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

Immune checkpoint inhibitors (ICIs)	**A new class of monoclonal antibodies that modulate the immune system to enhance anti-tumour immune response.**
Immune related adverse event (irAE)	**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.**

Index

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.[1] 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.[2] 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.[3] Onset is usually during the initial dosing period, with a median time to onset of 5-9 weeks depending on the organ/system involved.[4]

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 [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

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* or pregabalin*) have also been used for severe or refractory pruritus.

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**), with tapering over at least 1 month.

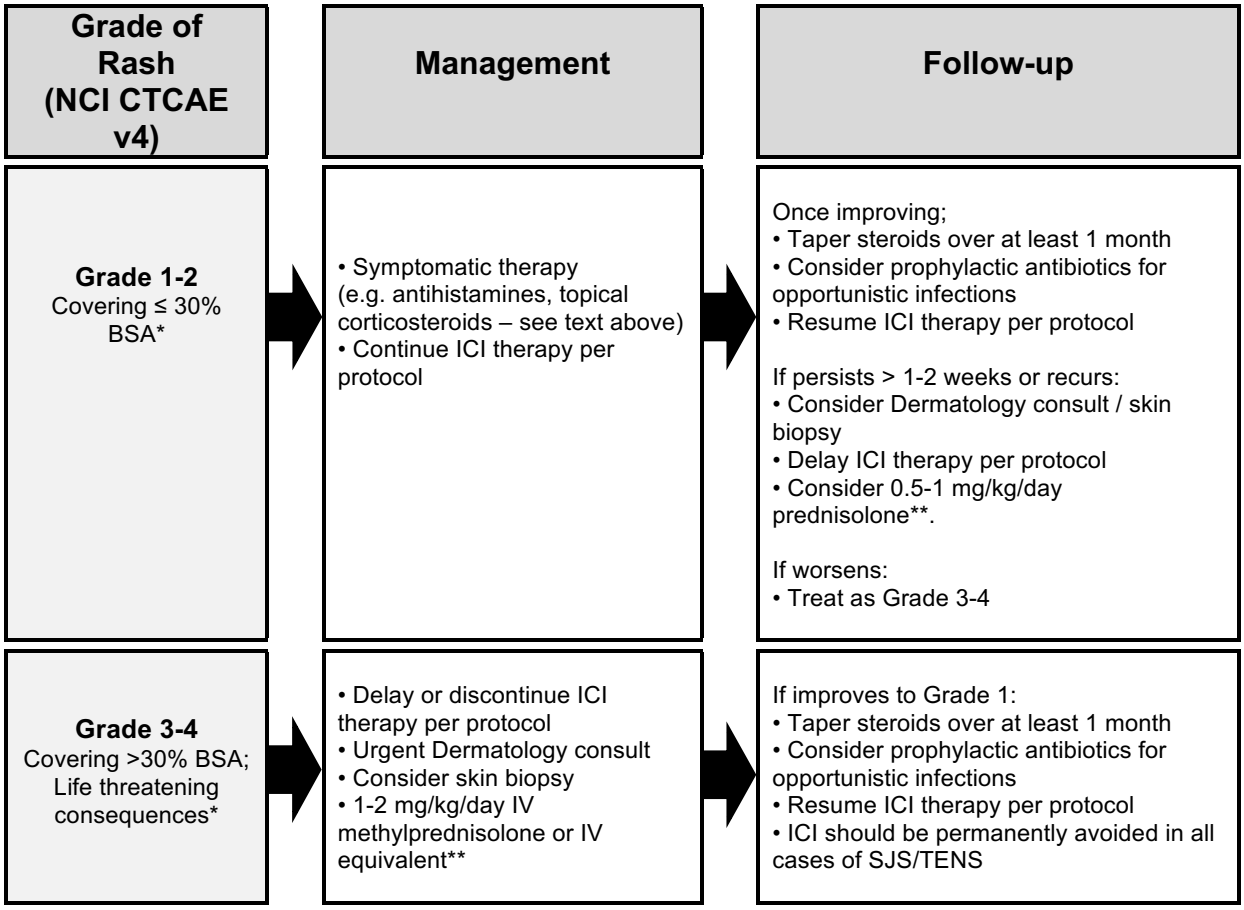
Severe rashes (Grade 3, >30% body surface area) require interruption or discontinuation of the ICI (See individual PI for further advice). Systemic corticosteroids should be commenced (IV Methylprednisolone 1-2mg/kg/day or PO Prednisolone 1-2mg/kg/day**), and tapered over at least 1 month once skin condition 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**), along with supportive treatment and other therapies as indicated. Once skin condition has significantly improved, taper steroids over at least 1 month.

