State if the document is a Trust Policy/Procedure or a Clinical Guideline / Drugs Therapeutic Committee Document	**Clinical Guidelines**

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Document author(s):	Nicola Farthing, Acute Oncology Service CNS Nicole Young, Acute Oncology Service CNS Admin support by Melissa Morawski
Document developed in consultation with:	Nicola Farthing, Acute Oncology Service CNS Nicole Young, Acute Oncology Service CNS Dr Anup Vinayan, Clinical Oncologist Dr Mawdsley, Clinical Oncologist Priya Shah Oncology Pharmacist
Staff with overall responsibility for development, implementation and review:	Acute Oncology Service Steering Group
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Target Audience:	All Trust Staff.
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Associated Trust Documents:	
Reason for current amendments:	New Treatment /new guideline

Contents

1.0 Introduction

This document aims to provide pathways to advise on appropriate management of Immunotherapy Related Adverse Events (irAEs). IrAEs can occur early, mostly within weeks to 3 months after initiation of immune checkpoint blockers. However, the first onset of irAEs has been documented as long as 1 year after discontinuation of treatment.
Immunotherapy drugs work with the body's immune system by increasing its natural ability to act against cancer cells.
Side effects can result in severe immune mediated adverse reactions, the most common are itchy skin rashes, diarrhoea leading to an inflammatory colitis type picture, thyroid, adrenal or pituitary dysfunction, pneumonitis, nephritis, hepatitis, uveitis, paresthesia and neuropathy can all occur. It is important to recognise and manage these adverse events early to reduce serious patient related morbidity and mortality.

The mainstay of immunotherapy toxicity management is corticosteroids which is immunosuppressive and therefore suppresses the T cell activating function of the treatment. The following serve as a general guide, it is important to inform the treating oncologist/haematologist as soon as possible or in the event of a hospital admission. It is also important to liaise with medical specialities such as the gastroenterology or endocrine team at L&D, as a proportion of patients may not respond to first line corticosteroids and will have to be admitted to hospital.

2.0 Definition

Immunotherapy is a type of cancer treatment that helps the immune system fight cancer by the use of cytokines and T cells (by the use of check point inhibitors and agonists of co-stimulatory receptors), manipulation of T cells, vaccines and oncolytic viruses. The principal behind these checkpoint inhibitors is to remove the physiological immune 'break' and stimulate the immune system to recognise tumour cells.

3.0 Background

These guidelines have been produced by the Luton & Dunstable University Hospital. The Acute Oncology Service makes recommendations based on evidence-based practice with an extensive review of the available literature to promote best practice in the management of Immunotherapy Related Adverse Events.

4.0 Objectives

1. For all immunotherapy toxicities to be graded according to the adverse event grading criteria & follow guidelines for management of toxicities.
2. To inform the treating oncologist/haematologist as soon as possible or in the event of a hospital admission.
3. To ensure that all patients admitted to hospital 'at risk' of irAEs are recognised.

4. To ensure that the patient has the most appropriate treatment based on a thorough and inclusive assessment of the symptoms.
5. To minimise the risk of upcoming oncological treatments being delayed or dose reduced due to irAEs.
6. To reduce the length of stay in hospital for patients with irAEs as a contributing factor for their admission.
7. To communicate with the Oncology/Haematology treating physician to ensure there is a plan for future treatments, to prevent readmission with further irAEs.
8. Any queries with regard to patients with irAEs should be referred to the:

Acute Oncology Service (Monday – Friday, 8:00am – 4:00pm).
07917553350 Bleep 011

Mount Vernon Cancer Centre (for oncology opinion):
SpR on Call 020 3826 2020

4.0 Monitoring

The guidance and pathway is based on this guidance and current best clinical practice. The pathway will be monitored through the Acute Oncology Service (AOS) who will have initial contact with all acutely admitted cancer patients. If the AOS team see that the pathway is not being followed they will educate, audit and report in accordance with the Trust's incident reporting guidelines. The medical teams to inform the GP via discharge letter of the patient's treatment and ongoing support needed

5.0 Communication

This guidance and the attached pathways are available on the hospital intranet and will be relayed to acute medical doctors in their induction.

