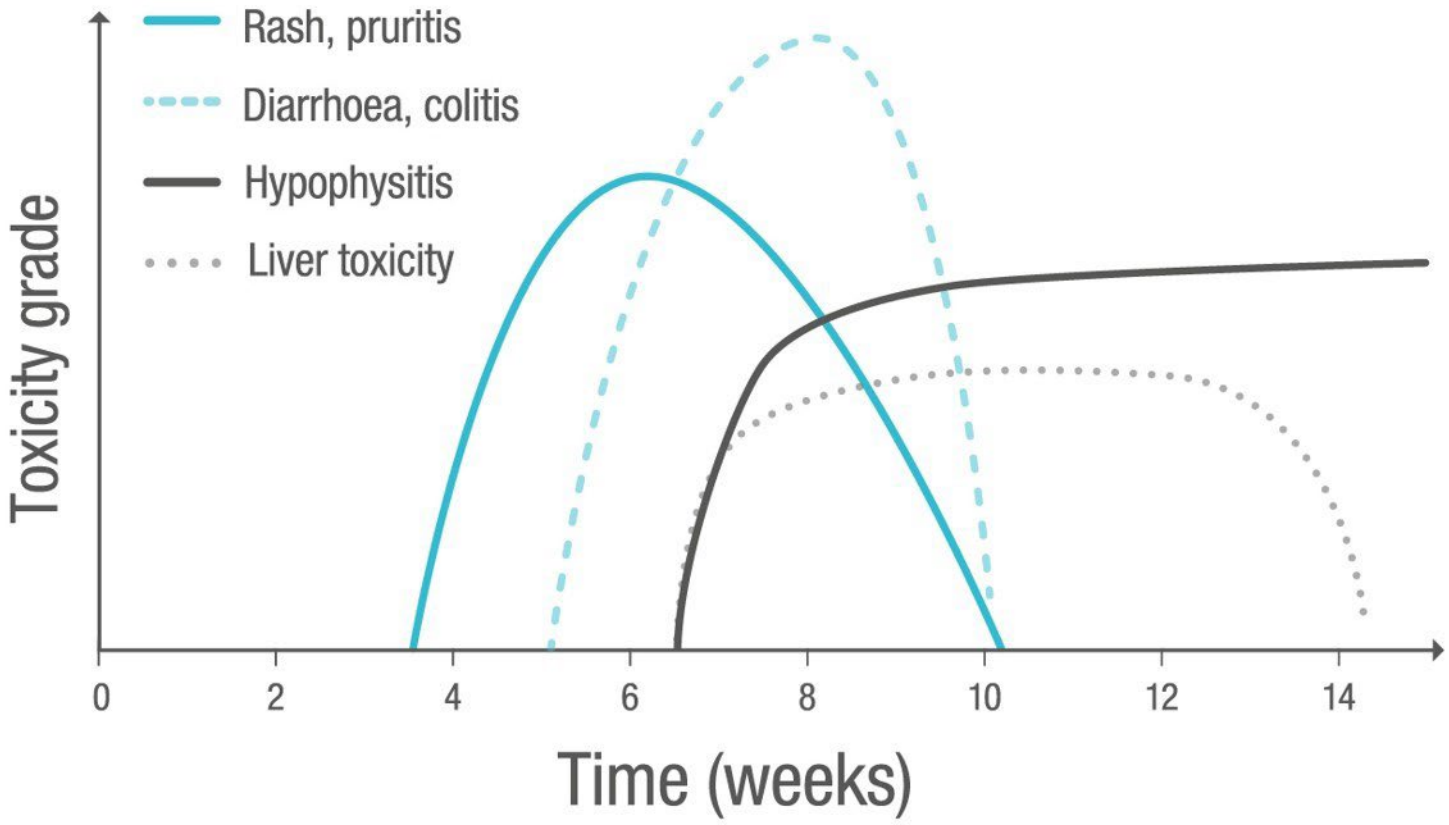
Incidence and epidemiology

Time to onset and resolution of occurrence of immuno-related adverse events following Ipilimumab treatment



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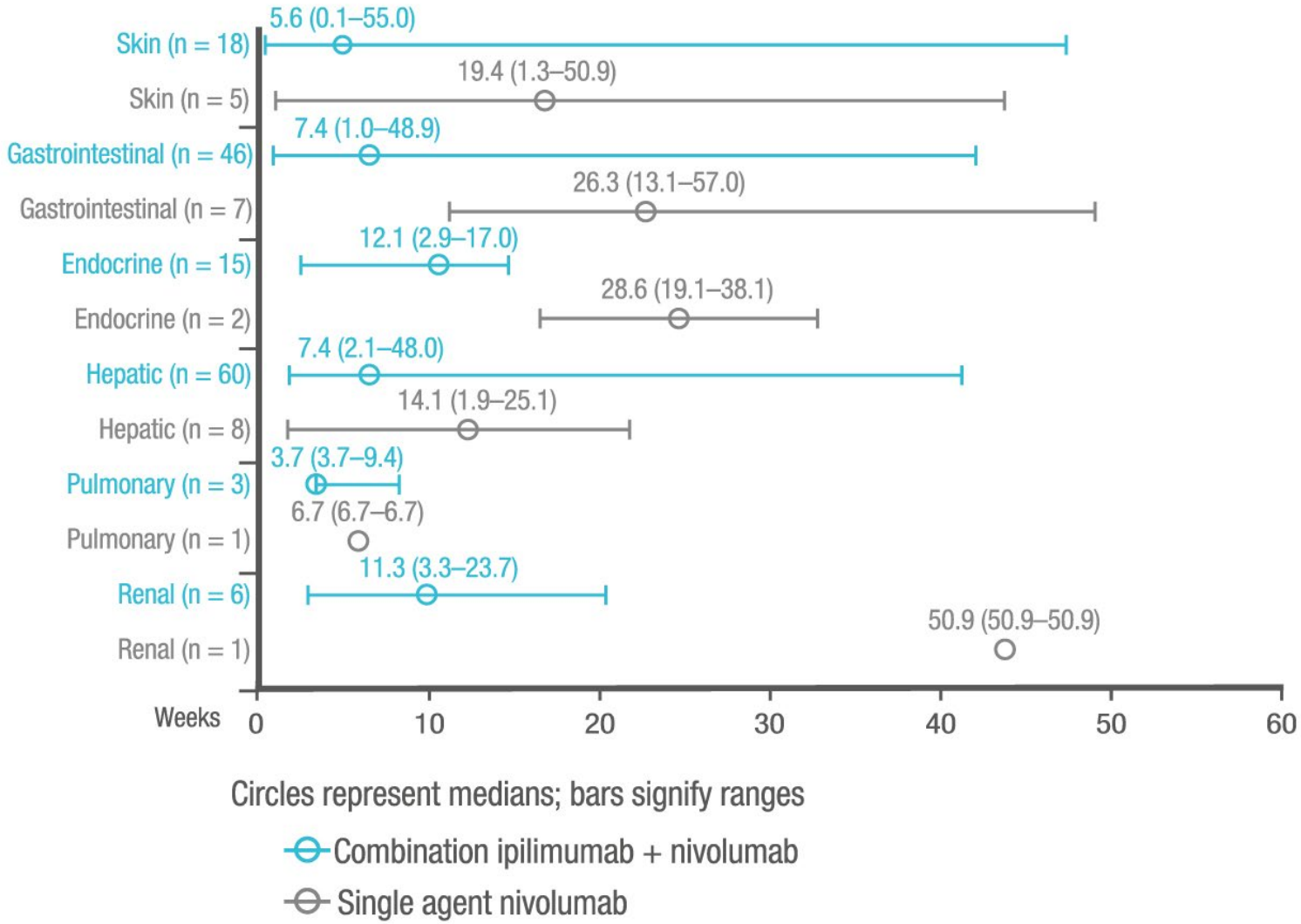
Incidence and epidemiology

