Management of toxicities from immunotherapy

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

J. Haanen, F. Carbonnel, C. Robert, K. Kerr, S. Peters, J. Larkin and K. Jordan, on behalf of the ESMO Guidelines Committee

*For details of author affiliations, correspondence and versions, please see the full version at esmo.org/Guidelines/Supportive-and-Palliative-Care
Incidence and epidemiology

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

Incidence and epidemiology

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

Reprinted with permission.

© 2018 ESMO. All rights reserved. esmo.org/Guidelines/Supportive-and-Palliative-Care/Management-of-Toxicities-from-Immunotherapy
## Summary of recommendations

<table>
<thead>
<tr>
<th>General aspects of immune-related adverse events (irAEs)</th>
<th>Generally occur within 3 months after initiation of ICPi treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tissue biopsy may be useful for higher grade (3-4) toxicities, when there is diagnostic doubt and management would be altered by the outcome</td>
</tr>
</tbody>
</table>

### 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
**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.
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 skin toxicity**

ICPi-related toxicity:
Management of skin rash/toxicity

**Symptom Grade**

- Grade 1: Skin rash, with or without symptoms, < 10% BSA
  - Avoid skin irritants, avoid sun exposure, topical emollients recommended
  - Topical steroids (mild strength) cream od +/- oral or topical antihistamines for itch
  - Proceed with treatment

- Grade 2: Rash covers 10–30% of BSA
  - Supportive management, as above
  - Topical steroids (moderate strength) cream od or (potent) cream bid +/- oral or topical antihistamines for itch
  - Proceed with ICPi treatment

- Grade 3: Rash covers > 30% BSA or grade 2 with substantial symptoms
  - Withhold ICPi
  - Topical treatments as above (potent)
  - Initiate steroids: if mild to moderate 0.5–1 mg/kg prednisolone od for 3 days then wean over 1–2 weeks; or if severe IV (methyl)prednisolone 0.5–1 mg/kg and convert to oral steroids on response, wean over 2–4 weeks
  - Recomence ICPi at G1/mild G2 after discussion with patient and consultant

- Grade 4: Skin sloughing > 30% BSA with associated symptoms (e.g. erythema, purpura, epidermal detachment)
  - IV (methyl)prednisolone 1–2 mg/kg
  - Seek urgent dermatology review
  - Discontinue ICPi treatment
  - Physical examination
  - Exclude other causes, e.g. viral illness, infection, other drug rash

**Assessment and Investigations**

- As above
  - Consider dermatology referral and skin biopsy

- As for grade 1
  - Dermatology review
  - Consider punch biopsy and clinical photography

- As for grade 1
  - Dermatology review
  - Punch biopsy
  - Clinical photography

© 2018 ESMO. All rights reserved. esmo.org/Guidelines/Supportive-and-Palliative-Care/Management-of-Toxicities-from-Immunotherapy
**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 atenolol 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

© 2018 ESMO. All rights reserved. esmo.org/Guidelines/Supportive-and-Palliative-Care/Management-of-Toxicities-from-Immunotherapy
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.
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

**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
**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 toxicities**

- **endocrinopathies**

  Type 1 diabetes mellitus
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

If > ULN – 3 x ULN repeat in 1 week

Re-check LFTs/INR/albumin every 3 days
Review medications, e.g., statins, antibiotics and alcohol history
Perform liver screen: Hepatitis A/B/C serology, Hepatitis E PCR, anti-ANA/SMA/LKM/LA/LP/LC, iron studies
Consider imaging for metastases/clot

As above; daily LFTs/INR/albumin
Perform US with Doppler
Low threshold to admit if clinical concern

As above; hepatology consult
Consider liver biopsy

© 2018 ESMO. All rights reserved. esmo.org/Guidelines/Supportive-and-Palliative-Care/Management-of-Toxicities-from-Immunotherapy
Immune related gastrointestinal toxicities

ICPi-related toxicity: Management of diarrhoea and colitis

1 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:
- Moderate: wean over 2–4 weeks
- Severe: wean over 4–8 weeks
- Steroids > 4 weeks: Consider PJP prophylaxis, regular random blood glucose, VitD level, start calcium/VitD supplement

