NICaN Checkpoint Inhibitor Immunotherapy Toxicity Management Guidelines

February 2025

Document Title	**NICaN Checkpoint-Inhibitor Immunotherapy Toxicity Management Guidelines**
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Document Purpose	This guidance has been produced to support the management of immune-related adverse events for patients receiving immunotherapy. Treatment decisions for individual patients requires the consideration of a multitude of factors, which cannot all be accounted for in a clinical guideline. The Clinical Guidelines provide a description of the range of treatment options available for a clinical scenario.
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Key Policy Statement(s)

Policy Principles

- **The relevant team should be kept informed through the daily handover sheet if any patient who has received immunotherapy contacts the helpline for advice, both during working day and out of hours. Clinical concerns should be discussed with the relevant team directly by telephone or face to face during working hours, or with the SpR on call (middle grade or Consultant on-call if in North-West Cancer Centre) out of hours.**

- Patients who have received immunotherapy are entitled to use the Oncology helpline for up to **12 months** from their last treatment, and may be admitted to the Northern Ireland Cancer Centre (NICC) and the North-West Cancer Centre (NWCC) as appropriate. This is due to the potential for delayed treatment-related toxicities with these drugs. **Patients who contact the Cancer Centre helpline but are redirected to the local hospital for capacity or medical reasons must be discussed with the relevant team or on-call team as above.**

- The use of systemic corticosteroids at baseline before starting immunotherapy, is to be avoided where possible because of their potential interference with the pharmacodynamic activity and efficacy of immunotherapy agents. However, systemic corticosteroids or other immunosuppressants can be used after starting treatment to treat immune-related adverse reactions. The use of systemic corticosteroids after starting immunotherapy treatment does not appear to impair efficacy, and corticosteroids should not be withheld from patients experiencing toxicity on this basis.

- This guide covers the management of patients who call the oncology helpline or present to hospital with symptoms. It does not fully cover onward management decisions with respect to modifying/discontinuing treatment thereafter.

- The contents of this guide should be used by the oncology team to give advice to other treating physicians if patients are acutely admitted outside NICC and NWCC

Date	Version	Author	Comments
September 2018	V1	Dr B Oladipo, Dr P Gallagher	
July 2022	V2	Dr B Oladipo, Dr P Gallagher	Updates on GI/liver/cardiac/rheumatological toxicity, and fatigue advice
February 2025	V3	Dr B Oladipo, Dr P Gallagher	Updates on GI/liver/skin/endocrine/renal/cardiac toxicity, baseline cardiac biomarker testing, bone protection advice, nurse led IO toxicity service pathway

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BACKGROUND

- Immunotherapy in this guideline refers to monoclonal antibodies which target the immune system and are used as systemic anti-cancer therapy

- The currently licensed/approved drugs target cytotoxic T lymphocyte-associated antigen 4 (CTLA4) and the programmed death-1 receptor (PD-1) or its ligand (PD-L1).

- These agents have become standard of care for an increasing number of indications and a growing number of patients will be exposed to these drugs with a chance of developing toxicities from these treatments.

- Immunotherapy use has introduced a new set of adverse events not previously seen in oncology. Increased awareness, early recognition and guideline-driven management is essential.

- **Some toxicities may present with symptoms that appear familiar from chemotherapy/targeted therapy use, but the aetiology and approach to management is completely different.**

- Immune-mediated adverse reactions can affect any organ system and be fatal. A high index of suspicion should be maintained if patients present with unexplained symptoms and senior medical advice should be sought.

- The specific immunotherapy regimens covered by the guideline include but are not limited to:

  - **Pembrolizumab**
  - **Nivolumab**
  - **Ipilimumab**
  - **Ipilimumab + Nivolumab (Ipi/Nivo) combination**
  - **Nivolumab/Relatlimab (Nivo/Rela) combination**
  - **Atezolizumab**
  - **Avelumab**
  - **Cemiplimab**
  - **Durvalumab**

  Other agents may be added as and when they are licensed or become NICE approved

- Use CTC adverse event grading criteria to assess/grade severity of toxicities, (unless otherwise recommended in this guidance) and institute management as per this recommendation in this guidance document

  Website: Common Terminology Criteria for Adverse Events (CTCAE) (eortc.be)

GASTROINTESTINAL TOXICITY (DIARRHOEA AND COLITIS/ENTEROCOLITIS)

See also Gastrointestinal toxicity management flowsheet (appendix I)

Symptoms include diarrhoea, abdominal pain and mucus or blood in stool. Most common initial symptoms are increased frequency of bowel motions +/- abdominal pain/cramps. If not proactively treated, bowel perforation and death can result.

Management steps

1. Exclude possible infection and arrange stool cultures/PCR as appropriate. In addition, send a stool sample for faecal calprotectin.
2. Do not wait for stool cultures results before commencing steroids (PO prednisolone or IV methylprednisolone) depending on grade. Anti-diarrhoeals (loperamide, codeine) are NOT recommended in the management of immunotherapy-related diarrhoea/colitis/enteritis
3. Ascertain the grade of the symptoms and treat as per below

GI toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhoea	Increase of <4 stools per day over baseline; mild increase in stoma output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in stoma output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in stoma output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated
Colitis/Enterocolitis	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/fever/ileus	Life-threatening consequences; urgent intervention indicated

Diarrhoea

Grade 1:

- Encourage increased oral fluid intake
- Baseline bloods, to include FBC, oncology profile (U&E, serum magnesium, calcium and phosphate, LFTs) and CRP
- If persistent grade 1 diarrhoea, or if diarrhoea of other potential confounding aetiology, send stool sample for faecal calprotectin. Consider stool microscopy and culture/PCR and Clostridium difficile screen
- Needs follow-up call within 24 hours to ensure symptoms are not progressing, and daily thereafter until symptoms improve. If symptoms fail to improve or worsen, then clinically re-assess grade and treat accordingly.
- Next dose of immunotherapy may be given, at treating consultant's discretion. Consider deferring treatment until diarrhoea resolved, especially for patients on ipilimumab or ipilimumab/nivolumab.

- If persistent grade 1 diarrhoea, consider referral for endoscopy
- Consider escalating treatment as per grade 2+ if there is clinical concern, no improvement after 3 days, or alarm symptoms present. These include:
    - Nocturnal diarrhoea
    - New incontinence
    - Organ dysfunction
    - Blood/mucous in stool, or abdominal pain (see colitis grading).

Grade 2:

- Assess patient clinically, to ensure no hypotension/electrolyte imbalance.
- Baseline bloods (FBC, U+E, serum magnesium, calcium and phosphate, LFTs and CRP) and abdominal x-ray
    - Admit for IV fluids and further abdominal imaging (consider CT) if any clinical concerns
- Send stool sample for faecal calprotectin, stool microscopy and culture/PCR and Clostridium difficile screen
- Commence PO prednisolone 1mg/kg daily (max 60mg/day) with Gastroprotection
- If not admitted, a follow-up call is needed within 24 hours to ensure symptoms are not progressing, and daily thereafter until symptoms improve. If symptoms fail to improve or worsen, then clinically re-assess grade and treat accordingly.
    - If no improvement after 3 days, consider escalating to management as per grade 3-4
- Consider referral for endoscopy
- Ensure the relevant team is informed and a tapering schedule for steroids/telephone assessments should be arranged with the team (see steroid tapering guidance, appendix XI)
- Omit next cycle of immunotherapy until symptoms resolve.

Grade 3 or 4:

- Admit for hydration and commence high dose IV methylprednisolone 2mg/kg
- Send stool sample for faecal calprotectin, stool microscopy and culture/PCR and Clostridium difficile screen
- Baseline bloods (FBC, U&E, serum magnesium, calcium and phosphate, LFTs, TFTs, cortisol & CRP)
- Arrange CT abdomen
- Arrange flexible sigmoidoscopy

- Screen for infliximab administration suitability on admission (to include TB history and quantiferon IGRA test, hepatitis screen, HIV, chest X-Ray (if chest CT not already performed) (see appendix XIII)
- Escalate to infliximab if no improvement on high dose steroids after 72 hours (see appendix XIII)
- Plan for 2 doses of infliximab 2 weeks apart as standard, regardless of initial response
- Commence steroid taper once symptoms have improved to grade 1 (or grade 2 if has received infliximab) (see steroid tapering guidance, appendix XI)
- Permanently discontinue immunotherapy for patients on ipilimumab or ipilimumab/nivolumab combination. For patients on single agent anti-PD-1/PD-L1 therapy, refer to SPC (http://emc.medicines.org.uk/) and discuss with consultant

Colitis/Enterocolitis

Grade 1:

- If diarrhoea, send a faecal calprotectin
- If no diarrhoea, to be followed up and monitored clinically by treating team
- Consider referral for endoscopy

Grade 2 and above:

- Admit for investigations and perform CT abdomen and refer for endoscopy. Consider NBM until investigations performed
- Commence steroids:
  - **If grade 2 colitis/enterocolitis and NO diarrhoea**: Commence PO prednisolone 1mg/kg with Gastroprotection (max 60mg/day), until treating team reviews
  - **If grade 2 colitis/enterocolitis with diarrhoea of ANY CTC grade; or grade ≥3colitis/enterocolitis with or without diarrhoea**: Treat as grade 3/4 diarrhoea as above.
- If symptoms persist with blood in stools, significant bowel inflammation seen on imaging, or clinical deterioration, urgent assessment by the gastroenterology team should be considered, as endoscopy and anti-TNFα therapy (infliximab, see appendix XIII) may be indicated.
- Refer to SPC and discuss with consultant regarding further cycles of treatment.

LIVER TOXICITY (HEPATITIS)

See also hepatotoxicity management flowsheet (appendix II)

Management steps

1. Assess for other causes of hepatic injury, including infections, tumour progression, or concomitant medication
2. Ascertain the degree of liver dysfunction according to CTCAE grade

Liver toxicity	Grade 1	Grade 2	Grade 3	Grade 4
ALT or AST	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Bilirubin	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal

Grade 1:

- Exclude other causes of hepatic injury, including infections, tumour progression, or concomitant medication
- Hold any potentially offending medication where possible
- Arrange regular repeat LFTs weekly to monitor for progression or resolution.
- If any associated symptoms such as (abdominal pain/nausea and vomiting), arrange liver imaging and consider admission
- Patients may continue immunotherapy under treating consultant's discretion. If on ipilimumab or ipilimumab/nivolumab combination, consider withholding next cycle of immunotherapy until LFTs normalise or at baseline.

Grade 2:

- As for grade 1, but arrange twice weekly LFTs initially
- Arrange USS liver +/- Doppler (to exclude thrombus) and perform Hepatology blood screen
    - Coagulation screen (or INR)
    - Serum Lactate

- Amylase
- Serum ferritin
- CK level
- If bilirubin elevated: Direct and indirect bilirubin
- Hepatitis A,B,C,E screen (+/-PCR)
- EBV, CMV (PCR)
- Liver autoimmune screen

- Commence oral prednisolone 1mg/kg daily (max 60mg/day), with Gastroprotection.
- Withhold immunotherapy until LFTs back to grade 0-1 or at baseline, and steroids have been appropriately tapered (see steroid tapering guidance, appendix XI)
- If LFTs do not improve (within 3 days), worsen, or relapse, then treat as per grade 3-4

Grade 3 or 4:

- Commence IV methylprednisolone (2 mg/kg) with Gastro-protection. An ambulatory pathway can be considered for suitable patients (Belfast Trust), if otherwise well
    - In cases where transaminases (ALT and/or AST) ≥ 400, elevated bilirubin, or altered synthetic liver function (low albumin and/or prolonged PT) commence PULSED IV methylprednisolone 1g OD (with Gastroprotection) for 3 days, and discuss with Hepatology (as may require additional immunosuppressive agent)
- Arrange liver imaging and exclude other causes as above.
- Perform full Hepatology screen (see above, for grade 2)
- For patients with LFT elevations that fail to improve after 3 days of corticosteroid therapy or with clinical deterioration, early discussion with the Hepatology team is advised to allow consideration of additional immunosuppressive agent (appendix XIV).
    - IV methylprednisolone (1 g) for 3 days is advised in cases where doubling time for ALT or AST is ≤ 24 hours despite 2mg/kg IV methylprednisolone
- For patients whose LFTs are improving on corticosteroid therapy but ALT and/or AST remain ≥ Grade 3 despite 5 days of IV methylprednisolone discussion with the hepatology team is advised to allow consideration of additional immunosuppressive agent (see appendices XI and XIV).
- Commence steroid taper once LFTs returned to ≤ grade 1 (if commencing an additional immunosuppressive agent, reduce steroids upon its commencement, see appendix XI)

  - In cases which flare on ≥ 2 episodes during steroid wean, discuss with Hepatology as an additional immunosuppressive agent (e.g. Mycophenolate mofetil/MMF or tacrolimus) may be required if patient not already on (see appendix XIV).

- Permanently discontinue immunotherapy for patients on ipilimumab or ipilimumab/nivolumab combination. For patients on single agent anti-PD-1/PD-L1 therapy, refer to SPC (http://emc.medicines.org.uk/) and discuss with consultant

LUNG TOXICITY (PNEUMONITIS)

See also lung toxicity management flowsheet (appendix III)

Management steps

1. Assess for other causes of respiratory symptoms, such as infections (including PJP), VTE and tumour progression
2. Suspected pneumonitis should be confirmed with an urgent high resolution CT chest. **Note: non-classical radiological appearances of pneumonitis can occur. Maintain a high index of suspicion with all abnormal chest imaging**
3. Once confirmed, treat according to CTC grade below

Lung toxicity	Grade 1	Grade 2	Grade 3	Grade 4
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)

Grade 1:

- Assess clinically and record/document O_2 saturation
- Baseline bloods to include profile FBC, oncology profile (U&E, serum magnesium, calcium and phosphate, LFTs) and CRP
- Consider withholding next cycle of immunotherapy. If next cycle is given, arrange weekly telephone assessment and reassess clinically if symptoms develop

Grade 2:

- Assess clinically and record/document O_2 saturation
  - Arrange sputum cultures and commence antibiotics if concurrent infection suspected
  - Urine legionella and pneumococcal antigen (consider also PJP PCR mycoplasma serology and Beta-D-glucan) to exclude atypical infection
- Commence oral prednisolone 1mg/kg daily (max 60mg), with Gastroprotection
- If not admitted, for daily telephone follow up calls, to ensure symptoms not progressive, and for clinical re-assessment after 3 days of steroids, or earlier if worsening symptoms

  - If symptoms persist (≥ 3 days), or worsen, reassess grade and treat accordingly (as per grade 3-4)

- Consider early referral to respiratory team opinion for bronchoscopy/ bronchoalveolar lavage, especially for persistent/recurrent symptoms
- Repeat high resolution CT chest to be performed within 4-6 weeks to assess for deterioration
- Withhold next cycle of immunotherapy
- Commence steroid taper once pneumonitis improved to ≤ grade 1 (see appendix XI)

Grade 3 and above:

- Admit to hospital
- Urgent respiratory physician input (consider bronchoscopy/ bronchoalveolar lavage)
- Baseline bloods and atypical pneumonia screen (as per grade 2), and consider pulmonary function tests
- Commence IV methylprednisolone 2mg/kg daily with Gastroprotection. (Up to 4mg/kg can be considered for patients very unwell)
- Commence oxygen therapy as indicated.
- Commence empirical antibiotic cover for pneumonia
- Commence PJP prophylaxis with co-trimoxazole 960mg/day Mon/Wed/Fri
- If medically unstable, liaise early with intensive care as respiratory support may be needed
- Stop immunotherapy
- Commence steroid taper once pneumonitis improved to ≤ grade 1 (see appendix XI)
- Additional immunosuppressant use for refractory cases, on advice of respiratory physicians. There is limited evidence to recommend the best agent, but infliximab, tacrolimus and mycophenolate mofetil are all options that can be considered.

SKIN TOXICITY (DERMATITIS/RASH AND PRURITUS)

See also skin toxicity management flowsheet (appendix IV)

Immunotherapy agents are associated with a variety of skin adverse reactions. The most common manifestation is of a drug reaction-type maculopapular rash and/or pruritus. Severe cutaneous adverse reactions (SCARs), such as Stephen Johnson's syndrome (SJS), toxic epidermal necrolysis and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have also been reported.