* Non-PBS and non-formulary indication

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

Skin irAE Management Algorithm



** 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.

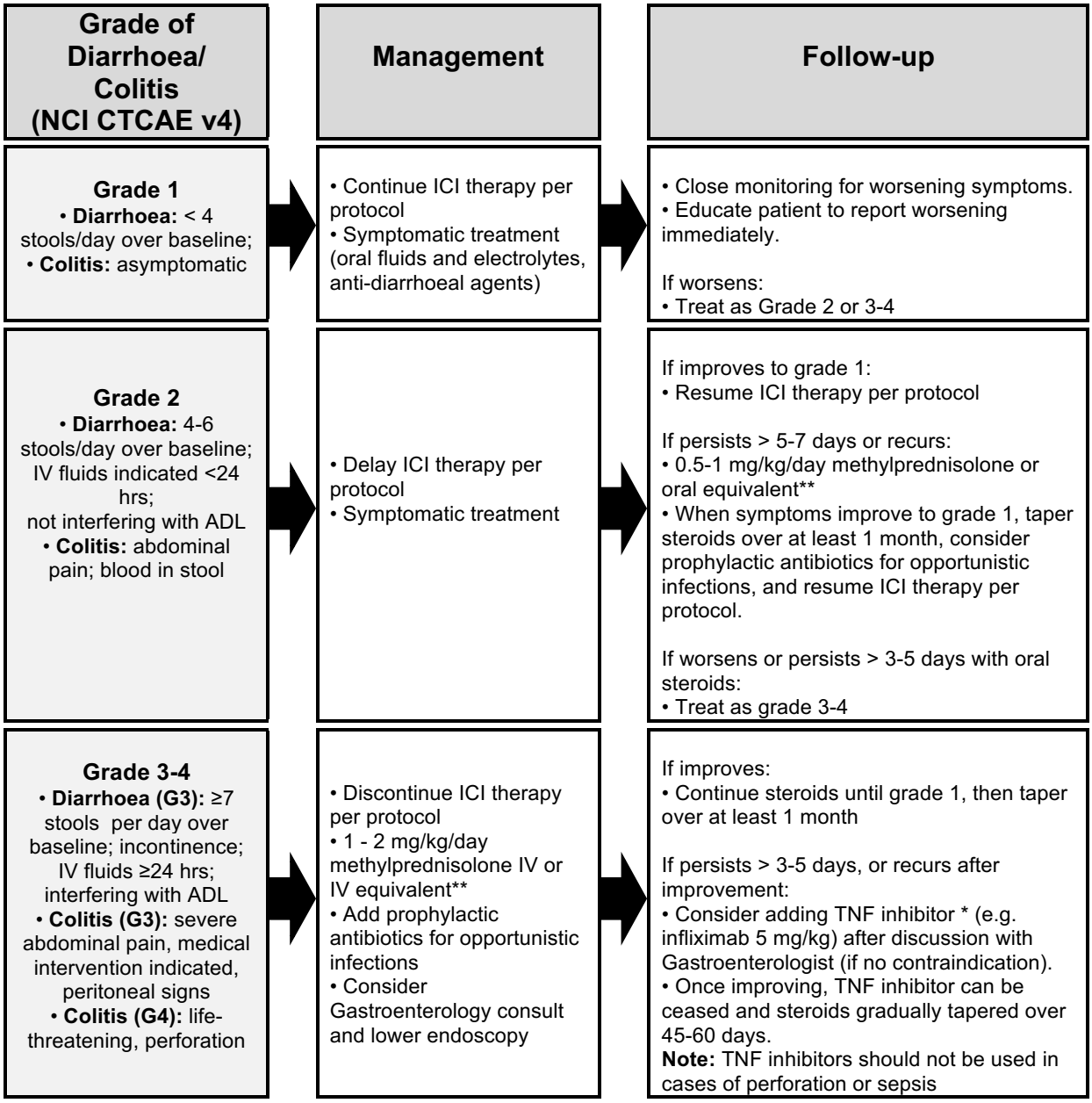
Severe diarrhoea/colitis (Grade 3 or 4) requires ICI therapy to be discontinued and admission to hospital. Intravenous fluid and electrolyte replacement is often necessary, and intravenous steroid therapy should be initiated (IV methylprednisolone 1-2mg/kg/day*). Once improving, change to an equivalent 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.



* 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 [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**), 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**). If LFTs improving after 48 hours, then can change to oral steroids (Prednisolone 1-2mg/kg/day**) and tapered over at least 1 month.

