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

Circles represent medians; bars signify ranges
- Combination ipilimumab + nivolumab
- Single agent nivolumab

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## Summary of recommendations

<table>
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<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>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>
<td></td>
</tr>
</tbody>
</table>

### Incidence and epidemiology

<table>
<thead>
<tr>
<th>Patient selection and baseline assessments</th>
<th>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</th>
</tr>
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<tbody>
<tr>
<td>Work-up should include: history, general physical condition, autoimmune diseases, baseline laboratory tests and radiological scans</td>
<td></td>
</tr>
<tr>
<td>• If current or previous autoimmune disease: risk of worsening of their autoimmune disease while on ICPI treatment</td>
<td></td>
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<tr>
<td>• If previous ipilimumab-related irAEs: risk of developing irAEs following anti-PD-1 treatment, and vice versa</td>
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<tr>
<td>Once irAEs have developed, prompt work-up and action are required</td>
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<tr>
<td>Pneumocystis prophylaxis should be considered for patients receiving long-term (&gt; 6 weeks) treatment with immunosuppressive drugs</td>
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<tr>
<td>The clinical outcome of patients on ICPI treatment is not affected by the use of immunosuppressive agents for the management of immune-related toxicities</td>
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### Immune-related skin toxicity

#### Diagnosis and pathology/molecular biology

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<tr>
<td>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</td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>A biological assessment, including blood cell count and liver and kidney tests, may be required to rule out dermatological emergencies</td>
</tr>
<tr>
<td>• In severe cases, ICPI treatment should be permanently discontinued, the patient hospitalised and symptomatic treatment initiated immediately</td>
</tr>
<tr>
<td>Severity of maculopapular rash should be classified according to the CTCAE version 4.0</td>
</tr>
</tbody>
</table>
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 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
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

**Immune related toxicities - endocrinopathies**

ICPi-related toxicity: Management of hypophysitis (cont’d)
### Summary of recommendations

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

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**Immune related toxicities - endocrinopathies**

*Type 1 diabetes mellitus*
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

Immune related hepatotoxicity
ICPi-related toxicity: Management of hepatitis

Steroid wean:
- Grade 1: ALT or AST > ULN – 3 x ULN
  - Continue treatment

Grade 2: ALT or AST 3–5 x ULN
  - Withhold ICPI treatment
    - If rising ALT/AST when re-checked, start oral prednisolone 1 mg/kg

Grade 3: ALT or AST 5–20 x ULN
  - Cease treatment
    - ALT/AST < 400 and normal bilirubin/INR/albumin: Oral prednisolone 1 mg/kg
    - ALT/AST > 400 or raised bilirubin/INR/low albumin: IV (methyl)prednisolone 2 mg/kg

Grade 4: ALT or AST > 20 x ULN
  - IV (methyl)prednisolone 2 mg/kg
    - Permanently discontinue treatment

Assessment and Investigations
- 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/SLA/LP/LC
- 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
**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)

2. Steroid wean duration:
   - Moderate: wean over 2–4 weeks
   - Severe: wean over 4–8 weeks

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

**Symptom Grade**

- **Mild (G1):** i.e. < 4 liquid stools per day over baseline, feeling well ICPI can be continued
- **Moderate (G2):** i.e. 4–6 liquid stools per day over baseline or abdominal pain or blood in stool or nausea or nocturnal episodes
  - Outpatient management if appropriate
  - If unwell, manage as per severe ICPI to be withheld
- **Severe (G3/4):** i.e. ≥ 7 liquid stools per day over baseline or ≥ 1 hour of eating
  - Requires hospitalisation and isolation until infection excluded
  - ICPI to be withheld

**Management escalation pathway**

1. Symptomatic Mx:
   - Oral fluids, loperamide, avoid high fibre/lactose diet
   - G1 and persists > 14 days or G2 and persists for > 3 days or worsens

2. **Prednisolone** 0.5–1 mg/kg (non-enteric coated) or consider oral budesonide 9 mg od if no bloody diarrhoea
   - Do not wait for sigmoidoscopy/colonoscopy to start

3. No improvement in 72 hours or worsening or absorption concern
   - At clinician discretion
   - IV (methyl)prednisolone 1–2 mg/kg
   - Gastroenterology input and ensure sigmoidoscopy is requested
   - No improvement in 72 hours or worsening

**Assessment and Investigations**

- **Baseline Investigations:** FBC, UEC, LFTs, CRP, TFFs
  - Stool microscopy for leucocytes/ova/parasites, culture, viral PCR, *Clostridium difficile* toxin and cryptosporidia
  - Culture for drug-resistant organisms

- **Outpatients:** Baseline tests as above
  - Consider in case of abdominal discomfort:
    - Abdominal X-ray for signs of colitis
    - Exclude steatorrhoea
  - Book sigmoid/colonoscopy (+/- biopsy)
  - Contact patient every 72 hours
  - Repeat baseline bloods at outpatient review

- **Inpatients:** Test as above, including sigmoid/colonoscopy
  - Consider CT abdomen/pelvis, repeat Abdominal X-ray as indicated
  - Daily FBC, UEC, LFTs, CRP
  - Review diet (e.g. nothing by mouth, clear fluids, TPN)
  - Early surgical review if bleeding, pain or distension