Steroid wean duration:
- Moderate: Wean over 2–4 weeks
- Severe: Wean over 4–8 weeks
- Steroids > 4 weeks: Consider PJP prophylaxis, regular random blood glucose, VitD level, start calcium/VitD supplement

© 2018 ESMO. All rights reserved. esmo.org/Guidelines/Supportive-and-Palliative-Care/Management-of-Toxicities-from-Immunotherapy
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)

<table>
<thead>
<tr>
<th>Summary of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common symptoms</td>
</tr>
<tr>
<td>Main biological abnormalities</td>
</tr>
<tr>
<td>Ruling out infection and cancer as causes</td>
</tr>
<tr>
<td>Further investigations</td>
</tr>
</tbody>
</table>
### Summary of recommendations

<table>
<thead>
<tr>
<th>Management</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-severe diarrhoea</td>
<td>Treatment with antidiarrhoeals, fluid and electrolyte supplementation, if required, and ICPIs can be continued</td>
</tr>
<tr>
<td>Persistent grade 2 / severe grade 3–4 / grade 1–2 with alarm symptoms</td>
<td>ICPI discontinuation and initiation of systemic corticosteroids (1 to 2 mg/kg IV daily)</td>
</tr>
<tr>
<td>Response to IV corticosteroids</td>
<td>Responding (within 3–5 days): switch to the oral form, treatment tapered over 8–12 weeks</td>
</tr>
<tr>
<td></td>
<td>Not responding: switch to infliximab 5 mg/kg (unless contraindicated)</td>
</tr>
<tr>
<td>Colonic perforation (with or without intra-abdominal abscess)</td>
<td>Emergency subtotal colectomy with ileostomy and endoscopy</td>
</tr>
</tbody>
</table>

### 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
### Summary of recommendations

<table>
<thead>
<tr>
<th>Anti-PD-1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common symptoms</strong></td>
</tr>
<tr>
<td><strong>Endoscopic findings</strong></td>
</tr>
</tbody>
</table>
| **Different patterns of GI irAEs** | • Acute colitis  
• Microscopic colitis  
• Upper GI involvement  
• Pseudo-obstruction |

<table>
<thead>
<tr>
<th>Combined anti-CTLA-4 and anti-PD-1 antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>With this combined treatment, pancreatitis and small bowel enteritis, which may be visible on CT scan, require ICPi treatment discontinuation and initiation of immunosuppression</td>
</tr>
</tbody>
</table>
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 embol; Sarcoidosis

---

**Symptom Grade**
- **Grade 1:** Radiographic changes only
  - Ground glass change, non-specific interstitial pneumonia

- **Grade 2:** Mild/moderate new symptoms
  - Dyspnoea, cough, chest pain

- **Grade 3 or 4:** Severe new symptoms
  - New/worsening hypoxia
  - Life threatening
  - Difficulty in breathing, ARDS

---

**Management escalation pathway**
- **Consider delay of treatment**
  - Monitor symptoms every 2–3 days
  - If worsens: Treat as grade 2 or 3–4

- **Withhold ICPI**
  - Start Ab if suspicion of infection
    - Fever, CRP, neutrophil counts
  - If no evidence of infection or no improvement with Ab after 48 hours, add in prednisolone 1 mg/kg/day orally
  - Consider Pneumocystis prophylaxis depending on the clinical context
  - High resolution CT +/- bronchoscopy and BAL pending appearances

- **Discontinue ICPI**
  - Admit patient, baseline tests as above
  - Methylprednisolone IV 2–4 mg/kg/day
  - High resolution CT and respiratory review
  - +/- bronchoscopy and BAL pending appearances
  - Cover with empiric antibiotic
  - Discuss escalation and ventilation

- **Add infliximab 5 mg/kg or MMF if concurrent hepatic toxicity**
  - Continue with IV steroids - wean as clinically indicated

---

**Assessment and Investigations**
- **Baseline indications:** Chest X-ray, Bloods (Hb/UE/C/FTs/FTTs/Ca/Esr/CRP)
- Consider sputum sample and screening for viral, opportunistic or specific bacterial (Mycoplasma, Legionella) infections depending on the clinical context