Time to onset of grade 3-4 treatment-related select adverse events



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Incidence and epidemiology

Summary of recommendations	
General aspects of immune-related adverse events (irAEs)	Generally occur within 3 months after initiation of ICPi treatment
	Tissue biopsy may be useful for higher grade (3-4) toxicities, when there is diagnostic doubt and management would be altered by the outcome
Patient selection and baseline assessments	Before starting treatment: patients' susceptibility to irAEs should be assessed and patients informed of the potential AEs, reporting directly to the treating physician or team
	Work-up should include: history, general physical condition, autoimmune diseases, baseline laboratory tests and radiological scans • If current or previous autoimmune disease: risk of worsening of their autoimmune disease while on ICPi treatment • If previous ipilimumab-related irAEs: risk of developing irAEs following anti-PD-1 treatment, and vice versa
	Once irAEs have developed, prompt work-up and action are required
	Pneumocystis prophylaxis should be considered for patients receiving long-term (> 6 weeks) treatment with immunosuppressive drugs
	The clinical outcome of patients on ICPi treatment is not affected by the use of immunosuppressive agents for the management of immune-related toxicities

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Immune-related skin toxicity

Diagnosis and pathology/molecular biology

Summary of recommendations
Any other aetiology of skin problem, such as infection, an effect of another drug or a skin condition linked to another systemic disease, should be ruled out
The severity of the reaction should be evaluated by a careful and thorough physical examination of the skin, including the mucosal areas, and patient's general health status
A biological assessment, including blood cell count and liver and kidney tests, may be required to rule out dermatological emergencies • In severe cases, ICPi treatment should be permanently discontinued, the patient hospitalised and symptomatic treatment initiated immediately
Severity of maculopapular rash should be classified according to the CTCAE version 4.0

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Immune-related skin toxicity

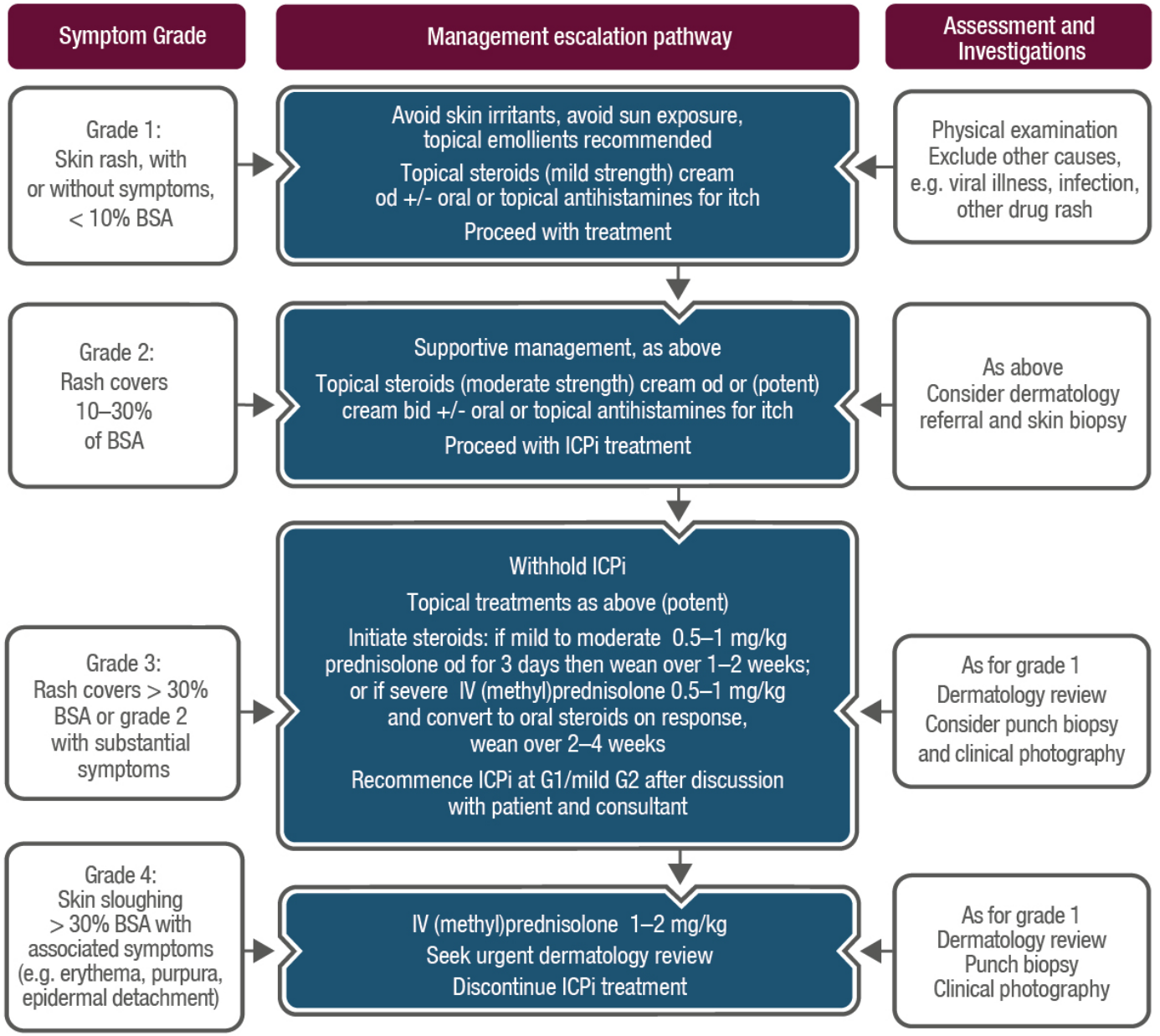
ICPi-related toxicity: Management of skin rash/toxicity

Recognised skin AEs include:

Most common: Erythema, maculopapular and pustulopapular rash

Rare: TEN, Steven-Johnson syndrome and DRESS

Vasculitis may also be present with purpuric rash



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Immune related toxicities - endocrinopathies

ICPi monitoring and management:
Thyroid function

Baseline Endocrine Panel:
TSH, FT4, T3* TFTs

Baseline abnormal values do not preclude treatment; discuss with endocrinologist if uncertain
*when indicated

Monitoring during treatment:
Anti-CTLA-4 (including combination with anti-PD-1)
· TFTs every cycle
· TFTs 4-6 weeks after cycle 4 (i.e. with restaging CT)
Late endocrine dysfunction can occur

Anti-PD-1/Anti-PD-L1
· TFTs every cycle for first 3 months, every second cycle thereafter (in case of 2-weekly schedule)
· Cortisol as indicated by symptoms/falling TSH

A falling TSH across two measurements with normal or lowered T4 may also suggest pituitary dysfunction and weekly cortisol measurements should be performed

If TSH is abnormal, refer to algorithm below. Iodine from CT scans may impact TFTs

Hypothyroidism: Low FT4 with elevated TSH or TSH > 10 with normal FT4

Treatment: Thyroxine 0.5–1.5 µg/kg (start low in elderly, if cardiac history)

Continue ICPi

Thyrotoxicosis (DDx thyroiditis, Grave's disease):

Investigations: Anti-TSH receptor Ab, anti-TPO Ab, nuclear medicine thyroid uptake scan

Treatment: Propranolol or atenonol for symptoms; consider carbimazole if anti-TSH receptor Ab-positive

