

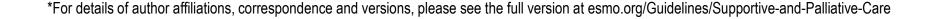
An ESMO Product

Management of toxicities from immunotherapy

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

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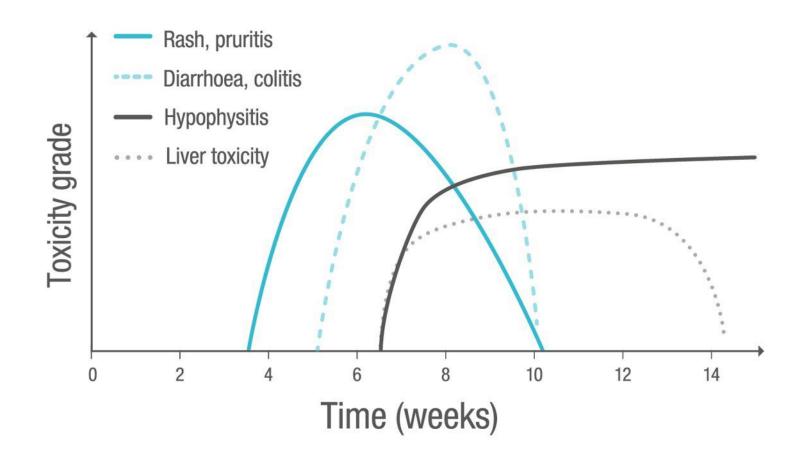




Incidence and epidemiology

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

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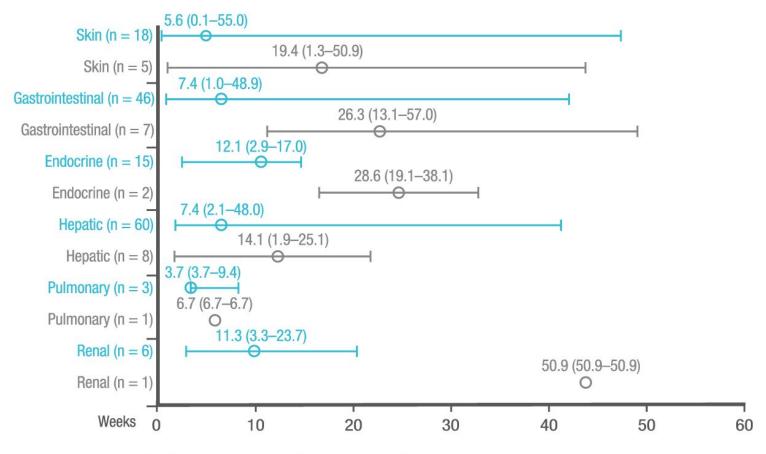




Incidence and epidemiology

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

Larkin J et al. Presented at ECC 2015;Abs330. Reprinted with permission.



Circles represent medians; bars signify ranges

- Combination ipilimumab + nivolumab
- Single agent nivolumab



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



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



Immune-related skin toxicity

ICPi-related toxicity:
Management of skin rash/toxicity

Recognised skin AEs include:

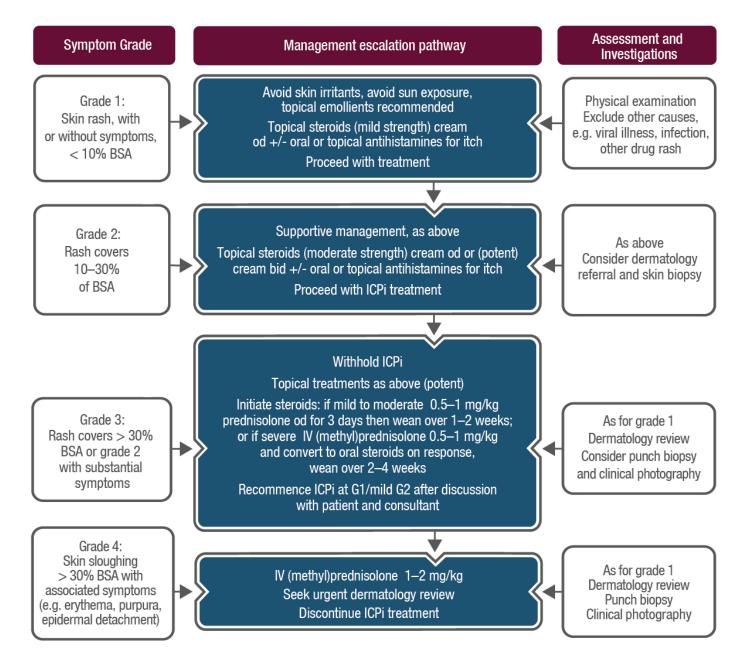
Most common: Erythema, maculopapular and