Dermatitis

Management steps

1. Consider other potential causes (e.g. infection, other drugs, other systemic illnesses associated with skin manifestations)
2. Assess severity, and manage (as below)
   - Grading according to CTCAE is a challenge for skin rashes. Instead, severity may be best assessed based on body surface area, tolerability, morbidity and duration. A pragmatic classification of mild, moderate or severe as shown below can be used

Skin toxicity	Mild	Moderate	Severe (any of the following)
Rash (acneiform or maculopapular)	• Localised macular or papular eruption • Asymptomatic	• Rash affecting ≤ 50% skin surface **and** • Symptoms such as pruritus or irritation affecting ADLs/sleep	• Rash covering >50% of body surface • Generalised • Exfoliative • Ulcerative • Bullous dermatitis

Mild

- Commence an emollient cream with paraffin content (e.g. Cetraben), and consider topical steroids such as 0.05% clobetasone butyrate (Eumovate) or 0.05% Alclometasone dipropionate (Modrasone) cream.
- Add PO antihistamines if associated pruritus (chlorphenamine 4mg QDS PRN, or non-sedating anti-histamines such as cetirizine or loratidine)
- Immunotherapy may continue
- Arrange follow-up reassessment within 1 week, to see if symptoms subside.
  - If rash persists for over one week with no improvement with topical steroids, arrange dermatology review. If rash worsens, reassess grade and treat accordingly

Moderate:

- Clinical assessment of patient with baseline bloods (FBC, U&E, serum magnesium, calcium and phosphate, LFTs and CRP)
- Consider photography of rash, to enable assessment of response to intervention
- Commence emollient cream with paraffin content (e.g. Cetraben), and high potency topical steroids such as 0.122% betamethasone valerate (Betnovate) cream BD
- Add PO antihistamines if associated pruritus (see grade 1)
    - If has already been using topical steroids/antihistamines for a mild rash with no improvement/worsening, arrange dermatology review
- Oral prednisolone 30-60mg/day can be considered for rashes that are extensive or fail to respond to topical steroids but does not reach severe classification (in liaison with dermatologists). Note oral steroids are rarely required and most cases can be managed with topical agents as guided by dermatology
- Arrange follow-up reassessment within 72 hours after intervention, to see if symptoms subside. If no improvement, arrange dermatology review
- Withhold next cycle of immunotherapy

Severe

- Admit patient and arrange urgent dermatology review
- Baseline bloods FBC, oncology profile (U&E, serum magnesium, calcium and phosphate, LFTs) and CRP
- Ensure adequate hydration; Consider IV fluids
- Regular anti-histamines
- If exfoliative/ulcerative or bullous dermatitis features are present, commence IV methylprednisolone 1mg/kg daily, with Gastro-protection, in liaison with dermatology
    - Note: the usual avoidance of corticosteroids for SJS is not applicable here, as the underlying mechanism is a T-cell immune-directed toxicity
- Consider IV antibiotics (if clinically indicated for supra-imposed infection, following swab of affected area).
- Consider Drug Reaction/Rash with Eosinophilia and Systemic Symptoms (DRESS) if any associated fever, lymphadenopathy or facial oedema. Perform Chest X-ray if any respiratory symptoms. Seek senior medical input
- Discontinue immunotherapy
- Commence steroid taper once symptoms improved to mild or resolved (see appendix XI)

Pruritus

Pruritus can occur without a visible rash. This can be graded using CTCAE grading below and managed accordingly

Skin toxicity	Grade 1	Grade 2	Grade 3
Pruritus	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., oedema, 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

Grade 1:

- Commence PO antihistamines, and treat any associated rash as per protocol
- Arrange follow-up telephone call within 72 hours, to see if symptoms subside.
    - If pruritus worsens, reassess grade and treat accordingly

Grade 2:

- Assess medically to evaluate if any associated rash present. Treat any associated rash as per protocol
- Commence PO antihistamines and arrange urgent dermatology input.
- Arrange follow-up telephone call within 72 hours, to see if symptoms subside
    - If patient already on topical agents/antihistamines with no improvement over 1 week, commence PO prednisolone 30-60mg daily with Gastroprotection, in liaison with dermatology.

Grade 3:

- Commence IV methylprednisolone 1mg/kg daily, with Gastro-protection. An initial trial of oral prednisolone 60mg as per grade 2 also reasonable
- Urgent dermatology review
- Treat any associated rash as per protocol.

ENDOCRINOPATHY

See also adrenal dysfunction (appendix V) and thyroid dysfunction (appendix VI) management flowsheets

- Checkpoint inhibitor immunotherapy can cause inflammation of the endocrine system organs, and may lead to thyroid dysfunction (hypo-or hyper-thyroidism), hypophysitis with subsequent hypopituitarism, primary adrenal insufficiency, and autoimmune diabetes mellitus. Arginine vasopressin deficiency (previously known as central diabetes insipidus) can occur as a result of hypophysitis but is rare.
- Patients may present with non-specific symptoms such as headache, fatigue, and hypotension, and may have electrolyte disturbances. These often resemble other disease-related causes such as brain metastasis or progressive underlying disease. Some cases are also detected on routine blood tests and have no or mild symptoms.
- **Always consider potential endocrinopathy such as adrenal insufficiency in patients who present with vague nonspecific symptoms, even in the absence of classical biochemical or clinical signs**.
- **Immunotherapy-induced type 1 diabetes mellitus is very rare, but should also be considered in acute presentations with elevated blood sugars, especially if features of diabetes ketoacidosis (DKA) are present. A high proportion of patients with immunotherapy induced diabetes present with DKA** (see page 23)
- **NOTE:** Other acute illnesses can lead to suppression of gonadotrophin and thyroid axis, which recovers as illness resolves. High dose glucocorticoids can suppress ACTH, TSH and gonadotrophins

Management steps

1. Assess symptoms and evaluate for any non-endocrine cause such as infection.
2. Baseline bloods including FBC, oncology profile (U&E, serum magnesium, calcium and phosphate, LFTs), random blood glucose and CRP.
3. Check if recent blood tests (TFTs, serum cortisol, routinely done 3-weekly) suggest any potential thyroid or adrenal dysfunction. Repeat TFTs and cortisol levels, if high index of suspicion

- Note: TFTs and cortisol levels are not routinely assayed out of hours, and a **telephone call to the laboratory is required** to ensure sample is prioritised.

4. Arrange full endocrine function panel with updated thyroid function tests, ACTH, FSH, LH, prolactin, oestrogen (in pre-menopausal females), and testosterone in males
5. Manage as per guidance for adrenal insufficiency and thyroid dysfunction as appropriate (see below) and see relevant flowsheets (see appendix V and appendix VI). These are the most common immune-mediated endocrinopathies seen with these agents.
6. Remember the possibility of Diabetic Ketoacidosis (DKA) and Hyperosmolar Hyperglycaemic states (HHS), in patients with markedly elevated blood glucose especially in absence of a prior diabetes history. Liaise with the endocrine team early in such cases.

The initial results may not be diagnostic as the condition may be evolving. Repeat the tests if clinical concerns remain.

Hypoadrenalism

Hypoadrenalism secondary to immunotherapy may occur as a result of hypophysitis leading to hypopituitarism, or more rarely as a result of primary adrenal failure. This should be suspected if a patient presents with unexplained severe dehydration, hypotension or shock, particularly if electrolyte disturbance (hyponatraemia/hyperkalaemia), nausea, and/or non-specific abdominal pain is present. Patients may present asymptomatic, but with a serum cortisol < lower limit of normal (LLN) on routine testing. Hypophysitis may present with headache and fatigue. Visual symptoms as a result of optic chiasm compression can occur but are rare. Treat accordingly, based on the presence/absence of symptoms, and the extent of serum cortisol decrease, as below.

- **NOTE:** If the patient is already on steroids (even if topical/inhaled), then serum cortisol can be suppressed.

- Patients with suspected hypoadrenalism should have an endocrine function panel performed (NOTE: ACTH is the most common hormone deficiency in hypophysitis and can be isolated):
  - U&E, LFT, TSH, Free T4, ACTH (must be SENT ON ICE to the lab IMMEDIATELY), LH, FSH & cortisol (between 6-10am if possible), prolactin, blood glucose +/- testosterone/oestrogen
  - Note: High dose glucocorticoids can result in suppression of TSH, LH and FSH

ASYMPTOMATIC

Serum cortisol >100nmol/L but lower than reference range for time of day

- Repeat 9am cortisol within 48 hours
- If 9am cortisol confirmed as low:
  - Perform endocrine function panel
    - Consider replacement dose oral hydrocortisone (15mg am with breakfast meal/5mg pm with evening meal) whilst awaiting results of endocrine function panel.
- Monitor regularly (before each cycle as a minimum) and act as per algorithm (see appendix V) if serum levels fall or endocrine panel confirms hypopituitarism
- Continue immunotherapy

Serum cortisol ≤100nmol/L and lower than reference range for time of day

- Repeat 9am cortisol within 24 hours, and perform endocrine function panel at same time.
- If high index of suspicion (morning cortisol level significantly low in absence of steroid treatment) consider immediate commencement of hydrocortisone replacement.
- To confirm hypoadrenalism in patients who have pre-emptively been started on hydrocortisone, omit pm dose day before and the morning dose on the day of the test (i.e. check levels 24 hours after last dose). The morning dose hydrocortisone should be taken after the test whilst awaiting results

- Discuss with endocrinology for further advice, if results remain uncertain
- Continue immunotherapy

SYMPTOMATIC

Mild/Non-life threatening symptoms with serum cortisol <lower limit of reference range for time of day:

- Symptoms may include
    - Tiredness/fatigue, headache, weight loss, susceptibility to infection, normal BP and no postural drop
- Repeat 9am cortisol within 24 hours, and perform endocrine function panel at same time
- If high index of suspicion (morning cortisol level significantly low in absence of steroid treatment) consider immediate commencement of hydrocortisone replacement. An initial dose of 30mg am with breakfast meal/10mg with evening meal should be used.
- To confirm hypoadrenalism in patients who have pre-emptively been started on hydrocortisone, omit pm dose day before and the morning dose on the day of the test (i.e. check levels 24 hours after last dose). The morning dose hydrocortisone should be taken after the test whilst awaiting results
- MRI head with pituitary views should be considered in patients with persistent headaches which do not settle after corticosteroid replacement, and/or new visual disturbance/ field defects, to assess for pituitary enlargement or other pathology such as brain metastases
- Refer to endocrinology for advice/further investigation
- Consider admission to hospital for IV fluids and observation, if cortisol ≤100 and symptoms significant
- May continue immunotherapy after hormone replacement is established

Severe symptoms or life-threatening/Adrenal Crisis

(**NOTE:** Serum cortisol < 450 nmol/L in severe/life-threatening illnesses is suggestive of adrenal insufficiency)

- Suspect if symptoms/signs of the following:
    - Dizziness/collapse or hypovolaemic shock
    - Hypotension (systolic BP ≤90mmHg) or postural hypotension (≥20mmHg drop in systolic BP)
    - Nausea/vomiting
    - Abdominal pain/tenderness/guarding
    - Fever

- Confusion, delirium or coma
- Hyponatraemia, hyperkalaemia, hypoglycaemia
- Pre-renal failure

- Admit for aggressive IV fluid hydration
- Send blood samples for TFTs and random cortisol **prior** to starting IV hydrocortisone, complete endocrine function panel.
    - Commence on 100mg hydrocortisone IV followed by 50mg 6 hourly (if adrenal insufficiency is suspected do not wait for results before starting IV steroids)
    - If co-existent immune toxicity of any grade also present (such as diarrhoea, hepatitis, etc.), use IV methylprednisolone 2mg/kg daily in place of hydrocortisone (with Gastroprotection).
- Screen for infection and treat any co-existent sepsis with appropriate antibiotics
- Seek urgent endocrinology input and senior medical advice.
- MRI head with pituitary views should be considered in patients with persistent headaches which do not settle after corticosteroid replacement, and/or new visual disturbance/ field defects, to assess for pituitary enlargement or other pathology such as brain metastases. If pituitary enlargement confirmed on imaging and symptoms are persistent, higher dose steroids may be needed initially for optic chiasm or other severe compressive symptoms before weaning to replacement dose.
- Further immunotherapy will depend on clinical recovery and establishment of replacement hormone

Note: ONCE ESTABLISHED ON STEROIDS

- Commence levothyroxine if free-T4 also low (do not commence before established on steroids)
- Gonadal hormone replacement should be considered for cases of hypophysitis with persistent, confirmed hypogonadism following recovery from acute illness
- Watch for polyuria/polydipsia and consider arginine vasopressin deficiency (previously known as central diabetes insipidus) if present, in collaboration with endocrine team

Thyroid dysfunction

Immunotherapy can lead to a hypo- or hyper- thyroid state. Management should be guided by the pattern of TFT's, and the presence or absence of symptoms, as below.

Hypothyroidism

This is not usually an acute presentation but should be considered if a patient presents with suggestive symptoms such as lethargy, constipation, low mood, cold intolerance and weight gain.

WARNING: IF SECONDARY HYPOTHROIDISM IS SUSPECTED (LOW TSH AND LOW/NORMAL T4) DO NOT COMMENCE THYROID HORMONE REPLACEMENT UNTIL CORTISOL RESULTS AVAILABLE AND CO-EXISTENT ADRENAL INSUFFICIENCY HAS BEEN EXCLUDED

- In such cases, a full endocrine function panel should be sent (see endocrinopathy section, page 17), alongside an updated random serum cortisol and TFTs

- Exclude concurrent infection

- Send blood samples for TFTs, and random cortisol level

- Treat symptomatically. Thyroid replacement not usually indicated unless TSH >10mIU/L AND free-T4 below reference range
  - Commence levothyroxine 50-75 micrograms daily (caution in high risk patients e.g. elderly patients or history of atrial fibrillation, consider a lower starting dose of 25 micrograms)
  - Re-check TFTs and cortisol with every treatment cycle
  - Increase levothyroxine in 25 microgram increments as needed at intervals of at least 6 weeks (note TSH may not fall for 4-6 weeks after commencing levothyroxine)

- Steroid therapy not usually indicated, unless other concurrent immune toxicities or hypoadrenalism present.

- Seek endocrinologist input, for cases very symptomatic, if multiple comorbidities present, or if unable to stabilise thyroid function

Hyperthyroidism

Hyperthyroidism is typically due to an acute autoimmune thyroiditis and is often transient and asymptomatic before a return to normal levels for a brief period, which is then followed by hypothyroidism. Rare cases of Grave's hyperthyroidism and thyroid eye disease have been described. Hyperthyroidism should be considered if patients present with classical symptoms such as hyper-activity, tremor, palpitations, insomnia, heat intolerance, unexplained weight loss or diarrhoea.

Particular caution should be taken in patients with pre-existing cardiac comorbidities including cardiomyopathy, heart failure and arrhythmias, as even temporary surges in thyroxine levels can lead to cardiac decompensation

- Exclude concurrent infection
- Perform an ECG to exclude atrial fibrillation or other arrhythmias
- See blood samples for TFTs level, and send a random cortisol level
- Most cases are self-limiting and improve/transition to primary hypothyroidism within a short number of weeks. Seek endocrine advice and consider testing for thyroid auto-antibodies (anti-TSH receptor, and anti-TPO) and nuclear medicine thyroid uptake scan, if persistent
- If symptomatic, treat with Propanolol 10mg QDS initially (for overt thyrotoxicosis, dose can be increased to 40mg QDS)
    - If thyrotoxicosis is severe or persistent, refer for endocrine advice

TSH receptor antibodies may be checked in persistent symptoms/thyroid eye disease as they are specific for Graves' disease

    - Steroids may be indicated on discussion with endocrinology in the presence of severe thyrotoxicosis (thyroid storm) or severe thyroid eye disease. (Prednisolone 0.5-1mg/kg/day, maximum 60mg/day). Otherwise steroid therapy is not indicated, unless other concurrent immune toxicities or hypoadrenalism is present.

- Re-check TFTs and cortisol every 2-3 weeks. If patients are clinically symptomatic with any of below, consider deferring the next cycle of immunotherapy until clinically improved
    - Dyspnoea at rest,
    - Profound fatigue
    - GI symptoms (nausea/vomiting or diarrhoea)
    - Tremors/agitation
    - Resting heart rate >100/min or new atrial fibrillation/other arrhythmias
    - Evidence of dysthyroid eye disease

  - Pre-existing cardiac comorbidity

- As most cases of hyperthyroidism are as a result of an acute thyroiditis, many patients become hypothyroid, at which point follow the algorithm for hypothyroidism (see page 21 and appendix VI)

- Carbimazole is rarely indicated, such as in cases of persistent hyperthyroidism or if concerns about symptoms/comorbidities are present. Carbimazole should therefore be avoided initially and only commenced upon endocrine team advice.