Painful thyroiditis – consider prednisolone 0.5 mg/kg and taper

If unwell, withhold ICPi and consider restarting when symptoms controlled

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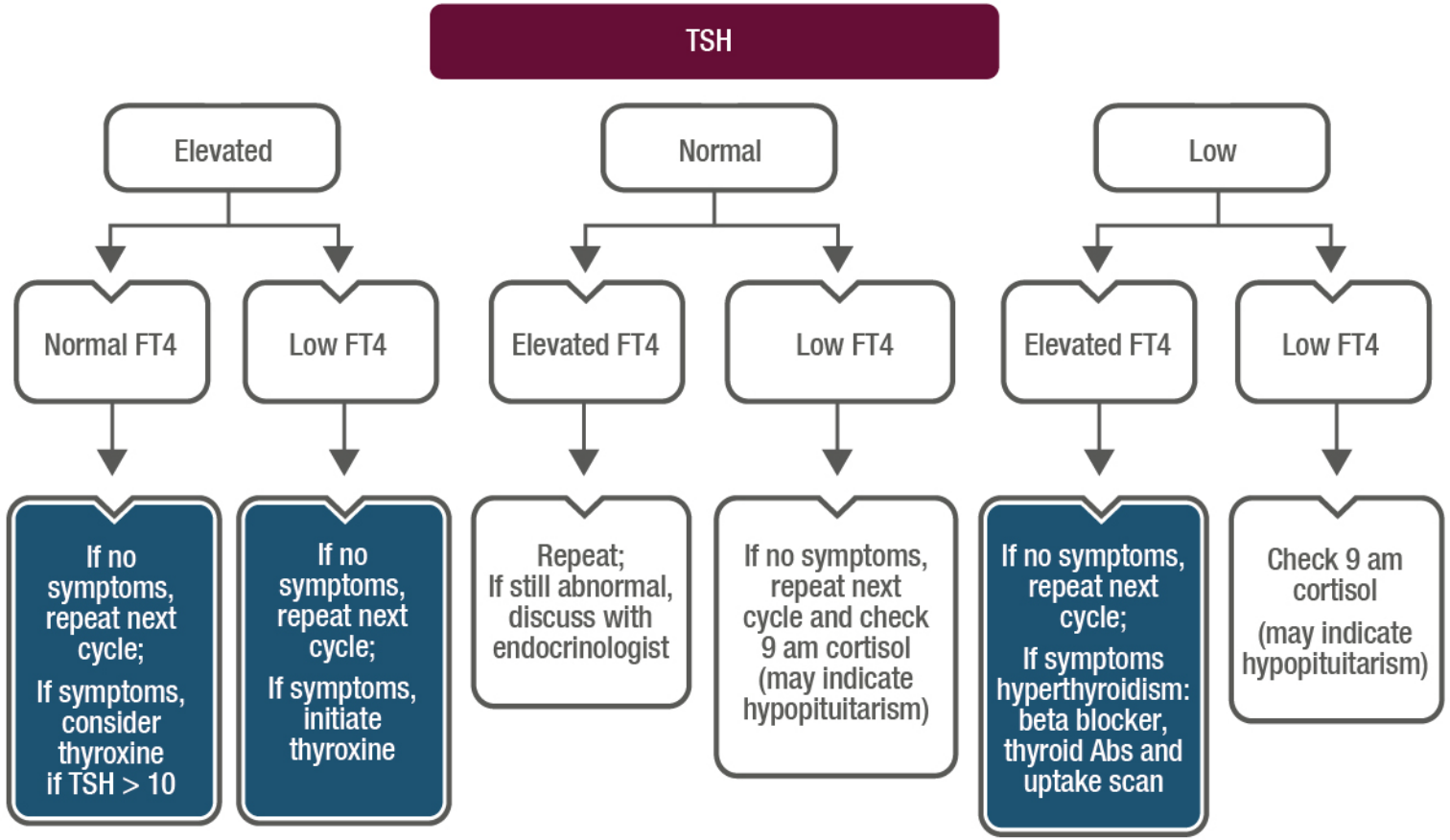
Immune related toxicities - endocrinopathies

ICPi monitoring and management: Thyroid function (cont'd)



Withhold ICPi if patient is unwell with symptomatic hyperthyroidism

Subclinical hyperthyroidism (low TSH, normal FT4) often precedes overt hypothyroidism

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Immune related toxicities - endocrinopathies

ICPi related toxicity: Management of hypophysitis

*Pituitary axis bloods: 9 am cortisol (or random if unwell and treatment cannot be delayed), ACTH, TSH/FT4, LH, FSH, oestradiol if premenopausal, testosterone in men, IGF1, prolactin. Mineralocorticoid replacement is rarely necessary in hypopituitarism

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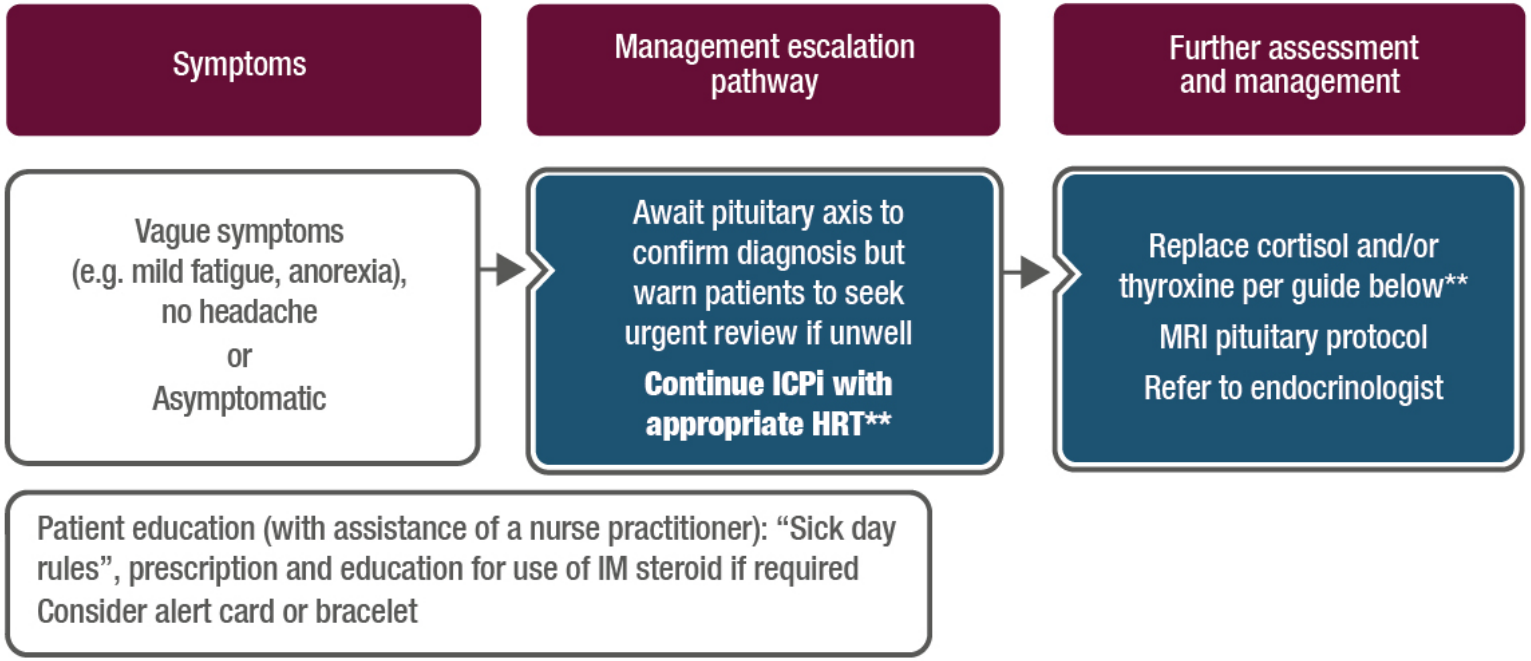
Immune related toxicities - endocrinopathies

ICPi-related toxicity: Management of hypophysitis (cont'd)



**Initial replacement advice for cortisol and thyroid hormones:

If 9 am cortisol < 250 nmol/L or random cortisol < 150 nmol/L and vague symptoms:

- Replace with hydrocortisone 20/10/10 mg
- If TFTs normal, 1–2 weekly monitoring initially (always replace cortisol for 1 week prior to thyroxine initiation)

If falling TSH +/- low FT4:

- Consider need for thyroxine replacement (guide is 0.5–1.5 mg/kg) based on symptoms and/or check 9 am weekly cortisol
- See thyroid section for further information regarding interpretation of an abnormal TSH/T4

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Immune related toxicities - endocrinopathies

Type 1 diabetes mellitus

Summary of recommendations
Blood glucose levels should be regularly monitored in patients treated with ICPi in order to detect the emergence of *de novo* DM
Patients with Type 2 DM may develop ketoacidosis, which should be treated according to standard local guidelines
The role of high-dose steroids in preventing total loss of pancreatic beta cells is unclear and is not recommended
C-peptide and antibodies against GAD and islet cells can distinguish between Type 1 and Type 2 DM
Restarting ICPi treatment can be considered once the patient has been regulated with insulin substitution

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Immune related hepatotoxicity