pustulopapular rash

Rare: TEN, Steven-Johnson syndrome

and DRESS

Vasculitis may also be present with purpuric rash





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

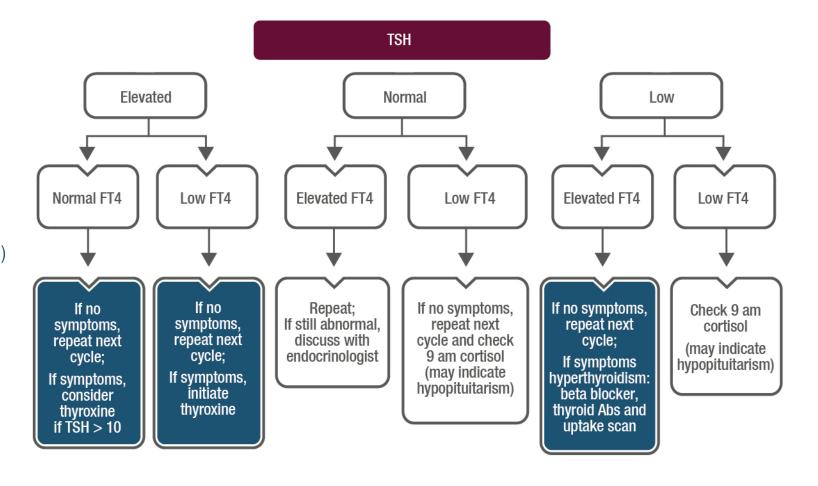
If unwell, withhold ICPi and consider restarting when symptoms controlled



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





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

Symptoms

Management escalation pathway

Further assessment and management

Severe mass effect symptoms, i.e. severe headache, any visual disturbance

or

Severe hypoadrenalism, i.e. hypotension, severe electrolyte disturbance Initiate IV (methyl)prednisolone

1 mg/kg after sending
blood tests for pituitary
axis assessment*

Analgesia as needed for headache (discuss with neurologist if resistant to paracetamol and NSAIDs)

Withhold ICPi

MRI pituitary protocol (also exclude brain metastases) Consider formal visual field assessment (if abnormal patient to inform

driver licensing agency)
Aim convert to prednisolone
and wean as symptoms allow
over 4 weeks to 5 mg

Do not stop steroids

Refer to or consult endocrinologist Monitor TFTs

Moderate symptoms, i.e. headache but no visual disturbance

10

Fatigue/mood alteration but haemodynamically stable, no electrolyte disturbance

Oral prednisolone
0.5–1 mg/kg od
after sending pituitary axis

If no improvement in 48 hours, treat as severe with IV (methyl)prednisolone as above

assessment

Withhold ICPi

MRI pituitary protocol (also exclude brain metastases),visual field assessment

Wean steroids based on symptoms over 2–4 weeks to 5 mg prednisolone

Do not stop steroids

Refer to or consult endocrinologist

Monitor TFTs



Immune related toxicities - endocrinopathies

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

Symptoms

Management escalation pathway

Further assessment and management

Vague symptoms (e.g. mild fatigue, anorexia), no headache or Asymptomatic Await pituitary axis to confirm diagnosis but warn patients to seek urgent review if unwell

Continue ICPi with appropriate HRT**

Replace cortisol and/or thyroxine per guide below** MRI pituitary protocol Refer to endocrinologist

Patient education (with assistance of a nurse practitioner): "Sick day rules", prescription and education for use of IM steroid if required Consider alert card or bracelet

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



^{**}Initial replacement advice for cortisol and thyroid hormones:

