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 Ipilimumab treatment
Incidence and epidemiology

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

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### 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>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>
<tr>
<td>Patient selection and baseline assessments</td>
<td>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</td>
</tr>
<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>
</tr>
<tr>
<td>• If previous ipilimumab-related irAEs: risk of developing irAEs following anti-PD-1 treatment, and vice versa</td>
<td></td>
</tr>
<tr>
<td>Once irAEs have developed, prompt work-up and action are required</td>
<td></td>
</tr>
<tr>
<td>Pneumocystis prophylaxis should be considered for patients receiving long-term (&gt; 6 weeks) treatment with immunosuppressive drugs</td>
<td></td>
</tr>
<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>
<td></td>
</tr>
</tbody>
</table>
### 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

ICPi-related toxicity:
Management of skin rash/toxicity

ICPi-related toxicity:
Management of skin rash/toxicity

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Immune related toxicities - endocrinopathies

ICPi monitoring and management:
Thyroid function

Baseline Endocrine Panel:
- TSH, FT4, T3* TFTs
Baseline abnormal values do not preclude treatment; discuss with endocrinologist if uncertain
*when indicated

Monitoring during treatment:
- Anti-CTLA-4 (including combination with anti-PD-1)
  - TFTs every cycle
  - TFTs 4-6 weeks after cycle 4 (i.e. with restaging CT)
Late endocrine dysfunction can occur
- Anti-PD-1/Anti-PD-L1
  - TFTs every cycle for first 3 months, every second cycle thereafter (in case of 2-weekly schedule)
  - Cortisol as indicated by symptoms/falling TSH

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

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

Hypothyroidism: Low FT4 with elevated TSH or TSH > 10 with normal FT4
Treatment: Thyroxine 0.5–1.5 μg/kg (start low in elderly, if cardiac history)
Continue ICPi

Thyrotoxicosis (DDx thyroiditis, Grave’s disease):
Investigations: Anti-TSH receptor Ab, anti-TPO Ab, nuclear medicine thyroid uptake scan
Treatment: Propranolol or 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

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Immune related toxicities - endocrinopathies

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

Withhold ICPi if patient is unwell with symptomatic hyperthyroidism
Subclinical hyperthyroidism (low TSH, normal FT4) often precedes overt hypothyroidism
**CLINICAL PRACTICE GUIDELINES**

# Immune related toxicities - endocrinopathies

ICPi related toxicity: Management of hypophysitis

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Management escalation pathway</th>
<th>Further assessment and management</th>
</tr>
</thead>
</table>
| 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*  
Anaegiesia 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 or Fatigue/mood alteration but haemodynamically stable, no electrolyte disturbance | **Oral prednisolone**  
0.5–1 mg/kg od after sending pituitary axis assessment  
If no improvement in 48 hours, treat as severe with IV (methyl)prednisolone as above  
**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 |

*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

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**Immune related toxicities - endocrinopathies**

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

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**Sick day rules**, prescription and education for use of IM steroid if required

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

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

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**Clinical Practice Guidelines**

**Symptom Grade**

<table>
<thead>
<tr>
<th>Grade 1:</th>
<th>ALT or AST &gt; ULN – 3 x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2:</td>
<td>ALT or AST 3–5 x ULN</td>
</tr>
<tr>
<td>Grade 3:</td>
<td>ALT or AST 5–20 x ULN</td>
</tr>
<tr>
<td>Grade 4:</td>
<td>ALT or AST &gt; 20 x ULN</td>
</tr>
</tbody>
</table>

**Management escalation pathway**

- Withhold ICPi treatment if rising ALT/AST when re-checked, start oral prednisolone 1 mg/kg
- Cease treatment if ALT/AST < 400 and normal bilirubin/INR/albumin: Oral prednisolone 1 mg/kg
- IV (methyl)prednisolone 2 mg/kg Permanently discontinue treatment
- IV (methyl)prednisolone 2 mg/kg

**Assessment and Investigations**

- If > ULN – 3 x ULN repeat in 1 week
- Re-check LFTs/INR/albunin 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/SmIgM/SmIgG/PrC, iron studies
- Consider imaging for metastases/clot

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

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

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

IV (methyl)prednisolone 1–2 mg/kg Gastroenterology input and ensure sigmoidoscopy/colonoscopy is requested

Symptomatic Mx: Oral fluids, loperamide, avoid high fibre/lactose diet

No improvement in 72 hours or worsening/absorption concern

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

No improvement in 72 hours or worsening

Infliximab 5 mg/kg
(if no perforation/sepsis/TB/hepatitis/NYHA III/IV CHF)