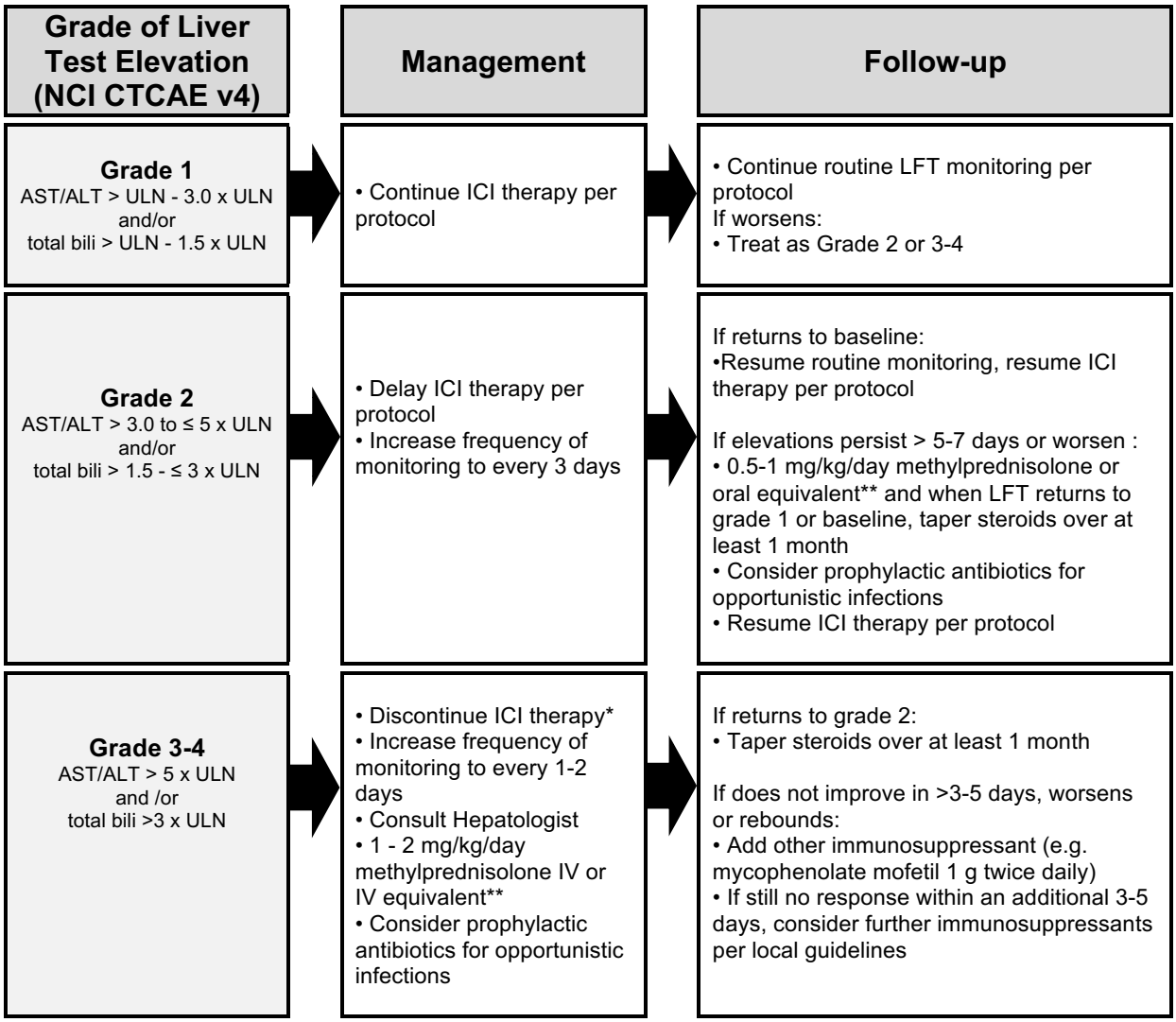
If no improvement after 72 hours of high dose intravenous steroids then consider addition of other immunosuppressive therapy (e.g. mycophenolate mofetil 500-1000mg twice daily).

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

** 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.



*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.