Type 1 Diabetes Mellitus

This should be suspected in patients with patients with unexpectedly elevated blood glucose, particularly in the absence of a prior history of diabetes or steroid use.

- **Ensure diabetic ketoacidosis is excluded** (Check capillary ketones, venous pH, U+E and bicarbonate). Refer to local Trust protocol for Diabetic Ketoacidosis (DKA) and Hyperosmolar Hyperglycaemic states (HHS) and follow regional DKA protocol. Liaise early with the Diabetic and endocrinology team if DKA or HHS present

- **Do not use high dose steroids, insulin will be required**

  - Treat symptomatically, with insulin and IV fluids and seek diabetic team input

- HbA1c is helpful in determining duration of hyperglycaemia but a normal value does not exclude new-onset type 1 diabetes
- Consider measuring diabetes antibody screen to distinguish between type 1 and type 2 diabetes. Discuss with endocrinology

- Immunotherapy may resume once blood sugar control achieved and symptoms controlled.

NEPHRITIS

See also renal toxicity (nephritis) management flowsheet (appendix VII)

Management steps

1. Exclude other causes of renal injury such as fluid loss (e.g. from diarrhoea or vomiting), tumour-related renal obstruction or concomitant medication for all patients**. Note – immunotherapy induced nephritis is rare and renal dysfunction from other causes is very common, hence a period of initial monitoring whilst addressing the common causes is preferred before making the diagnosis**
2. Perform urinalysis (assess for haematuria and proteinuria) for all grade 2 and above
3. Assess grade of nephritis (based on creatinine elevation as below)

Renal disorders	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine increased Or Acute kidney injury	Creatinine 1-1.5 x baseline level	Creatinine 1.5 - 3 x baseline level	Creatinine >3 x baseline level or >350 μmol/L Hospitalisation indicated	Creatinine >6 x ULN Life-threatening consequences; dialysis indicated

Grade 1:

- Review current medications, consider holding/adjusting medications (ACE/ARB/NSAID/Trimethoprim/Diuretics, PPI etc.)
- Assess of intravascular volume, including blood pressure lying/standing, and heart rate)
- Treat intercurrent infection if present
- If intravascular volume depleted and/or any associated symptoms such as vomiting/diarrhoea/suspicion of sepsis, consider admission for IV fluids and further investigations
- If well allow home, encourage increased oral fluids and arrange regular repeat U+Es (at least weekly) to monitor for progression or resolution
- if creatinine risen by additional 30% during monitoring (even if still grade 1), contact nephrology team for advice

Grade 2:

- Review medication, treat intercurrent infection and assess intravascular volume as per grade 1
- Perform urinalysis to assess for evidence of blood or protein, and protein) and send urine for albumin:creatinine ratio (ACR). Send MSSU if indicated
- Arrange USS renal tracts to exclude obstructive cause

- If all other causes of renal impairment excluded and/or creatinine fails to improve despite intervention and after a period of monitoring:
    1. Commence PO Prednisolone 1mg/kg (max 60mg od)
    2. Consider checking the following
        - MPO and PR3 ANCA
        - Anti GBM
        - Complement C3,C4
        - If thrombocytopenic- blood film- LDH- reticulocyte count- bilirubin- haptoglobins
    3. Contact the nephrology team
    - Check U+E daily and if creatinine fails to improve or rises by additional 30% on oral steroids after ≥2 weeks, re-discuss with nephrology team to consider treating as grade 3+
    - Consider renal biopsy if atypical features (rising creatinine, positive serology, significant blood and protein on dipstick, urine ACR >30mg/mmol)
    - Commence steroid taper ((see appendix XI) once renal function is stable, even if not yet grade 1. **Note full renal function recovery may be slow in these patients and may not return fully to baseline**
    - Defer immunotherapy until grade ≤1, and prednisolone has been appropriately tapered (see appendix XI)

<u>Grade 3-4:</u>

- Admit patient and contact nephrology team
- Perform investigations/assessments as per grade 2, and review concomitant medications
- Commence IV methylprednisolone 2mg/kg daily
- Daily U+E with strict fluid balance +/- daily weight monitoring
- Discontinue immunotherapy
- Consider renal biopsy with renal team input in patients with persistent/worsening creatinine despite 2 weeks of high dose steroids, as additional immunosuppression may be required
- Commence taper after 5 days of IV Methylprednisolone 2mg/kg. Reduce to oral prednisolone 60mg od, then taper by 10mg/week (see appendix XI)

NEUROPATHY

See also neurological toxicity management flowsheet (appendix VIII) and complex neurological toxicity guidance (appendix IX)

Checkpoint inhibitor immunotherapy has been associated with serious immune-related neurological adverse reactions, including Myasthenia Gravis, Guillain-Barré syndrome, other demyelination syndromes, transverse myelitis, posterior reversible leukoencephalopathy, encephalitis and aseptic meningitis. Polyneuropathies (including motor and/or sensory) can also occur and early specialist input is essential. It is important to exclude other potential causes of any new neurological impairment.

Management steps

1. Exclude other causes of neuropathy such as CNS metastatic disease spread/progression, infections, metabolic syndromes and concomitant medication
2. Ascertain the grade of the symptoms and treat as per below
3. Refer to appendix IX for specific management of more complex neurological syndromes. To be used in conjunction with neurology.

Neurological toxicity	Grade 1	Grade 2	Grade 3	Grade 4
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
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

Grade 1:

- Assess for any co-existent sensory neuropathy symptoms, or symptoms of brain/spinal cord disease and perform neurological examination to document clinical signs.
- Exclude other causes: Send bloods for Vitamin B12/folate/TFT/diabetic screen, alcohol history, and concomitant medication. Consider paraneoplastic autoantibody screen.
- Regular close monitoring:
  - Advise patient to contact helpline if symptoms worsen. Follow-up telephone call or assessment within 1 week
- May continue immunotherapy, but can consider deferral of next dose for 1 week to monitor for any progression

- If symptoms worsen, reassess grade and treat accordingly

Grade 2:

- Assessment and investigations (including bloods, alcohol history and concomitant medications) as per grade 1
- Arrange urgent MRI Spine and CT or MRI brain, to evaluate for CNS disease.
- Commence oral steroids with prednisolone 1mg/kg daily (max 60mg/day) with Gastroprotection.
- Defer immunotherapy
- Consider neurology referral
- If not admitted, needs follow-up call within 48 hours to ensure symptoms are not progressing.
    - If symptoms progressive, reassess grade and treat accordingly.

Grade 3 and above:

- Admit to hospital for investigations and arrange urgent MRI Spine and brain imaging, to evaluate for CNS disease.
- Exclude other causes with investigations as per grade 1
- Daily neurological assessment
- Commence IV methylprednisolone 2mg/kg daily with Gastroprotection.
- Urgent neurology referral.
    - Consider lumbar puncture, nerve conduction studies and electromyography , in liaison with neurology
- Discontinue immunotherapy permanently

RHEUMATOLOGICAL TOXICITIES

Rheumatological and musculoskeletal toxicities from immune checkpoint inhibitor treatment have been observed in approximately 10% of patients.

- Inflammatory arthritis syndromes are some of the major clinical presentations encountered BUT presentations can vary from mono/oligo-arthritis to polyarthritis, (teno-)synovitis and enthesitis
    - Auto-antibodies, including rheumatoid factor and anti-CCP, are often negative and should therefore not be used to exclude a diagnosis
- Polymyalgia rheumatica (PMR) -like syndromes may also be observed, and acute-phase reactants (ESR, CRP) may be negative
    - Proximal myalgia (pain/discomfort) +/- weakness are common presenting features
- Myositis is less common but is potentially fatal as it is frequently associated with myocarditis and/or myasthenia gravis
    - Initial presentation of myositis may be clinically similar to a PMR-like syndrome BUT an elevated creatine kinase is observed in the majority of patients with myositis (it is usually within normal range for PMR-like syndromes)
    - Most reported cases occur early (within first 1-2 months from treatment initiation) but can also occur as a later-occurring toxicity.
    - Diplopia and ptosis also commonly reported and may be related to associated myasthenia gravis
- Additional systemic manifestations can occur, including sicca syndrome, vasculitis and sarcoidosis/sarcoid-like reactions

It is not within the scope of this guidance to provide in-depth management of all potential rheumatological immune-related toxicities, but management of more common rheumatological toxicities will be discussed

- Prompt referral to a rheumatologist for assessment and management should be considered

Inflammatory arthritis syndromes and Myalgia/Polymyalgia-like syndrome

These can present with joint pain/arthralgia, joint stiffness and joint swelling. Management is dependent on severity and may vary from simple analgesia, low-high dose systemic corticosteroids, disease modifying anti-rheumatic drugs (DMARDs) and biologic agents. Patients requiring DMARDs or biologic agents should have rheumatology involvement.

The goal in managing these toxicities is to relieve the patient's symptoms to an acceptable level with a management strategy which permits both the maintenance of quality of life and continuation of immune checkpoint therapy.

- If required, the lowest dose of corticosteroid +/- DMARD required to relieve symptoms should be used

Management steps

1. Consider other potential causes symptoms, such as cancer progression, paraneoplastic syndromes, degenerative changes, trauma, septic joint, crystal arthropathies and other non-rheumatic causes of arthralgia

2. All patients should have examination of affected joints for swelling and tenderness. Consider x-ray of affected joints to exclude metastases and evaluate for joint erosions
3. Check ESR and CRP, and if any myalgia MUST have a CK checked. If CK elevated, please refer to myositis guidance
4. Assess CTCAE grade and manage as per grade (below)

Rheumatological toxicity	Grade 1	Grade 2	Grade 3-4
Arthritis	Mild pain, with inflammation, erythema or joint swelling	Moderate pain associated with signs of inflammation, erythema, or joint swelling Limiting instrumental ADL	Severe pain associated with signs of inflammation, erythema, or joint swelling Irreversible joint damage Limiting self-care ADL
Myalgia	Mild stiffness and pain	Moderate stiffness and pain Limiting instrumental ADL	Severe stiffness and pain Limiting self-care ADL

Grade 1:

- Manage pain with simple analgesia such as paracetamol and/or NSAIDs (if patient can tolerate)
- Continue on checkpoint inhibitor immunotherapy
- If symptoms remain intolerable/unacceptable despite current management, treat as per grade 2 guidance

Grade 2:

- Consider autoimmune blood panel including ANA, RF, and anti-CCP,
- For mono-/oligo-arthritis consider intra-articular corticosteroid injection (under rheumatology) depending on size of joint(s) and number of joints involved
- If symptoms inadequately controlled on optimal analgesia, commence PO low-dose prednisolone 10-20 mg/day (do not co-prescribe prednisolone and NSAID), with Gastroprotection
    - If prednisolone dose >10 mg/day, hold checkpoint inhibitor immunotherapy
    - If symptoms improve, commence slow steroid taper over 4-6 weeks
    - Checkpoint inhibitor immunotherapy can be continued/recommenced if prednisolone dose ≤ 10 mg/day
    - If unable to wean PO low-dose prednisolone due to recurrent symptoms, hold immunotherapy and refer to rheumatology
- If symptoms remain intolerable/unacceptable despite low dose prednisolone for 4 weeks:
    - Refer to rheumatology
    - Hold immunotherapy
    - Treat as per grade 3-4 guidance

Grade 3-4:

- Hold checkpoint inhibitor immunotherapy

- Perform autoimmune blood panel including ANA, RF, and anti-CCP, and anti-inflammatory markers (ESR and CRP)
- Refer to rheumatology
- Consider intra-articular corticosteroid injection (under rheumatology) depending on size of joint(s) and number of joints involved
- Commence PO prednisolone 0.5-1 mg/kg with Gastroprotection
    - Commence steroid taper once symptoms improved to ≤ grade 1 (see appendix XI)
    - If symptoms fail to improve within 4 weeks, or symptoms worsen despite high dose oral prednisolone, discuss with rheumatology for consideration of commencing a DMARD or biologic (anti-TNFα or anti-IL-6 agent. Caution should be exercised with anti-IL-6 agents as they can rarely cause intestinal perforation and should NOT be used in patients with co-existent colitis)

Myositis

Myositis is a rare but potentially life-threatening toxicities associated with checkpoint inhibitor immunotherapy.

- Diagnosis can be challenging and involves exclusion of other potential causes. The possibility of an immune-checkpoint inhibitor associated myositis being responsible for suspected symptoms, is higher in the presence of other immune-related toxicities.
- Diagnosis and management should involve rheumatology
- Cardiac evaluation (serum troponin and ECG) should be performed on any patient presenting with myositis, to assess for associated myocarditis. For further evaluation of suspected myocarditis see myocarditis section and appendix X)

Presentation

- Myositis can present with myalgia and proximal myopathy, mimicking a polymyalgia-like condition
- Symptoms of a co-existent myasthenia gravis syndrome may be present (e.g. with ptosis, diplopia, dysphagia, dysarthria, dysphonia, respiratory failure) or co-existent myocarditis

Investigations

Should aim to not only confirm a diagnosis of myositis but to exclude other more common causes of symptoms;

- Serum creatine kinase (CK) is elevated in the majority of cases of myositis.
- Serum inflammatory markers (ESR and CRP)
- Serum troponin can be elevated in cases of myositis and myocarditis
- Electromyography (EMG) may reveal a myopathic pattern in cases of myositis
- Limb MRI may be useful in diagnosing myocarditis (discuss with rheumatology)
- Muscle biopsy can be considered

Consider cardiac evaluation to assess for co-existent myocarditis (see myocarditis section, pg 32)

Management

- Corticosteroids are the initial treatment of choice. Dosing varies dependent on severity
    - Initial dosing of 0.5-1mg/kg (maximum 60mg) PO prednisolone OD if mild weakness/pain
    - Escalate to methylprednisolone 1-2mg/kg IV OD in severe cases (some patients may also benefit from pulsed methylprednisolone 1g IV for 3 days)
- Immune checkpoint inhibition should be permanently discontinued in moderate- severe cases of myositis and ALL cases of myocarditis (irrespective of severity)
- Cardiology input is required for management of co-existent cardiac impairment or arrhythmias/AV nodal block secondary to myocarditis

- Corticosteroids should be weaned over a period of AT LEAST 4-6 WEEKS

Additional immunosuppressive treatment for myositis/myocarditis

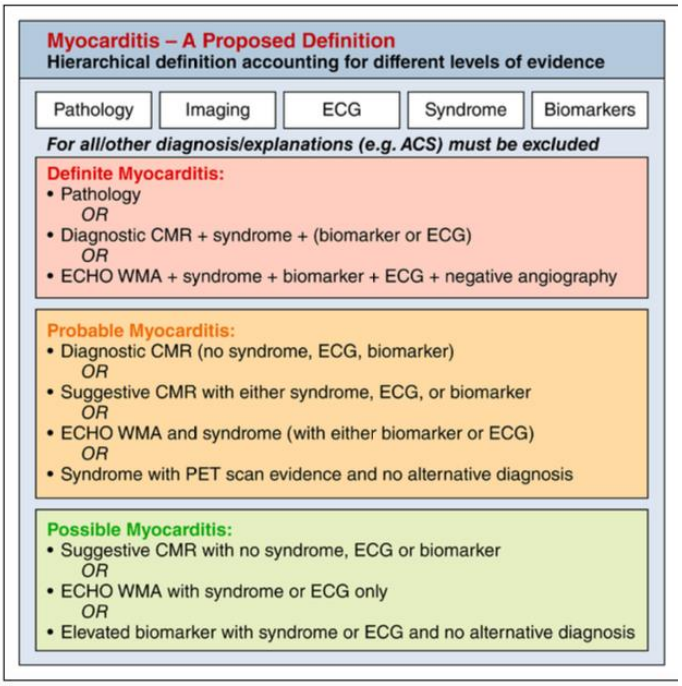
- The decision of when to use an additional immunosuppressive treatment, and which to use, should be made on a case-by-case basis and should have multi-disciplinary involvement
- Plasmapheresis or IV immunoglobulin have been used in severe myositis
- Additional agents used/listed below have been reported –discuss with the relevant specialty
    - Mycophenolate mofetil, methotrexate, azathioprine. Infliximab, Rituximab or anti-IL6 agents.

