MEDICAL PRACTICE GUIDELINE: MANAGEMENT OF IMMUNE RELATED ADVERSE EVENTS ASSOCIATED WITH USE OF IMMUNE CHECKPOINT INHIBITORS

Key alerts

Contact the On-Call Medical Oncologist to discuss management in all cases (contact via SCGH switchboard on 6457 3333). The On-Call Immunologist can also be consulted if deemed clinically necessary.

Management must always be individualised for each patient and this guideline should only be applied where no contraindications exist.

Definitions

<table>
<thead>
<tr>
<th>Immune checkpoint inhibitors (ICIs)</th>
<th>A new class of monoclonal antibodies that modulate the immune system to enhance anti-tumour immune response.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune related adverse event (irAE)</td>
<td>Immune-mediated side-effects of immune checkpoint inhibitor therapy resulting from dysregulation of the immune system. May result in severe or life-threatening inflammation of a range of organs/systems.</td>
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1. Introduction

Immune Checkpoint Inhibitors (ICIs) are a new class of immune modulating monoclonal antibodies currently used in the management of advanced melanoma, and also undergoing trials in other malignancies such as lung cancer. These drugs target molecules expressed on either the surface of T lymphocytes (CTLA-4, PD-1) or on the tumour cells themselves (PD-L1), and allow an anti-tumour immune response to be generated. See appendix 1 for a list of ICIs currently in use.

The use of ICIs has been associated with a range of immune related adverse events (irAEs) involving numerous organs/systems. These irAEs are common, affecting well over half of patients treated with ICIs. Combination therapy with two ICIs (e.g. ipilimumab plus nivolumab) is becoming more frequent and has been shown to result in significantly higher rates of irAEs. Toxicity appears to be mechanism-related, and dose-dependent to some extent. Most irAEs are reversible and mild or moderate severity, although can be severe or life-threatening. Toxicity may occur at any time during treatment, and is some cases late-onset toxicity can occur even after treatment has been discontinued. Onset is usually during the initial dosing period, with a median time to onset of 5-9 weeks depending on the organ/system involved.

Management of irAEs depends on the affected organ(s)/system(s), and often involves temporary immunosuppression. When immunosuppression is used, appropriate prophylaxis for opportunistic infections should be considered. The guidelines on the management of specific irAEs provided in this document are based on current available evidence from the literature, although no prospective trials have been conducted. Referral to other relevant specialties should also be considered e.g. Endocrinology for hypophysitis.

NB. Grading used in this document follows the NCI CTCAE version 4.03 (see appendix 3).
2. General Management Principles

Adverse Event Grading

Mild irAEs (Grade 1) generally do not require interruption of ICI therapy. Symptomatic management and increased monitoring may be all that is required. If there is progression then treat as per higher grade.

Moderate irAEs (Grade 2) usually require ICI therapy to be withheld while treatment is commenced. Cautious reintroduction of ICI therapy may be considered once the irAE has improved to Grade 0 or 1. Moderate dose corticosteroids may be required.

Severe irAEs (Grade 3 or 4) generally require ICI therapy to be permanently discontinued. While there are reports of ICI therapy being resumed following resolution of severe irAEs, there are no published guidelines. High dose systemic corticosteroids are usually required, with tapering once there is objective improvement.

Corticosteroids and other immunosuppressive therapy

High dose steroids are usually initiated with either oral prednisolone 1-2 mg/kg/day (usually to a maximum of 100mg) or intravenous methylprednisolone 1-4 mg/kg/day depending on indication (up to 250-500mg in some cases). Patients commenced on intravenous corticosteroids (e.g. methylprednisolone) can be switched to an equivalent dose of an oral steroid (e.g. prednisolone) once sustained clinical improvement is observed. Steroid tapering over at least 1 month is generally recommended, although a more prolonged taper may be required in some cases. Steroid dose may need to be increased if symptoms worsen during tapering.

There is no evidence that treatment of irAEs with high dose corticosteroids impairs the anti-tumour effect of ICI therapy.

Other immunosuppressive drugs may also be required for severe irAEs (refer to specific organ/system guidelines in this document). Non-formulary indications will require an Individual Patient Approval (IPA) to be submitted.

Prophylactic antibiotics should be considered for patients receiving prolonged corticosteroids or other immunosuppressive medications.

Interruption and resumption of ICI therapy

ICI therapy should be permanently discontinued in patients who experience severe irAEs (see above).

Patients who experience moderate irAEs should have ICI therapy interrupted. Resumption of ICI therapy may be considered once there has been significant improvement (Grade 0 or 1). ICI therapy generally should not be recommenced while the patient is still receiving immunosuppressive doses of corticosteroids (≥ 10mg/day prednisolone or equivalent), or other immunosuppressive therapy.\(^5\)
3. Management Guidelines

3.1 Skin\textsuperscript{3, 4, 6}

Skin toxicity is the most common irAE associated with ICIs, and is usually the earliest to develop with average time to onset of 3-4 weeks.

Rash and/or pruritus may occur in over 50% of patients treated with Ipilimumab, most of which are not severe. By comparison, rash and pruritus occur in 11% and 6% respectively in patients receiving Nivolumab. The typical rash with ICIs is described as reticular, erythematous and maculopapular, usually affecting trunk and/or limbs.

Other less common skin manifestations include vitiligo (up to 10%) and alopecia, and rarely severe rashes such as Stevens Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN) may occur.

Non-inflammatory causes need to be ruled out.