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



Immune related hepatotoxicity

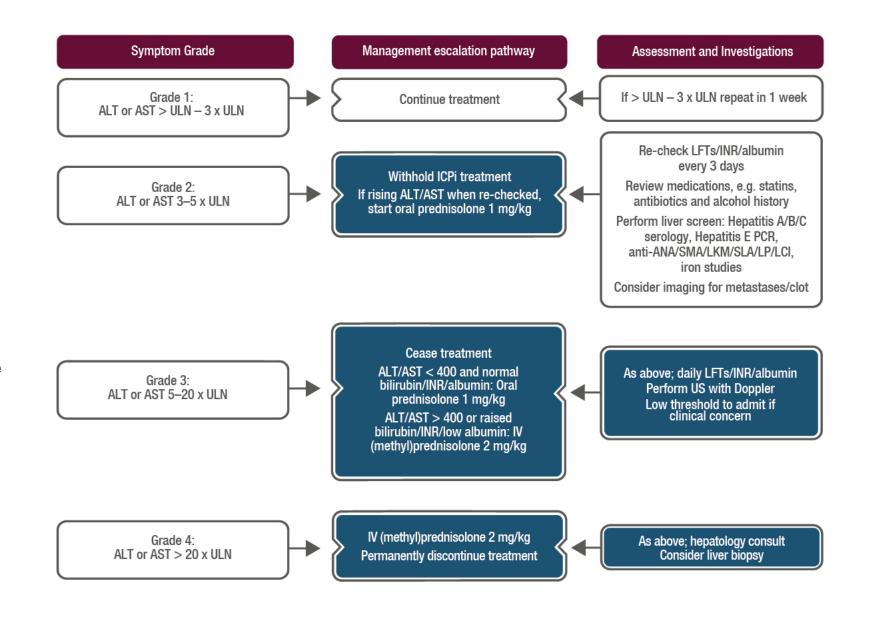
ICPi-related toxicity: Management of hepatitis

Steroid wean:

- Grade 2: Once grade 1, wean over 2 weeks; reescalate 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





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:

¹Moderate: wean over 2–4 weeks ²Severe: wean over 4–8 weeks

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

Assessment and Investigations **Symptom Grade** Management escalation pathway Baseline Investigations: FBC, UEC, Mild (G1): i.e. < 4 liquid stools per Symptomatic Mx[†]: Oral fluids, LFTs. CRP. TFTs day over baseline, feeling well loperamide, avoid high fibre/lactose diet Stool microscopy for leucocytes/ova/ ICPi can be continued parasites, culture, viral PCR, Clostridium difficile toxin and cryptosporidia G1 and persists > 14 days or G2 and Culture for drug-resistant organisms Moderate (G2): i.e. 4-6 liquid stools persists for > 3 days or worsens per day over baseline or abdominal pain or blood in stool or nausea or nocturnal episodes Outpatients: Baseline tests as above Outpatient management if appropriate Consider in case of abdominal discomfort: Prednisolone^{1*} 0.5-1 mg/kg (non-enter-If unwell, manage as per severe Abdominal X-ray for signs of colitis ic coated) or consider oral budesonide ICPi to be withheld Exclude steatorrhea 9 mg od if no bloody diarrhoea Book sigmoido/colonoscopy (+/- biopsy) Do not wait for sigmoidoscopy/ Contact patient every 72 hours colonoscopy to start Severe (G3/4): i.e. Repeat baseline bloods at outpatient review ≥ 7 liquid stools per day over baseline or No improvement in 72 hours or if episodes within worsening or absorption concern 1 hour of eating Inpatients: Test as above, including Requires hospitalisation sigmoido/colonoscopy and isolation until Αt Consider CT abdomen/pelvis, repeat infection excluded IV (methyl)prednisolone^{2*} 1–2 mg/kg clinician Abdominal X-ray as indicated ICPi to be withheld Gastroenterology input and ensure discretion Daily FBC, UEC, LFTs, CRP sigmoido/colonoscopy is requested Review diet (e.g. nothing by mouth, clear fluids, TPN) Early surgical review if bleeding, pain or distension No improvement in 72 hours or worsening Steroid wean duration: · Moderate: Wean over 2-4 weeks Medications: (Methyl)prednisolone 1-2 mg/kg IV Infliximab 5 mg/kg · Severe: Wean over 4-8 weeks (if no perforation/sepsis/TB/hepatitis/NYHA III/IV CHF) Loperamide 4 mg first dose then 2 mg Steroids > 4 weeks: 30 minutes before each meal and after each loose stool Can repeat 2 weeks later Consider PJP prophylaxis, regular until 12 hours without diarrhoea (max 16 mg/day) Must have had flexsigmoido/colonoscopy prior random blood glucose, VitD level, Other immunosuppressive treatment options: start calcium/VitD supplement MMF 500-1000 mg bid or tacrolimus