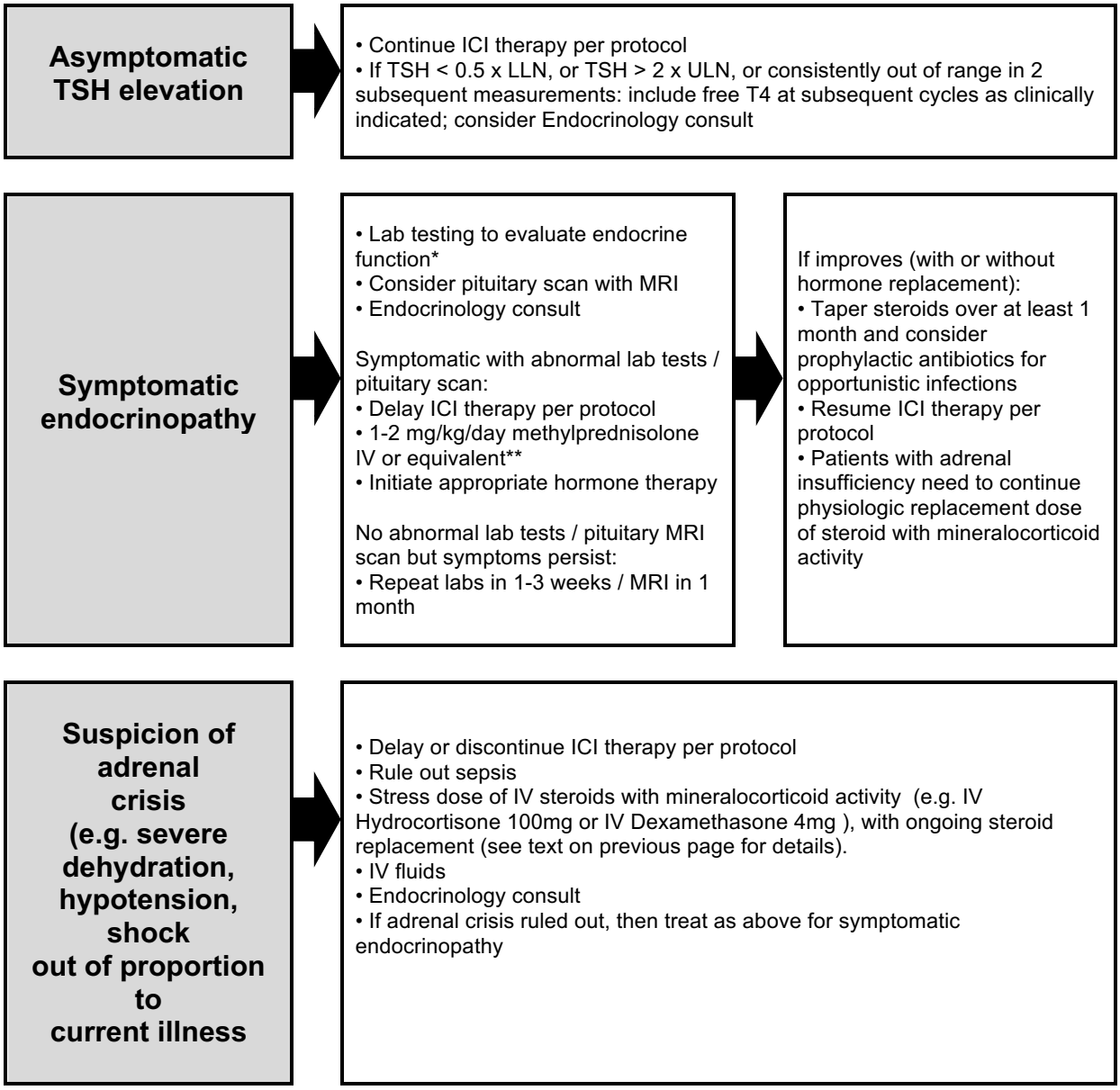
Moderate or severe hypothyroidism (Grade 2-4) requires interruption of ICI therapy. Thyroxine replacement should be commenced and dose titrated as required. Consider treatment with high dose corticosteroids (Prednisolone 1-2mg/kg/day or equivalent**), with tapering over at least 1 month once improvement 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



*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

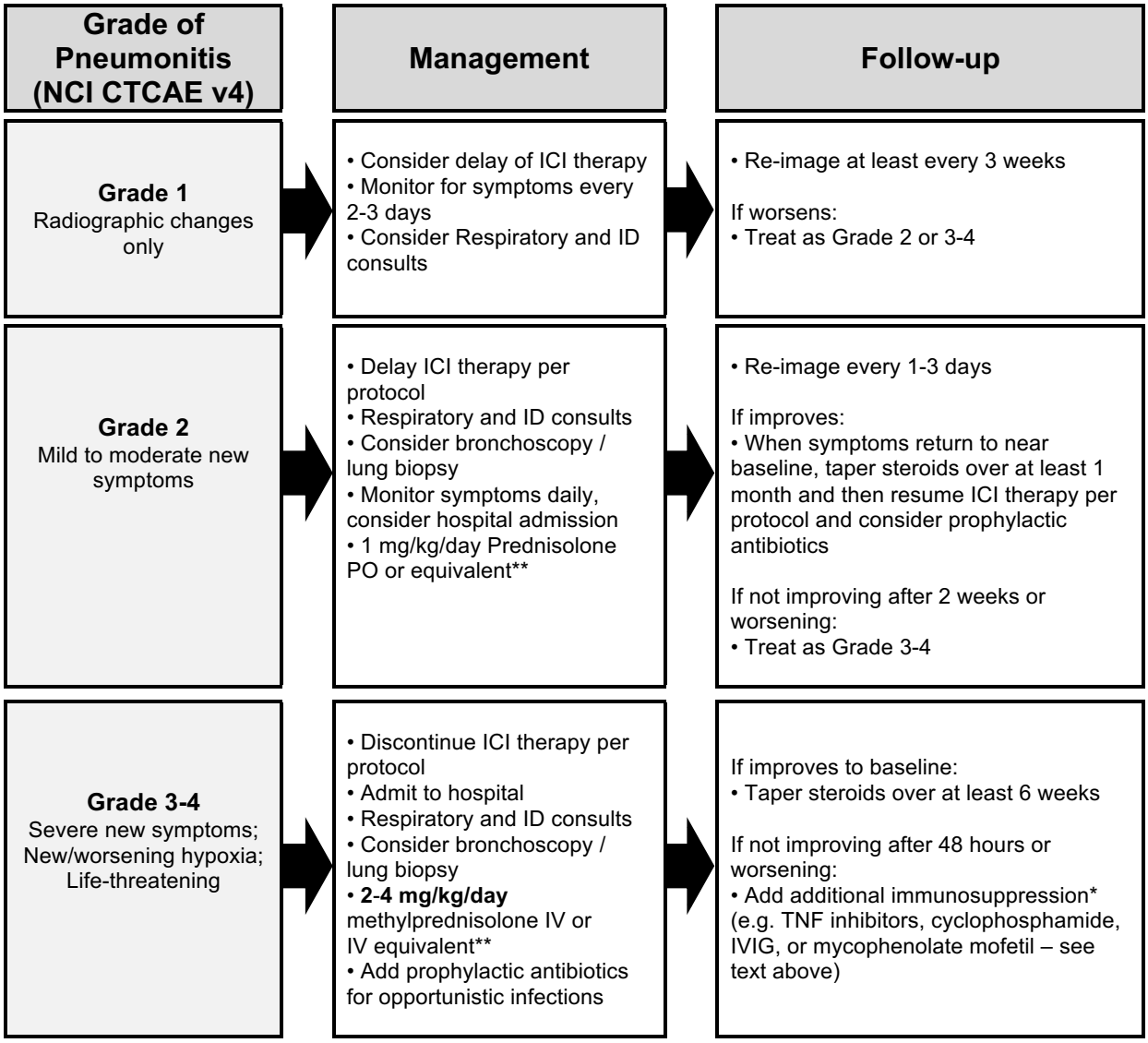
For radiographic changes suggestive of pneumonitis only (Grade 1) interruption of ICI therapy should be considered with increased clinical monitoring and repeat imaging.