Management

\textit{Pruritus}

Mild or moderate pruritus (Grade 1 or 2) can generally be managed with emollients and oral antihistamines ± topical corticosteroids (e.g. 1% hydrocortisone).

Constant intense or widespread pruritus (Grade 3) may warrant high dose oral antihistamines or oral corticosteroids. GABA agonists (e.g. gabapentin\textsuperscript{*} or pregabalin\textsuperscript{*}) have also been used for severe or refractory pruritus.

\textit{Rash}

Most rashes are mild or moderate (Grade 1 or 2) and can be effectively treated with topical corticosteroids alone, without interruption to ICI therapy. If rash is persistent or progressive then ICI therapy may need to be interrupted and oral corticosteroids started (PO Prednisolone 0.5-1mg/kg/day\textsuperscript{**}), with tapering over at least 1 month.

Severe rashes (Grade 3, >30% body surface area) require interruption or discontinuation of the ICI (See individual PI for further advice). Systemic corticosteroids should be commenced (IV Methylprednisolone 1-2mg/kg/day or PO Prednisolone 1-2mg/kg/day\textsuperscript{**}), and tapered over at least 1 month once skin condition has significantly improved. Urgent Dermatology review should be requested.

Severe rashes (Grade 4, e.g. SJS/TEN) require permanent discontinuation of the ICI. Systemic corticosteroids should be commenced (IV Methylprednisolone 1-2mg/kg/day or equivalent\textsuperscript{**}), along with supportive treatment and other therapies as indicated. Once skin condition has significantly improved, taper steroids over at least 1 month.

\textsuperscript{*} Non-PBS and non-formulary indication
\textsuperscript{**} Also refer to General Management Principles on page 4 regarding steroid dosing.
# Skin irAE Management Algorithm

<table>
<thead>
<tr>
<th>Grade of Rash (NCI CTCAE v4)</th>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1-2</strong>&lt;br&gt;Covering ≤ 30% BSA*&lt;br&gt;- Symptomatic therapy (e.g. antihistamines, topical corticosteroids – see text above)&lt;br&gt;- Continue ICI therapy per protocol</td>
<td><strong>Once improving:</strong>&lt;br&gt;- Taper steroids over at least 1 month&lt;br&gt;- Consider prophylactic antibiotics for opportunistic infections&lt;br&gt;- Resume ICI therapy per protocol&lt;br&gt;If persists &gt; 1-2 weeks or recurs:&lt;br&gt;- Consider Dermatology consult / skin biopsy&lt;br&gt;- Delay ICI therapy per protocol&lt;br&gt;- Consider 0.5-1 mg/kg/day prednisolone**.&lt;br&gt;If worsens:&lt;br&gt;- Treat as Grade 3-4</td>
<td><strong>If improves to Grade 1:</strong>&lt;br&gt;- Taper steroids over at least 1 month&lt;br&gt;- Consider prophylactic antibiotics for opportunistic infections&lt;br&gt;- Resume ICI therapy per protocol&lt;br&gt;- ICI should be permanently avoided in all cases of SJS/TENS</td>
</tr>
<tr>
<td><strong>Grade 3-4</strong>&lt;br&gt;Covering &gt;30% BSA; Life threatening consequences*&lt;br&gt;- Delay or discontinue ICI therapy per protocol&lt;br&gt;- Urgent Dermatology consult&lt;br&gt;- Consider skin biopsy&lt;br&gt;- 1-2 mg/kg/day IV methylprednisolone or IV equivalent**</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Also refer to General Management Principles on page 4 regarding steroid dosing.**

Adapted from Reference 5.
3.2 Gastrointestinal ¹, 6, 7, 8, 9

Diarrhoea is a common side-effect of ICI therapy, occurring in 30-45% of patients receiving anti-CTLA-4 therapy (severe in up to 18%). The reported incidence of diarrhoea is lower with PD-1 inhibitors, with diarrhoea in 10-20% of patients (3% severe). Onset is usually about 6 weeks after initiation of ICI therapy.

Approximately 5-10% of patients receiving ICIs develop evidence of colitis (abdominal pain, mucous or blood in stools, or radiological or histological evidence of colitis). Rare complications of colitis include bowel obstruction and perforation.

Infectious causes of diarrhoea/colitis always need to be excluded before steroids or other immunosuppression is commenced.

The use of prophylactic steroids (oral budesonide) has not been shown to be effective at preventing the development of diarrhoea or colitis caused by ICIs.

Management

**Diarrhoea / Colitis**

Mild (Grade 1) diarrhoea can be managed symptomatically with oral fluid and electrolyte replacement and anti-diarrhoeal agents (e.g. loperamide). Persistent or worsening diarrhoea, or blood in stools, should be investigated further to exclude infection or colitis, which may include stool MC&S and sigmoidoscopy/colonoscopy with biopsy. ICI therapy can usually be continued.

Moderate diarrhoea/colitis (Grade 2) may require ICI therapy to be withheld. Symptomatic treatment with fluids/electrolytes and anti-diarrhoeal agents (e.g loperamide or diphenoxylate hydrochloride/atropine sulphate) should be given. Systemic steroids (IV methylprednisolone 0.5-1mg/kg/day or Prednisolone 0.5-1mg/kg/day*) may be required.

Severe diarrhoea/colitis (Grade 3 or 4) requires ICI therapy to be discontinued and admission to hospital. Intravenous fluid and electrolyte replacement is often necessary, and intravenous steroid therapy should be initiated (IV methylprednisolone 1-2mg/kg/day*). Once improving, change to an equivalent dose of an oral steroid (e.g. prednisolone), with tapering over at least 1 month.

