Guidelines for Management of Immunotherapy-Related Adverse Events

These guidelines apply to all patients who are receiving, or have received, treatment with any of the immune checkpoint inhibitors; ipilimumab, pembrolizumab, nivolumab, atezolizumab or avelumab

For details regarding prescribing, administration, and the routine monitoring requirements for patients on immune checkpoint inhibitors, see the relevant protocol available at http://stlukescanceralliance.co.uk/

Immune-related adverse events (irAEs) usually occur within weeks to 3 months after initiation of immune checkpoint blockers. However, first onset of an immune-related adverse event may occur up to 1 year after discontinuing treatment.

For management of immune-related adverse events, follow the relevant pathway(s) below:

- Skin toxicity
- Colitis
- Hepatitis
- Endocrinopathies: Thyroid, Diabetes, Hypophysitis
- Pneumonitis
- Nephritis
- Neurological
- Other

Steroid taper guidance

Length of steroid taper is dictated by severity of the irAE.
Guidance on the recommended length of taper can be found in each pathway.
Regular monitoring during tapering is advised, as there is a risk of irAE recurrence.
For out-patients, the options are:
- to emphasise to the patient to telephone if ANY new symptom or worsening symptom, and to monitor in clinic at least every 2 weeks or
- to pro-actively monitor by telephone, once or twice weekly, throughout the taper.

Tapering guidance:
- If on IV methylprednisolone, continue for 5 days, then switch to oral prednisolone, if possible.
- For oral prednisolone, reduce the dose in 10mg/day steps every 7 days, or as resolution of toxicity allows.
- Once steroid dose is 10mg/day, consider reducing to 5mg/day for 7 days, then to zero, as appropriate.
- If signs or symptoms of adrenal suppression, steroids will need to have a prolonged wean in steps of less than 5mg, or consider physiological replacement with hydrocortisone +/- endocrinology review.

While on steroids, regular random blood glucose monitoring is required:
- pre-existing diabetes may require escalation in oral hypoglycaemic agents or insulin
- if new hyperglycaemia is detected, manage accordingly; endocrinology advice may be sought

Consider calcium/vitamin D supplement if steroids continue > 4 weeks
Monitor for oral candidiasis.

Immunotherapy may be restarted within 12 weeks after the last dose, only if an adverse reaction remains at Grade ≤ 1 and the corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day.
Immune-related Skin Toxicities

These are the most common adverse events, including maculopapular rash, pruritis and vitiligo. However severe skin adverse events are rare, and they do not usually require dose reductions or treatment discontinuation.

Symptom Grade

Grade 1: Skin rash with or without symptoms, < 10% BSA

Avoid skin irritants and sun exposure. Recommend regular emollient use. Initiate topical Betnovate or Dermovate cream once daily +/- oral antihistamine for itch

Proceed with immunotherapy

Investigations

Skin examination: Exclude other causes, e.g. viral illness, infection, other drug rash

Grade 2: Skin rash covers 10% to 30% of BSA (or diffuse but light rash not associated with any symptoms)

Supportive management as above

Initiate topical Dermovate cream once or twice daily +/- oral antihistamine for itch

Proceed with immunotherapy, but check weekly for improvement – if the rash does not resolve, interrupt immunotherapy until reverted to grade 1.

Investigations

As above

Consider dermatology referral and consider skin biopsy

Grade 3: Skin rash covers > 30% of BSA, or Grade 2 with substantial symptoms

Withhold immunotherapy.

Use topical Dermovate cream twice daily.

Initiate systemic steroids:

If mild – moderate; oral prednisolone 0.5 - 1mg/kg/day (max 60mg/day) for 3 days, then taper over 1-2 weeks.

If severe, methylprednisolone IV 0.5 - 1mg/kg/day, and convert to oral prednisolone on response; wean over 2 – 4 weeks.

Once resolved to G1/mild G2, Consultant and patient decision to re-start immunotherapy.