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



* 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

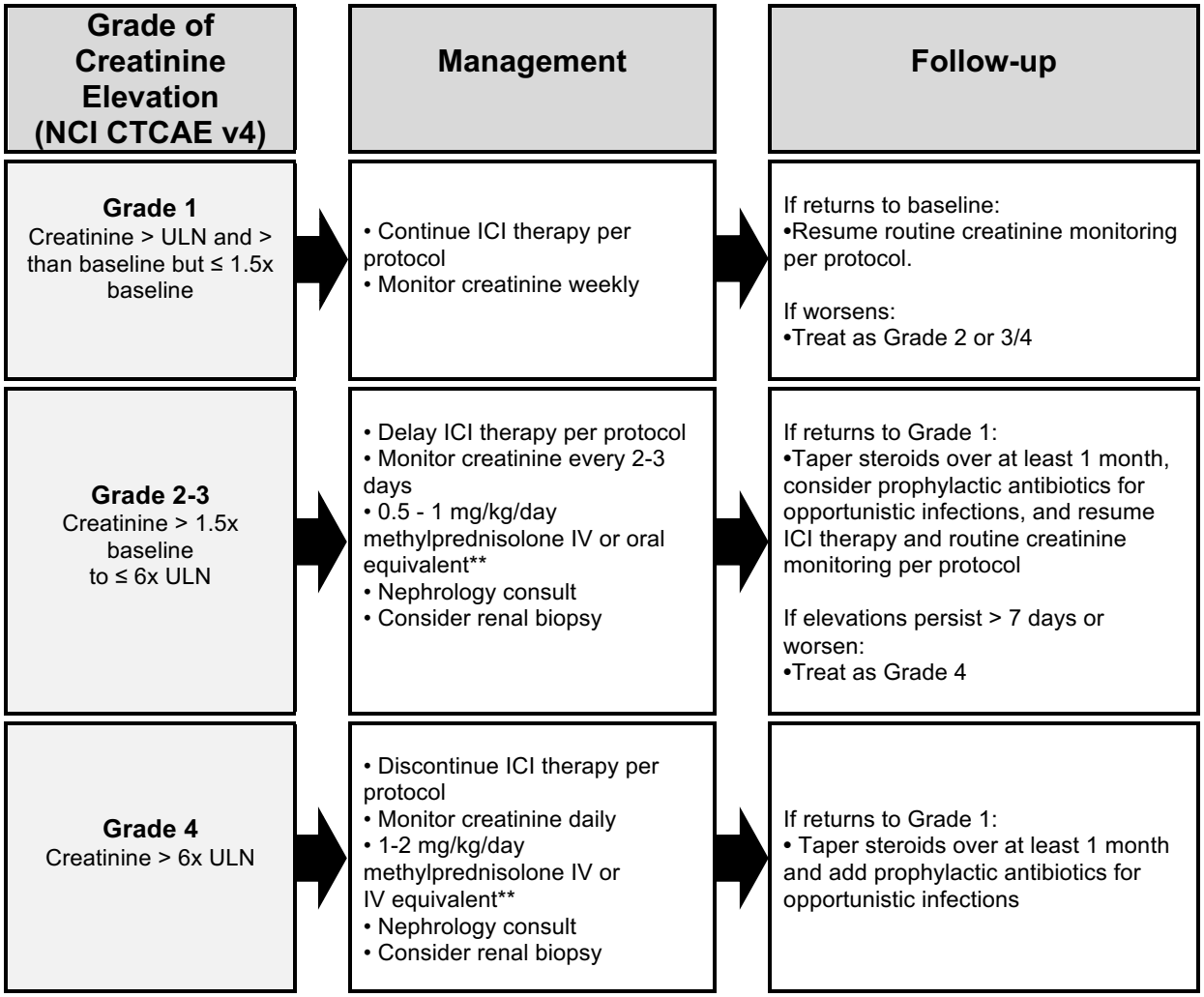
Mild renal impairment (Grade 1) requires increased monitoring of renal function, but ICI therapy can usually be continued.