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 <i>Clostridium difficile</i> toxin content of stools and investigation of GI metastases	
Further investigations	Flexible endoscopy can confirm the diagnosis of enterocolitis	



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	

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



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



Immune related pneumonitis toxicities

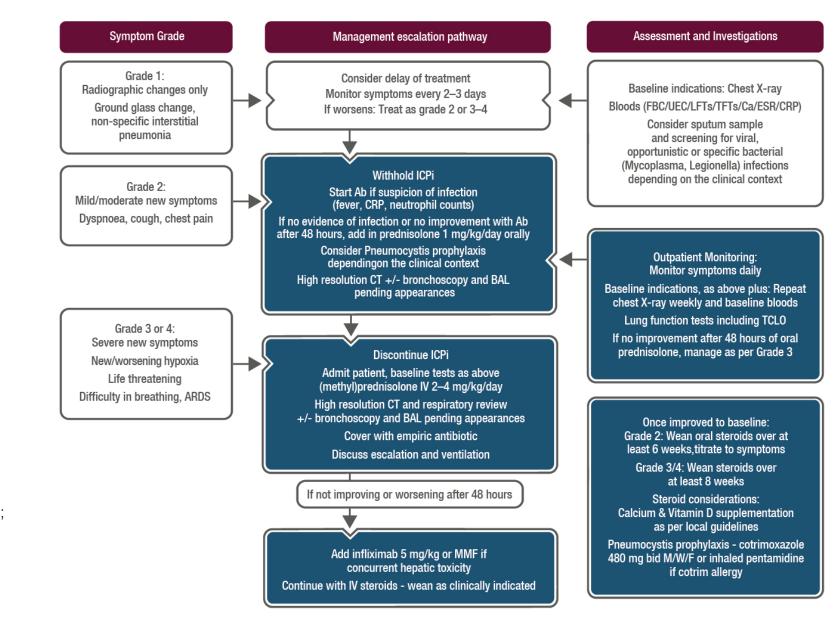
ICPi-related toxicity: Management of pneumonitis

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





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



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 \leq 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



Rare immunerelated 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

Symptom Grade Assessment and Investigations Management escalation pathway Mild: No interference with Comprehensive neurological examination Low threshold to withhold ICPi and monitor function, symptoms not Diabetic screen, B12/folate, symptoms for another week versus continue concerning to patient HIV. TSH, consider vasculitic ICPi; close monitoring for any progression & autoimmune screen. Any mild cranial nerve review alcohol history & other medications problem should be managed as 'moderate' Consider need for MRI/MRA brain or spine (exclude CVA, Withhold ICPi structural cause) Moderate: Some Initial observation reasonable or initiate interference with ADL. prednisolone 0.5-1 mg/kg (if progressing, e.g. symptoms concerning from mild) and/or pregabalin or duloxetine for pain As above to patient Resume ICPi once returns to grade 1 Consider NCS/EMG for lower motor neurone motor and/or sensory change Consider pulmonary If worsening symptoms, manage as per severe function/sniff/diaphragmatic function tests Consider neurological consult Severe: Limits self-care Withhold ICPi and admit patient and aids warranted. Initiate (methyl)prednisolone 2 mg/kg IV MRI brain/spine advised life threatening, e.g. Involve neurologist in care NCS/EMG respiratory problems Lumbar puncture Daily neurological review Pulmonary function assessment +/- daily vital capacity



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



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

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)

Suggested Investigations

Lumbar puncture – M/C/S (normal Gram stain, WBCs $< 500/\mu L$, normal glucose), PCR for HSV, cytology

CNS imaging to exclude brain metastases and leptomeningeal disease

Management approach

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 lqG

(Methyl)prednisolone 2 mg/kg (or consider 1 g/day) Neurology consultation Plasmapheresis may be required if non-steroid responsive