6.0 References

European Society for Medical Oncology (2017) Management of toxicities from immunotherapy: ESMO clinical practice guidelines. Available at: http://www.esmo.org/Guidelines/Supportive-and-Palliative-Care/Management-of-Toxicities-from-Immunotherapy

Kent and Medway Cancer Collaborative (2017) Guidelines for the management of Immune-related toxicities. Available at: http://www.kentmedwaycancerguide.nhs.uk/EasysiteWeb/getresource.axd?AssetID=466828&type=full&servicetype=Attachment

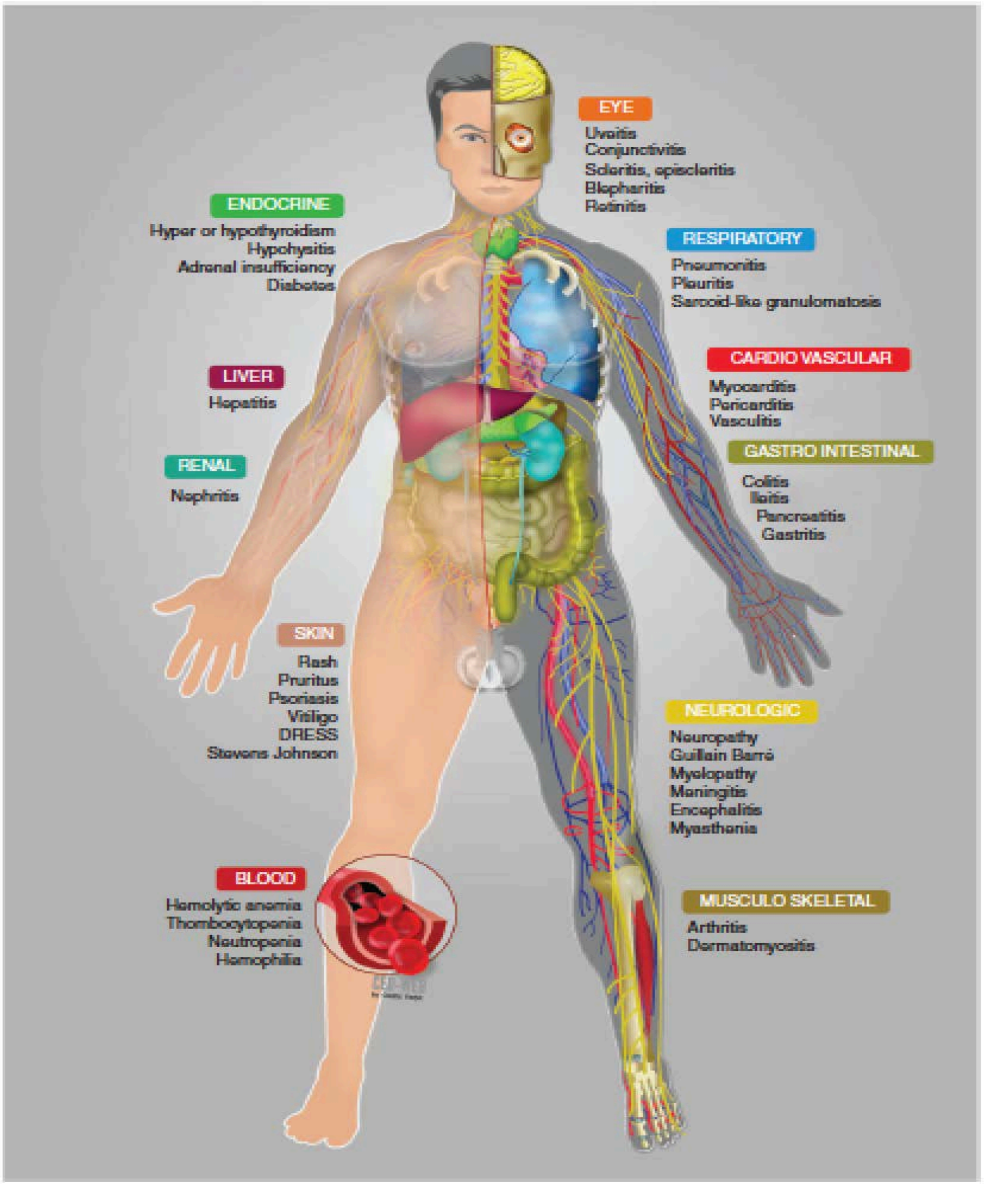
Velindre Cancer Centre (2016) Immunotherapy toxicity guidelines. Available at: http://www.velindrecc.wales.nhs.uk/sitesplus/documents/1087/Immunotherapy%20Guidelines%20version%201%20%28Oct%202016%29.pdf

These guidelines have been adapted from the Clatterbridge Cancer Centre's Immunotherapy Guidelines.