Investigations

As for Grade 1

Dermatology review
Consider punch biopsy and clinical photography

Grade 4: Skin sloughing > 30% of BSA, with associated symptoms such as erythema, purpura, epidermal detachment

Initiate methylprednisolone IV 1 - 2mg/kg/day

Urgent dermatology review
Permanently discontinue immunotherapy

Investigations

As for Grade 1

Dermatology review
Punch biopsy and clinical photography
### Immune-related Colitis

#### Symptom Grade

**Grade 1**
- (< 4 stools day over baseline)
- Feeling well.
- *Immunotherapy may continue*

**Grade 2**
- (4 – 6 stools/day over baseline)
- or abdominal pain
- or blood in stool
- or nausea
- or nocturnal episodes.
- *Withhold immunotherapy*

**Grade 3 - 4**
- (> 6 stools/day over baseline)
- Requires hospitalisation and isolation until infection excluded.
- *Withhold immunotherapy*

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#### Management

**Symptomatic management with oral fluids and loperamide (max 16mg/day; if this is ineffective, do NOT persist with other anti-diarrhoeals)**
- Avoid high fibre and lactose.

**G1 and symptoms persist for > 14 days, OR**
- G2 and persists for > 3 days or worsens

- Initiate oral prednisolone
  - 0.5 – 1 mg/kg/day (max 60mg/day)
  - (non-enteric coated)

**No improvement in 72 hours, or worsening, or absorption concern**

**Consider a dose of infliximab 5mg/kg IV**
- (if no perforation, sepsis, TB, hepatitis or moderate/severe heart failure)
  - *Must have had sigmoidoscopy prior to infliximab*

- A repeat infliximab dose after 2 weeks may occasionally be required.

#### Investigations

**All below tests required for Grade 2, and consider for Grade 1, according to clinical setting:**
- FBC, U&Es, LFTs, TFTs, CRP
- Stool microscopy for leukocytes, ova, parasites, C. difficile, cryptosporidia, viral PCR.
- Culture stool for drug-resistant organisms

**Outpatients: tests as above.**
- Plus consider in case of abdominal discomfort, abdominal x-ray for signs of colitis.
- Exclude steatorrhea.
- Book sigmoidoscopy (+/- biopsy)
- Contact patient every 72 hours.

**Inpatients: tests as above, including sigmoidoscopy.**
- Consider CT abdomen, and repeat abdominal x-ray as indicated.
- Daily FBC, U&Es, LFTs, CRP.
- Review diet, e.g. NBM, clear fluids, TPN
- Early surgical review if bleeding, pain or distension.
- Daily stool chart.

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Once symptoms of colitis have resolved, the dose of steroid may be gradually tapered over 2-4 weeks (if moderate colitis) or 4 – 8 weeks (if severe colitis). Too-rapid de-escalation is known to risk incomplete treatment of colitis.
Immune-related Hepatitis

**Symptom Grade**

- **Grade 1:**
  - ALT/AST > ULN to 3 x ULN
  - Proceed with immunotherapy
  - Monitor LFTs weekly while > ULN – 3 x ULN

- **Grade 2:**
  - ALT/AST > 3 - 5 x ULN
  - Withhold immunotherapy.
  - If AST/ALT is rising when re-checked, or persistent longer than 1-2 weeks, initiate oral prednisolone 1mg/kg/day (max 60mg/day).
  - Once resolved to G1, wean steroids over 2 weeks; re-escalate if worsening; treatment may be resumed once prednisolone ≤ 10mg.
  - If no improvement despite steroids, increase dose to 2mg/kg/day (methyl)prednisolone and permanently discontinue immunotherapy.

- **Grade 3:**
  - ALT/AST 5 - 20 x ULN
  - Permanently discontinue immunotherapy.
  - ALT/AST < 400 and normal bilirubin/INR/albumin: initiate oral prednisolone 1mg/kg/day* (max 60mg/day)
  - ALT/AST > 400 or raised bilirubin/INR/low albumin: initiate methylprednisolone IV 2mg/kg/day*

- **Grade 4:**
  - ALT/AST > 20 x ULN
  - Permanently discontinue immunotherapy.
  - Initiate methylprednisolone IV 2mg/kg/day*