MYOCARDITIS

See also myocarditis diagnosis and management sheet (appendix X)

Myocarditis is a rare but potentially life-threatening toxicity associated with checkpoint inhibitor immunotherapy.

- Most reported cases occur early (within first 1-2 months from treatment initiation) but can also occur as a later-occurring toxicity.
- Diagnosis can be challenging and involves exclusion of other potential causes. The possibility of an immune-checkpoint inhibitor associated myocarditis being responsible for suspected symptoms, is higher in the presence of other immune-related toxicities. Risk is also elevated in patients treated with combination immune-checkpoint inhibitor therapy.
- It can co-occur with an immune-related myasthenia gravis syndrome
- Diagnosis and management should involve cardiology
    - A diagnostic approach for myocarditis has been described (Bonaca M et al, 2019) and may classify the diagnosis as definite, probable or possible myocarditis



Diagnosis of myocarditis (Bonaca et al, *2019*) CMR Cardiac MRI; WMA Wall motion abnormality

Presentation

- Myocarditis may be sub-clinical, or present with symptoms, ranging from mild to severe/life-threatening. Presentations can be with acute-coronary-syndrome (ACS) like episodes, new onset heart failure, acute arrhythmias or a chronic cardiac impairment. Consider in patients presenting with;
    - Chest pain
    - Dyspnoea
    - Orthopnoea, paroxysmal nocturnal dyspnoea
    - Palpitations
    - Unexplained fatigue

  - New arrhythmias or heart block
  - Cardiogenic shock
- Symptoms of a co-existent myasthenia gravis syndrome may be present (e.g. with ptosis, diplopia, dysphagia, dysarthria, dysphonia, respiratory failure)

Investigations

Should aim to not only confirm a diagnosis of myositis/myocarditis but to exclude other more common causes of symptoms.

Serum investigations

- Serum troponin can be elevated in cases of myositis and myocarditis
- Serum NT-pro BNP and BNP elevation may occur in myocarditis
- Serum creatine kinase (CK) is often elevated. CK-MB is more cardio-specific
- Serum inflammatory markers (ESR and CRP)

Baseline testing

- All patients commencing immunotherapy should have a baseline pre-treatment ECG available for future reference
- Baseline cardiac biomarker testing (troponin is the most sensitive marker for myocarditis) prior to commencement of immunotherapy may also be useful particularly in select cases with pre-existing cardiac vulnerability- specifically cardiomyopathy, heart failure, significant ischaemic heart disease and arrhythmias. This may enable risk assessment to select the appropriate immunotherapy regimen and allow interpretation of an elevated result if repeated testing is required after treatment starts.
- Note elevated baseline levels are not a clear predictor for immunotherapy myocarditis developing, and not a reason in itself not to proceed with treatment.
  - If baseline troponin elevated (i.e. >50, or 25-50 + any other concern) – consider rechecking in 1-2 weeks to ensure not rising but may not be a reason not to proceed/continue with treatment. Note renal impairment/other factors can affect basal levels
  - If persistently elevated on recheck, request echo and refer for cardiology advice. Ongoing IO therapy should be a clinical risk/benefit decision made in conjunction with cardiology

There is a separate ‘Baseline Cardiac testing’ consensus statement currently under local review and applicability will be guided by ongoing local data collection. (Baseline Cardiac Assessment in Individuals Receiving Immune Checkpoint Inhibitors - A Joint Consensus Statement V1.0.pdf). This can be used for reference.

ECG and EMG studies

- Electrocardiography (ECG) +/- telemetry may show non-specific changes in myocarditis, and other causes for these should also be considered. Examples include;

- New PR prolongation
- New heart/atrioventricular block
- Ventricular arrhythmias or frequent premature ventricular complexes/ectopics
- ST depression
- Diffuse T-wave inversion
- Telemetry may show tachy- or brady-arrhythmias

Imaging

- Echocardiography should be undertaken in ALL cases of suspected myocarditis. Findings may include (but not limited to);
  - Impairment of left ventricular ejection fraction (LVEF)
  - Abnormal diastolic function in presence of normal LVEF
  - Regional wall motion abnormalities
  - Developmental of a pericardial effusion
- Cardiac MRI may demonstrate features consistent with myocarditis to support the diagnosis (when requesting, should specify to evaluate for myocarditis)

Invasive tests

- Coronary angiography is useful for excluding significant coronary artery disease as a cause of patient's symptoms/clinical presentation (under cardiology advice)
- Endo-myocardial biopsy is the gold standard diagnostic test for myocarditis, but should only performed by experienced clinicians in experienced centres, and therefore is not recommended as a routine investigation under this guideline

Management

Early involvement of cardiology is recommended, especially for presentations with arrhythmias, atrioventricular block, heart failure or cardiogenic shock.

- Corticosteroids are the initial treatment of choice.
  - Initiate methylprednisolone 2mg/kg IV OD
  - For severe cases or cases not responding to initial methylprednisolone treatment, IV methylprednisolone 1g OD is recommended
  - Response to corticosteroid treatment in myocarditis can be monitored using serum troponin
- Immune checkpoint inhibition should be permanently discontinued in all cases of myocarditis (irrespective of severity)
- Cardiology input is required for management of co-existent cardiac impairment or arrhythmias/AV nodal block secondary to myocarditis
- Corticosteroids should be weaned over a period of AT LEAST 4-6 WEEKS. See appendix XI (special considerations) for more information

Additional immunosuppressive treatment for myocarditis

- The decision of when to use an additional immunosuppressive treatment, and which to use, should be made on a case-by-case basis and should have multi-disciplinary involvement

- Additional agents suggested for use in case series include; Mycophenolate mofetil (MMF), tacrolimus, anti-thymocyte globulin, abatacept, alemtuzumab and infliximab. Note infliximab should only be used with caution if LVEF is impaired
- Plasmapheresis or IV immunoglobulin may also be beneficial in severe myocarditis

Specific cardiac supportive therapies are usually also indicated according to the dominant cardiac manifestations present. This should be guided by cardiology

Ocular TOXICITY

- Checkpoint inhibitor immunotherapy can cause uveitis, iritis or episcleritis.
- Maintain high index of suspicion if patients complain of new–onset eye pain, photophobia, blurred vision or unexplained redness. Symptoms may be subtle and there should be a low threshold for deferring treatment and referring to Eye Casualty for assessment.
- Non-urgent cases may be discussed directly with the Ophthalmology uveitis team for a fast-track outpatient clinic opinion.
- Topical corticosteroid eye drops are usually adequate, but management should be guided by eye specialists.
- Consider high dose steroids for immune-related eye disorders not responding to topical immunosuppressive therapy, or if posterior/pan-uveitis diagnosed at ophthalmology (grade 3 uveitis). Seek ophthalmology advice.

PYREXIA

- Checkpoint inhibitor immunotherapy can cause pyrexia in the absence of infection, as an inflammatory immune response. It may occur as a precursor for specific organ immune toxicity (e.g. hepatitis), or concurrent with established toxicity, after immunotherapy. It may also be associated with the underlying malignancy as a paraneoplastic phenomenon
- There is accumulating evidence to suggest antibiotics may be detrimental to immunotherapy patients' outcome, by altering the gut microbiome. Antibiotics should therefore not be routinely commenced when patients on immunotherapy present with pyrexia and no clinical focus of infection
- Septic screen should be performed at presentation, to exclude infection, but antibiotics can be withheld whilst results are awaited, unless there are clinical concerns. Symptomatic measures such as paracetamol may be employed.

- If corticosteroids are required to treat organ toxicity according to grade, associated pyrexia often settles quickly. Corticosteroids are however not recommended for use as routine treatment for isolated pyrexia with no organ immune toxicity.

- Persistent/refractory cases should be discussed with microbiology team for advice, and pyrexia of unknown origin work-up should be considered, to exclude occult infection.

FATIGUE

Fatigue is a frequently reported toxicity of immune-checkpoint inhibitor treatment and is often non-specific. However, consideration should be given to other potential toxicities contributing to fatigue including (see below). If any of these are present, please refer to the appropriate guidance for its management.

- Hypothyroidism: Check TFTs
- Hypoadrenalism: Check early morning cortisol +/- synacthen test
- Hypopituitarism: Check TFTs, cortisol and remaining pituitary panel (particularly consider serum testosterone in males, and FSH + oestrogen in females)
- Diabetes mellitus: Check random blood glucose and HbA1c
- Myocarditis: Evaluate for other clinical features and consider additional investigations (as per myocarditis section).
- Anaemia
- Rheumatological toxicities

OTHER IMMUNE RELATED ADVERSE EVENTS (PANCREATITIS, HAEMOLYTIC ANAEMIA, ETC)

- Exclude other potential causes and seek early input from relevant specialty

- If other causes excluded, consider as potentially immune-related, and treat with high dose steroids according to clinical severity/CTC grade

    - Persistent and/or clinically significant grade 2: PO prednisolone 1mg/kg daily (max. 60mg/day) with Gastro-protection till treating team review

    - Grade 3 or higher: IV methylprednisolone 2mg/kg with Gastroprotection

- **Refer to ASCO and ESMO guidance (Ref 3-4) for guidance of more rare and complex immune toxicities, and seek specialist advice**

IMPLEMENTATION OF POLICY

5.1 Dissemination

For circulation to all staff involved in the administration of SACT to adult patients receiving checkpoint inhibitor immunotherapy throughout the Network (including private facilities / non-statuary domiciliary providers).
Raise awareness locally with regards to the implementation of the guidelines.

5.2 Resources

This should include training, awareness raising, testing of new documentation associated with the policy etc. and who is responsible for this.

5.3 Exceptions

Treatment decisions for individual patients requires the consideration of a multitude of factors, which cannot all be accounted for in a clinical guideline. The Clinical Guidelines provide a description of the range of treatment options available for a clinical scenario.

6.0 MONITORING

Provide detail of any inherent key performance indicators (KPI) relevant to the successful implementation of this policy.
Describe the process for monitoring the effectiveness of all of the above and who and how this will be done. This monitoring should include any section 75 implications of implementing the policy.

7.0 EVIDENCE BASE / REFERENCES

Please see references section below

8.0 CONSULTATION PROCESS

Please see page 2 for a list of authors and consultees

9.0 APPENDICES / ATTACHMENTS

Please see pages 40-62

10.0 EQUALITY STATEMENT

In line with duties under the equality legislation (Section 75 of the Northern Ireland Act 1998), Targeting Social Need Initiative, Disability discrimination and the Human Rights Act 1998, an initial screening exercise to ascertain if this policy should be subject to a full impact assessment has been carried out.
The outcome of the Equality screening for this policy is:

Major impact ☐

Minor impact ☐

No impact. ☐

SIGNATORIES

(Policy – Guidance should be signed off by the author of the policy and the identified responsible director).

_____ **Date:** _____
Name
Title

_____ **Date:** _____
Name
Title

_____ **Date:** _____
Name
Title

_____ **Date:** _____
Name
Title

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Appendices

Immunotherapy-related GI Toxicity (Diarrhoea and Colitis/Enterocolitis)

- Exclude possible infection, and arrange stool cultures as appropriate.
- Do **NOT** wait for stool cultures results before commencing steroids

GRADE 1 (Mild)

Any of the following

- Increase < 4 stools/day over baseline; mild increase in stoma output
- Asymptomatic colitis (clinical or diagnostic observations only)

Assess patient

Investigations:

- Baseline bloods (FBC, U+E, serum magnesium + calcium + phosphate, LFTs and CRP)
- If persistent also send faecal calprotectin

Consider Stool microscopy/culture (or PCR) and C. difficile screen

Treatment:

- Encourage fluids
- Avoid high fibre and lactose

Actions

- Telephone assessment daily
- May continue immunotherapy (if on ipilimumab or ipi/nivo, consider withholding immunotherapy)
- Consider early endoscopy/biopsy if any alarm symptoms present (see page 7), or if persistent grade 1 diarrhoea

Symptoms persist (≥3 days) or alarm symptoms present

- Treat as per Grade 2

Symptoms improve

- Continue immunotherapy

GRADE 2 (Moderate)

Any of the following

- Increase 4-6 stools/day over baseline; moderate increase in stoma output
- Mild-moderate abdominal pain
- Mucus in stool

If any Grade 2 colitis combined with diarrhoea of ANY CTC grade, treat as per Grade 3+4

Assess patient

Investigations:

- Baseline bloods (as per grade 1)
- Abdominal x-ray, consider CT abdomen
- Faecal calprotectin
- Stool microscopy/culture (or PCR) and C. difficile screen
- Monitor stool/stoma output (with Bristol stool chart)

Treatment:

- Commence PO prednisolone (1mg/kg/day, max 60mg) with Gastroprotection
- Stop any antidiarrheal therapy to avoid masking worsening symptoms
- Fluid replacement as appropriate. Admit for IVF if hypotensive or electrolyte imbalance

Actions

- If not admitted; daily follow-up phone call until improved
- Defer immunotherapy
- Consider referral for endoscopy/biopsy

Symptoms improve (To ≤ Grade 1)

- Initiate steroid taper (see appendix XI)

Symptoms persist (≥3 days) **or Symptoms worsen**

- Treat as per Grade 3-4

GRADE 3-4 (Severe)

Any of the following

- **≥7 stools/day over baseline *or* significant increase in stoma output**
- Severe abdominal pain
- Fever
- Dehydration
- Blood in stool
- Incontinence
- Limiting ADL's

ADMIT patient

Investigations:

- Baseline bloods as per grade 1; also TFTs and cortisol
- Baseline AXR and CT Abdomen
- Faecal calprotectin
- Stool microscopy/culture (or PCR) and C. difficile screen
- Screen for Infliximab suitability on admission (to include: TB history and IGRA quantiferon, hepatitis screen, HIV, chest X-Ray)
- Refer to gastroenterology to consider endoscopy with biopsies

Treatment:

- IV hydration and fluid balance
- IV Methylprednisolone 2 mg/kg/day + Gastroprotection

Actions

- Daily stool chart
- Dietician review
- Omit and consider discontinuation of immunotherapy (see page 8)

Symptoms improve (To ≤ Grade 1)

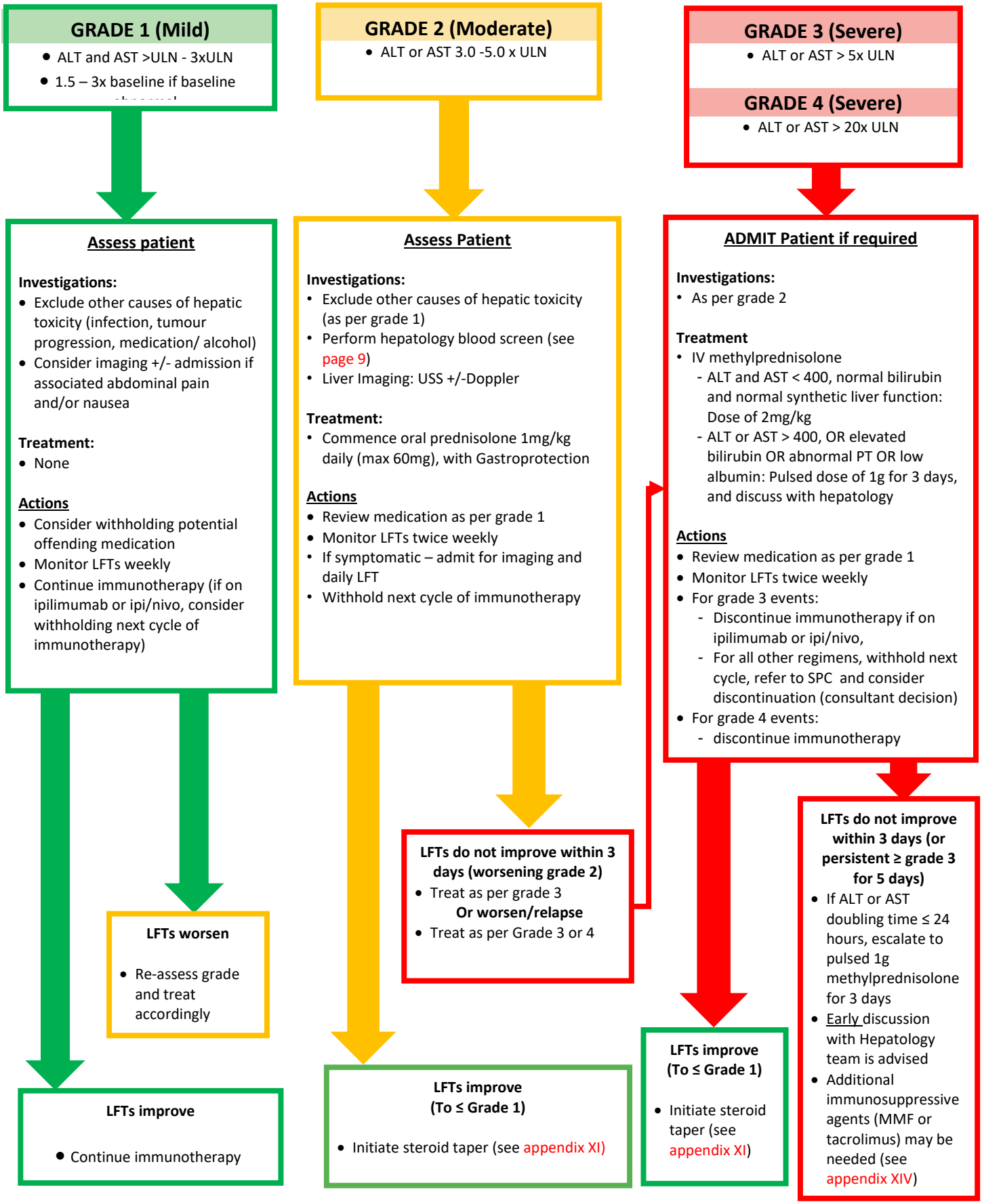
- Initiate steroid taper (see appendix XI)