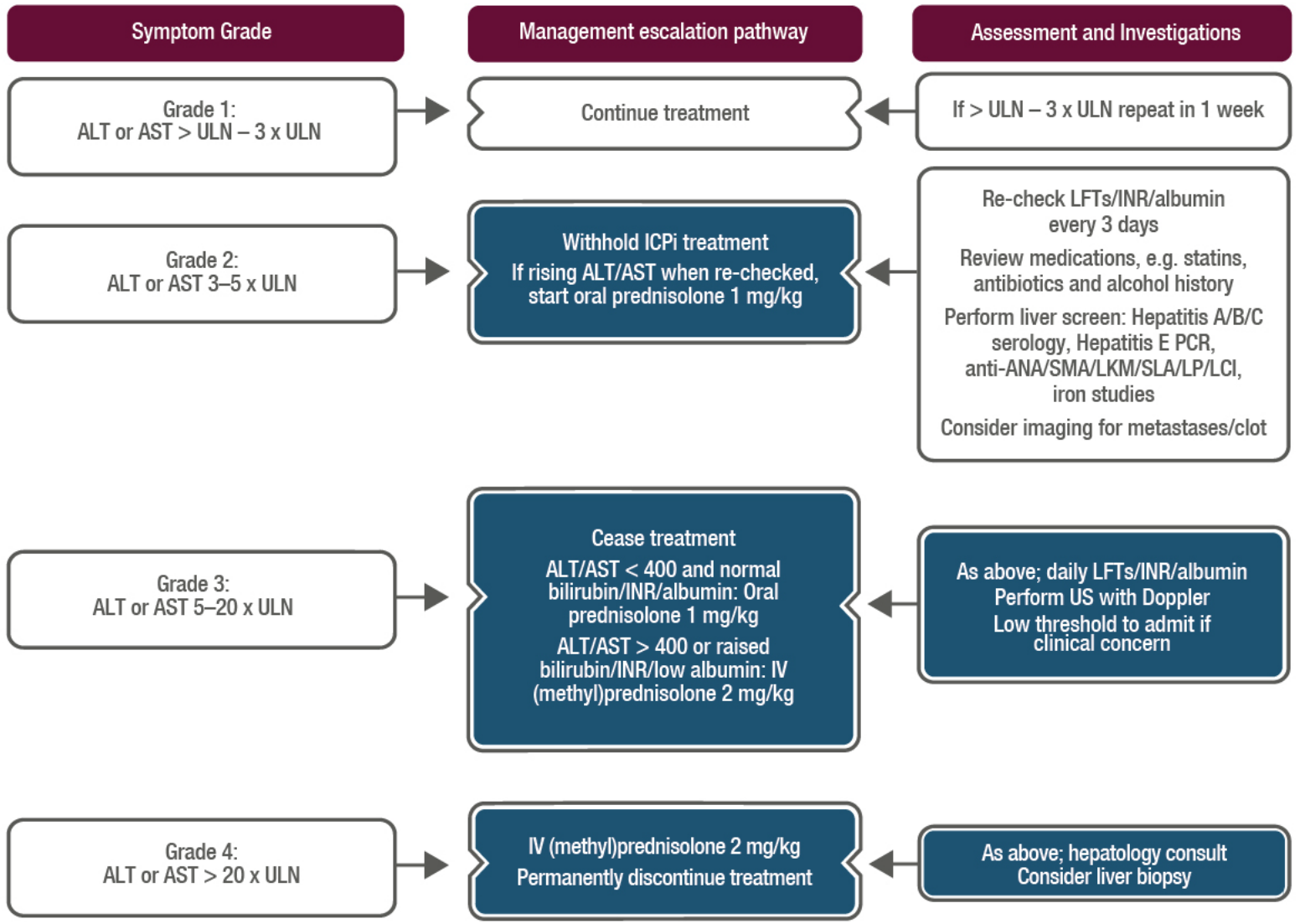
ICPi-related toxicity: Management of hepatitis

Steroid wean:

- Grade 2: Once grade 1, wean over 2 weeks; re-escalate if worsening; treatment may be resumed once prednisolone ≤ 10 mg
- Grade 3/4: Once improved to grade 2, can change to oral prednisolone and wean over 4 weeks; for grade 3, re-challenge only at consultant discretion

Worsening despite steroids:

- If on oral change to IV (methyl)prednisolone
- If on IV add MMF 500–1000 mg bid
- If worse on MMF, consider addition of tacrolimus
- A case report has described the use of anti-thymocyte globulin in steroid + MMF-refractory fulminant hepatitis



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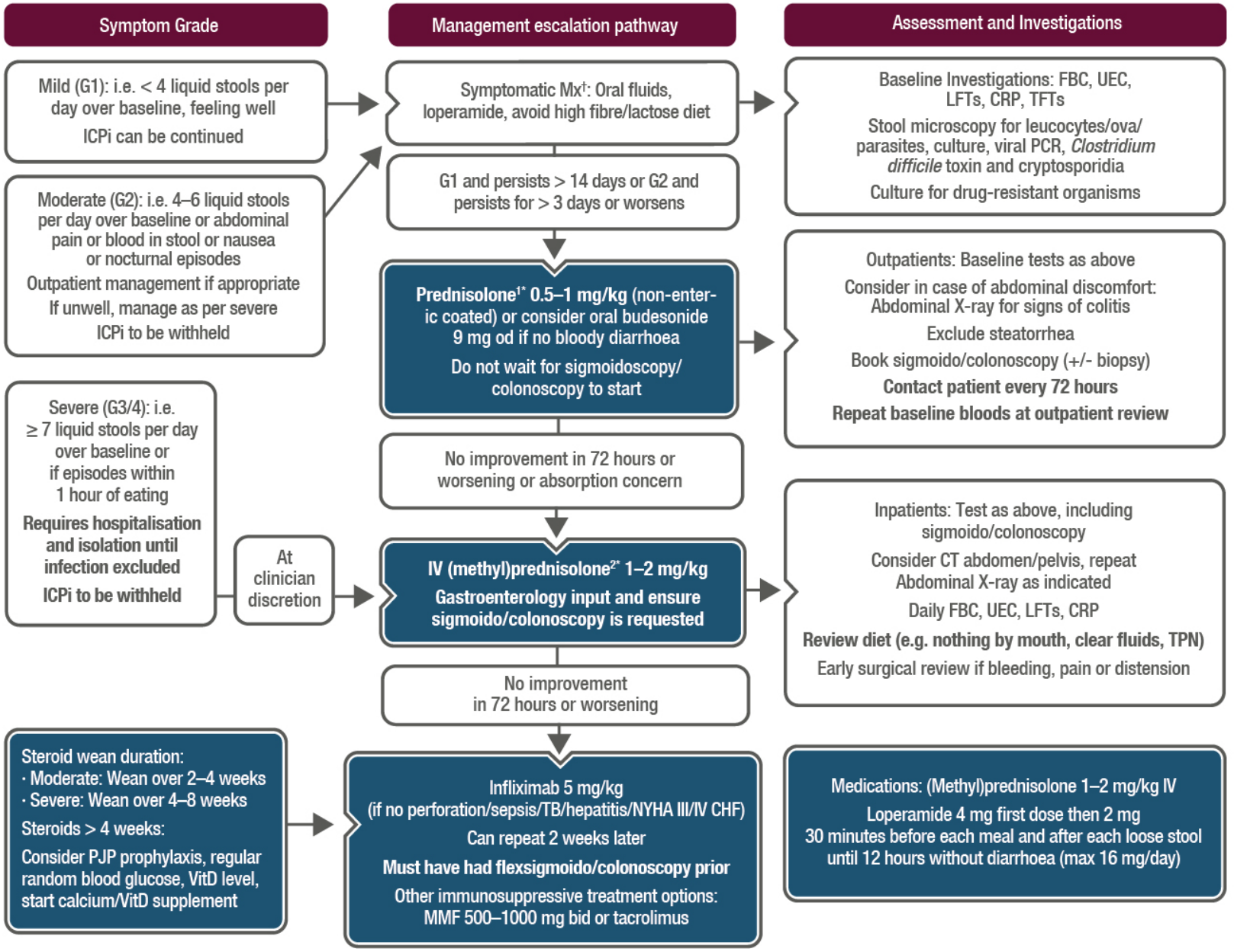
Immune related gastrointestinal toxicities

ICPi-related toxicity: Management of diarrhoea and colitis

†Loperamide 4 mg first dose then 2 mg 30 minutes before each meal and after each loose stool until 12 hours without diarrhoea (max 16 mg/day)

Steroid wean duration:
[1]Moderate: wean over 2–4 weeks
[2]Severe: wean over 4–8 weeks

*Steroids > 4 weeks: Consider PJP prophylaxis, regular random blood glucose, VitD level, start calcium/VitD supplement



CLINICAL PRACTICE GUIDELINES

Immune related gastrointestinal toxicities

GI toxicity of ICPIs (most commonly observed with anti-CTLA-4 alone or anti-CTLA-4 + anti-PD-1/PD-L1)