Can repeat 2 weeks later

Must have had flexisigmoid/colonoscopy prior

Other immunosuppressive treatment options:
MMF 500–1000 mg bid or tacrolimus

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)

Outpatients: Baseline tests as above

Consider in case of abdominal discomfort:
Abdominal X-ray for signs of colitis
Exclude steatorrhea
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

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

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 if episodes within 1 hour of eating
Requires hospitalisation and isolation until infection excluded
ICPi to be withheld

At clinician discretion

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

Baseline Investigations: FBC, UEC, LFTs, CRP, TFTs

Stool microscopy for leukocytes/ova/parasites, culture, viral PCR, C. difficile toxin and cryptosporidia

Culture for drug-resistant organisms

Assessment and Investigations
## 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

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

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

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### Summary of recommendations

<table>
<thead>
<tr>
<th>Anti-PD-1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common symptoms</strong></td>
<td>Diarrhoea, nausea/vomiting and abdominal pain, with a median time to symptom onset of 3 months</td>
</tr>
<tr>
<td><strong>Endoscopic findings</strong></td>
<td>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>
</tbody>
</table>
| **Different patterns of GI irAEs** | • Acute colitis  
• Microscopic colitis  
• Upper GI involvement  
• Pseudo-obstruction |

#### Combined anti-CTLA-4 and anti-PD-1 antibodies

With this combined treatment, pancreatitis and small bowel enteritis, which may be visible on CT scan, require ICPi treatment discontinuation and initiation of immunosuppression.

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**Immune related gastrointestinal toxicities**

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

<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>
## 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>
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</tbody>
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## 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

### Rare immune-related toxicities

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

**Symptom Grade**
- **Moderate:** Some interference with ADL, symptoms concerning to patient

**Symptom Grade**
- **Severe:** Limits self-care and aids warranted, life threatening, e.g. respiratory problems

**Management escalation pathway**
- **Low threshold to withhold ICPi and monitor symptoms for another week versus continue ICPi; close monitoring for any progression**

**Management escalation pathway**
- **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

**Management escalation pathway**
- **If worsening symptoms, manage as per severe**

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

**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)

**Assessment and Investigations**
- **As above**
  - Consider NCS/EMG for lower motor neurone motor and/or sensory change
  - Consider pulmonary function/sniff/diaphragmatic function tests
  - Consider neurological consult

**Assessment and Investigations**
- **MRI brain/spine advised**
  - NCS/EMG
  - Lumbar puncture
  - Pulmonary function assessment
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

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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

<table>
<thead>
<tr>
<th>Suspected syndrome</th>
<th>Suggested Investigations</th>
<th>Management approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aseptic meningitis:</td>
<td>Lumbar puncture – M/C/S (normal Gram stain, WBCs &lt; 500/μL, normal glucose), PCR for HSV, cytology</td>
<td>Exclude bacterial and ideally viral infections prior to high-dose steroids</td>
</tr>
<tr>
<td>Exclusion of infective causes paramount</td>
<td>CNS imaging to exclude brain metastases and leptomeningeal disease</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 afebrile, vomiting; normal cognition/cerebral function (distinguishes from encephalitis)</td>
<td></td>
<td></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>Consider concurrent empiric antiviral (IV acyclovir) and antibacterial therapy</td>
</tr>
<tr>
<td>Exclusion of infective and metabolic causes paramount</td>
<td>CNS imaging</td>
<td>As above for aseptic meningitis</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 serology</td>
<td>Suggest concurrent IV acyclovir until PCR result obtained</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/syphilis/ANA/anti-Ro and anti-La Abs, TSH, anti-aquaporin-4 IgG</td>
<td>Plasmapheresis may be required if non-steroid responsive</td>
</tr>
</tbody>
</table>
## 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 |
### 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 |
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
## Rare immune-related toxicities

**Rheumatological toxicity**

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<th>Summary of recommendations</th>
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<tbody>
<tr>
<td>Mild or moderate symptoms</td>
<td>Analgesia with paracetamol and/or NSAIDs is recommended; moderate symptoms may respond to prednisolone</td>
</tr>
<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>
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

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### Summary of recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
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</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>
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<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>
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<tr>
<td>Acute tubulo-interstitial nephritis with lymphocytic infiltration is a frequent biopsy finding.</td>
</tr>
</tbody>
</table>
### Summary of recommendations

<table>
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<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>
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<th>Haematological toxicities</th>
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<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>
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<tr>
<th>Allograft rejection</th>
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<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>
Disclaimer and how to obtain more information

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

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

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