In patients with severe diarrhoea/colitis who do not improve after 48-72 hours of high dose steroid therapy, consider treatment with a TNF inhibitor (e.g Infliximab 5mg/kg every 2 weeks, similar to approach used in Inflammatory Bowel Disease) after discussion with a gastroenterologist. This is a non-PBS and non-formulary indication therefore an Individual Patient Approval (IPA) is required before treatment can be commenced. TNF inhibitors should not be used in cases of bowel perforation or sepsis. Once symptoms are improving, TNF inhibitor therapy can be discontinued and steroids tapered gradually over 45-60 days. Recurrence of symptoms during steroid weaning may require an increase in steroid dose or repeat treatment with a TNF inhibitor.

* Also refer to General Management Principles on page 4 regarding steroid dosing.
**Gastrointestinal irAE Management Algorithm**

Infectious causes of diarrhoea/colitis should be excluded before further treatment.

<table>
<thead>
<tr>
<th>Grade of Diarrhoea/Colitis (NCI CTCAE v4)</th>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong></td>
<td>Diarrhoea: &lt; 4 stools/day over baseline; Colitis: asymptomatic</td>
<td>• Continue ICI therapy per protocol&lt;br&gt;• Symptomatic treatment (oral fluids and electrolytes, anti-diarrhoeal agents)</td>
</tr>
<tr>
<td><strong>Grade 2</strong></td>
<td>Diarrhoea: 4-6 stools/day over baseline; IV fluids indicated &lt;24 hrs; not interfering with ADL&lt;br&gt;Colitis: abdominal pain; blood in stool</td>
<td>• Delay ICI therapy per protocol&lt;br&gt;• Symptomatic treatment</td>
</tr>
<tr>
<td><strong>Grade 3-4</strong></td>
<td>Diarrhoea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL&lt;br&gt;Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs&lt;br&gt;Colitis (G4): life-threatening, perforation</td>
<td>• Discontinue ICI therapy per protocol&lt;br&gt;1 - 2 mg/kg/day methylprednisolone IV or IV equivalent**&lt;br&gt;Add prophylactic antibiotics for opportunistic infections&lt;br&gt;Consider Gastroenterology consult and lower endoscopy</td>
</tr>
</tbody>
</table>

* Non-PBS and non-formulary indication. Individual Patient Approval (IPA) required prior to commencing treatment.

** Also refer to General Management Principles on page 4 regarding steroid dosing.

Adapted from Reference 5.
3.3 Hepatic \cite{1,7}

Immune-mediated hepatitis causing asymptomatic hepatotoxicity (elevated transaminases and/or bilirubin) occurs in 3-9\% of patients receiving ICIs. Onset is typically 3-9 weeks after initiation of ICI therapy. Some patients may also experience fever and malaise. Fulminant hepatitis is rare.

Other possible causes of worsening liver function tests need to be considered, including viral hepatitis, liver metastases or effects of other drugs. Appropriate investigations should be performed to exclude these conditions, which may include liver biopsy. Hepatology consult should be requested.

Management

*Elevated ALT/AST and/or bilirubin*

Mild elevation (Grade 1) does not require interruption of ICI therapy. Liver function test should continue to be monitored routinely.

Moderate elevation (Grade 2) may require ICI therapy to be delayed, with increased frequency of monitoring (every 3-5 days). If LFTs return to baseline, then ICI can be resumed. If elevation persists after 7 days then steroid therapy may be required (Prednisolone 0.5-1mg/kg/day\textsuperscript{**}), which should be tapered over at least 30 days once LFTs improving. ICI may be resumed once Grade 0/1.

Severe elevation (Grade 3 or 4) requires discontinuation of ICI and treatment with intravenous steroids (IV Methylprednisolone 1-2mg/kg/day\textsuperscript{**}). If LFTs improving after 48 hours, then can change to oral steroids (Prednisolone 1-2mg/kg/day\textsuperscript{**}) and tapered over at least 1 month.

If no improvement after 72 hours of high dose intravenous steroids then consider addition of other immunosuppressive therapy (e.g. mycophenolate mofetil 500-1000mg twice daily).

TNF inhibitors (e.g. infliximab) are not recommended for treatment of hepatitis induced by ICIs due to its potential for hepatotoxicity.

\textsuperscript{**} Also refer to General Management Principles on page 4 regarding steroid dosing.
Hepatic irAE Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue ICI therapy. Consider imaging for obstruction.