Immunotherapy Related Adverse Effects (irAEs)

irAEs are typically mild to moderate in severity, if they are left unrecognised or untreated, they can become life-threatening. These toxicities can be managed effectively in almost all patients by using established guidelines that stress vigilance and the use of corticosteroids and other immunosuppressive agents when necessary. **For treatment advice on irAEs please see Management guidelines for Immunotherapy Related Adverse Effects.** These guidelines cover initial management of common immunotherapy related toxicities.

Think could this be an irAEs



Please contact the treating oncologist for advice ASAP or
Acute Oncology Service (Monday – Friday, 8:00am – 4:00pm).
07917553350 Bleep 011

Mount Vernon Cancer Centre (for oncology opinion):
SpR on Call 020 3826 2020

Luton & Dunstable University Hospital

Immune-Related Adverse Event: Diarrhoea

Gastrointestinal (GI) irAEs are among the most common and although they are typically mild to moderate in severity, if they are left unrecognised or untreated, they can become life-threatening. These toxicities can be managed effectively in almost all patients by using established guidelines that stress vigilance and the use of corticosteroids and other immunosuppressive agents when necessary.

Mild (Grade 1)

- <4 stools/day over baseline
- or mild increase in ostomy output

in the absence of abdominal pain, mucous/blood in stools

Investigations:
- Baseline bloods (FBC, U&E, LFTs, TFTs, cortisol & CRP)
- Stool microscopy and culture
- C. difficile toxin
- Faecal calprotectin

Treatment:
- Loperamide (use with caution as may mask symptoms of worsening colitis)
- Encourage fluids
- Avoid high fibre and lactose

Actions:
- Telephone assessment within 3 days
- Consider continuing immunotherapy (if on combination anti-PD1/CTLA4 consider withholding immunotherapy)

Symptoms: PERSIST (>5 days) or WORSEN or are associated with deranged U&E's

Moderate (Grade 2)

If **any** of the following symptoms are present:

- 4-6 stools/day over baseline *or* moderate increase in ostomy output
- Moderate abdominal pain/cramps/discomfort
- Mucous in stool

Clinical Assessment

Investigations:
- As per mild (Grade 1)
- CMV viral load + PCR (brown top blood sample)
- Abdominal X-ray (consider CT Abdo/pelvis

Treatment:
(Commence treatment; do not wait for investigation results)
- Prednisolone 0.5-1 mg/kg/day (max. 60mg/day) + PPI cover
- Fluid balance and replacement as appropriate (inc. diarolyte sachets)

Actions:
- Omit next dose of immunotherapy
- Daily telephone monitoring
- Gastroenterology advice/review (consider endoscopy)

Assess response to treatment within 72 hours

Symptoms: Resolve or improve to mild see steroid tapering guidance

PERSISTANT or WORSEN or RELAPSE

Severe or life-Threatening (Grade 3 + 4)

If any of the following symptoms are present:

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

Admit Patient

Investigations:
- As per moderate (Grade 2)
- Daily bloods (FBC, U&E, LFTs & CRP)
- CT abdomen/pelvis
- Screen for Infliximab administration suitability on admission (to include- TB Eli spot test, hepatitis screen, HIV, chest X-Ray (if chest CT not already performed)
- Endoscopy with biopsies (inc. CMV staining)

Treatment:
- IV hydration and fluid balance
- IV methylprednisolone 2mg/kg/day (or IV hydrocortisone 100mg QDS) + PPI cover
- Antibiotics are not required as standard

Use analgesia with CAUTION

Actions:
- Daily stool chart
- Refer and consider transfer to gastroenterology
- Dietician review
- Omit and consider discontinuation of immunotherapy

Review patient daily, if no improvement within 72 hours, seek gastroenterology advice for further advice and management

Interrupt SACT immunotherapy until discussed with Acute Oncology team. Please contact on-call oncology/haematology team for advice. Ensure that Acute Oncology/Haematology team are informed of admission

Luton & Dunstable University Hospital

Immune-Related Adverse Event: Endocrinopathies – Adrenal Crisis

Immunotherapy has been causatively associated with a number of endocrinopathies that may present with nonspecific symptoms, which may resemble other causes such as brain metastasis or underlying disease.