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



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

ULN – upper limit of normal

Adapted from Reference 5.

3.7 Neurological [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**) 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**) 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

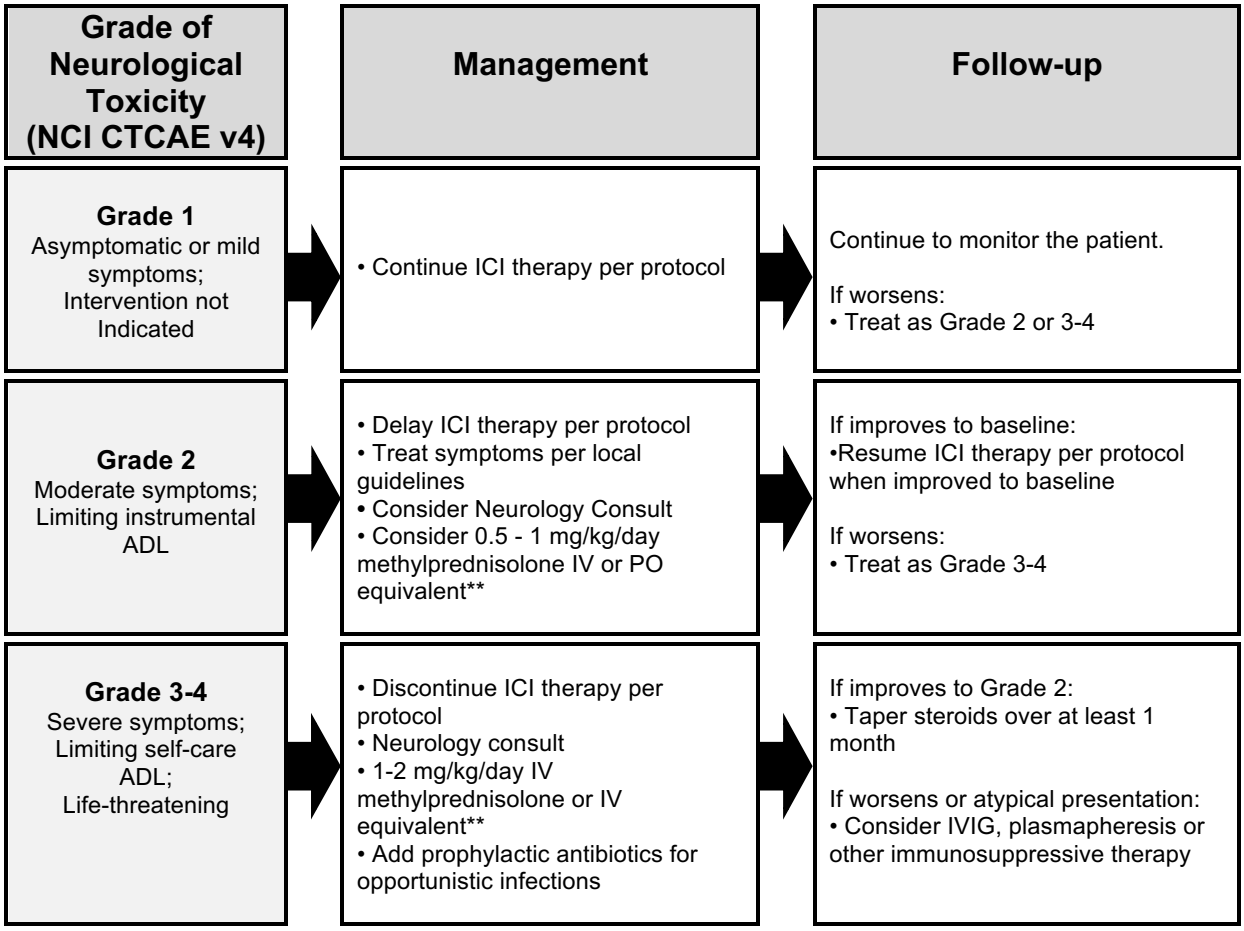
Management of GBS related to ICI therapy should be managed similarly to other forms of GBS, with plasmapheresis or intravenous immunoglobulin. ICI therapy should be discontinued. Cases of GBS related to ICI therapy have also been treated with high dose corticosteroids with good effect, which does differ 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.