<table>
<thead>
<tr>
<th>Grade of Liver Test Elevation (NCI CTCAE v4)</th>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1&lt;br&gt;Ast/ALT &gt; ULN - 3.0 x ULN and/or total bili &gt; ULN - 1.5 x ULN</td>
<td>• Continue ICI therapy per protocol</td>
<td>• Continue routine LFT monitoring per protocol&lt;br&gt;If worsens: • Treat as Grade 2 or 3-4</td>
</tr>
<tr>
<td>Grade 2&lt;br&gt;Ast/ALT &gt; 3.0 to ≤ 5 x ULN and/or total bili &gt; 1.5 - ≤ 3 x ULN</td>
<td>• Delay ICI therapy per protocol&lt;br&gt;• Increase frequency of monitoring to every 3 days</td>
<td>If returns to baseline: • Resume routine monitoring, resume ICI therapy per protocol&lt;br&gt;If elevations persist &gt; 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent** and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month&lt;br&gt;• Consider prophylactic antibiotics for opportunistic infections&lt;br&gt;• Resume ICI therapy per protocol</td>
</tr>
<tr>
<td>Grade 3-4&lt;br&gt;Ast/ALT &gt; 5 x ULN and/or total bili &gt;3 x ULN</td>
<td>• Discontinue ICI therapy*&lt;br&gt;• Increase frequency of monitoring to every 1-2 days&lt;br&gt;• Consult Hepatologist&lt;br&gt;• 1 - 2 mg/kg/day methylprednisolone IV or IV equivalent**&lt;br&gt;• Consider prophylactic antibiotics for opportunistic infections</td>
<td>If returns to grade 2: • Taper steroids over at least 1 month&lt;br&gt;If does not improve in &gt;3-5 days, worsens or rebounds: • Add other immunosuppressant (e.g. mycophenolate mofetil 1 g twice daily)&lt;br&gt;• If still no response within an additional 3-5 days, consider further immunosuppressants per local guidelines</td>
</tr>
</tbody>
</table>

*ICI therapy may be delayed rather than discontinued if Ast/ALT ≤ 8 x ULN and total bilirubin ≤ 5 x ULN.

** Also refer to General Management Principles on page 4 regarding steroid dosing. The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

ULN – upper limit of normal

Adapted from Reference 5.
3.4 Endocrine \(^1,10\)

Hypopituitarism caused by autoimmune hypophysitis is the most common endocrine complication related to ICI therapy, occurring in 1-6% of patients treated with CTLA-4 inhibitors. Hypophysitis has a mean onset 6 weeks after initiation of ICI therapy, with symptoms including headache, nausea, vertigo, behavioural changes and visual disturbance. Hypopituitarism usually manifests as secondary hypoadrenalism, hypothyroidism and hypogonadism. Diabetes insipidus has also been reported.

Primary hypothyroidism and hypoadrenalism have also been reported less frequently. In general, PD1 inhibitors have lower rates of endocrine complications.

Investigation of suspected hypophysitis includes measurement of serum hormone levels, including pituitary (ACTH, TSH, FSH, LH, prolactin), adrenal (cortisol), thyroid (T4, T3) and gonadal (testosterone in males). Measurement of electrolytes and glucose is also indicated. Brain imaging (including pituitary) with MRI should be performed to investigate for hypophysitis, and to exclude other differentials such as brain metastases or infection. Endocrinology consultation is recommended.

Management

Hypophysitis

Hypopituitarism due to autoimmune hypophysitis may be irreversible (particularly secondary hypoadrenalism) and necessitate permanent hormone replacement. ICI therapy usually needs to be withheld (and may need to be permanently discontinued), and treatment with short-term high dose steroids (IV Methylprednisolone 1-2mg/kg/day or equivalent**) is recommended, with tapering over at least 1 month once improvement in symptoms. In patients with secondary hypoadrenalism, the steroid dose should only be tapered down to a physiologic replacement dose. Patient suspected to have hormonal abnormalities secondary to ICI should always be discussed with the Endocrine team.

Hypoadrenalism

Adrenal crisis with hypovolaemic shock may be life-threatening if not recognised and treated promptly and requires emergency treatment with intravenous steroids with mineralocorticoid activity (e.g. IV Hydrocortisone 100mg or IV Dexamethasone 4mg) along with other supportive treatment, including intravenous fluid resuscitation. Ongoing high dose steroid replacement is required in the short-term (e.g. IV Hydrocortisone 50mg 8-hourly) until clinically stable. Long-term steroid replacement therapy (e.g. Hydrocortisone or Prednisolone) will be required at a physiologic dose, with additional ‘stress’ doses required during times of acute illness.

Hypothyroidism

Mild hypothyroidism (Grade 1) requires no change to treatment. Moderate or severe hypothyroidism (Grade 2-4) requires interruption of ICI therapy. Thyroxine replacement should be commenced and dose titrated as required. Consider treatment with high dose corticosteroids (Prednisolone 1-2mg/kg/day or equivalent**), with tapering over at least 1 month once improvement in symptoms.

Hypogonadism

Testosterone replacement is indicated in males with secondary hypogonadism related to ICI therapy.

** Also refer to General Management Principles on page 4 regarding steroid dosing.
**Endocrine irAE Management Algorithm**

**Asymptomatic TSH elevation**
- Continue ICI therapy per protocol
- If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include free T4 at subsequent cycles as clinically indicated; consider Endocrinology consult

**Symptomatic endocrinopathy**
- Lab testing to evaluate endocrine function*
- Consider pituitary scan with MRI
- Endocrinology consult

Symptomatic with abnormal lab tests / pituitary scan:
- Delay ICI therapy per protocol
- 1-2 mg/kg/day methylprednisolone IV or equivalent**
- Initiate appropriate hormone therapy

No abnormal lab tests / pituitary MRI scan but symptoms persist:
- Repeat labs in 1-3 weeks / MRI in 1 month

If improves (with or without hormone replacement):
- Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections
- Resume ICI therapy per protocol
- Patients with adrenal insufficiency need to continue physiologic replacement dose of steroid with mineralocorticoid activity

**Suspicion of adrenal crisis (e.g. severe dehydration, hypotension, shock out of proportion to current illness**
- Delay or discontinue ICI therapy per protocol
- Rule out sepsis
- Stress dose of IV steroids with mineralocorticoid activity (e.g. IV Hydrocortisone 100mg or IV Dexamethasone 4mg), with ongoing steroid replacement (see text on previous page for details).
- IV fluids
- Endocrinology consult
- If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy

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*Lab testing should include relevant hormones, electrolytes and glucose.