Symptoms persist (≥Grade 2 for ≥3 days, or flare during steroid taper))

- Escalate to infliximab (see appendix XIII and special considerations)

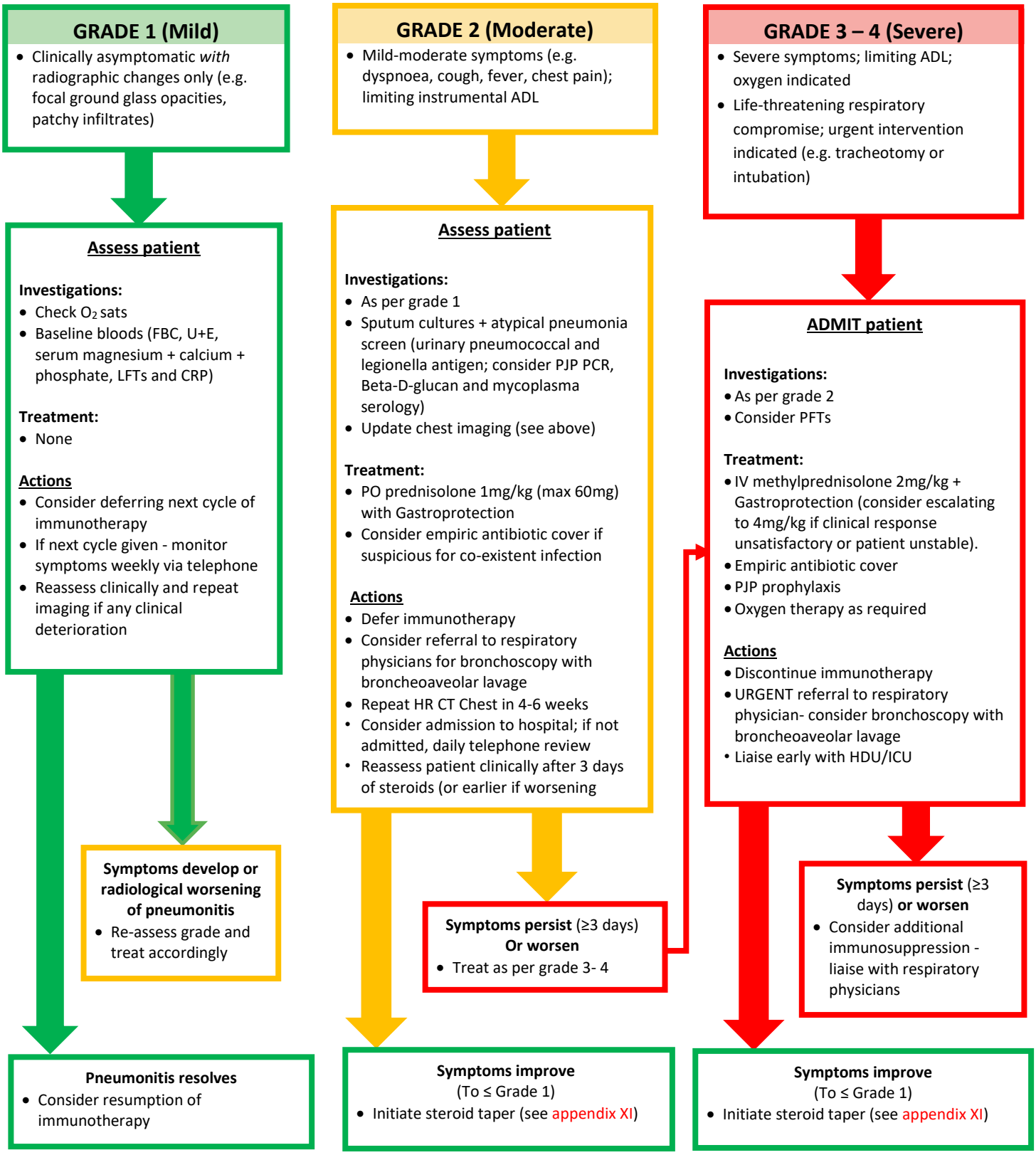
Immunotherapy-related Hepatotoxicity

- Assess for other causes of hepatic injury, including infections, tumour progression, or concomitant medication/alcohol
- Ascertain the degree of liver dysfunction according to CTCAE grade and treat accordingly (as below)



Immunotherapy-related Lung Toxicity (Pneumonitis)

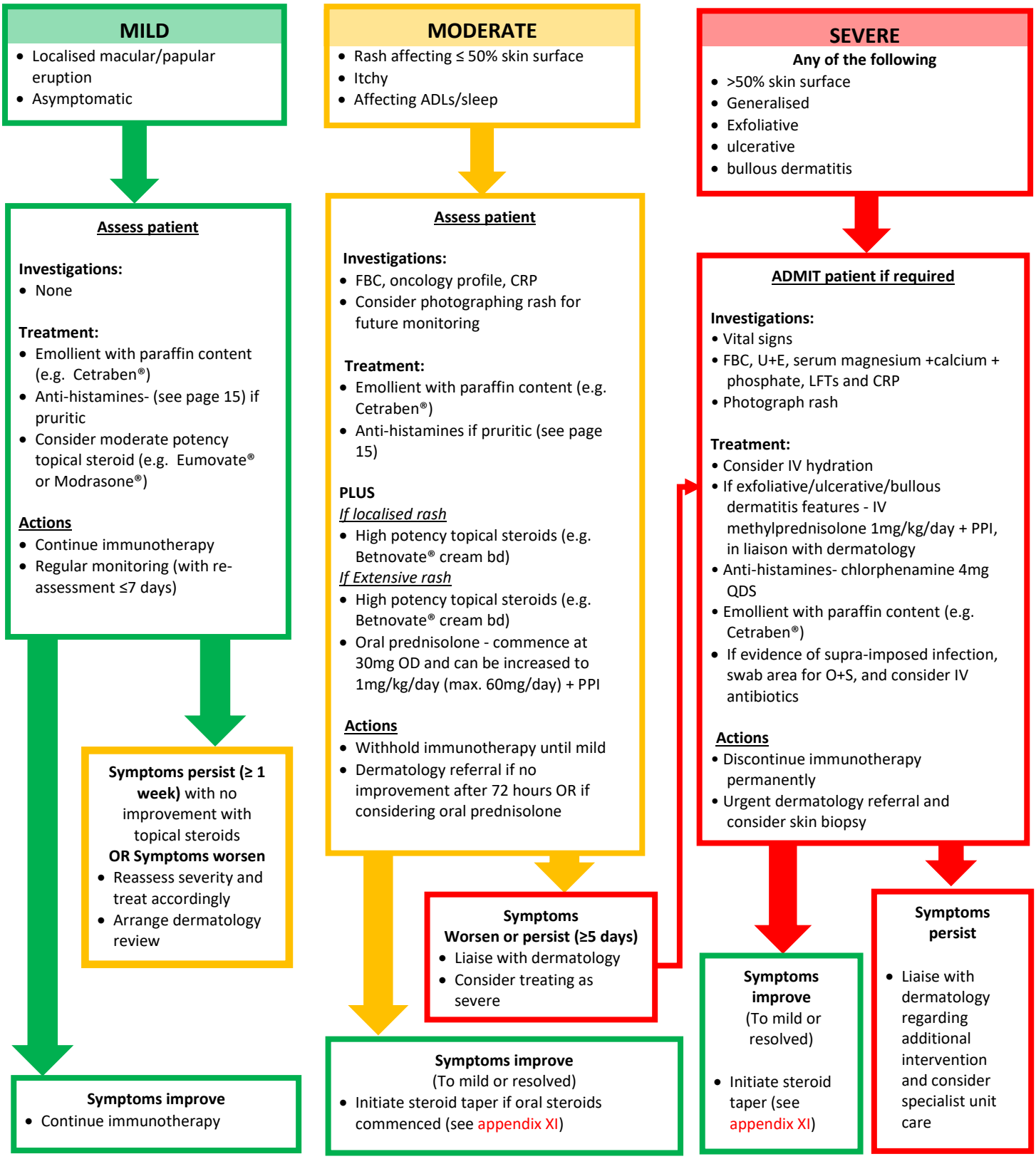
- Assess for other causes of respiratory symptoms, such as infections (including PJP), VTE and tumour progression
- All patients should have a CXR. Suspected pneumonitis should be confirmed with an urgent **HIGH RESOLUTION CT scan of Chest**.
- Once confirmed, grade pneumonitis as per CTCAE and treat accordingly (as below)
- Please note that a slower taper of steroids is recommended for pneumonitis (see appendix XI)



Immunotherapy-related Skin toxicity

Note: All rashes associated with blistering/mucosal involvement or significant systemic symptoms/organ dysfunction require urgent dermatology input and discontinuation of immunotherapy

- Consider other potential causes (e.g. infection, other drugs, other systemic illnesses associated with skin manifestations)
- If pruritus WITHOUT an associated rash, please refer to NICaN immunotherapy toxicity management guidance document, (see page 16)



Immunotherapy-related adrenal dysfunction

CAUTION: Accurate drug history is essential. If the patient is already on steroids (even if topical/inhaled), then serum cortisol and ACTH can be suppressed. Discuss with endocrinology team before considering replacement.

NOTE: If co-existent immune toxicity of any grade present (such as diarrhoea, hepatitis, etc.) with confirmed hypoadrenalism, use IV Methylprednisolone 1-2mg/kg daily in place of hydrocortisone (with Gastroprotection).

Endocrine function panel if required, consists of U&E, LFT, TSH, Free T4, ACTH, LH, FSH & cortisol (between 9-11am if possible), prolactin, blood glucose +/- testosterone/oestrogen (NOTE: High dose glucocorticoids cause ACTH suppression and can also suppress TSH and gonadotrophins)

MILD (GRADE 1)

- **Asymptomatic,** cortisol lower than reference range for time of day noted on routine blood test
- **Hypoadrenalism is possible if cortisol is <100nmol/L**

Assess patient

Cortisol >100nmol/L but lower than reference range for time of day:

Investigations:
- Repeat 9am level within 48 hours
- Complete endocrine function panel, if 9am levels confirmed as low

Action:
- Consider replacement hydrocortisone 15mg am/5mg pm if 9am cortisol confirmed as low, pending results of full endocrine screen
- Monitor regularly (before each cycle as a minimum) and act as per algorithm if serum levels fall or endocrine panel confirms hypopituitarism
- Continue immuno-therapy

Cortisol ≤100nmol/L and lower than reference range for time of day:

Investigations:
- Repeat 9am level within 24 hours and complete endocrine function panel at the same time
- Commence hydrocortisone 30mg am/10mg pm, pending results.

Action:
- Consult endocrinology for advice/ further investigation

MODERATE (GRADE 2)

- Mild/Non-life-threatening symptoms with cortisol lower than reference range for time of day
- Symptoms may include tiredness/fatigue, headache, weight loss, susceptibility to infection,
- Normal BP, with no postural drop

Assess patient

Investigations:
- Repeat 9am level within 24 hours and complete endocrine function panel at the same time

Treatment:
- Commence hydrocortisone 30mg am/10mg pm pending full endocrine screen results
- **Consider admission to hospital for IV fluids and observation, if cortisol <100 and symptoms significant**

Action:
- Refer to endocrinology for advice/ further investigation
- Consider MRI brain with pituitary views if persistent headaches/new visual symptoms which do not settle with hydrocortisone replacement
- May continue immunotherapy after hormone replacement established

SEVERE (GRADE 3 + 4)

- **Severe or Life-threatening symptoms**
- **Suspect adrenal crisis if:**
  - Hypotension (SBP <90mm Hg)
  - Postural hypotension (>20mm Hg drop)
  - Dizziness/Collapse/shock
  - Nausea/ Vomiting
  - Abdominal pain/ tenderness/guarding
  - Fever
  - Confusion/ delirium, Coma,
  - Hyponatraemia/hyperkalaemia/
  - hypoglycaemia
  - Pre-renal/renal failure

Serum cortisol < 450 nmol/L in presence of severe/life-threatening illness is suggestive of adrenal insufficiency

ADMIT patient

Urgent Intervention required
- Immediate management with an ABCDE approach
- Aggressive IV fluid hydration
- **Send endocrine panel PRIOR to commencing steroids**
- Commence on 100mg hydrocortisone IV followed by 50mg 6 hourly immediately/without awaiting blood tests
- Screen for concomitant infections and if suspected infection, also treat with antibiotics
- Urgent Endocrinology referral
- Consider MRI head with pituitary images if persistent headaches/new visual symptoms which do not settle with hydrocortisone replacement

Follow local Trust guidance or Society for Endocrinology [SfE] guidelines for management of adrenal crisis: www.endocrineconnections.com/content/5/5/G1

Further immunotherapy will depend on clinical recovery and establishment of replacement hormones

Remember the clinical picture may be evolving, and initial results may not fit. Repeat if clinical concerns remain.

ONCE ESTABLISHED ON STEROIDS, commence levothyroxine and/or gonadal hormones (if confirmed deficient). Watch for polyuria/polydipsia and consider arginine vasopressin deficiency if present, in collaboration with endocrine team.

Immunotherapy-related Thyroid dysfunction

Immunotherapy can cause hypo- or /hyperthyroidism. Hyperthyroidism is typically due to thyroiditis and asymptomatic, before returning to normal levels for a brief period, then hypothyroidism. Primary hypothyroidism can also occur. Both groups require long term replacement in almost all cases.

****Remember to exclude hypoadrenalism in all cases, before commencing thyroxine replacement****

*****Patients presenting with hyperthyroidism who have pre-existing cardiac comorbidities, including cardiomyopathy, heart failure and arrhythmias, should be closely monitored, as even temporary surges in thyroxine levels can lead to cardiac decompensation*****

ASYMPTOMATIC (MILD)

- Asymptomatic with biochemical changes

Investigations

- TSH, T4 levels. If hyperthyroidism check TSH receptor autoantibodies.
- If secondary hypothyroidism suspected (low TSH and low or normal T4), check ACTH, LH, FSH & random cortisol, prolactin, oncology profile + testosterone in males/oestrogen in pre-menopausal females
- In hyperthyroidism, perform ECG to exclude atrial fibrillation or other arrhythmias

Hyperthyroidism

TSH <0.27 mIU/L and Free T4 > 22pmol/L

(If TSH low and T4 normal or low, need to exclude pituitary dysfunction)

Treatment:

- Rarely a role for steroids (except painful thyroiditis/significant thyroid swelling, severe thyrotoxicosis or severe thyroid eye disease), discuss with endocrinologist before commencing steroids

Actions:

- Recheck TFT's and cortisol 2-3 weekly.

The majority of cases become hypothyroid within a matter of weeks.