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

Neurological irAE Management Algorithm



** 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.

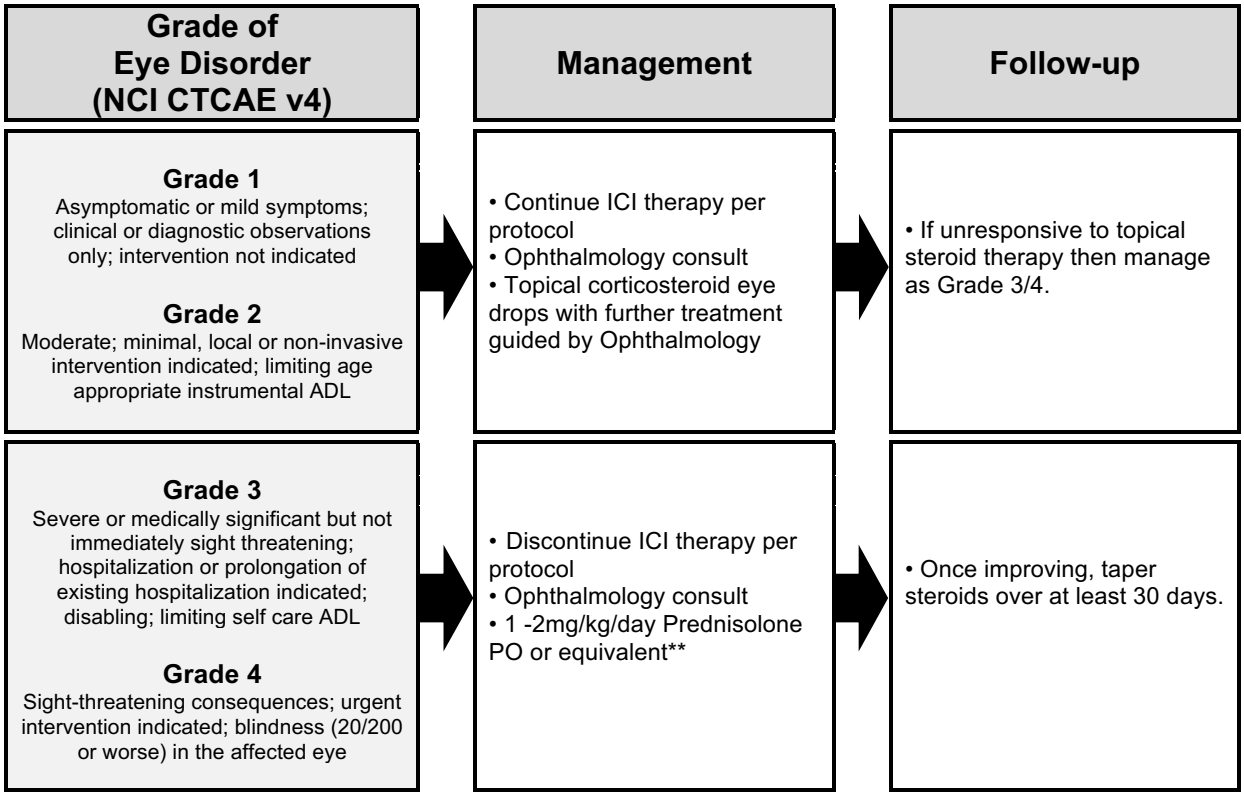
Management

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



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

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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]):			
Breach legislative requirements	☐	*Impact on Patient Quality of Care*	☒
Breach National/State/Hospital Policy	☐	*Impact on Patient Safety*	☒
Breach professional standards	☐	*Misconduct*	☐
Breach SCGH Mission & Values	☐	*Other:*	☐

8. Document Endorsement

Endorsing Authority	
Endorsed by	Dr Joanna Dewar, Head of Department, Medical Oncology Dr Andrew McLean-Tooke, Head of Department, Immunology **Medical Executive Committee **Drug and Therapeutics Committee
Policy Author	Dr Jack Bourke, Department of Immunology
Executive Sponsor	**Dr David Joske, Medical Co-Director, Medical Specialties Division
Initial Endorsement	DDMMYYYY
Last Amended	N/A
Next Review Date	DDMMYYYY **3 years**
Version	1
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

Class	Drug Name
Anti CTLA-4	Ipilimumab
Anti PD-1	Pembrolizumab Nivolumab
Anti PD-L1	None currently in use in Australia

9.2 Appendix 2: Summary of drugs used for irAE management;

Refer to individual algorithms for details.