** Also refer to General Management Principles on page 4 regarding steroid dosing.

LLN – lower limit of normal
ULN – upper limit of normal

Adapted from Reference 5.
3.5 Pulmonary $^6, ^{11}, ^{12}$

PD-1 inhibitors have been associated with pneumonitis in 3-5% of patients, and may be fatal in rare cases. Pulmonary inflammatory conditions have also been reported less frequently in patients receiving CTLA-4 inhibitors. Pneumonitis should be considered in any patient receiving ICI therapy who presents with cough or dyspnoea, and appropriate imaging performed. Infective causes also need to be excluded, and empiric antibiotics should be considered. Further investigation may include bronchoscopy.

There are also case reports of diffuse, PET positive lymphadenopathy and a sarcoid-like syndrome (mediastinal lymphadenopathy with non-caseating granulomata, elevated ACE level) in patients receiving ICI therapy.

Management

*Pneumonitis*

For radiographic changes suggestive of pneumonitis only (Grade 1) interruption of ICI therapy should be considered with increased clinical monitoring and repeat imaging.

Moderate pneumonitis (Grade 2) requires ICI therapy to be withheld and corticosteroid therapy (Prednisolone 1mg/kg/day or equivalent**) to be commenced. Close clinical monitoring and frequent repeat imaging should be performed to assess for response to treatment. Steroids should be tapered over at least 1 month once significant improvement in symptoms. Always consult Respiratory team, and also consider consulting Infectious Diseases.

Severe pneumonitis (Grade 3 or 4) requires permanent discontinuation of ICI therapy. High dose systemic corticosteroids should be commenced (IV Methylprednisolone 2-4mg/kg/day or equivalent**) with tapering over at least 6 weeks once significant improvement in symptoms. If worsening, or failing to improve after 48 hours, addition of other immunosuppressives or immunomodulators (e.g. cyclophosphamide, mycophenolate mofetil*, TNF inhibitors e.g. infliximab*, or intravenous immunoglobulin therapy†) could be considered. For non-formulary indications an Individual Patient Approval (IPA) is required before commencing treatment. Although there is no published evidence to guide the use of other immunosuppressive drugs in this setting, it may be reasonable to use an approach comparable to that used in other severe acute/fulminant interstitial lung diseases.

* Non-PBS and non-formulary indication
** Also refer to General Management Principles on page 4 regarding steroid dosing.
† Non-National Blood Authority (NBA) approved indication
# Pulmonary irAE Management Algorithm

<table>
<thead>
<tr>
<th>Grade of Pneumonitis (NCI CTCAE v4)</th>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
</table>
| **Grade 1** Radiographic changes only | • Consider delay of ICI therapy  
• Monitor for symptoms every 2-3 days  
• Consider Respiratory and ID Consults | • Re-image at least every 3 weeks  
If worsens:  
• Treat as Grade 2 or 3-4 |
| **Grade 2** Mild to moderate new symptoms | • Delay ICI therapy per protocol  
• Respiratory and ID Consults  
• Consider bronchoscopy / lung biopsy  
• Monitor symptoms daily, consider hospital admission  
• 1 mg/kg/day Prednisolone PO or equivalent**  
• Re-image every 1-3 days  
If improves:  
• When symptoms return to near baseline, taper steroids over at least 1 month and then resume ICI therapy per protocol and consider prophylactic antibiotics  
If not improving after 2 weeks or worsening:  
• Treat as Grade 3-4 |
| **Grade 3-4** Severe new symptoms; New/worsening hypoxia; Life-threatening | • Discontinue ICI therapy per protocol  
• Admit to hospital  
• Respiratory and ID Consults  
• Consider bronchoscopy / lung biopsy  
• 2-4 mg/kg/day methylprednisolone IV or IV equivalent**  
• Add prophylactic antibiotics for opportunistic infections | If improves to baseline:  
• Taper steroids over at least 6 weeks  
If not improving after 48 hours or worsening:  
• Add additional immunosuppression* (e.g. TNF inhibitors, cyclophosphamide, IVIG, or mycophenolate mofetil – see text above) |

* Non-formulary indications require an Individual Patient Approval prior to commencing treatment.

** Also refer to General Management Principles on page 4 regarding steroid dosing.

Adapted from Reference 5.
3.6 Renal 6, 13, 14

Nephrotoxicity due to ICI therapy is rare. There are only a few reported cases of acute renal failure with CTLA-4 inhibitors, including several cases of acute granulomatous tubulointerstitial nephritis and one case of membranous lupus nephritis. Onset of renal disease ranges from 6-12 weeks after initiation of ICI therapy.

Other causes of renal impairment need to be considered, including other drugs.

Management

**Acute renal impairment**

Mild renal impairment (Grade 1) requires increased monitoring of renal function, but ICI therapy can usually be continued.

Moderate renal impairment (Grade 2 or 3) requires ICI therapy to be withheld, with close monitoring of renal function. Moderate dose corticosteroids (Prednisolone 0.5-1mg/kg/day or equivalent**) may be required, with tapering over at least 1 month once creatinine has improved significantly. Renal biopsy may be considered in consultation with Nephrology team.