Summary of recommendations	
Most common symptoms	Diarrhoea, abdominal pain, hematochezia, weight loss, fever and vomiting, mouth ulcers, anal lesions and extra-intestinal manifestations (Upper GI symptoms and endoscopic lesions have been reported)
Main biological abnormalities	Anaemia, increased serum CRP and low serum albumin levels
Ruling out infection and cancer as causes	Bacterial enteropathogens and *Clostridium difficile* toxin content of stools and investigation of GI metastases
Further investigations	Flexible endoscopy can confirm the diagnosis of enterocolitis

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CLINICAL PRACTICE GUIDELINES

Immune related gastrointestinal toxicities

GI toxicity of ICPis – management, follow-up and long-term implications

Summary of recommendations	
Management	
Non-severe diarrhoea	Treatment with antidiarrhoeals, fluid and electrolyte supplementation, if required, and ICPis can be continued
Persistent grade 2 / severe grade 3–4 / grade 1-2 with alarm symptoms	ICPi discontinuation and initiation of systemic corticosteroids (1 to 2 mg/kg IV daily)
Response to IV corticosteroids	Responding (within 3–5 days): switch to the oral form, treatment tapered over 8–12 weeks Not responding: switch to infliximab 5 mg/kg (unless contraindicated)
Colonic perforation (with or without intra-abdominal abscess)	Emergency subtotal colectomy with ileostomy and endoscopy
Follow-up and long-term implications	
Corticosteroids or infliximab treatment does not affect response and OS of patients treated with ipilimumab	
Reintroduction of ICPi in patients previously experiencing enterocolitis is associated with a high risk of relapse - discuss on an individual basis	

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CLINICAL PRACTICE GUIDELINES

Immune related gastrointestinal toxicities

GI toxicity of ICPIs (most commonly observed with anti-CTLA-4 alone or anti-CTLA-4 + anti-PD-1/PD-L1)

Summary of recommendations	
Anti-PD-1	
Common symptoms	Diarrhoea, nausea/vomiting and abdominal pain, with a median time to symptom onset of 3 months
Endoscopic findings	Normal mucosa through mild erythema to severe inflammation and histological findings include lamina propria expansion, villus blunting, intra-epithelial neutrophils and increased crypt/gland apoptosis
Different patterns of GI irAEs	• Acute colitis • Microscopic colitis • Upper GI involvement • Pseudo-obstruction
Combined anti-CTLA-4 and anti-PD-1 antibodies	
With this combined treatment, pancreatitis and small bowel enteritis, which may be visible on CT scan, require ICPi treatment discontinuation and initiation of immunosuppression	

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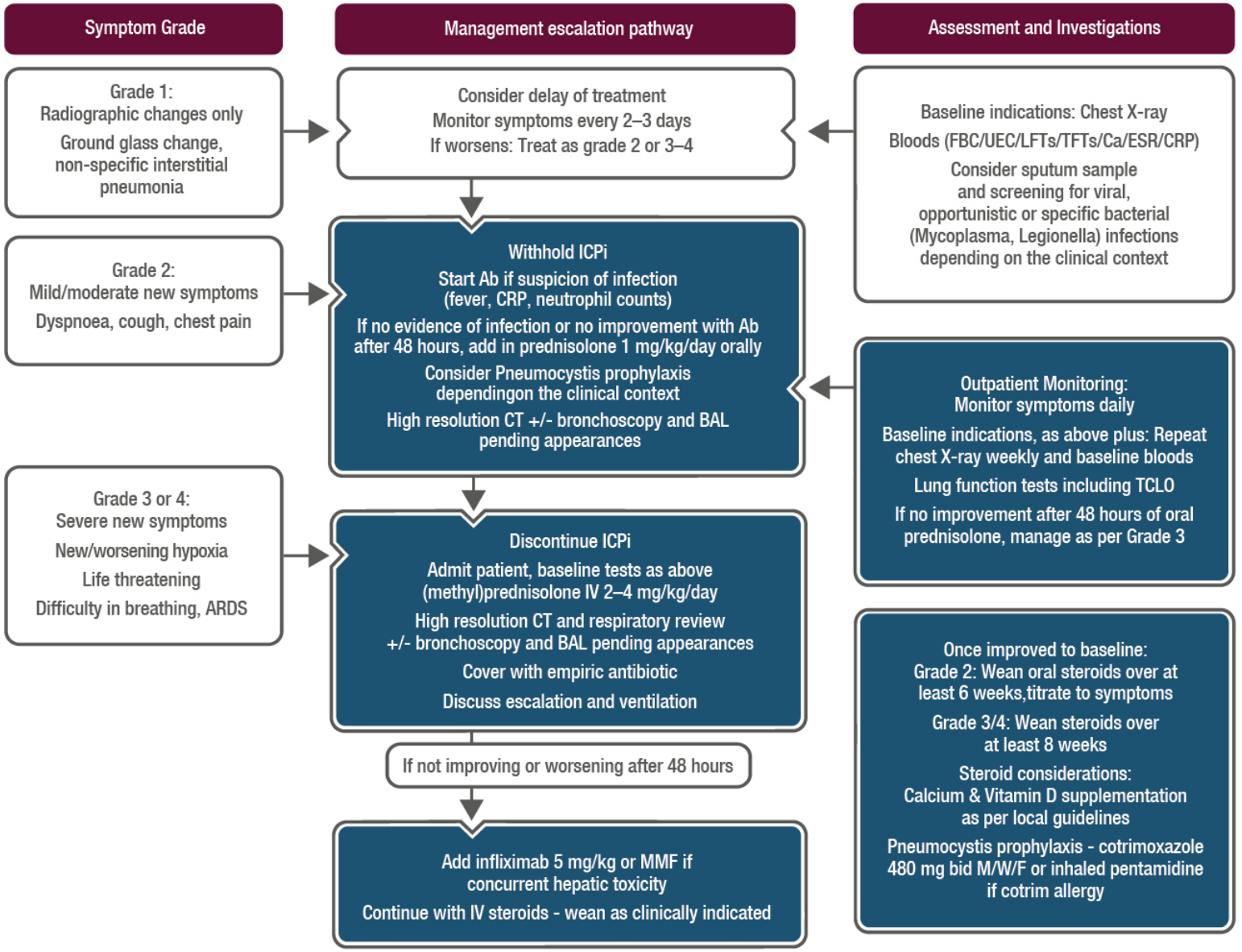
Immune related pneumonitis toxicities

ICPi-related toxicity: Management of pneumonitis

History:
Pulmonary hypertension/respiratory; disease/connective tissue disease; Influenza/Mycobacterium; tuberculosis exposure; Smoking history; Travel history; Allergy history including exposure to home/occupational aeroallergens

Differential Diagnosis:
Pneumonia (including atypical, pneumocystis, tuberculosis); Lymphangitis; Usual interstitial pneumonias; Pulmonary oedema; Pulmonary emboli; Sarcoidosis



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Immune related pneumonitis toxicities

Any new respiratory symptom require prompt investigation to formally exclude lung toxicity and all patients presenting with pulmonary symptoms should be assessed by CT

Summary of recommendations	
Radiological features	• Ground glass opacities • A cryptogenic organising pneumonia-like appearance • Interstitial pneumonia pattern • Characteristics of hypersensitivity pneumonitis
Lung biopsy	Generally not required for patient management, unless there is doubt as to the aetiology of pulmonary infiltrates, when a VATS biopsy is the method of choice
Bronchoscopy with BAL	Supports the identification of infections and is recommended in any symptomatic pneumonia

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Immune related pneumonitis toxicities

Management of pneumonitis

Summary of recommendations	
Immune-related pneumonitis is documented or suspected	Immunosuppressive treatment should be started immediately
When no possibility to rule out infection using bronchoscopy	Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment for grade ≥ 3 pneumonitis
Grade 1–2	Oral prednisone 1 mg/kg daily or equivalent with clinical assessment every 2–3 days initially is recommended, with additional radiological assessments for grade 2 pneumonitis, and possible ICPi treatment interruption. Following recovery, steroids should be tapered over 4–6 weeks and ICPi treatment reintroduction delayed until the daily steroid dose is ≤ 10 mg of oral prednisone
Grade 3–4 moderate-to-severe cases	Hospitalisation, treatment with high dose IV (methyl)prednisolone 2–4 mg/kg/day or equivalent and permanent discontinuation of ICPi treatment is recommended • If there is no improvement after 2 days, additional immunosuppressive strategies, such as infliximab, MMF or cyclophosphamide, are recommended • Steroids should be tapered slowly over at least 6 weeks to prevent recurrence