<table>
<tr><th rowspan="2">System</th><th colspan="4">Adverse Event Grade</th></tr>
<tr><th>1</th><th>2</th><th>3</th><th>4</th></tr>
<tr><td>Skin</td><td colspan="2">Antihistamines
Topical steroids

If persistent:
Prednisolone 0.5 - 1 mg/kg/day</td><td colspan="2">Methylprednisolone 1 – 2 mg/kg/day</td></tr>
<tr><td>Gastrointestinal</td><td colspan="2">Anti-diarrhoeal agents
Fluid and electrolyte replacement

If persistent Grade 2:
Prednisolone 0.5 - 1 mg/kg/day</td><td colspan="2">Methylprednisolone 1 – 2 mg/kg/day

If refractory:
Consider TNF inhibitor
(e.g. Infliximab 5mg/kg)</td></tr>
<tr><td>Hepatic</td><td colspan="2">Monitor

If persistent:
Methylprednisolone 0.5 - 1 mg/kg/day</td><td colspan="2">Methylprednisolone 1 – 2 mg/kg/day

If refractory:
Other immunosuppression
(e.g. Mycophenolate mofetil 1g bd)</td></tr>
<tr><td rowspan="3">Endocrine</td><td colspan="4"></td></tr>
<tr><td>Endocrinopathy</td><td>Monitor</td><td colspan="2">Methylprednisolone 1 – 2 mg/kg/day
Appropriate hormone replacement as required</td></tr>
<tr><td>Adrenal crisis</td><td colspan="3">Hydrocortisone 100mg or Dexamethasone 4mg + ongoing replacement
Intravenous fluid resuscitation</td></tr>
<tr><td>Pulmonary</td><td>Monitor</td><td>Prednisolone
1mg/kg/day</td><td>Methylprednisolone 2 – 4 mg/kg/day

If refractory:
Consider other immunosuppression
(e.g. TNF inhibitor, cyclophosphamide,
IVIG, Mycophenolate mofetil)</td></tr>
<tr><td>Renal</td><td>Monitor</td><td colspan="2">Methylprednisolone 0.5 - 1 mg/kg/day</td><td>Methylprednisolone
1 – 2 mg/kg/day</td></tr>
<tr><td rowspan="2">Neurological</td><td rowspan="2">Monitor</td><td rowspan="2">Methylprednisolone
0.5 - 1 mg/kg/day</td><td>Methylprednisolone 1 – 2 mg/kg/day</td></tr>
<tr><td>If progression or Atypical features:
Consider IVIG, Plasmapharesis or
additional immunosuppression</td></tr>
<tr><td>Ophthalmic</td><td colspan="2">Topical corticosteroid eye drops</td><td colspan="2">Prednisolone 1 - 2 mg/kg/day</td></tr>
</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;

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

National Cancer Institute (NCI) - Common Terminology Criteria for Adverse Events v4.03 (CTCAE)

Adverse Event	Grade				
	1	2	3	4	5
SKIN					
Pruritus	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g. edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	-	-
Rash – maculo-papular	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL	-	-
Stevens-Johnson syndrome	-	-	Skin sloughing covering <10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Skin sloughing covering 10 - 30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Death
Toxic epidermal necrolysis	-	-	-	Skin sloughing covering >=30% BSA with associated symptoms (e.g., erythema, purpura, or epidermal detachment)	Death
GASTROINTESTINAL					
Diarrhoea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care	Life-threatening consequences; urgent intervention indicated	Death
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
HEPATIC					
ALT and/or AST increased	ALT/AST >ULN - 3.0 x ULN	ALT/AST >3.0 - 5.0 x ULN	ALT/AST >5.0 - 20.0 x ULN	ALT/AST >20.0 x ULN	-
Bilirubin increased	Bilirubin >ULN - 1.5 x ULN	Bilirubin >1.5 - 3.0 x ULN	Bilirubin >3.0 - 10.0 x ULN	Bilirubin >10.0 x ULN	-
ENDOCRINE					
Adrenal insufficiency	Asymptomatic; clinical or diagnostic observations only; intervention not indicated.	Moderate symptoms; medical intervention indicated.	Severe symptoms; hospitalization indicated.	Life-threatening consequences; urgent intervention indicated.	Death
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated.	Symptomatic; thyroid replacement therapy indicated; limiting instrumental ADL.	Severe symptoms; limiting self care ADL; hospitalization indicated.	Life-threatening consequences; urgent intervention indicated.	Death
Hyperthyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated.	Symptomatic; thyroid suppression indicated; limiting instrumental ADL.	Severe symptoms; limiting self care ADL; hospitalization indicated.	Life-threatening consequences; urgent intervention indicated.	Death

Hypophysitis	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	Moderate; minimal, local or non-invasive; intervention indicated; limiting age appropriate instrumental ADL.	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL.	Life-threatening consequences; urgent intervention indicated.	Death
PULMONARY					
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
RENAL					
Acute kidney injury	Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline	Creatinine 2 - 3 x above baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
NEUROLOGICAL					
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated	Death
Peripheral sensory neuropathy	Asymptomatic; loss of deep tendon reflexes or paraesthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Myositis	Mild pain	Moderate pain associated with weakness; pain limiting instrumental ADL	Pain associated with severe weakness; limiting self care ADL	-	-
Nervous system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
OPHTHALMIC					
Uveitis	Asymptomatic; clinical or diagnostic observations only	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis	Blindness (20/200 or worse) in the affected eye	-
Eye disorders – Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental ADL	Severe or medically significant but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye	-