**Management**

**Investigations**

- Re-check LFTs/INR/albumin every 3 days.
- Review concurrent medicines, e.g. statins, antibiotics, alcohol.
- Perform liver screen: Hep A/B/C/E, anti-ANA/SMA/LKM/SLA/LP/LCI & iron studies
- Consider imaging for metastases / clot

- As above, but daily LFTs/INR/albumin
- Perform US with Doppler
- Low threshold to admit patient if concerned.
- Refer to hepatologist for advice, in steroid-refractory cases

- As above, but Hepatology consult
- Consider liver biopsy

* Once improved to G2, can change to oral prednisolone and wean over 4 weeks
* If worsening hepatitis despite steroids;
  - if on oral, change to IV methylprednisolone
  - if on IV, add in mycophenolate mofetil 500 – 1000mg bd po or IV (Consultant decision only, pink form required)
Immune-related Endocrinopathies

**Hypothyroidism:** Low $T_4$ with elevated TSH, or TSH > 10 with normal $T_4$.

Hypothyroidism may be managed with replacement therapy (start dose of thyroxine 25mcg od, check TFTs 4-weekly and adjust accordingly) without immunotherapy treatment interruption (and without corticosteroids).

Consider referral to endocrinologist.

**Hyperthyroidism:** Low TSH with elevated $T_4$.

*N.B. A falling TSH across 2 measurements, with normal or lowered $T_4$, may suggest pituitary dysfunction, and weekly cortisol levels should be performed.*

Note that subclinical hyperthyroidism (low TSH, normal $T_4$) often precedes overt hypothyroidism.

Withhold immunotherapy if patient is unwell with symptomatic hyperthyroidism. **Refer to endocrinologist.**

If painful thyroiditis, consider prednisolone 0.5mg/kg/day (max 60mg/day) and then taper.

Immunotherapy may re-start once symptoms controlled and prednisolone ≤ 10mg/day.

**Diabetes:** The emergence of either Type 1 or Type 2 diabetes occurs in < 1% of patients treated with immune checkpoint inhibitors.

Steroids will negatively influence diabetic control, and it is unclear whether they will prevent total loss of beta cells in the islands of Langerhans, so they are not routinely recommended in this setting.

Withhold immunotherapy until diabetic control has been achieved.
**Immune-related Hypophysitis**

Inflammation of the anterior lobe of the pituitary gland. Very rare in patients treated only with PD-1/PD-L1 antibodies. Headache or visual disturbances require differentiation between cerebral metastases, leptomeningeal disease, cerebrovascular disease or hypophysitis.

### Symptoms
- Severe headache, any visual disturbance or severe hypoadrenalism (hypotension, severe electrolyte disturbance)
- Moderate symptoms (headache but no visual disturbance) or fatigue / mood alteration but haemodynamically stable, no electrolyte disturbance
- Vague symptoms (mild fatigue, anorexia), no headache or asymptomatic (i.e. identified on routine testing)

### Management
- **Severe headache, any visual disturbance or severe hypoadrenalism**
  - Withhold immunotherapy.
  - Initiate methylprednisolone IV 1mg/kg/day after sending bloods for pituitary axis assessment*.
  - Analgesia as needed for headache (discuss with neurologist if resistant to paracetamol and NSAIDs)
- **Moderate symptoms (headache but no visual disturbance) or fatigue / mood alteration but haemodynamically stable, no electrolyte disturbance**
  - Withhold immunotherapy.
  - Initiate oral prednisolone 0.5 – 1mg/kg/day (max 60mg/day) after sending bloods for pituitary axis assessment*
  - If no improvement in 48 hours, treat as severe with IV methylprednisolone as above
- **Vague symptoms (mild fatigue, anorexia), no headache or asymptomatic (i.e. identified on routine testing)**
  - Proceed with immunotherapy.
  - Send bloods for pituitary axis and await results to confirm diagnosis, but warn patient to seek urgent review if unwell.
  - Initiate appropriate hormone replacement therapy