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CLINICAL PRACTICE GUIDELINES

Rare immune-related toxicities

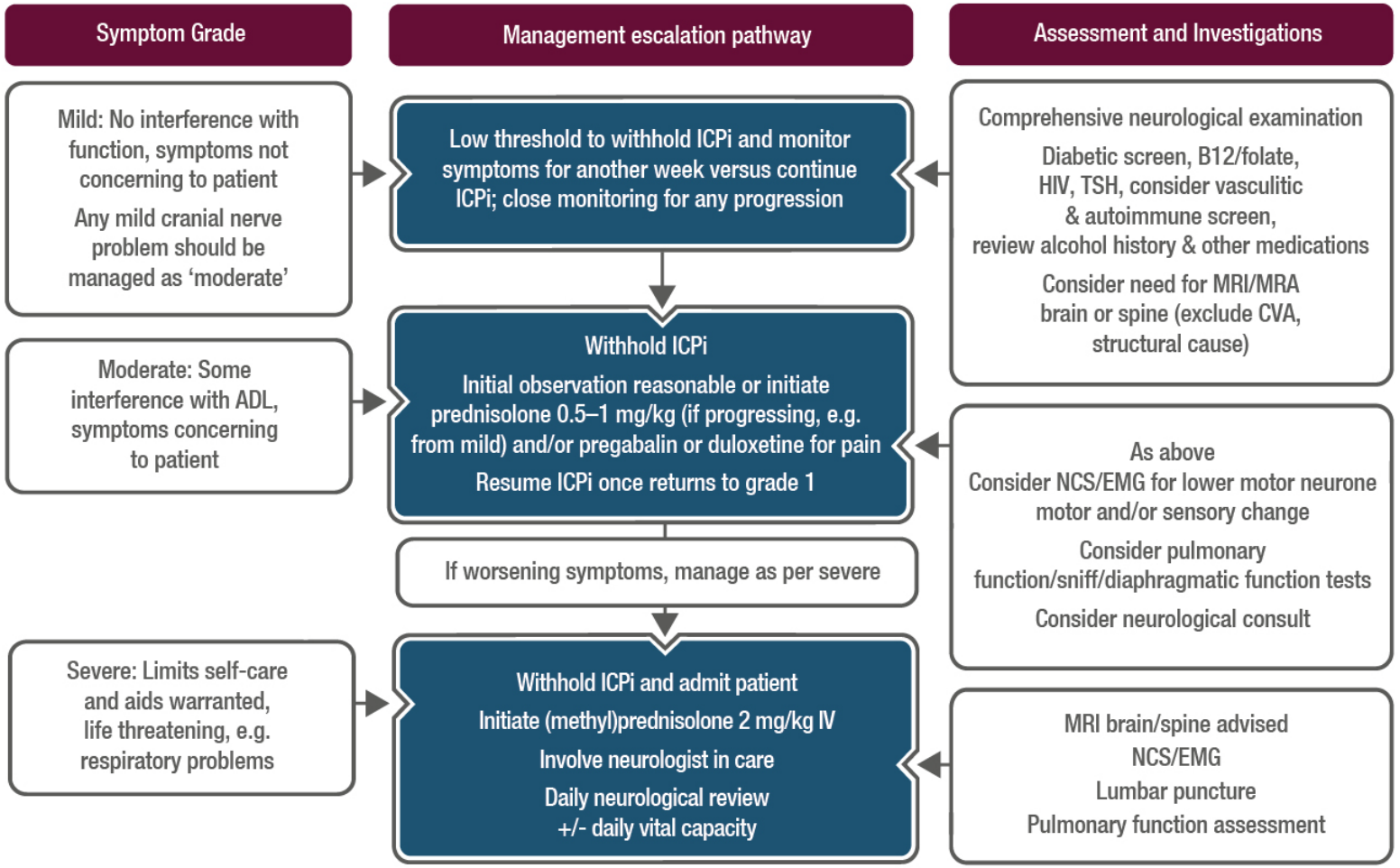
ICPi-related toxicity: Management of suspected peripheral neurological toxicity: mild, moderate or severe

Advice on steroid wean:

- Conversion from IV to oral steroids at clinician discretion once improvement noted
- Suggested oral prednisolone taper for 4–8 weeks
- Consider PJP prophylaxis/Vitamin D if > 4-week duration

Multidisciplinary team involvement:

- Physiotherapy, occupational therapy and speech therapy as appropriate, ophthalmology review for ocular/cranial nerve issues
- Orthotic devices, e.g. for foot drop, should be considered



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Rare immune-related toxicities

ICPi-related toxicity: Management of suspected peripheral neurological toxicity: Guillain-Barré and Myasthenia Gravis syndromes

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

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 packtest with neurological input Repetitive nerve stimulation and single fibre EMG	Steroids indicated (oral or IV 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

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CLINICAL PRACTICE GUIDELINES

Rare immune-related toxicities

ICPi-related toxicity: Management of suspected central neurological toxicity

Other syndromes reported:
Posterior Reversible Leucoencephalopathy Syndrome (PRES), Vogt-Harada-Koyanagi syndrome, demyelination, vasculitic encephalopathy, generalised seizures

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 IV (methyl)prednisolone 1–2 mg/kg if very unwell Consider concurrent empiric antiviral (IV 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/mm3 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 IV 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

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Rare immune-related toxicities

Neurological toxicity

Summary of recommendations	
Time frame	A range of neurological events have been described with a time of onset from 6 to 13 weeks
Assessment	Progression of the underlying cancer, seizure activity, infection and metabolic derangement should be ruled out as causes and nerve conduction studies and lumbar puncture may assist in diagnosis
Management	• Early consultation with a neurologist is advised • For all but mild (grade 1) neurological symptoms, ICPi therapy should be withheld until the cause is determined • Prednisolone 0.5–1 mg/kg should be considered for moderate symptoms • High-dose oral prednisolone 1–2 mg/kg or IV equivalent is recommended for significant neurological toxicity • Plasmapheresis or IVIg may be required for the treatment of myasthenia and GBS

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Rare immune-related toxicities

Cardiac toxicity

Summary of recommendations	
Circumstances	Cardiac side effects have been reported to occur after treatment with ipilimumab, pembrolizumab and nivolumab and the incidence is higher with the combination of ipilimumab and nivolumab compared with nivolumab alone
Management	• Early consultation with a cardiologist is recommended • High-dose corticosteroids should be instituted rapidly if ICPi-induced cardiac side effects are suspected • Escalation to other immunosuppressive drugs, such as infliximab, MMF and ATG, is recommended if symptoms do not respond promptly to steroids