SYMPTOMATIC (MODERATE)

- Symptomatic or severe biochemical disturbance

Investigations

- TSH, T4 levels. If hyperthyroidism check TSH receptor autoantibodies. If persistent hypothyroidism check anti-TPO antibodies
- If secondary hypothyroidism suspected (low TSH and low or normal T4), check ACTH, LH, FSH & random cortisol, prolactin, oncology profile + testosterone in males/oestrogen in pre-menopausal females
- In hyperthyroidism, perform ECG to exclude atrial fibrillation

Hypothyroidism

TSH of >10mIU/L and Free T4 < 12 pmol/L

Treatment:

- Levothyroxine 50 – 75 mcg/day (consider lower starting dose of 25 mcg/day in higher risk patients: e.g. elderly, pre-existing cardiac history)

Actions:

Check cortisol prior to commencing replacement

- Recheck TFTs and cortisol with each cycle of treatment
- Increase Levothyroxine in 25mcg increments as needed at intervals of at least 6 weeks
- Refer to endocrinologist if multiple comorbidities present, very symptomatic or unable to stabilise thyroid function

Hyperthyroidism

TSH <0.27 mIU/L and Free T4 > 22pmol/L

(If TSH low and T4 normal or low, need to exclude pituitary dysfunction)

Treatment:

- B-blocker- propranolol 10mg QDS initially
- Carbimazole-rarely indicated due to the transient nature of hyperthyroidism. If persistent, significant symptoms, multiple comorbidities or associated with anti-TSH antibodies consider in collaboration with an endocrinologist
- Steroids may be indicated, on discussion with endocrinology, in severe thyrotoxicosis or severe thyroid eye disease (Prednisolone 0.5-1mg/kg/day, max 60 mg/day)

Actions:

- Recheck TFT's and cortisol 2-3 weekly. Most cases become hypothyroid within weeks.
- Consider radioiodine thyroid scan and anti-TSH/antithyroid peroxidase antibodies if persistent, on endocrine advice

Once hypothyroid- manage as per hypothyroidism algorithm

Immunotherapy-related renal toxicity (Nephritis)

- Exclude other causes of renal injury such as fluid loss (e.g. from diarrhoea or vomiting), tumour-related renal obstruction or concomitant medication for all patients.
- Consider renal biopsy in all cases if atypical features (rising creatinine, positive serology, significant blood and protein on dipstick, urine ACR >30mg/mmol

GRADE 1 (Mild)

- Serum creatinine: 1 – 1.5x baseline level

Assess patient

Investigations:
- Baseline bloods (FBC, U+E, serum magnesium + calcium + phosphate, LFTs, CRP)
- Assess intravascular volume – lying/standing BP/HR

Treatment:
- If well, allow home and encourage oral fluids
- Consider admission for IVF if intravascular volume depleted/suspicion of sepsis

Actions:
- Weekly U+E monitoring
- Review potentially nephrotoxic medication
- if creatinine risen by additional 30% then contact nephrology team
- May continue immunotherapy

Renal function worsens (creatinine rise >30%)

- Reassess grade and discuss with nephrology

Renal function improves

- Continue immunotherapy

GRADE 2 (Moderate)

- Serum creatinine: 1.5 - 3x baseline level

Assess patient

Investigations
- Baseline bloods as per grade 1
- Review medication, treat intercurrent infection and assess intravascular volume
- Send urinalysis (evidence of blood +/- protein) and send urine for albumin:creatinine ratio (ACR) +/- MSSU
- Arrange USS renal tracts

Treatment
- If other causes excluded and/or creatinine doesn't improve despite intervention - Commence PO prednisolone (1mg/kg/day, max 60mg) with Gastroprotection
- Contact Nephrology
- Fluid replacement as appropriate. Admit for IVF if hypotensive or electrolyte imbalance

Action
- Withhold immunotherapy
- Monitor U+E daily
- Consider sending
  - MPO and PR3 ANCA
  - Anti GBM
  - Complement C3, C4
  - If thrombocytopenic- blood film- LDH- reticulocyte count- bilirubin- haptoglobins
- Consider renal biopsy if rising creatinine, positive serology, significant blood and protein on dipstick, urine ACR >30mg/mmol)

Renal function fails to improve or creat worsens by >30% after ≥2 weeks steroids or becomes grade 3+
-Repeat urinalysis/ACR
-Contact nephrology team and consider treating as grade 3+

Renal dysfunction improves/stable
(even if not yet grade 1)
- Initiate steroid taper (see appendix XI)

GRADE 3-4 (Severe)

Any of the following
- Creatinine >3 x baseline or >350 mmol/L
- Hospitalization or dialysis indicated

ADMIT patient

Investigations:
- As per grade 2

Treatment:
- IV hydration
- Strict fluid balance+/- daily weight monitoring
- IV methylprednisolone 2 mg/kg/day + Gastroprotection

Actions:
- Daily U+E
- Stop immunotherapy
- Urgent nephrology referral

Renal dysfunction persists or worsens despite 2 weeks of high dose steroids

- Repeat urinalysis/ACR
- Consider renal biopsy with renal team input and potential additional immunosuppression

Renal dysfunction improves/stable
(even if not yet grade 1)
- Initiate steroid taper (see appendix XI)

Immunotherapy-related neurological toxicity

Note: Below offers a simplistic overview management approach to immune-mediated neurotoxicity but complex neurological syndromes including Guillain Barre, Myasthenia Gravis, encephalitis and aseptic meningitis can occur. Liaise early with neurology and refer to appendix IX for more difficult cases

GRADE 1 (Mild)

- Asymptomatic
- Not interfering with normal function

Assess patient

Investigations:
- Neurological examination
- Baseline bloods (FBC, U+E, serum magnesium + calcium + phosphate, LFTs, CRP, glucose + HbA1c, TFTs, Vitamin B12, folate)

Treatment:
- None

Actions:
- Regular close monitoring for progression, follow up assessment/telephone review in one week
- Review medication/alcohol history
- May continue immunotherapy, but can consider deferring next immunotherapy dose to monitor for progression

Symptoms worsen
- Reassess grade and treat accordingly

Symptoms improve
- Continue immunotherapy

GRADE 2 (Moderate)

Any of the following
- Sensory alteration such as paraesthesia (including tingling)
- Cranial nerve symptoms or signs
- Interfering with function BUT NOT ADLs

Assess patient

Investigations:
- As per grade 1
- Urgent MRI Spine and CT or MRI Brain

Treatment:
- Commence prednisolone 1mg/kg od (max 60mg/day) with Gastroprotection

Actions:
- Withhold treatment until ≤ grade 1
- Review medication/alcohol history as per grade 1
- Consider seeking neurology advice
- If not admitted, follow up telephone review within 48 hours

Symptoms persist (≥5 days) **or worsen**
- Liaise with neurology and consider treating as severe

Symptoms improve
(To ≤ Grade 1)
- Initiate steroid taper (see appendix XI)

GRADE 3 - 4 (Severe)

Any of the following
- Severe
- Disabling
- Limiting self-care ADLs
- Life threatening symptoms

ADMIT patient

Investigations:
- Urgent neurology input
- Daily neurological examination with regular NEWS and GCS score as appropriate
- Baseline bloods as per grade 1
- Urgent MRI Spine and CT/MRI Brain
- Consider lumbar puncture, nerve conduction studies and electromyography, in liaison with neurology

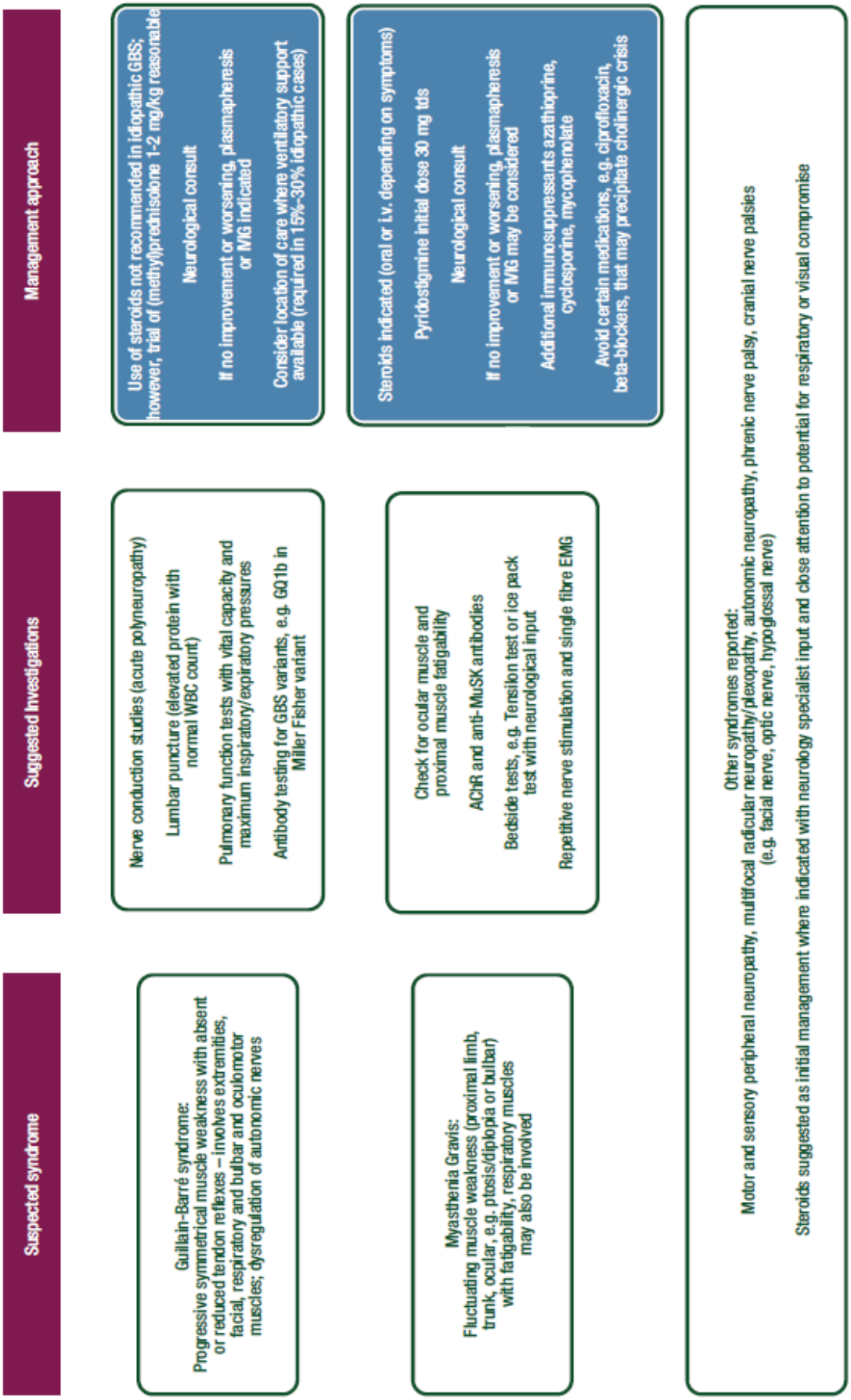
Treatment:
- IV methylprednisolone 2 mg/kg/day + Gastroprotection

Actions:
- Discontinue immunotherapy permanently
- Urgent neurology referral
- Alcohol history, medication review and exclude other potential causes

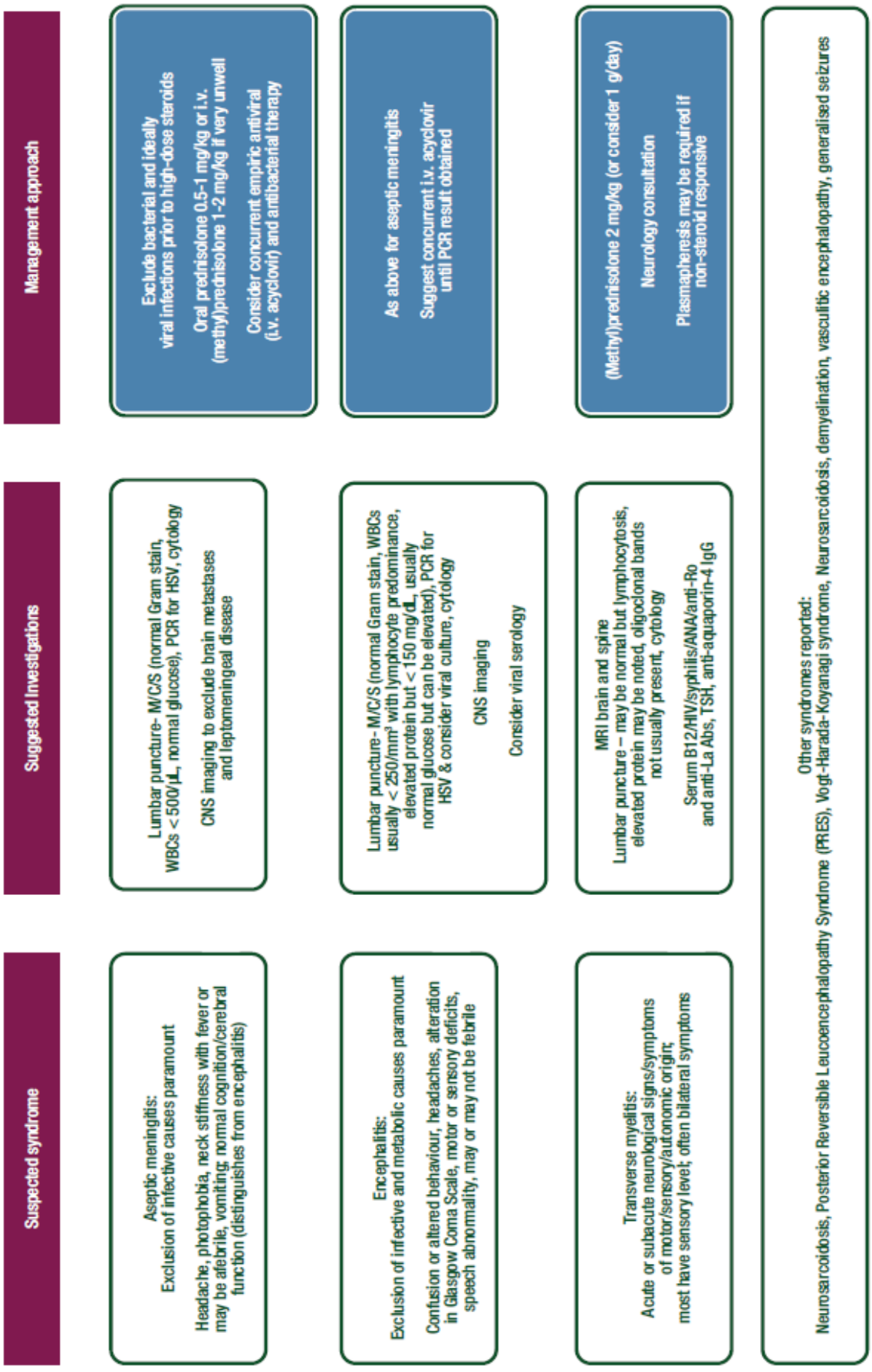
Symptoms persist (≥3 days) **or worsen**
- Liaise with neurology regarding additional intervention (may require additional immunosuppression or IVIG)

Symptoms improve
(To ≤ Grade 1)
- Initiate steroid taper (see appendix XI)

Complex Neurological Toxicity Management- Guillain Barré syndrome



Complex neurological toxicity management- Aseptic meningitis



Immunotherapy-related Myocarditis

- Diagnosis can be challenging and involves exclusion of other potential causes.
- The possibility of an immune-checkpoint inhibitor associated myositis/myocarditis being responsible for suspected symptoms, is higher in the presence of other immune-related toxicities (it may co-occur with myositis and/or myasthenia gravis).
- Diagnosis and management should involve cardiology.