Rare immunerelated 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



Rare immunerelated 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



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

Management escalation pathway Assessment and Investigations Symptom Grade Grade 1: Initiate analgesia with Complete rheumatological history regarding DDx Mild pain with above and examination of all joints and skin paracetamol and ibuprofen inflammation, Continue ICPi Consider plain X-ray/imaging to exclude erythema or joint swelling metastases if appropriate Autoimmune blood panel (as above) Grade 2: Complete history and examination as above; Escalate analgesia and use diclofenac Moderate pain associated autoimmune blood panel or naproxen or etoricoxib with the above, limits US +/- MRI imaging of affected joints If inadequately controlled, initiate instrumental ADL prednisolone 10-20 mg or consider Consider early referral to a rheumatologist intra-articular steroid injections for large joints Consider withholding ICPi and resuming upon symptom control, prednisolone < 10 mg; if worsens treat as per grade 3 Withhold ICPi Grade 3: Initiate prednisolone 0.5-1 mg/kg Severe pain; irreversible As for grade 2 If failure of improvement after 4 weeks joint damage; disabling; Seek rheumatologist advice and review or worsening in meantime, refer patient limits self-care ADL to rheumatologist (consider anti-TNFa therapy)



Rare immunerelated 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 $TNF\alpha\text{-blocking}$ agents is recommended



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

Assessment and Investigations Management escalation pathway **Symptom Grade** Review hydration status, medications, urine test/culture if urinary tract infection symptoms Continue ICPi Grade 1: Dipstick urine and send for Creatinine 1.5 x baseline Repeat creatinine weekly protein assessment UPCR or > ULN-1.5 x ULN If worsens, manage as per criteria below If obstruction suspected: Renal ultrasound +/- doppler to exclude obstruction/clot Withhold ICPi: hydration and review creatinine in 48–72 hours; if not improving, As above discuss with nephrologist and need for Renal ultrasound +/- doppler to biopsy and if attributed to irAE, initiate exclude obstruction/clot steroids (oral prednisolone 0.5–1 mg/kg) Grade 2: If proteinuria: For 24 hour Creatinine > 1.5-3 xRepeat creatinine/K+ every 48 hours collection or UPCR baseline or > 1.5-3 x ULN If returns to grade 1/baseline -If blood: Phase contrast recommence ICPi (if on steroids, microscopy and GN screen* only once < 10 mg prednisolone) if nephrologist recommends If not attributed to irAE - may continue ICPi Advise patient to notify if oliquric



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

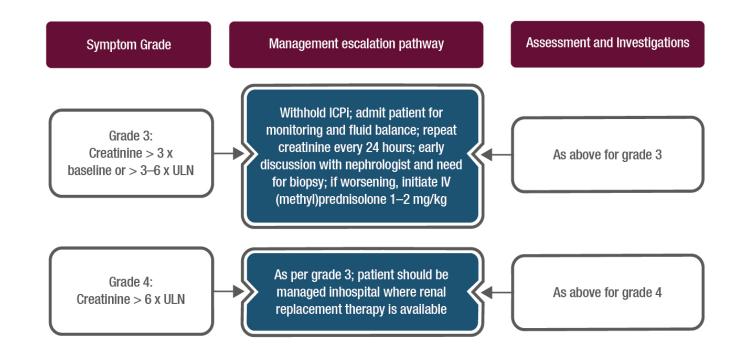
Confounding diagnoses include dehydration, recent IV contrast, urinary tract infection, medications, hypotension or hypertension

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

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





Rare immunerelated 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



Rare immunerelated 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



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.

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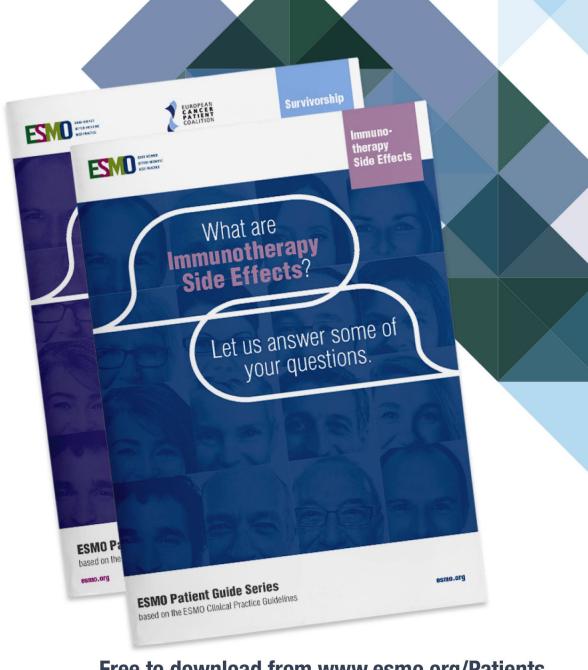
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