Severe renal impairment (Grade 4) requires permanent discontinuation of ICI therapy, with daily monitoring of renal function. High dose corticosteroids (IV Methylprednisolone 1-2mg/kg/day or Prednisolone 1-2mg/kg/day**) should be commenced, with tapering over at least 1 month once creatinine has improved significantly. Renal biopsy may be considered.

** Also refer to General Management Principles on page 4 regarding steroid dosing.
Renal irAE Management Algorithm

<table>
<thead>
<tr>
<th>Grade of Creatinine Elevation (NCI CTCAE v4)</th>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 &lt;br&gt; Creatinine &gt; ULN and &gt; than baseline but ≤ 1.5x baseline</td>
<td>• Continue ICI therapy per protocol&lt;br&gt;• Monitor creatinine weekly</td>
<td>If returns to baseline:&lt;br&gt;• Resume routine creatinine monitoring per protocol.</td>
</tr>
<tr>
<td>Grade 2-3 &lt;br&gt; Creatinine &gt; 1.5x baseline to ≤ 6x ULN</td>
<td>• Delay ICI therapy per protocol&lt;br&gt;• Monitor creatinine every 2-3 days&lt;br&gt;• 0.5 - 1 mg/kg/day methylprednisolone IV or oral equivalent**&lt;br&gt;• Nephrology consult&lt;br&gt;• Consider renal biopsy</td>
<td>If returns to Grade 1:&lt;br&gt;• Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume ICI therapy and routine creatinine monitoring per protocol</td>
</tr>
<tr>
<td>Grade 4 &lt;br&gt; Creatinine &gt; 6x ULN</td>
<td>• Discontinue ICI therapy per protocol&lt;br&gt;• Monitor creatinine daily&lt;br&gt;• 1-2 mg/kg/day methylprednisolone IV or IV equivalent**&lt;br&gt;• Nephrology consult&lt;br&gt;• Consider renal biopsy</td>
<td>If returns to Grade 1:&lt;br&gt;• Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections</td>
</tr>
</tbody>
</table>

** Also refer to General Management Principles on page 4 regarding steroid dosing.

ULN – upper limit of normal

Adapted from Reference 5.
3.7 Neurological\textsuperscript{1, 15, 16, 17, 18}

Transient peripheral neuropathies (sensory and/or motor) occur in <1% of patients treated with ICIs. Isolated cases of other neurological cases have also been reported, including Guillain-Barre syndrome (GBS), myasthenia gravis (MG), aseptic meningitis, autonomic neuropathy and myositis.

Management

Neuropathy

Mild neuropathy (Grade 1) may be self-limiting and often requires no treatment.

Moderate neuropathy (Grade 2) that is persistent or worsening may require interruption of ICI therapy and a course of oral steroids (Prednisolone 0.5-1mg/kg/day\textsuperscript{*}) tapered over 1 month.

Severe neuropathy (Grade 3 or 4) requires permanent cessation of ICI therapy and steroid therapy (IV Methylprednisolone 1-2mg/kg/day or Prednisolone 1-2mg/kg/day\textsuperscript{*}) tapered over at least 1 month. If atypical features are present, or if progression occurs despite treatment, then other immunosuppression, plasmapheresis or intravenous immunoglobulin may be required.

Guillain-Barre syndrome

Management of GBS related to ICI therapy should be managed similarly to other forms of GBS, with plasmapheresis or intravenous immunoglobulin. ICI therapy should be discontinued. Cases of GBS related to ICI therapy have also been treated with high dose corticosteroids with good effect, which does differ from treatment of other forms of GBS where corticosteroids are not beneficial.

Myasthenia Gravis

Management of MG related to ICI therapy should be managed similarly to other forms of MG. ICI therapy should be discontinued. Cases of myasthenia gravis related to ICI therapy have been treated effectively with high dose corticosteroids as well as plasmapheresis and intravenous immunoglobulin. Use of high dose corticosteroids alone may be associated with transient worsening of weakness in MG.

\textsuperscript{*} Also refer to General Management Principles on page 4 regarding steroid dosing.
### Neurological irAE Management Algorithm

<table>
<thead>
<tr>
<th>Grade of Neurological Toxicity (NCI CTCAE v4)</th>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong>&lt;br&gt;Asymptomatic or mild symptoms; Intervention not indicated</td>
<td>• Continue ICI therapy per protocol</td>
<td>Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4</td>
</tr>
<tr>
<td><strong>Grade 2</strong>&lt;br&gt;Moderate symptoms; Limiting instrumental ADL</td>
<td>• Delay ICI therapy per protocol&lt;br&gt;• Treat symptoms per local guidelines&lt;br&gt;• Consider Neurology Consult&lt;br&gt;• Consider 0.5 - 1 mg/kg/day methylprednisolone IV or PO equivalent**</td>
<td>If improves to baseline:&lt;br&gt;• Resume ICI therapy per protocol when improved to baseline&lt;br&gt;If worsens: • Treat as Grade 3-4</td>
</tr>
<tr>
<td><strong>Grade 3-4</strong>&lt;br&gt;Severe symptoms; Limiting self-care ADL; Life-threatening</td>
<td>• Discontinue ICI therapy per protocol&lt;br&gt;• Neurology consult&lt;br&gt;• 1-2 mg/kg/day IV methylprednisolone or IV equivalent**&lt;br&gt;• Add prophylactic antibiotics for opportunistic infections</td>
<td>If improves to Grade 2:&lt;br&gt;• Taper steroids over at least 1 month&lt;br&gt;If worsens or atypical presentation:&lt;br&gt;• Consider IVIG, plasmapheresis or other immunosuppressive therapy</td>
</tr>
</tbody>
</table>

** Also refer to General Management Principles on page 4 regarding steroid dosing.

Adapted from Reference 5.
3.8 Ophthalmic ¹,¹⁹

Episcleritis or uveitis occur in <1% of patients receiving ICIs, with median onset 2 months after initiation of therapy. Symptoms may include eye pain and redness, photophobia, dryness and blurred vision. Other immune-mediated ophthalmic disease may also occur, including orbital inflammation, blepharitis, conjunctivitis, scleritis, peripheral ulcerative keratitis and optic neuritis. Ophthalmology consultation is recommended.