**Medications:** (Methyl)prednisolone 1–2 mg/kg IV
- 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)

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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)

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

### Management

<table>
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<tr>
<th>Condition</th>
<th>Treatment/Action</th>
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<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>
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<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>
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<tbody>
<tr>
<td>Common symptoms: Diarrhoea, nausea/vomiting and abdominal pain, with a median time to symptom onset of 3 months</td>
</tr>
<tr>
<td>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</td>
</tr>
<tr>
<td>Different patterns of GI irAEs: Acute colitis, Microscopic colitis, Upper GI involvement, Pseudo-obstruction</td>
</tr>
<tr>
<td>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</td>
</tr>
</tbody>
</table>
ICPi-related toxicity: Management of pneumonitis toxicities

**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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**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

**Assessment and Investigations**
- Baseline indications: Chest X-ray
  - Bloods (FBC/UEC/LFTs/TTFs/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 TCLO
- 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

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

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**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.

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<td><strong>Radiological features</strong></td>
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<tr>
<td><strong>Lung biopsy</strong></td>
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<tr>
<td><strong>Bronchoscopy with BAL</strong></td>
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# Summary of recommendations

<table>
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<tr>
<th>Immune-related pneumonitis is documented or suspected</th>
<th>Immunosuppressive treatment should be started immediately</th>
</tr>
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<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><strong>Grade 1–2</strong></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>
</tbody>
</table>
| **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 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

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 IVg indicated
Consider location of care where ventilatory support available (required in 15–30% idiopathic cases)

Steroids indicated (oral or IV depending on symptoms)
Pyridostigmine initial dose 30 mg tds
Neurological consult
If no improvement or worsening, plasmapheresis or IVg may be considered
Additional immunsuppressants 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

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<th>Suspected syndrome</th>
<th>Suggested Investigations</th>
<th>Management approach</th>
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<tr>
<td>Aseptic meningitis:</td>
<td>Lumbar puncture – M/C/S (normal Gram stain, WBCs &lt; 500/µl, normal glucose),</td>
<td>Exclude bacterial and ideally viral infections prior to high-dose steroids</td>
</tr>
<tr>
<td>Exclusion of infective causes paramount</td>
<td>PCR for HSV, cytology</td>
<td>Oral prednisolone 0.5–1 mg/kg or IV (methyl)prednisolone 1–2 mg/kg if very unwell</td>
</tr>
<tr>
<td>Headache, photophobia, neck stiffness with fever or may be febrile, vomiting; normal cognition/cerebral function (distinguishes from encephalitis)</td>
<td>CNS imaging to exclude brain metastases and leptomeningeal disease</td>
<td>Consider concurrent empiric antiviral (IV acyclovir) and antibacterial therapy</td>
</tr>
<tr>
<td>Encephalitis:</td>
<td>Lumbar puncture – M/C/S (normal Gram stain, WBCs usually &lt; 250/mm3 with lymphocyte predominance, elevated protein but &lt; 150 mg/dL, usually normal glucose but can be elevated), PCR for HSV &amp; consider viral culture, cytology</td>
<td>As above for aseptic meningitis</td>
</tr>
<tr>
<td>Exclusion of infective and metabolic causes paramount</td>
<td>CNS imaging</td>
<td>Suggest concurrent IV acyclovir until PCR result obtained</td>
</tr>
<tr>
<td>Confusion or altered behaviour, headaches, alteration in Glasgow Coma Scale, motor or sensory deficits, speech abnormality, may or may not be febrile</td>
<td>Consider viral serology</td>
<td></td>
</tr>
<tr>
<td>Transverse myelitis:</td>
<td>MRI brain and spine</td>
<td>(Methyl)prednisolone 2 mg/kg (or consider 1 g/day)</td>
</tr>
<tr>
<td>Acute or subacute neurological signs/symptoms of motor/sensory/autonomic origin; most have sensory level; often bilateral symptoms</td>
<td>Lumbar puncture – may be normal but lymphocytosis, elevated protein may be noted, oligoclonal bands not usually present, cytology</td>
<td>Neurology consultation</td>
</tr>
<tr>
<td></td>
<td>Serum B12/HIV/sero/ANA/anti-Ro and anti-La Abs, TSH, anti-aquaporin-4 IgG</td>
<td>Plasmapheresis may be required if non-steroid responsive</td>
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</tbody>
</table>
**Rare immune-related toxicities**

**Neurological toxicity**

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<td><strong>Time frame</strong></td>
</tr>
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<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 |
Summary of recommendations

<table>
<thead>
<tr>
<th>Circumstances</th>
<th>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</th>
</tr>
</thead>
</table>
| 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>
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<tr>
<th>Mild or moderate symptoms</th>
<th>Analgesia with paracetamol and/or NSAIDs is recommended; moderate symptoms may respond to prednisolone</th>
</tr>
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<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

**Rheumatological toxicity**
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>
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<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>
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</tbody>
</table>

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**Rare immune-related toxicities**

**Renal toxicity**
# Rare immune-related toxicities

**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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