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Immune related toxicities

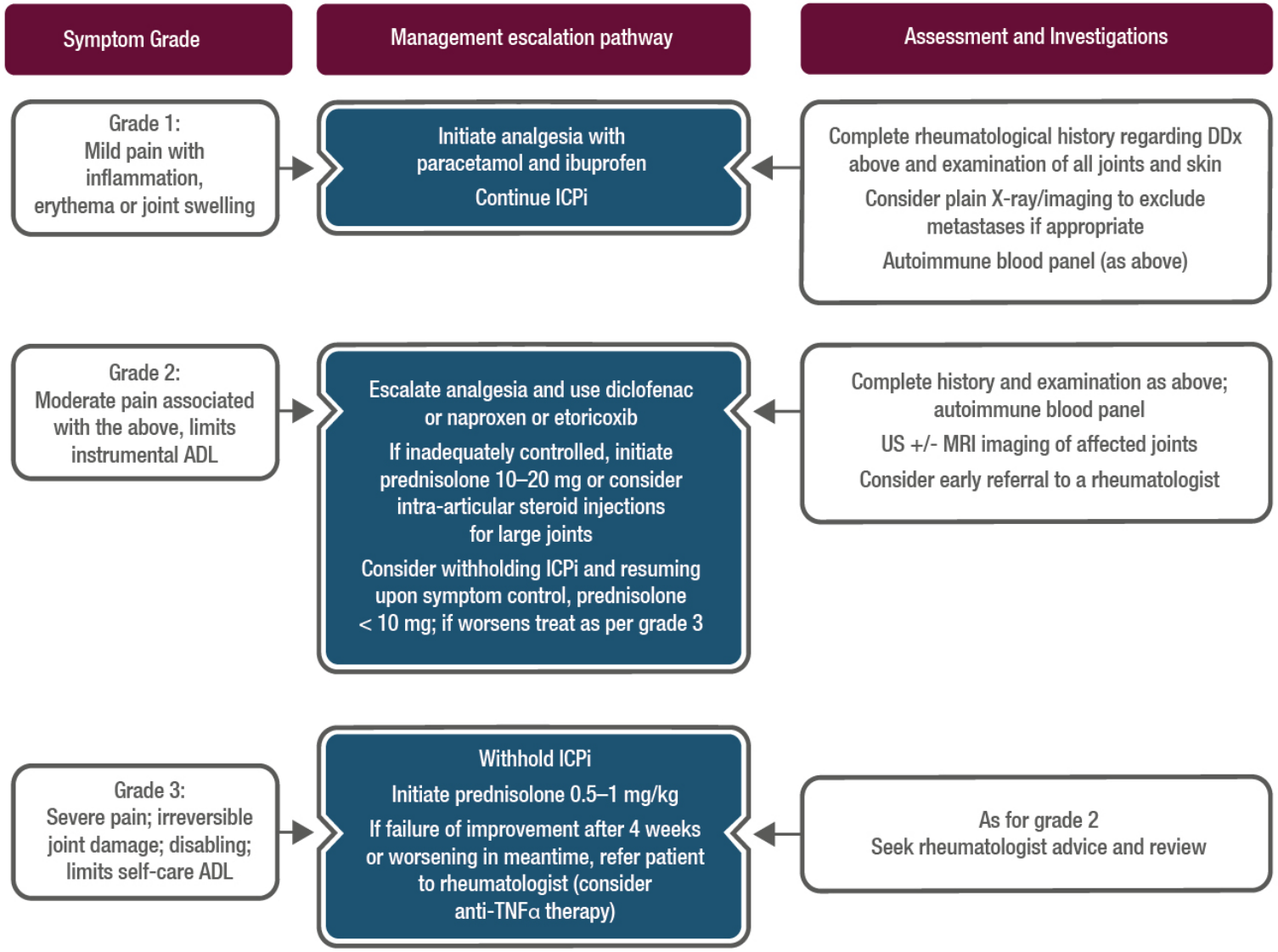
ICPi-related toxicity: Management of arthralgia

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 in the CPG 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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Rare immune-related toxicities

Rheumatoligical toxicity

Summary of recommendations	
Mild or moderate symptoms	Analgesia with paracetamol and/or NSAIDs is recommended; moderate symptoms may respond to prednisolone
Severe symptoms	Consultation with a rheumatologist and the use of high dose corticosteroids and TNFα-blocking agents is recommended

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CLINICAL PRACTICE GUIDELINES

Rare immune-related toxicities

ICPi-related toxicity: Management of nephritis: **grade 1-2**

Renal injury occurs in around 1–4% of patients treated with ICPis, usually in a pattern of acute tubulo-interstitial nephritis with a lymphocytic infiltrate

Attention needs to be paid to the patient's baseline creatinine, not just abnormal results per biochemistry ULN

Confounding diagnoses include dehydration, recent IV contrast, urinary tract infection, medications, hypotension or hypertension

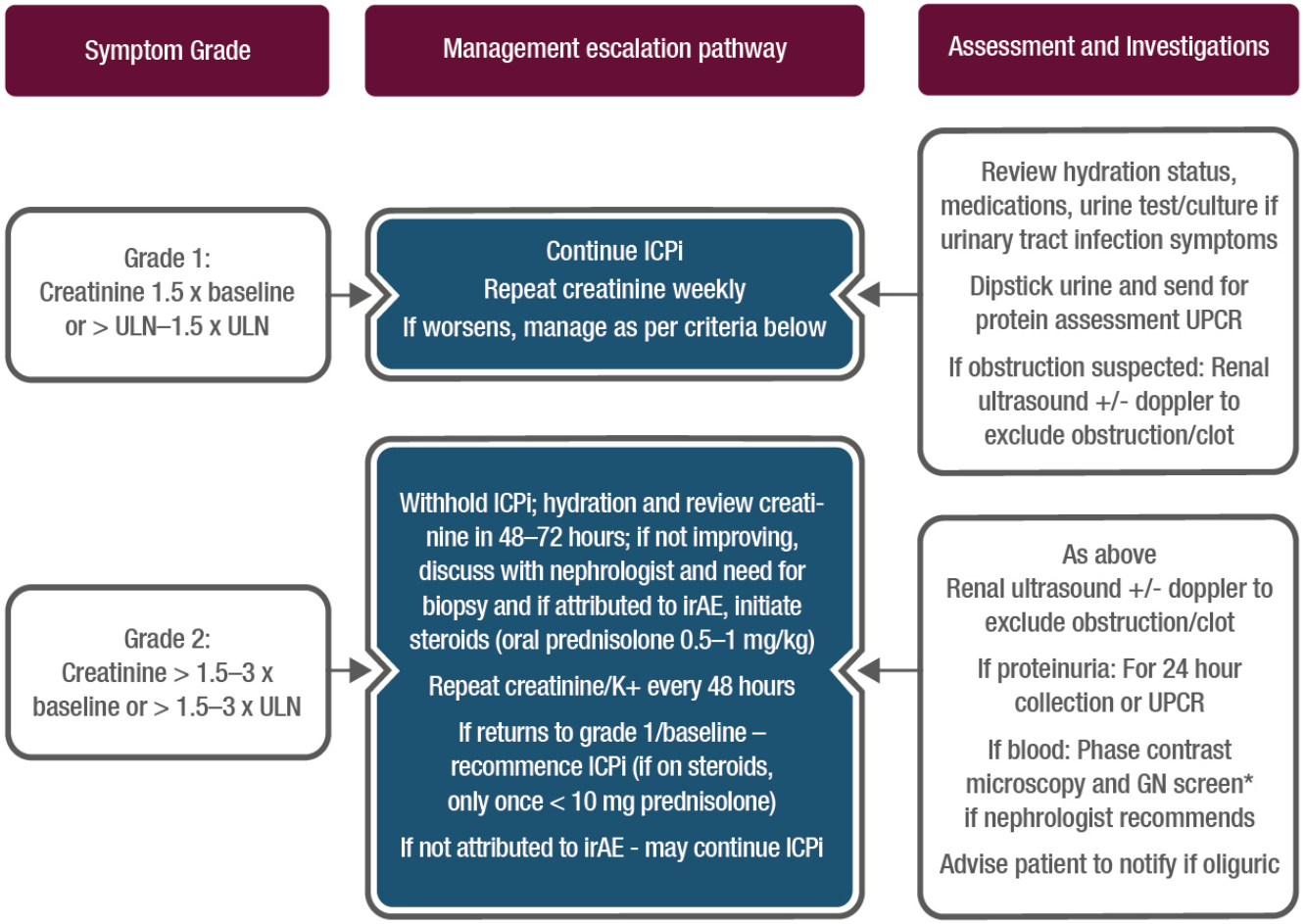
Early consideration for renal biopsy is helpful which may negate the need for steroids and determine if renal deterioration related to ICPis or other pathology

Oliguria should prompt inpatient admission for careful fluid balance and plan for access to renal replacement therapy

Steroid wean: Begin to wean once creatinine grade 1; grade 2 severity episode: wean steroids over 2–4 weeks; grade 3–4 episode: wean over ≥ 4 weeks

If on steroids for > 4 weeks–PJP prophylaxis, calcium/vitamin D supplementation, gastric protection and check afternoon glucose for hyperglycaemia

*GN screen: ANA, complement C3, C4, ANCA, anti-GBM, hepatitis B and C, HIV, immunoglobulins and protein electrophoresis



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Rare immune-related toxicities

ICPi-related toxicity: Management of nephritis: **grade 3-4**

Renal injury occurs in around 1–4% of patients treated with ICPis, usually in a pattern of acute tubulo-interstitial nephritis with a lymphocytic infiltrate

Attention needs to be paid to the patient's baseline creatinine, not just abnormal results per biochemistry ULN

Confounding diagnoses include dehydration, recent IV contrast, urinary tract infection, medications, hypotension or hypertension

Early consideration for renal biopsy is helpful which may negate the need for steroids and determine if renal deterioration related to ICPis or other pathology

Oliguria should prompt inpatient admission for careful fluid balance and plan for access to renal replacement therapy