### Further assessment
- **Severe headache, any visual disturbance or severe hypoadrenalism**
  - Refer to endocrinologist.
  - MRI pituitary.
  - Aim to convert to prednisolone and wean over 4 weeks to 5mg.
  - **Do not stop steroids**
  - Monitor TFTs
- **Moderate symptoms (headache but no visual disturbance) or fatigue / mood alteration but haemodynamically stable, no electrolyte disturbance**
  - Refer to endocrinologist.
  - MRI pituitary.
  - Wean steroids based on symptoms over 2-4 weeks to 5mg prednisolone.
  - **Do not stop steroids**
  - Monitor TFTs
- **Vague symptoms (mild fatigue, anorexia), no headache or asymptomatic (i.e. identified on routine testing)**
  - Refer to endocrinologist.
  - MRI pituitary.
  - Wean steroids based on symptoms over 2-4 weeks to 5mg prednisolone.
  - Do not stop steroids
  - Monitor TFTs

### Pituitary axis bloods:
- 9am cortisol* (or random if unwell and cannot delay)
- ACTH, TSH, T4, LH, FSH, oestradiol if premenopausal, testosterone in men, IGF-1, prolactin

*Caution, if the patient is already on steroids, then serum cortisol will likely be suppressed; discuss with endocrinology before commencing replacement.
Immune-related Pneumonitis

All patients presenting with pulmonary symptoms such as an upper respiratory infection, new cough, shortness of breath or hypoxia should be assessed by CT. Monitor carefully, as fatal and life-threatening cases of pneumonitis have been reported.

### Symptom Grade

- **Grade 1:** Radiographic changes only
  - Non-specific interstitial pneumonia

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

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

### Management

- **Consider delay of immunotherapy**
  - Monitor symptoms every 2 – 3 days
  - If worsens, treat as grade 2 or grade 3 - 4

- **Withhold immunotherapy**
  - Start antibiotics if suspicious of infection
    - (fever, CRP, neutrophil count)
  - If no evidence of infection, or no improvement after 48 hours, add in oral prednisolone
    - 1mg/kg/day (max 60mg/day)
  - Once resolved to baseline, wean steroids over 4 - 6 weeks, titrate to symptoms.

- **Permanently discontinue immunotherapy.**
  - Admit patient, baseline tests as above.
  - Initiate methylprednisolone IV
    - 2 – 4 mg/kg/day
  - Refer to chest physician
    - High resolution CT +/- bronchoscopy and BAL pending appearances
    - Cover with empiric antibiotics
    - Discuss escalation and ventilation

- **Add infliximab**
  - 5mg/kg or mycophenolate mofetil 500 – 1000mg bd (po or IV) if concurrent hepatitis
  - Continue with IV steroids – wean as clinically indicated over at least 8 weeks

### Investigations

- **Chest x-ray**
  - +/- high resolution CT
  - FBC, U&Es, LFTs, TFTs / Ca / ESR / CRP
  - Sputum for culture
  - O₂ sats

- **Out-patient monitoring:**
  - Monitor symptoms daily
  - Baseline tests as above, plus bloods weekly
  - Lung function tests including TCLO (transfer factor for CO)

- **No improvement after 48 hrs of oral prednisolone, manage as G3**

- **No improvement or worsening after 48 hours**

- **Once resolved to baseline, wean steroids over ≥ 6 weeks.**

- **Ensure funding approval obtained**

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Reason for Update: need for single toxicity management document

Approved by Chair of Alliance Chemotherapy Group: Dr J De Vos

Version: 1b

Date: 16.10.17

Supersedes: information included in individual immunotherapy protocols

Review Date: October 2019

Prepared by: S Taylor

Checked by: Dr M Ajaz
Immune-related Nephritis

### Symptoms

- **Grade 1:** Creatinine 1.5 x baseline or ULN – 1.5 x ULN
- **Grade 2:** Creatinine >1.5 – 3 x baseline or >1.5 - 3 x ULN
- **Grade 3:** Creatinine > 3 x baseline or >3 - 6 x ULN
- **Grade 4:** Creatinine > 6 x ULN

### Management

- **Continue immunotherapy.**
  - Repeat serum creatinine weekly.
  - If worsens, manage as criteria below.

- **Continue immunotherapy.**
  - Repeat serum creatinine weekly.
  - If diagnostic tools are already in place, refer to nephrologist as above.