---

**Outpatient Monitoring:**
- Monitor symptoms daily
- Baseline indications, as above plus: Repeat chest X-ray weekly and baseline bloods
- Lung function tests including TCLD
- If no improvement after 48 hours of oral prednisolone, manage as per grade 3

**Once improved to baseline:**
- Grade 2: Wean oral steroids over at least 6 weeks, titrate to symptoms
- Grade 3/4: Wean steroids over at least 3 weeks

Steroid considerations:
- Calcium & Vitamin D supplementation as per local guidelines
- Pneumocystis prophylaxis - cotrimoxazole 480 mg bid M/W/F or inhaled pentamidine if cotrim allergy
### Immune related pneumonitis toxicities

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

<table>
<thead>
<tr>
<th>Summary of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radiological features</strong></td>
</tr>
<tr>
<td>• Ground glass opacities</td>
</tr>
<tr>
<td>• A cryptogenic organising pneumonia-like appearance</td>
</tr>
<tr>
<td>• Interstitial pneumonia pattern</td>
</tr>
<tr>
<td>• Characteristics of hypersensitivity pneumonitis</td>
</tr>
<tr>
<td><strong>Lung biopsy</strong></td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td><strong>Bronchoscopy with BAL</strong></td>
</tr>
<tr>
<td>Supports the identification of infections and is recommended in any symptomatic pneumonia</td>
</tr>
</tbody>
</table>
Immune related pneumonitis toxicities

Management of pneumonitis

### Summary of recommendations

<table>
<thead>
<tr>
<th>Immune-related pneumonitis is documented or suspected</th>
<th>Immunosuppressive treatment should be started immediately</th>
</tr>
</thead>
<tbody>
<tr>
<td>When no possibility to rule out infection using bronchoscopy</td>
<td>Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment for grade ≥ 3 pneumonitis</td>
</tr>
<tr>
<td>Grade 1–2</td>
<td>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</td>
</tr>
<tr>
<td>Grade 3–4 moderate-to-severe cases</td>
<td>Hospitalisation, treatment with high dose IV (methyl)prednisolone 2–4 mg/kg/day or equivalent and permanent discontinuation of ICPI treatment is recommended</td>
</tr>
<tr>
<td></td>
<td>• If there is no improvement after 2 days, additional immunosuppressive strategies, such as infliximab, MMF or cyclophosphamide, are recommended</td>
</tr>
<tr>
<td></td>
<td>• Steroids should be tapered slowly over at least 6 weeks to prevent recurrence</td>
</tr>
</tbody>
</table>
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

Symptom Grade
- Mild: No interference with function, symptoms not concerning to patient
- Any mild cranial nerve problem should be managed as ‘moderate’

Management escalation pathway
- Low threshold to withhold ICPI and monitor symptoms for another week versus continue ICPI; close monitoring for any progression
- Withhold ICPI
  - Initial observation reasonable or initiate prednisolone 0.5–1 mg/kg (if progressing, e.g. from mild) and/or pregabalin or duloxetine for pain
  - Resume ICPI once returns to grade 1
- If worsening symptoms, manage as per severe

Assessment and Investigations
- Comprehensive neurological examination
- Diabetic screen, B12/folate, HIV, TSH, consider vasculitic & autoimmune screen, review alcohol history & other medications
- Consider need for MRI/MRA brain or spine (exclude CVA, structural cause)
- As above
  - Consider NCS/EMG for lower motor neurone motor and/or sensory change
  - Consider pulmonary function/sniff/diaphragmatic function tests
  - Consider neurological consult

Withhold ICPI and admit patient
- Initiate (methyl)prednisolone 2 mg/kg IV
- Involve neurologist in care
- Daily neurological review
  +/- daily vital capacity

MRI brain/spine advised
- NCS/EMG
- Lumbar puncture
- Pulmonary function assessment

© 2018 ESMO. All rights reserved. esmo.org/Guidelines/Supportive-and-Palliative-Care/Management-of-Toxicities-from-Immunotherapy
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