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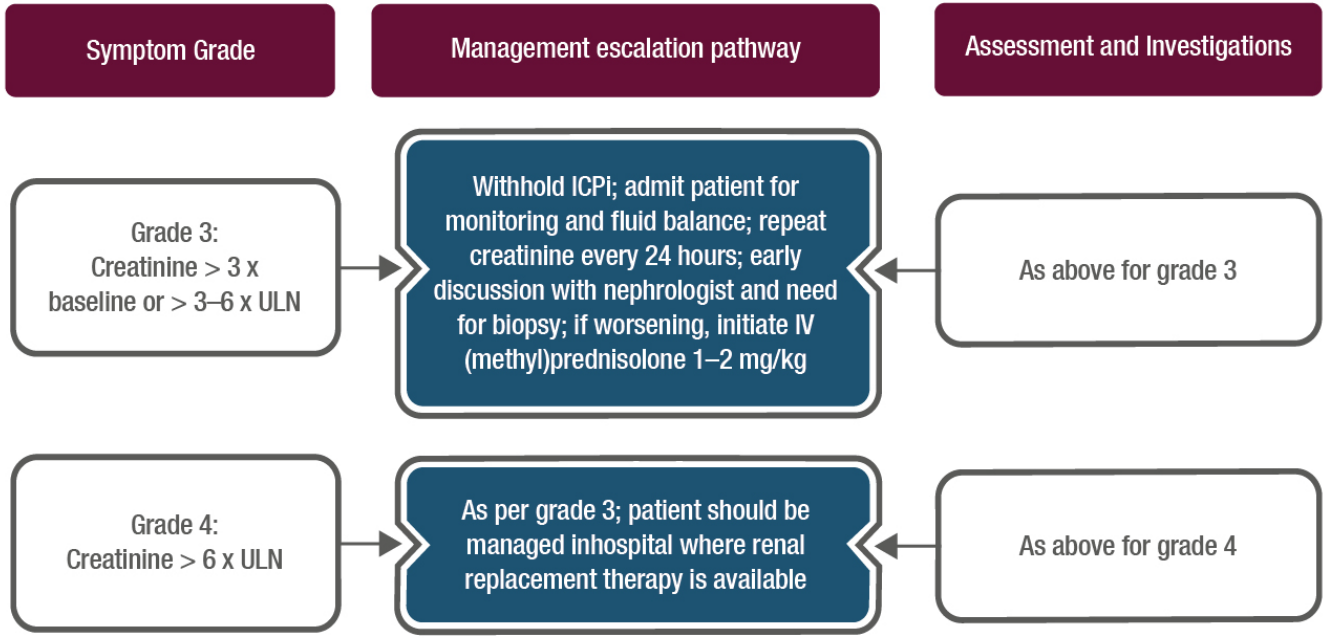

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Rare immune-related toxicities

Renal toxicity

Summary of recommendations
Serum sodium, potassium, creatinine and urea prior to every ICPi treatment infusion is recommended
Initial management involves stopping nephrotoxic drugs, ruling out infection and urinary tract obstruction and correcting hypovolaemia
For significant renal dysfunction, ICPi treatment should be withheld and consideration given to the use of systemic (methyl)prednisolone 0.5–2 mg or equivalent
In the event of severe renal dysfunction, a nephrologist should be consulted
Renal biopsy may be used to clarify a difficult differential diagnosis
Acute tubulo-interstitial nephritis with lymphocytic infiltration is a frequent biopsy finding

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Rare immune-related toxicities

Ocular toxicities
Haematological toxicities
Allograft rejection

Summary of recommendations
Ocular toxicities
Topical corticosteroids are recommended for episcleritis and anterior uveitis and systemic corticosteroids for severe ocular inflammation and orbital inflammation
Intravitreal anti-VEGF treatment is recommended for choroidal neovascularisation
Haematological toxicities
The optimal treatment for immune-related haematological AEs is unknown and initiation of high-dose corticosteroids and other immunosuppressive drugs should be performed in close collaboration with a haematologist
Allograft rejection
Use of ICPis may induce graft rejection. The risk of allograft rejection is probably lowest for anti-CTLA-4

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Disclaimer and how to obtain more information

This slide set provides you with the most important content of the full ESMO Clinical Practice Guidelines (CPGs) on the management of toxicities from immunotherapy. Key content includes diagnostic criteria, staging of disease, treatment plans and follow-up.

The ESMO CPGs are intended to provide you with a set of recommendations for the best standards of care, using evidence-based medicine. Implementation of ESMO CPGs facilitates knowledge uptake and helps you to deliver an appropriate quality of focused care to your patients.

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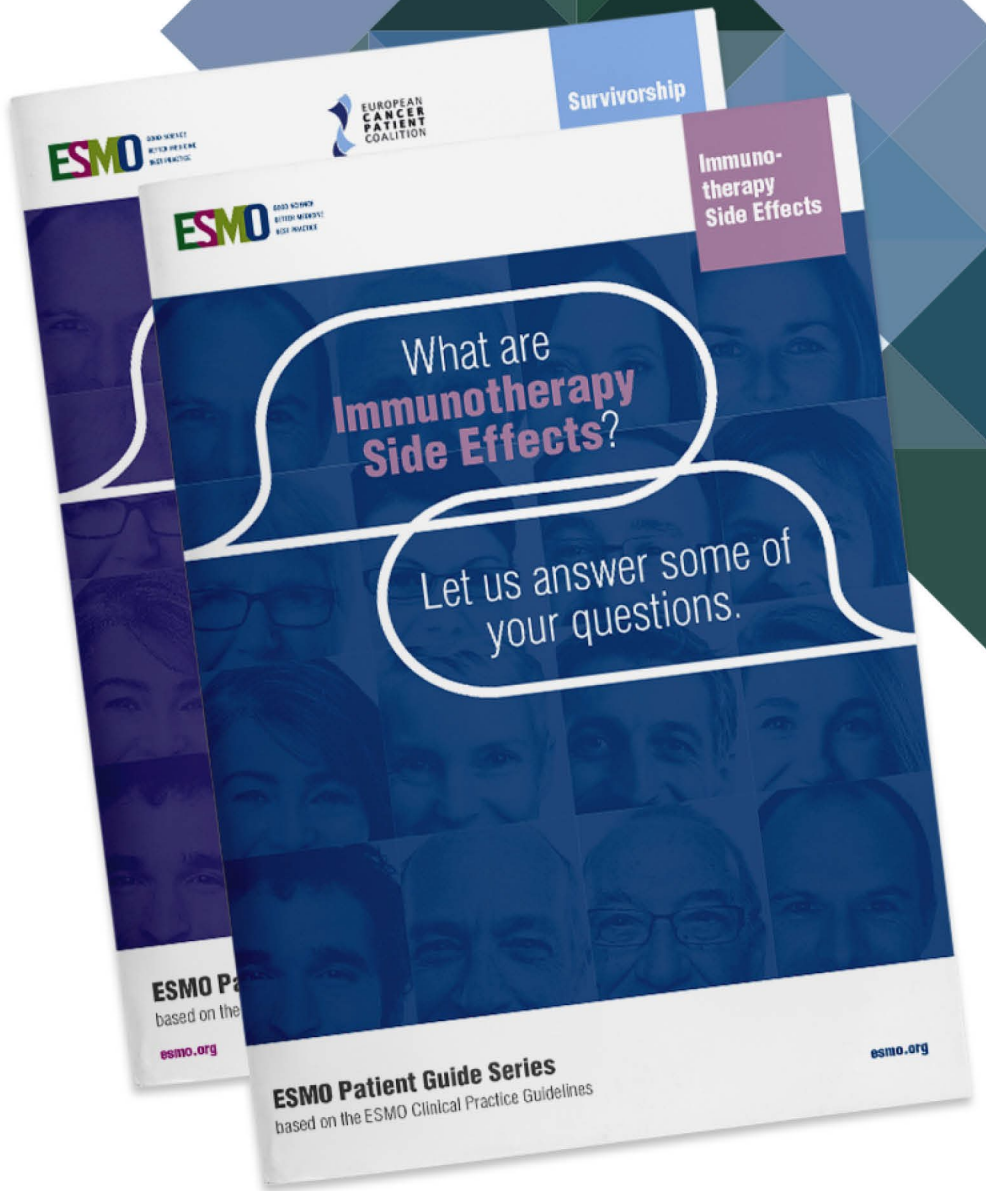

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