- **Withhold immunotherapy.**
  - Encourage hydration and review creatinine in 48 – 72 hours; if not improving, discuss with nephrologist and need for biopsy.
  - If considered an irAE, initiate oral prednisolone 0.5 – 1mg/kg/day (max 60mg/day)
  - Repeat creatinine and K+ every 48 hours.
  - Immunotherapy may re-commence once creatinine recovered to Grade 1/ baseline and prednisolone ≤ 10mg/day

- **Withhold immunotherapy.**
  - Admit patient for monitoring and fluid balance.
  - Repeat creatinine every 24 hours.
  - Discuss with nephrologist need for biopsy.
  - If worsening, initiate methylprednisolone IV 1-2mg/kg/day.

- **As for Grade 3.**
  - Patient should be managed in a hospital where renal replacement therapy is available.
  - Permanently discontinue immunotherapy.

### Further assessment

- **Review hydration status & other medications, & consider UTI.**
  - Dipstick urine and send for protein assessment.
  - Urine protein:creatinine ratio (UPCR)
  - If obstruction suspected, renal ultrasound.

- **As above**
  - Consult with nephrologist
  - Renal ultrasound +/- doppler to exclude obstruction/clot.
  - If proteinuria, for 24 hour collection or UPCR.
  - If blood: phase contrast microscopy and glomerulonephritis screen, if nephrologist recommends.
  - Advise patient to notify if oliguric.
  - (Oliguria requires inpatient admission)

- **As above**
  - Refer to nephrologist

- **As above**
  - Refer to nephrologist

### Steroid wean:

- Begin to wean once resolved to Grade 1. For G2 severity, wean over 2-4 weeks.
- For G3/4 episode, wean over ≥4 weeks.
A range of neurological events have been described, including polyneuropathy, facial nerve palsy, myasthenia gravis, Guillain Barré syndrome, encephalitis and aseptic meningitis.

It is important to rule out progression of the cancer, infection, or other medications as the cause of the symptoms.

**Symptom Grade**

Mild: no interference with function, symptoms not concerning to patient.

(Manage mild cranial nerve problem as moderate)

Moderate: some interference with ADL, symptoms concerning to patient

Severe: limits self care, life-threatening, e.g. respiratory problems

**Management**

Low threshold to delay immunotherapy and monitor symptoms for another week, versus continue immunotherapy.

Monitor closely for any progression

Withhold immunotherapy.

Initial observation reasonable, or initiate oral prednisolone 0.5 - 1mg/kg/day (max 60mg/day) if, for example, progressing from mild and /or requiring medicines for pain e.g. pregabalin

Once resolved to grade 1, resume immunotherapy.

If worsening symptoms, manage as severe

Permanently discontinue immunotherapy.

Admit patient, and initiate methylprednisolone IV 2mg/kg/day.

Involve neurologist in care.

Daily neurological review.

**Investigations**

Comprehensive neurological exam.

Diabetic screen, B12/folate, HIV, TSH, consider vasculitic & autoimmune screen, review alcohol history and other medicines.

Consider need for MRI brain or spine (exclude CVA, structural cause)

Consult with neurologist

As above.

Consider nerve conduction studies/electromyography for motor and/or sensory change.

Consider pulmonary function tests.

Refer to neurologist.

See below for specific disorders.

MRI brain/spine advised.

Nerve conduction studies/electromyography.

Lumbar puncture.

Pulmonary function assessment.

Refer to neurologist.

See below for specific disorders.

Multidisciplinary team involvement, as appropriate

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Reason for Update: need for single toxicity management document

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Supersedes: information included in individual immunotherapy protocols

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Prepared by: S Taylor

Checked by: Dr M Ajaz
Guillain-Barré Syndrome
Progressive symmetrical muscle weakness with absent or reduced tendon reflexes. Refer to neurologists for specialist input.

Suggested investigations:
nerve conduction studies; lumbar puncture; pulmonary function tests with vital capacity and maximum inspiratory/expiratory pressures; antibody testing for GBS variants, e.g. GQ1b in Miller Fisher variant.