<table>
<thead>
<tr>
<th>Suspected syndrome</th>
<th>Suggested Investigations</th>
<th>Management approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>Nerve conduction studies (acute polynueropathy) 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</td>
<td>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)</td>
</tr>
<tr>
<td>Myasthenia Gravis: Fluctuating muscle weakness (proximal limb, trunk, ocular, e.g. ptosis/diplopia or bulbar) with fatigability, respiratory muscles may also be involved</td>
<td>Check for ocular muscle and proximal muscle fatigability AChR and anti-MuSK antibodies Bedside tests, e.g. Tension test or ice pack test with neurological input Repetitive nerve stimulation and single fibre EMG</td>
<td>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</td>
</tr>
</tbody>
</table>
## 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

- **Meningitis:**
  - Exclusion of infective causes paramount
  - Headache, photophobia, neck stiffness with fever or may be afebrile, vomiting; normal cognition/cerebral function (distinguishes from encephalitis)

- **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

- **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/TPPA/ANA/anti-Ro and anti-La Abs, TSH, anti-aquaporin-4 IgG

### Suggested Investigations

- **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

- **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 serology

- **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/TPPA/ANA/anti-Ro and anti-La Abs, TSH, anti-aquaporin-4 IgG

### 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

- **As above for aseptic meningitis**
  - Suggest concurrent IV acyclovir until PCR result obtained

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

**Neurological toxicity**

<table>
<thead>
<tr>
<th>Summary of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time frame</strong></td>
</tr>
<tr>
<td><strong>Assessment</strong></td>
</tr>
</tbody>
</table>
| **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 |
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.
Summary of recommendations

<table>
<thead>
<tr>
<th>Mild or moderate symptoms</th>
<th>Analgesia with paracetamol and/or NSAIDs is recommended; moderate symptoms may respond to prednisolone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe symptoms</td>
<td>Consultation with a rheumatologist and the use of high dose corticosteroids and TNFα-blocking agents is recommended</td>
</tr>
</tbody>
</table>
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.

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.
### Summary of recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum sodium, potassium, creatinine and urea prior to every ICPi treatment infusion is recommended</td>
</tr>
<tr>
<td>Initial management involves stopping nephrotoxic drugs, ruling out infection and urinary tract obstruction and correcting hypovolaemia</td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>In the event of severe renal dysfunction, a nephrologist should be consulted</td>
</tr>
<tr>
<td>Renal biopsy may be used to clarify a difficult differential diagnosis</td>
</tr>
<tr>
<td>Acute tubulo-interstitial nephritis with lymphocytic infiltration is a frequent biopsy finding</td>
</tr>
</tbody>
</table>

---

**Rare immune-related toxicities**

**Renal toxicity**
### Summary of recommendations

<table>
<thead>
<tr>
<th>Ocular toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical corticosteroids are recommended for episcleritis and anterior uveitis and systemic corticosteroids for severe ocular inflammation and orbital inflammation</td>
</tr>
<tr>
<td>Intravitreal anti-VEGF treatment is recommended for choroidal neovascularisation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Haematological toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Allograft rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of ICPis may induce graft rejection. The risk of allograft rejection is probably lowest for anti-CTLA-4</td>
</tr>
</tbody>
</table>
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.

This slide set contains information obtained from authentic and highly regarded sources (www.esmo.org). Although every effort has been made to ensure that treatment and other information are presented accurately in this publication, the ultimate responsibility rests with the prescribing physician. Neither the publisher nor the ESMO Guidelines Committee can be held responsible for errors or for any consequences arising from the use of information contained herein. For detailed prescribing information on the use of any product or procedure discussed herein, please consult the prescribing information or instructional material issued by the manufacturer.

The slide set can be used as a quick reference guide to access key content on evidence-based management and individual slides may be used for personal presentation in their present version and without any alterations. All rights reserved.

© 2018 European Society for Medical Oncology
Please visit www.esmo.org or oncologypro.esmo.org to view the full guidelines.
Discover the ESMO Patient Guide Series

Based on the ESMO Clinical Practice Guidelines and designed to assist your patients, their relatives and caregivers to better understand the nature of different types of cancer, evaluate the best available treatment choice and address patient concerns.

Available titles include:

- Immunotherapy-Related Side Effects and their Management
- Survivorship

The ESMO Patient Guides Series is developed in collaboration with EONS and patient organisations, and each title is available in several languages.

Free to download from www.esmo.org/Patients