Management

Mild or moderate episcleritis/uveitis (Grade 1 or 2), or other immune-mediated ocular diseases, can generally be managed with topical corticosteroids (e.g. prednisolone drops). If unresponsive to topical steroid therapy then manage as Grade 3/4. Other treatments may be used under the direction of Ophthalmology.

Severe episcleritis/uveitis (Grade 3 or 4), or other immune-mediated ocular diseases, usually require permanent cessation of ICI therapy with commencement of systemic corticosteroids (Prednisolone 1-2mg/kg/day or equivalent**) tapered over at least 30 days.

** Also refer to General Management Principles on page 4 regarding steroid dosing.
# Ophthalmic irAE Management Algorithm

<table>
<thead>
<tr>
<th>Grade of Eye Disorder (NCI CTCAE v4)</th>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
</table>
| Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated | • Continue ICI therapy per protocol  
• Ophthalmology consult  
• Topical corticosteroid eye drops with further treatment guided by Ophthalmology | • If unresponsive to topical steroid therapy then manage as Grade 3/4. |
| Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL | | |
| Grade 3: Severe or medically significant but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL | • Discontinue ICI therapy per protocol  
• Ophthalmology consult  
• 1 -2mg/kg/day Prednisolone PO or equivalent** | • Once improving, taper steroids over at least 30 days. |
| Grade 4: Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye | | |

** Also refer to General Management Principles on page 4 regarding steroid dosing.
4. References


5. Acknowledgements

This guideline is based on the Fiona Stanley Hospital Clinical Guideline “Immune Related Adverse Events Associated with Use of Immune Checkpoint Inhibitors” (Reference #: FSH-IMM-GUI-0002).
6. Disclaimer
Printed or personally saved electronic copies of this policy are considered uncontrolled. Access current version from Sir Charles Gairdner Hospital Intranet (CHiPs).

7. Risk Statement

**RISK STATEMENT:**
Non-compliance with this policy will (please tick all that apply [right click on box, change properties, checked]):

<table>
<thead>
<tr>
<th>Breach legislative requirements</th>
<th>Impact on Patient Quality of Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breach National/State/Hospital Policy</td>
<td>Impact on Patient Safety</td>
</tr>
<tr>
<td>Breach professional standards</td>
<td>Misconduct</td>
</tr>
<tr>
<td>Breach SCGH Mission &amp; Values</td>
<td>Other:</td>
</tr>
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</table>

8. Document Endorsement

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Endorsed by</td>
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<tr>
<td>Policy Author</td>
</tr>
<tr>
<td>Executive Sponsor</td>
</tr>
<tr>
<td>Initial Endorsement</td>
</tr>
<tr>
<td>Last Amended</td>
</tr>
<tr>
<td>Next Review Date</td>
</tr>
<tr>
<td>Version</td>
</tr>
</tbody>
</table>

**References (Standards):**
- NSQH Standard/s: Standard 1: Governance for Safety and Quality in Health Service Organisations
- Framework
- Legislation / overarching policy
- Related Documents: Appendix 1: List of Immune Checkpoint Inhibitors
  Appendix 2: Summary of drugs used for irAE management
  Appendix 3: Common Terminology Criteria for Adverse Events v4.03 (CTCAE)
9. Appendices

9.1 Appendix 1: List of Immune Checkpoint Inhibitors

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti CTLA-4</td>
<td>Ipilimumab</td>
</tr>
<tr>
<td>Anti PD-1</td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td></td>
<td>Nivolumab</td>
</tr>
<tr>
<td>Anti PD-L1</td>
<td>None currently in use in Australia</td>
</tr>
</tbody>
</table>
## 9.2 Appendix 2: Summary of drugs used for irAE management;

Refer to individual algorithms for details.

<table>
<thead>
<tr>
<th>System</th>
<th>Adverse Event Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>1</strong></td>
</tr>
<tr>
<td>Skin</td>
<td>Antihistamines Topical steroids</td>
</tr>
<tr>
<td></td>
<td>If persistent: Prednisolone 0.5 - 1 mg/kg/day</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Anti-diarrhoeal agents Fluid and electrolyte replacement</td>
</tr>
<tr>
<td></td>
<td>If persistent Grade 2: Prednisolone 0.5 - 1 mg/kg/day</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Monitor</td>
</tr>
<tr>
<td></td>
<td>If persistent: Methylprednisolone 0.5 - 1 mg/kg/day</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Endocrinopathy Monitor</td>
</tr>
<tr>
<td></td>
<td>Appropriate hormone replacement as required</td>
</tr>
<tr>
<td></td>
<td>Adrenal crisis Hydrocortisone 100mg or Dexamethasone 4mg + ongoing replacement</td>
</tr>
<tr>
<td></td>
<td>Intravenous fluid resuscitation</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Monitor Prednisolone 1mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>If refractory: Consider other immunosuppression (e.g. TNF inhibitor, cyclophosphamide, IVIG, Mycophenolate mofetil)</td>
</tr>
<tr>
<td>Renal</td>
<td>Monitor Methylprednisolone 0.5 - 1 mg/kg/day</td>
</tr>
<tr>
<td>Neurological</td>
<td>Monitor Methylprednisolone 0.5 - 1 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>If progression or Atypical features: Consider IVIG, Plasmapharesis or additional immunosuppression</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>Topical corticosteroid eye drops</td>
</tr>
</tbody>
</table>
9.3 Appendix 3: National Cancer Institute (NCI) - Common Terminology Criteria for Adverse Events v4.03 (CTCAE)