Use of steroids is not recommended in idiopathic GBS; however a trial of methylprednisolone IV 1-2mg/kg/day is reasonable.
If no improvement or worsening, plasmapheresis or IVIG indicated *(IVIG request form required).*
Consider ventilation – required in 15-30% of idiopathic cases.

Myasthenia Gravis
Fluctuating muscle weakness with fatigability, respiratory muscles may be involved. Refer to neurologists for specialist input.

Suggested investigations:
Check for ocular muscle and proximal muscle fatigability; AChR and anti-muscle specific kinase antibodies; Tensilon test or ice pack test with neurological input; repetitive nerve stimulation and single fibre electromyography.

Steroids indicated (oral or IV depending on symptoms).
Pyridostigmine initial dose 30mg tds.
If no improvement or worsening, plasmapheresis or IVIG may be considered *(IVIG request form, with supporting signature, required)*
Consider additional immunosuppressants (e.g. azathioprine, cyclosporine, mycophenolate)
Avoid medicines which may precipitate cholinergic crisis, e.g. beta blockers, some antibiotics

Aseptic meningitis
Exclusion of infective causes paramount.

Suggested investigations:
lumbar puncture (M/C/S, PCR for Herpes simplex, cytology); CNS imaging to exclude brain metastases or leptomeningeal disease

Exclude bacterial and ideally viral infections prior to high-dose steroids.
Oral prednisolone 0.5 – 1mg/kg/day (max 60mg/day) or methylprednisolone IV 1-2mg/kg if very unwell.
Consider concurrent empiric antiviral and antibacterial therapy.

Encephalitis
Exclusion of infective and metabolic causes paramount.
Suggested investigations:
lumbar puncture (M/C/S, PCR for Herpes simplex, cytology, consider viral culture); CNS imaging; consider viral serology

Exclude bacterial and ideally viral infections prior to high-dose steroids.
Oral prednisolone 0.5 – 1mg/kg/day (max 60mg/day) or methylprednisolone IV 1-2mg/kg if very unwell.
Concurrent IV aciclovir suggested until PCR result obtained.
Transverse myelitis
Acute or subacute neurological symptoms/signs of motor/sensory/autonomic origin.
Refer to neurologists for specialist input.

Suggested investigations:
MRI brain and spine; lumbar puncture; serum B12/HIV/syphilis/ANA/anti-Ro and anti-La Abs; TSH; anti-aquaporin-4 IgG

(Methyl)prednisolone 2mg/kg/day suggested.
Plasmapheresis may be required if non-steroid responsive.

Other Immune-related toxicities

a) Cardiac
Myocarditis, pericarditis, arrhythmias and cardiomyopathy have been reported.
Early referral to a cardiologist is recommended.
High dose corticosteroids have been used successfully and should be instituted rapidly.
Immunotherapy should be permanently discontinued in the event of any Grade 3 or Grade 4 myocarditis.

b) Rheumatology
Mild or moderate myalgia and/or arthralgia occurs in 2-12% of patients.
For mild or moderate symptoms, analgesia with paracetamol and/or NSAIDs is recommended.
Continue immunotherapy.
If moderate symptoms are inadequately controlled with NSAIDs and/or paracetamol, initiate prednisolone 10-20mg once daily, and withhold immunotherapy until prednisolone ≤ 10mg/day.
If severe symptoms, refer to a rheumatologist, withhold immunotherapy and consider high dose corticosteroids.

c) Ocular
Ocular toxicities are rare.
Topical corticosteroid eye drops may be used in the case of episcleritis or anterior uveitis.
Systemic steroids are required for severe ocular inflammation and orbital inflammation.
Intravitreal anti-vascular endothelial growth factor (VEGF) is indicated for choroidal neovascularisation.

N.B.
Ipilimumab should be permanently discontinued in the event of any other Grade 3 or 4 irAE.
Pembrolizumab or nivolumab should be permanently discontinued in the event of any other Grade 4, or recurrent Grade 3, irAE.

References:
Management of Toxicities from Immunotherapy; ESMO Clinical practice Guidelines for diagnosis, treatment and follow-up; Haanen, J et al; Annals of Oncology 2017; 28 (Supplement 4): iv119–iv142