CLINICAL FEATURES

May be sub-clinical, or present with symptoms, ranging from mild to severe/life-threatening. Presentations can be with acute-coronary-syndrome (ACS) like episodes, new onset heart failure or a chronic cardiac impairment. Consider in patients presenting with;

- Chest pain
- Dyspnoea
- Orthopnoea, paroxysmal nocturnal dyspnoea
- Palpitations
- Unexplained fatigue
- New arrhythmias or heart block
- Cardiogenic shock

INVESTIGATIONS

SERUM TESTS
- Creatine Kinase (CK)
- Troponin
- NT-pro BNP and BNP
- Inflammatory markers (ESR and CRP)

ECG +/- TELEMETRY

Changes may be non-specific but may include
- New PR prolongation or new heart/atrioventricular block
- Ventricular arrhythmias or frequent ventricular ectopics
- ST depression
- Diffuse T-wave inversion

IMAGING TESTS

Echocardiographic features may include
- Impaired LVEF/LVSF or diastolic dysfunction
- Regional wall motion abnormalities
- Co-existent pericardial effusion

Cardiac MRI may demonstrate features consistent with myocarditis

INVASIVE TESTS
- Coronary angiography to exclude significant coronary artery disease as cause of symptoms (as required)
- Endo-myocardial biopsy is gold-standard BUT should only performed in experienced centres

DIAGNOSIS

DEFINITE MYOCARDITIS
- Pathological diagnosis

OR
- Diagnostic Cardiac MRI + clinical syndrome + (either: biomarker or ECG changes)

OR
- ECHO wall motion abnormality + clinical syndrome + biomarker + ECG changes + negative angiography

PROBABLE MYOCARDITIS
- Diagnostic Cardiac MRI (no clinical syndrome, ECG changes or biomarker)

OR
- Suggestive Cardiac MRI + (either: clinical syndrome, ECG changes or biomarker)

OR
- ECHO wall motion abnormality + clinical syndrome + (either: biomarker + ECG changes)

POSSIBLE MYOCARDITIS
- Suggestive Cardiac MRI + (no clinical syndrome, ECG changes or biomarker)

OR
- ECHO wall motion abnormality + (either: clinical syndrome or ECG changes)

OR
- Elevated biomarker + (either: clinical syndrome or ECG changes) AND NO ALTERNATIVE DIAGNOSIS

MANAGEMENT

CORTICOSTEROID TREATMENT
- IV Methylprednisolone 2mg/kg OD
- For severe cases not responding to initial methylprednisolone – IV methylprednisolone 1g OD is recommended
- Response to corticosteroid can be monitored using serum troponin
- Steroid weaning should occur over a period of AT LEAST 4-6 weeks
- **Immunotherapy should be discontinued permanently in all cases of myocarditis**
- Cardiology input required for management of co-existent cardiac impairment/arrhythmias/AV nodal block secondary to myocarditis

ADDITIONAL IMMUNOSUPPRESSIVE TREATMENT
- The decision of when to use an additional immunosuppressive treatment, and which to use, should be made on a case-by-case basis and should have multi-disciplinary involvement
- Experience of additional immunosuppressive agents in myocarditis suggested for use in case series include; Mycophenolate mofetil (MMF), anti-thymocyte globulin, abatacept, alemtuzumab. Note infliximab should only be used with caution if LVEF is impaired.
- Plasmapheresis or IV immunoglobulin may also be beneficial in severe myocarditis

Steroid tapering guidance and supportive measures

Note: steroids may be required for several weeks and symptoms may flare requiring dose re-escalation

Monitoring and advice on steroid dose according to symptoms should be led and documented by the treating team. For patients not admitted (or after discharge), clear communication and lines of responsibility for patient contact, blood test monitoring and steroid dose advice must be established between the treating team, helpline staff, AOHU specialty doctors, acute oncology team or specialist nurses, as appropriate. If in doubt, seek senior advice.

ORAL STEROID TAPERING

Initiate corticosteroid taper over 3-6 weeks once toxicity is grade 1 or resolved

Tapering guidance:

- Reduce prednisolone dose by 10mg every 3 days (as toxicity allows) until dose is 10mg/day.
- Once steroid dose is 10mg/day, reduce by 5mg every 5 days then stop. Slower taper by 1mg/week can be considered once down to 5mg/day, especially if duration of steroid use was extended by toxicity flares.
- Monitor patient by telephone at least once weekly during taper till steroids discontinued.

Patients who have received ipilimumab or ipi/nivo should have LFTs checked weekly, regardless of the toxicity being managed with steroids

INTRAVENOUS STEROID TAPERING*

Initiate corticosteroid taper over at least 6 weeks once toxicity is grade 1 or less

Tapering guidance:

- Continue IV methylprednisolone 2mg/kg/day for a total of 5 days then switch to oral prednisolone 1- 1.5mg/kg/day x 3 days, then reduce to 60mg/day prednisolone.
- Patient can be discharged if toxicity remains settled once the switch to oral steroids is established
- Reduce prednisolone dose by 10mg every 7 days (as toxicity allows) until dose is 10mg/day.
- Once steroid dose is 10mg/day, reduce by 5mg every week then stop. Slower taper by 1mg/week can be considered once down to 5mg/day, especially if duration of steroid use was extended by toxicity flares.

Upon discharge:

- Monitor patient by telephone at least twice weekly during taper until toxicity is grade 1 or resolved, then at least once weekly till steroids discontinued.

Patients who have received ipilimumab or ipi/nivo should have LFTs checked weekly, regardless of the toxicity being managed with steroids

***See below special considerations/subsequent management for specific organ toxicities**

SPECIAL CONSIDERATIONS

Patients receiving steroids for Pneumonitis

Patients with pneumonitis may require a slower steroid taper given the risk of recurrent pneumonitis during tapering

- For patients with grade 2 pneumonitis, taper steroids over at least 4-6 weeks
- For patients with grade 3-4 pneumonitis, taper steroids over at least 6 weeks
- For patients whose symptoms flare during steroid taper, reassess for other potential causes (e.g. infection, VTE)

Patients receiving steroids for nephritis

Grade 2 nephritis

- Commence taper after 1 week oral prednisolone 60mg od- taper by 10mg/week
- Taper can commence once creatinine stable/improved, even if not yet grade 1
- If renal dysfunction fails to improve or worsens on oral steroids after ≥2 weeks, repeat urinalysis/ACR and discuss with renal team to consider treating as per grade 3-4

Grade 3-4 nephritis:

- Commence taper after 5 days of IV Methylprednisolone 2mg/kg. Reduce to oral prednisolone 60mg od, then taper by 10mg/week
- Taper can commence once creatinine stable/improved, even if not yet grade 1
- If there is a sustained rise x 1 week in creatinine levels during taper or while on IV Methylprednisolone, or stable but failure to improve x 2 weeks- recheck urinalysis/ACR and discuss with renal team to consider renal biopsy +/- additional immunosuppression.

Patients who fail to respond to steroids and require Infliximab for colitis/diarrhoea

- IV Methylprednisolone for grade 3+ colitis with escalation for infliximab if no response by day 3. All should have baseline faecal calprotectin sent and flexible sigmoidoscopy requested at presentation
- For those that respond to steroids- follow current standard steroid taper process as appendix XI
- Escalate to biological therapy with infliximab for those who fail to respond to IV Methylprednisolone by day 3. **Plan for 2 doses of infliximab 2 weeks apart as standard in this context and regardless of initial response**
- Steroid taper after infliximab- after first dose, step down IV methylprednisolone to oral Prednisolone 60mg x 3 days, then 40mg to reduce by 10mg/week
- For patients already on or completed a steroid wean, and prior IV Methylprednisolone who then develop symptom flare, escalate Prednisolone to the last effective dose at the time infliximab is commenced
- If symptoms not resolved at week 4, or any flare during taper- recheck faecal calprotectin and link back in with GI team to consider 3rd dose infliximab at week 6 (or Vedolizumab depending on clinical context, and as guided by GI team). Steroids can temporarily be re-escalated by to the lowest last effective dose

Patients who receive additional immunosuppressive agent (e.g. mycophenolate or tacrolimus) for hepatitis

Patients who develop grade 3+ hepatitis for the first time during steroid wean after a grade 2 event should be treated with IV Methylprednisolone if not previously received, with the relevant grade 3 flowchart followed

- For patients on IV methylprednisolone and requiring an additional agent due to no response, reduce steroid dose to prednisolone 60mg OD once additional agent has been initiated.
- For patients already on a steroid wean, and prior IV Methylprednisolone escalate Prednisolone to the last effective dose at the time additional agent is introduced
- LFTs should be checked weekly (FBP should also be checked due to risk of myelosuppression).
- Reduce prednisolone by 10mg/week once a fall in transaminase levels is established (regardless of grade). Once prednisolone dose is 10mg/day, reduce by 5mg/week then stop.
- Additional agent e.g. (Mycophenolate or tacrolimus) should be weaned/discontinued only after steroids have been stopped for ≥ 2 weeks AND transaminase levels are normal (see appendix XIV). Continue weekly LFT checks for at least an additional 2 weeks after immunosuppression completed, to ensure no flare.
- Consult with hepatology if flare in transaminase levels occurs during steroid taper, to discuss change of additional immunosuppression (e.g. addition of tacrolimus, see appendix XIV) and/or escalation of steroid dose as appropriate.

Note patients on tacrolimus require trough level check after 24-48 hours. The therapeutic index is low and side effects can occur hence clinical assessment of persistent symptoms during taper is advised, to see if linked to tacrolimus

Patients receiving steroids for myocarditis
Consider a slow wean – example below
IV Methylprednisolone 1g OD for 3/7.
Then to 4mg/kg/day (or 500mg) for 3/7.
Then to 2mg/kg/day for 3/7
Then to 1mg/kg/day for 3 days
Then reduce by 10mg/week till at 10mg OD, then reduce to 5mg OD x 1 week then stop

Supportive measures: for patients on steroids/additional immunosuppression

1. Remember gastroprotection for all patients (e.g. Omeprazole 20mg OD)
2. Ensure a clear steroid tapering schedule and monitoring protocol for toxicity flare is established, and ensure any additional supportive measures (as below) are implemented for all patients, to minimize risk of steroid complications (see checklist for patients being treated with steroids for immune-related toxicities- appendix XII)

Hyperglycaemia:

- Check baseline HbA1c at steroid initiation and random afternoon blood sugar monitoring (BM) should be undertaken whilst on treatment.

- If new hyperglycaemia is detected, diabetic team advice should be sought. Pre-existing diabetes may require escalation in oral hypoglycaemic agents or insulin.

- Refer to relevant trust guidelines for the management of steroid-induced diabetes

Bone health:
DEXA scan and commencement of a bisphosphonate (e.g. Alendronic acid 70 mg once weekly), is recommended in all patients who have been commenced on IV Methylprednisolone for grade 3+ toxicity
They should be commenced while awaiting DEXA scan result, and should continue throughout duration of steroids irrespective of DEXA scan result. (Patients on bisphosphonate must also receive calcium and vitamin D supplementation)
**For patients treated with oral steroids for toxicity <G3, assess fracture risk (https://cks.nice.org.uk/topics/osteoporosis-prevention-of-fragility-fractures/background-information/risk-factors/), request DEXA AND commence bisphosphonate if any additional risk factors present

Proximal myopathy:

- Common and can be debilitating especially for patients on prolonged duration of steroids. Can restrict patient activities of daily living and overall fitness, especially in association with steroid weight gain

- Offer physiotherapy input for strengthening exercises and link in to the hospital or community team early (see appendix XVI)

Insomnia:

- Potentially distressing if prolonged. Offer advice and counselling on sleep management

- Advise patients to take their steroid dose in the morning after breakfast.

- Offer short-term PRN use of sedatives such as Zopiclone.

Steroid-induced psychosis:

- Monitor patients on steroids for changes in mood and behaviour
- Consider discussion with psychiatry team if unsure of diagnosis and for advice on managing symptoms

Opportunistic infections:

- Consider PJP prophylaxis for steroid doses >prednisolone 25mg OD for > 6/52 (or shorter if at risk; e.g. with pneumonitis).
- Seek advice if additional immunosuppressive agents used. Patients receiving mycophenolate may be considered for CMV prophylaxis with valganciclovir, especially if CMV IgG negative and lymphopenic.
- Monitor oral cavity for candidiasis, and treat with Nystatin or Fluconazole as required.

Checklist for patients on steroids for management of immune-related toxicities **FACTORS TO CONSIDER IN ALL PATIENTS**	**Tick when plan made**
Plan for steroid taper (or maintenance) documented	
Steroid prescription plan clearly documented in patient notes and transcribed to discharge letter/communicated to GP	
Arrangements for steroid wean to be conducted at CNS IO toxicity clinic (Belfast Trust)	
Arrangements for next CT scans/re-staging scans	
Commenced on Calcium and Vitamin D supplementation?	
HbA1c checked at initiation or during steroid therapy?	
*DEXA requested AND bisphosphonate commenced for all patients who have been commenced IV Methylprednisolone (if appropriate)	
**DEXA requested AND bisphosphonate commenced for all patients who have been commenced oral steroids and have additional fracture risk as per below (if appropriate)	
Is PJP prophylaxis required?***	Y/N
• If yes, has it been commenced	

*DEXA scan and commencement of a bisphosphonate (e.g. Alendronic acid 70 mg once weekly), is recommended in all patients who have been commenced on IV Methylprednisolone for grade 3+ toxicity

They should be commenced while awaiting DEXA scan result, and should continue throughout duration of steroids irrespective of DEXA scan result. (Patients on bisphosphonate must also receive calcium and vitamin D supplementation)

**For patients treated with oral steroids for toxicity <G3, assess fracture risk (https://cks.nice.org.uk/topics/osteoporosis-prevention-of-fragility-fractures/background-information/risk-factors/), request DEXA AND commence bisphosphonate if any additional risk factors present

*** PJP prophylaxis recommended in patients anticipated to remain on PO or IV steroids at a dose equivalent to ≥ 25mg prednisolone for 6 weeks or longer (lower threshold for patients with additional risk factors e.g. Pneumonitis)

Infliximab administration guidance

Infliximab should only be given after discussion with a medical oncology consultant
Prescribe the biosimilar brand in current use at the time, for all doses. Check with pharmacy if unsure

PRE- INFUSION SCREENING AT BASELINE

1. Tuberculosis

- Full TB History (Check family history, travel history and profession)
- Chest x-ray prior to starting treatment

2. Routine blood tests

The following should all be completed prior to starting Infliximab:

- HIV serology
- Hepatitis screen
- Quantiferon IGRA test
- VZV serology
- Recent FBC, U&E, LFT, ESR and CRP

Discuss with lab to ensure virology is processed urgently
Note IGRA TB test processed by labs (Belfast trust) Monday-Thursday only, and has strict cut off times for collection.

3. Stool samples

Three negative sets of stool samples are required prior to treatment. Send each set for:

- Faeces microscopy and culture/PCR
- C. Difficile screen
- Cryptosporidium and Giardia

** Discuss with lab to ensure these are processed urgently Ensure these are sent early as urgent analysis can take >24 hours (three full sets of the above are preferable but not essential) **

4. Vaccinations

- Check the patient's vaccination history prior to starting Infliximab.
- No live vaccines in the last four weeks

5. Infection

Ensure no evidence of sepsis, or clinically manifested infection.

CONSENT

- Give the patient an information sheet
- Document informed consent prior to administration – documentation of verbal consent is adequate.

PRESCRIPTION AND ADMINISTRATION

- Stat. dose of **hydrocortisone 100mg IV** given prior to infusion.
- Stat. dose of **chlorphenamine 10mg IV** to be given prior to infusion.
- Prescription of **INFLIXIMAB 5mg/kg**, added to a 250mL sodium chloride 0.9%, to be given over 2 hours.

Supportive medication

- Ensure that 'as required' paracetamol, chlorphenamine, hydrocortisone and adrenaline are prescribed on the drug chart.
  - Paracetamol 1g PO/IV QDS PRN
  - Chlorphenamine 10-20mg IV PRN
  - Hydrocortisone 100 - 200mg IV PRN
  - Adrenaline 1:1000 0.5ml IM

TREATMENT OF AN INFUSION REACTION

Minor (e.g. fever, chills, headache, nausea, mild rash and pruritus)

- Discontinue infusion temporarily and give:
  - Hydrocortisone 100 - 200mg IV
  - Chlorphenamine 10-20mg IV
  - Paracetamol 1g PO/IV
- If good response, restart the infusion at a slow rate as recommended in the nursing protocol
- If no response to the above treatment, obtain help from a senior doctor urgently

Moderate to severe reaction (urticaria, tachycardia, hypotension, respiratory distress, reduced SaO2, swollen lips, reduced GCS)

- Discontinue infusion immediately
- Resuscitation (ABCDE approach) with O2 and IV fluids
- Administer
  - Hydrocortisone 100 - 200mg IV
  - Chlorphenamine 10-20mg IV
  - Paracetamol 1g PO / IV
  - Adrenaline 1:1000 0.5ml IM if required
- Obtain senior help

Additional Immunosuppressive Agents Used In Hepatotoxicity/Hepatitis

GENERAL PRINCIPLES

- Cases for which additional immunosuppressive agents are being considered should be discussed with the hepatology team.
- Mycophenolate Mofetil (MMF) is the recommended first-line agent in steroid-refractory immune-related hepatitis
- Tacrolimus (Prograf) can also be recommended in the following situations;
    - An alternative first-line agent when MMF is not advised (particularly in cases of co-existent diarrhoea/colitis, as MMF may exacerbate diarrhoea)
    - As an alternative to MMF if LFTs rising significantly and a rapid response is desired
    - In addition to MMF if transaminases are not improving after a week on MMF (or sooner if rising rapidly and grade 4). This should be guided by hepatology.
- Usual starting doses are described below. Further escalation in doses may be necessary depending on response of LFTs (discussion with hepatology is recommended)
- LFTs should be checked at least weekly, to guide treatment. Monitoring of FBP and renal function should also be performed due to risk of myelosuppression/renal impairment.
- Aim to limit duration of immunosuppression (from commencement of corticosteroids) to a MAXIMUM of 3 months, if LFTs have normalised.
- Following weaning and discontinuation of additional immunosuppression, continue with weekly LFT checks for a further 2 weeks to ensure no flare.