Endocrine Function Panel:

U&E, LFT, TSH, Free T4, Free T3, ACTH, LH, FSH & Cortisol (between 9-11am if possible), prolactin, blood glucose +/- testosterone/oestrogen

CAUTION if the patient is on steroids (prednisolone/dexamethasone) then serum cortisol will likely be suppressed – please discuss with the endocrinology team before commencing replacement

Asymptomatic
Indentified on routine blood tests

Biochemical alteration in cortisol with serum level <400nmol/L

Hypoadrenalism is likely if cortisol is <100nmol/L

Cortisol 100-400nmol/L

Investigations:
- Repeat cortisol at 9am < 48 hours
- Complete endocrine function panel if outstanding

Actions:
- Monitor regularly (before each cycle as a minimum) and act as per algorithm if serum levels fall
- Continue immuno-therapy

Cortisol <100nmol/L

Investigations:
- Repeat cortisol at 9am < 24 hours
- Complete endocrine panel if outstanding

Treatment:
- Replace with hydrocortisone 10mg/5mg/5mg

Actions:
- Refer to endocrinology for advice/further investigation
- Give emergency advice about hydrocortisone
- Continue immunotherapy

Symptomatic
Mild/Non-life threatening

Suspect endocrinopathy based on symptoms

Tiredness/fatigue, headache, weight loss, susceptibility to infection, normal BP with no postural drop

Investigations
- 9am cortisol and ACTH
- MRI brain with pituitary cuts

Cortisol (9am) > 400 nmol/L

Adrenal insufficiency unlikely

Actions:
- Consider other causes of symptoms
- Continue immuno-therapy

Cortisol (9am) 100-400 nmol/L

Adrenal insufficiency possible

Actions:
- Endocrine referral
- Complete standard endocrine panel plus IGF-1
- Continue immuno-therapy

Cortisol (9am) <100nmol/L

Adrenal insufficiency likely

Treatment:
- Commence hydrocortisone 10mg/5mg/5mg

Actions:
- Endocrine referral
- Complete standard endocrine panel plus IGF-1
- Give emergency advice about hydrocortisone
- Continue immuno-therapy

Sympo-matic
Severe or Life – Threatening
Suspect adrenal crisis-
Hypotension (SBP <90mm Hg)
Postural hypotension (>20mm Hg drop)
Dizziness/Collapse
Hypovolemic shock
Nausea/Vomiting
Abdominal pain/tenderness/guarding
Fever
Confusion/delirium
Coma
Hyponatraemia/hyperkalaemia/ Hypoglycaemia
Pre-renal/renal failiure

Admit Patient

Immediate intervention
- Send endocrine panel
- Immediate management with an ABCDE approach
- Commence IV hydrocortisone 100mg immediately without awaiting blood tests
- Urgent endocrinology referral
- Rule out superadded infections

Society of Endocrinology (SfE) guidelines for adrenal crisis: www.endocrineconnections.com/content/5/5/G1*

Next steps are dependent on blood results

Emergency advice regarding hydrocortisone is outlined in the SfE guidance*

If thyroid function is also compromised within a hypopituitary picture ensure cortisol is replaced prior to commencement of thyroid replacement (for which grade 1 hypothyroidism guidelines should be instituted)

Interrupt SACT immunotherapy until discussed with Acute Oncology team. Please contact on-call oncology/haematology team for advice. Ensure that Acute Oncology/Haematology team are informed of admission

Luton & Dunstable University Hospital

Immune-Related Adverse Event: Endocrinopathies – Thyroid Dysfunction

Immunotherapy has been causatively associated with a number of endocrinopathies, including hypo/hyperthyroidism. Observational studies have shown that there is a typical pattern of thyroid specific biochemical disturbance presenting with asymptomatic hyperthyroidism, before the return to normal levels for a brief period. This is nearly always followed by the development of, in some cases profound, hypothyroidism which is frequently persistent and requires long term thyroid replacement. Smaller subsets of patients develop isolated hypothyroidism over a period of weeks. Both groups appear to require long term replacement in a majority of cases.