Grades
Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

**Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

**Grade 2** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.

**Grade 3** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.

**Grade 4** Life-threatening consequences; urgent intervention indicated.

**Grade 5** Death related to AE.

Further details of organ-specific grading criteria are included in the attached table below.

Information on other adverse events can be found in the CTCAE Quick Reference document available online;

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SKIN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>Mild or localized; topical intervention indicated</td>
<td>Intense or widespread; intermittent; skin changes from scratching (e.g. edema, papulation, exoriation, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL</td>
<td>Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rash – maculo-papular</td>
<td>Macules/papules covering &lt;10% BSA with or without symptoms (e.g., pruritus, burning, tightness)</td>
<td>Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL</td>
<td>Macules/papules covering &gt;30% BSA with or without associated symptoms; limiting self care ADL</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Stevens-Johnson syndrome</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Death</td>
</tr>
<tr>
<td>Toxic epidermal necrolysis</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Death</td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Increase of &lt;4 stools per day over baseline; mild increase in ostomy output compared to baseline</td>
<td>Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline</td>
<td>Increase of &gt;=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Colitis</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
<td>Abdominal pain; mucus or blood in stool</td>
<td>Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td><strong>HEPATIC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT/AST increased</td>
<td>ALT/AST &gt;ULN - 3.0 x ULN</td>
<td>ALT/AST &gt;3.0 - 5.0 x ULN</td>
<td>ALT/AST &gt;5.0 - 20.0 x ULN</td>
<td>ALT/AST &gt;20.0 x ULN</td>
<td>-</td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>Bilirubin &gt;ULN - 1.5 x ULN</td>
<td>Bilirubin &gt;1.5 - 3.0 x ULN</td>
<td>Bilirubin &gt;3.0 - 10.0 x ULN</td>
<td>Bilirubin &gt;10.0 x ULN</td>
<td>-</td>
</tr>
<tr>
<td><strong>ENDOCRINE</strong></td>
<td></td>
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</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated.</td>
<td>Moderate symptoms; medical intervention indicated.</td>
<td>Severe symptoms; hospitalization indicated.</td>
<td>Life-threatening consequences; urgent intervention indicated.</td>
<td>Death</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated.</td>
<td>Symptomatic; thyroid replacement therapy indicated; limiting instrumental ADL.</td>
<td>Severe symptoms; limiting self care ADL; hospitalization indicated.</td>
<td>Life-threatening consequences; urgent intervention indicated.</td>
<td>Death</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated.</td>
<td>Symptomatic; thyroid suppression indicated; limiting instrumental ADL.</td>
<td>Severe symptoms; limiting self care ADL; hospitalization indicated.</td>
<td>Life-threatening consequences; urgent intervention indicated.</td>
<td>Death</td>
</tr>
<tr>
<td>Condition</td>
<td>Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated</td>
<td>Moderate; minimal, local or non-invasive; intervention indicated; limiting age appropriate instrumental ADL</td>
<td>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated.</td>
<td>Death</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>PULMONARY</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
<td>Symptomatic; medical intervention indicated; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self care ADL; oxygen indicated</td>
<td>Life-threatening respiratory compromise; urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>Creatinine level increase of &gt;0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline</td>
<td>Creatinine 2 - 3 x above baseline</td>
<td>Creatinine &gt;3 x baseline or &gt;4.0 mg/dL; hospitalization indicated</td>
<td>Life-threatening consequences; dialysis indicated</td>
<td>Death</td>
</tr>
<tr>
<td>NEUROLOGICAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral motor neuropathy</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
<td>Moderate symptoms; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self care ADL; assistive device indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>Asymptomatic; loss of deep tendon reflexes or paraesthesia</td>
<td>Moderate symptoms; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>Myositis</td>
<td>Mild pain</td>
<td>Moderate pain associated with weakness; pain limiting instrumental ADL</td>
<td>Pain associated with severe weakness; limiting self care ADL</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Nervous system disorders - Other, specify</td>
<td>Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated</td>
<td>Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL</td>
<td>Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
<tr>
<td>OPHTHALMIC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uveitis</td>
<td>Asymptomatic; clinical or diagnostic observations only</td>
<td>Anterior uveitis; medical intervention indicated</td>
<td>Posterior or pan-uveitis</td>
<td>Blindness (20/200 or worse) in the affected eye</td>
<td>-</td>
</tr>
<tr>
<td>Eye disorders – Other, specify</td>
<td>Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated</td>
<td>Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL</td>
<td>Severe or medically significant but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL</td>
<td>Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye</td>
<td>-</td>
</tr>
</tbody>
</table>