***SHARED CARE GUIDANCE FOR MANAGEMENT OF THESE MEDICATIONS ARE AVAILABLE AT https://ipnsm.hscni.net/red-amber/

Mycophenolate Mofetil

- Usual starting dose is 500mg BD
- If no response to mycophenolate mofetil (MMF) after 2 weeks, re-discuss case with hepatology team, as may benefit from addition of tacrolimus (Prograf)
- Weaning can commence when corticosteroid treatment has been discontinued for ≥ 2 weeks AND LFTs have normalised
    - Reduce by 500mg BD every 2 weeks (if LFTs not fully normalised or fluctuate, consider a slower wean to 250mg BD then stop)

Tacrolimus (Prograf)

- Starting dose dependent on weight and renal function and should be guided by hepatology
- For patients ≥ 60 kg and normal renal function usual starting dose 3mg BD
- For patients < 60 kg, renal impairment or frail consider lower starting dose
- Tacrolimus levels should be checked 24-48 hours after starting and repeated within the following 2 weeks
- Once a therapeutic range is confirmed by 2 checks, further levels only needed in the following circumstances:
    - If symptoms change (to check if reference range exceeded causing side effects)- especially when LFTs are improved to grade 0/1
    - If LFTs flare (to check if sub-therapeutic)
    - If patient has commenced any new drugs that can interact (https://www.drugs.com/drug_interactions.html)
- If levels are sub-therapeutic but transaminases improving regardless, dose adjustment is not needed
- Ensure renal function is monitored as drug-induced renal injury can occur
- Note tacrolimus can be poorly tolerated by some patients and this should be considered if new symptoms develop whilst on the drug
- Weaning can commence when corticosteroid treatment has been discontinued for ≥ 2 weeks AND LFTs have normalised
    - Reduce by 1mg BD every 2 weeks OR
    - Can be discontinued at any point (without weaning) if patient has been on immunosuppression > 3 months (from commencement of corticosteroid treatment) AND LFTs have normalised

- Shared care guidelines are available and should be communicated to primary care to inform them that the patient is on tacrolimus, however drug dispensing and monitoring will continue to take place through the hospital in secondary/tertiary care
- Note tacrolimus is brand-specific. Prograf brand is typically used and the same brand used on initiation should be maintained throughout treatment

Patients on both Mycophenolate Mofetil (MMF) and Tacrolimus (Prograf)

- Weaning can commence when corticosteroid treatment has been discontinued for ≥ 2 weeks AND LFTs have normalised. Mycophenolate should be weaned/discontinued first
  - Reduce Mycophenolate Mofetil by 500mg BD every 2 weeks (if LFTs not fully normalised or fluctuate, consider a slower wean to 250mg BD then stop)
  - If LFTs remain normal for 2 weeks since discontinuation of MMF, tacrolimus can be weaned by 1g BD every 2 weeks (or can be discontinued at any point (without weaning) if patient has been on immunosuppression > 3 months (from commencement of corticosteroid treatment) AND LFTs have normalised)

Mycophenolate mofetil Patient information

What is Mycophenolate Mofetil?

Mycophenolate mofetil is a drug that has been used to treat patients who have inflammation caused by the body's own immune cells. The drug is often used following the transplant of organs such as heart, kidney and liver as their immune cells need to be "switched off" to stop them from attacking the donor organ.

You are being prescribed this drug because your immune cells are causing inflammation in your liver as a side effect of your anti-cancer immunotherapy treatment.

How should Mycophenolate Mofetil be taken?

- Swallow tablets whole, do not suck or chew them. They can be taken before or after meals.
- Your specialist will tell you what dose to take, and these instructions should be followed
- If you miss a dose take it as soon as you realise. However, if you do not realise until the next day, skip the missed dose and carry on as before. **Do not take double the dose.**

Taking Mycophenolate may reduce your body's resistance to infections. Try to keep away from people who you know are ill and report any sign of infection to the hospital using the chemotherapy helpline number.

Mycophenolate tablets can be stopped if required. They do not need to be gradually reduced down unlike steroids.

If you have not had chickenpox or shingles and come into contact with someone affected you should inform the hospital immediately, using the chemotherapy helpline. Acquiring chickenpox when your immune system is suppressed can lead to serious illness.

Your doctors will also need to know if you have been exposed to or had TB.

Can I have immunisations while I am on Mycophenolate?

Live vaccines should be avoided while you are taking Mycophenolate and up to six months after you start treatment. Inform your hospital oncology doctors or nurses before receiving immunisations. Inactivated vaccines are safe but may not work as well during treatment with mycophenolate.

What are the possible side effects?

Normally this treatment is tolerated well. You may however have some unwanted reactions.

- Initially you may feel nausea after tablets, which is often relieved by taking them after food. Spreading the dose evenly throughout the day may also help.
- General tiredness can occur at first but wears off with continued use or reduced dose.
- Your blood count is monitored regularly because Mycophenolate can reduce your blood count. Levels return to normal when treatment is reduced or stopped. If you experience unexpected bruising or bleeding, inform your oncology doctors or nurses immediately using the chemotherapy helpline
- There are other less common side effects including headache, impaired liver function and jaundice. Lymphoma a blood cancer has been reported but is very rare. Patients have very rarely developed a brain infection called PML while taking mycophenolate. Tell your doctor right away if you have any of the following symptoms- weakness on one side of the body, confused or have problems thinking or you cannot control your muscles. In cases of serious effects the treatment is stopped completely.

Are there any other precautions I need to take?

While taking Mycophenolate you may become more sensitive to the harmful effects of sunlight. As a result there is an increased risk of skin cancer. It is therefore advisable to limit the amount of sunlight and ultraviolet light you get by wearing protective clothing and using sunscreen with a high protective factor.

Mycophenolate and pregnancy?

Mycophenolate can cause serious side effects this includes an increased risk of pregnancy loss (miscarriage) and a higher risk of birth defects.

If you are premenopausal female who can become pregnant – you should have a negative pregnancy test prior to starting Mycophenolate. You should use two reliable forms of contraception before starting Mycophenolate therapy, during therapy and for six weeks after stopping therapy. Please discuss this with your GP.

If you inadvertently become pregnant on treatment stop your medication immediately and contact your doctor.

Sexually active men (including vasectomised men) should use condoms during treatment and for at least 90 days after Mycophenolate cessation. In addition female partners of male patients using Mycophenolate should use highly effective contraception during treatment and for a total of 90 days after the patient's last dose of any Mycophenolate containing product. This is because Mycophenolate can be passed to female partners through semen.

If you are male and your partner becomes pregnant the risks are unknown. The advice to avoid fathering children is a precautionary measure.

This information leaflet dose not list all the side effects of Mycophenolate. For further details please read the drug information sheet that comes with your prescription, or discuss with your hospital oncology doctors or nurses.

ONCOLOGY HELPLINE NUMBER (BELFAST CANCER CENTRE): 028 9504 5555

NURSE LED IO TOXICITY SERVICE REFERRAL PATHWAY (BELFAST TRUST) FOR PATIENTS REQUIRING STEROIDS TO MANAGE AN IMMUNOTHERAPY INDUCED ADVERSE EVENT

1. Assessment
   - Assess patient and identify grade of toxicity

2. Bloods
   - Ensure required bloods are taken
   - Send baseline HbA1c
   - If new hyperglycaemia detected arrange for patient to attend PTU for glucometer and training for home monitoring
   - If pre-existing diabetes educate patients about risk of hyperglycaemia and consider liaising with diabetic team regarding escalation of hypoglycaemic agents / Insulin

3. Guidelines
   - Refer to NICaN Checkpoint Inhibitor Immunotherapy Toxicity Management Guidelines

4. Steroids
   - Commence oral PREDNISOLONE or IV METHYLPREDNISOLONE depending on severity of toxicity
   - If sending patient home with oral steroids and supportive medication please make sure they have >2 week supply

5. Supportive medication for all patients on steroids
   - Gastroprotection
     E.g. OMEPRAZOLE 20mg OD
   - Bone protection
     E.g. ADCAL D3 TT BD
   - Prophylactic bisphosphonate therapy (following satisfactory dental check)
     E.g. ALENDRONIC ACID 70 mg once weekly
   - PJP prophylaxis
     E.g. CO-TRIMOXAZOLE 480mg BD on Mondays, Wednesdays and Fridays

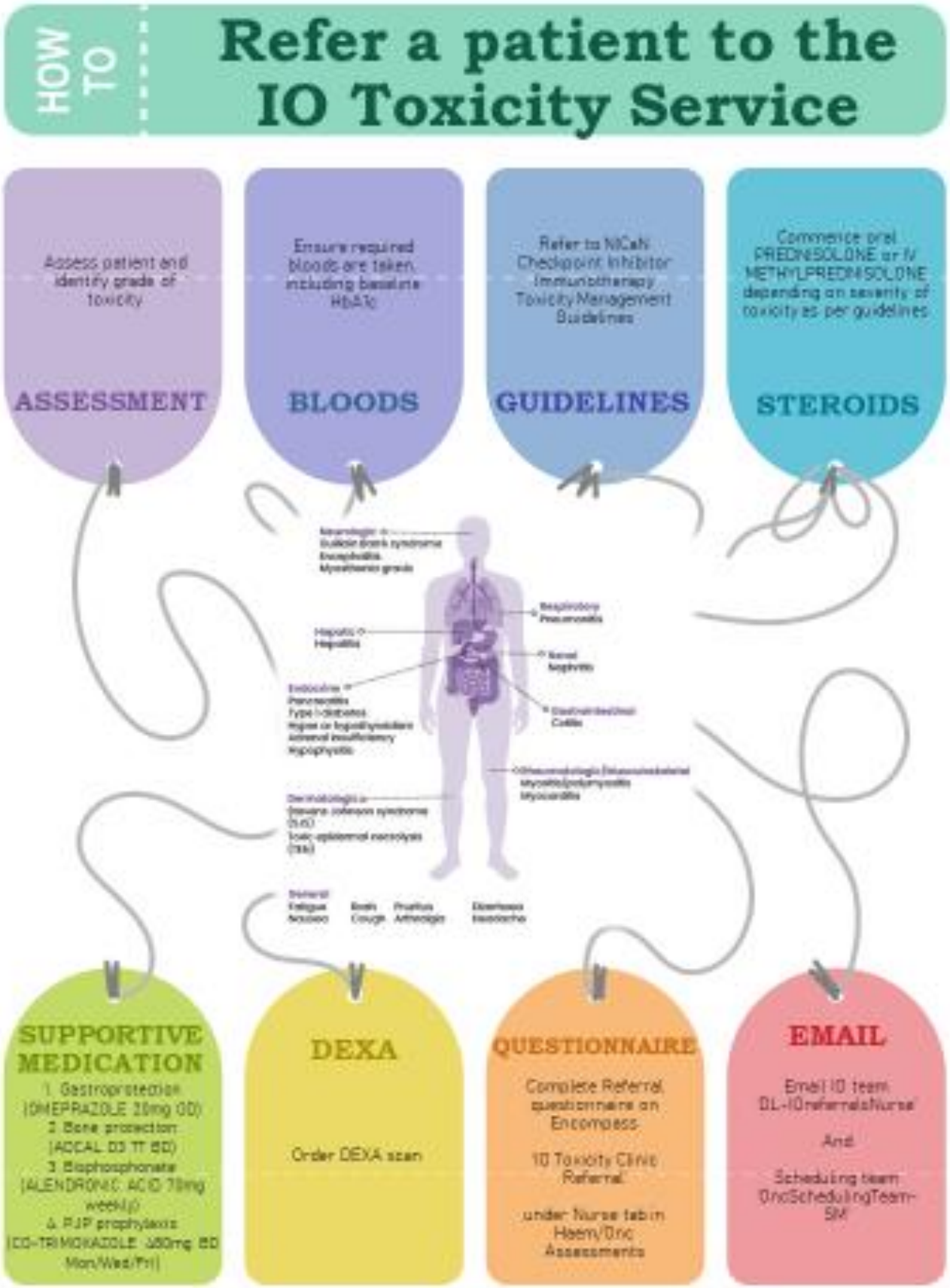
6. Order DEXA scan

7. Complete referral questionnaire on Encompass
   This can be found by clicking on the following:
   - 'Haem /Onc Assessments'
   - 'Nurse'
   - 'IO Toxicity Clinic Referral'
   - In the referral please include:
   1. Toxicity
   2. Suggested plan for steroid wean e.g. reduce by 10mg every 7 days
   3. Suggested date for first phone call
   - If patient has completed steroid wean and symptoms flare/recur please re-refer using the same pathway and complete a new IO Toxicity Clinic Referral questionnaire.

8. Email
   Email referral to:
   - IO team 'DL-IOreferralsNurse'

and
   - Scheduling team 'OncSchedulingTeam-SM'

Appendix XV: Nurse led IO Toxicity service referral pathway



Community Physiotherapy Referrals

AREA	REFERRAL SYSTEM	PHONE / E-MAIL
SOUTH & EAST BELFAST	CALL MANAGEMENT	028 90 565565
NORTH & WEST BELFAST	CALL MANAGEMENT	028 90 635300
SOUTH EASTERN HSC TRUST	E-MAIL REFERRAL	cbo.physiotherapy@setrust.hscni.net
WESTERN HSC TRUST	CALL MANAGEMENT	028 71 864399
SOUTHERN HSC TRUST	E-MAIL REFERRAL	ahp.cbu@southerntrust.hscni.net
NORTHERN HSC TRUST	E-MAIL REFERRAL	physiocentralbooking@northerntrust.hscni.net

List of abbreviations

Abbreviation	Meaning	Abbreviation	Meaning
ACTH	Adrenocorticotropic hormone	nmol/L	Nanomoles per litre
BD	Bis die (Twice daily)	OD	Omni die (Once daily)
BP	Blood pressure	PCR	Polymerase chain reaction
CK	Creatine Kinase	PD-1	Programmed death protein 1
CMV	Cytomegalovirus	PD-L1	Programmed death-ligand 1
CNS	Central nervous system	PJP	Pneumocystis jiroveci pneumonia
CRP	C-reactive protein	pmol/L	Picomoles per litre
CT	Computed tomography	PO	Per os (Oral administration)
CTC(AE)	Common terminology criteria (for adverse events)	PPI	Proton-pump inhibitor
EBV	Epstein-Barr virus	PT	Prothrombin time
FBC	Full blood count	QDS	Quater die sumendum (4 times daily)
FSH	Follicle-stimulating hormone	RVH	Royal Victoria Hospital
HIV	Human immunodeficiency virus	T3	Triiodothyronine
HSV	Herpes simplex virus	T4	Thyroxine
IV	Intravenous	TB	Tuberculosis
kg	Kilogram	TFT	Thyroid function test
LFT	Liver function test	TNF	Tumour necrosis factor
LH	Luteinising hormone	TPO	Thyroid peroxidase
LLN	Lower limit of normal	TSH	Thyroid-stimulating hormone
mg	Milligram	U+E	Urea and electrolytes
mIU/L	Milli-International units per litre	UKONS	UK Oncology Nursing Society
mmHg	Millimetre of mercury	VTE	Venous thromboembolism
MRI	Magnetic resonance imaging		