Mild (Grade 1)

Asymptomatic with biochemical changes

Investigations

TSH, Free T4, Free T3, ACTH, LH, FSH & cortisol, prolactin, blood glucose +/- testosterone

Hyperthyroidism

TSH <0.40 mU/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, discuss with endocrinologist before commencing steroids

Actions:

- Recheck TFT's and cortisol within 2 weeks and fortnightly thereafter. N.B. the majority of cases become hypothyroid within a matter of weeks.

Once hypothyroid – manage as per hypothyroidism algorithm

Hypothyroidism

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

Treatment:
Levothyroxine 50mcg/day

Actions:

- Recheck TFT's and cortisol with next cycle of treatment
- Increase Levothyroxine in 25mcg increments
- Discuss with endocrinologist to identify best pathway for long-term management and monitoring (primary/secondary care)
- Refer to endocrinologist if unable to stabilise thyroid function

Moderate (Grade 2)

Symptomatic or severe biochemical disturbance

Investigations

TSH, Free T4, Free T3, ACTH, LH, FSH & cortisol, prolactin, blood glucose +/- testosterone

Hyperthyroidism

TSH <0.40 mU/L and Free T4 > 22pmol/L

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

Treatment:

- Consider steroids, 0.5mg-1mg/kg/day (max. 60mg/day)
- B-blocker- Propranolol 40-80mg daily
- Carbimazole-rarely indicated due to the transient nature of hyperthyroidism. If persistent or associated with anti – TSH antibodies consider in collaboration with an endocrinologist

Actions:

- Recheck TFT's and cortisol within 2 weeks and fortnightly thereafter. N.B. the majority of cases become hypothyroid within a matter of weeks.

Once hypothyroid – manage as per hypothyroidism algorithm

Hypothyroidism

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

Treatment:
Levothyroxine 50mcg/day

Actions:

- Recheck TFT's and cortisol with next cycle of treatment
- Increase Levothyroxine in 25mcg increments
- Refer to endocrinologists if unable to stabilise thyroid function

Interrupt SACT immunotherapy until discussed with Acute Oncology team. Please contact on-call oncology/haematology team for advice. Ensure that Acute Oncology/Haematology team are informed of admission

Luton & Dunstable University Hospital

Immune-Related Adverse Event: Hepatoxicity

Hepatic transaminases (ALT/AST) and bilirubin must be evaluated before each dose of immunotherapy, as early laboratory changes indicate emerging immune-related hepatitis. Elevations in LFTs may develop in the absence of clinical symptoms. This guidance should be used in context of baseline LFTs and presence of known liver metastases. No dose adjustment is required for mild hepatic impairment but data is limited for use of these drugs in moderate/severe hepatic impairment and patients should be closely monitored for elevation in LFTs from baseline.

Prior to commencement of immunotherapy all patients should have LFTs checked

Moderate (Grade 2)

ALT >3 to ≤5 x ULN

Clinical Assessment

Investigations:

- Regular LFTs, direct and indirect bilirubin and clotting profile
- Imaging of liver to rule out PD & thromboembolism (Consider CT or USS)
- Hepatitis viral panel (hepatitis A, B and C)

Treatment:

- Commence prednisolone 1mg/kg/day (max 60mg OD)

Actions:

- Withhold dose until the adverse reaction resolves to Grade 0 – 1 (or returns to baseline)
- Review medications (e.g. statins, antibiotics)
- **Re-check LFTs and INR every 3 days**

Symptoms: Resolve or improve to Mild
See steroid tapering guidance

Biochemical abnormality PERSISTS (≥ 3 days) WORSEN or RELAPSE

Severe or Life – Threatening (Grade 3/4)

ALT >5 x ULN (Grade 4 >20 x ULN)

Clinical Assessment

Investigations:

- As per moderate hepatoxicity
- Daily LFTs and INR

Treatment

- Consider hospital admission depending on clinical condition and severity of liver abnormalities
- Consider prophylactic antibiotics after discussion with microbiology

Grade 3

- Oral prednisolone 1mg/kg/day (max. 60mg/day) if ALT/AST ≤400; OR IV hydrocortisone 100-200mg QDS

Grade 4

- IV methylprednisolone 2mg/kg/day

Actions:

- Referral to hepatologists for further advice
- If Grade 3, withhold next cycle of treatment
- If Grade 4 discontinue treatment permanently
- Consider antibiotic prophylaxis while on methylprednisolone after discussion with microbiology

Symptoms: Resolve or improve to mild
See steroid tapering guidance

Review patient daily, if no improvement within 72 hours, seek hepatologist for further management

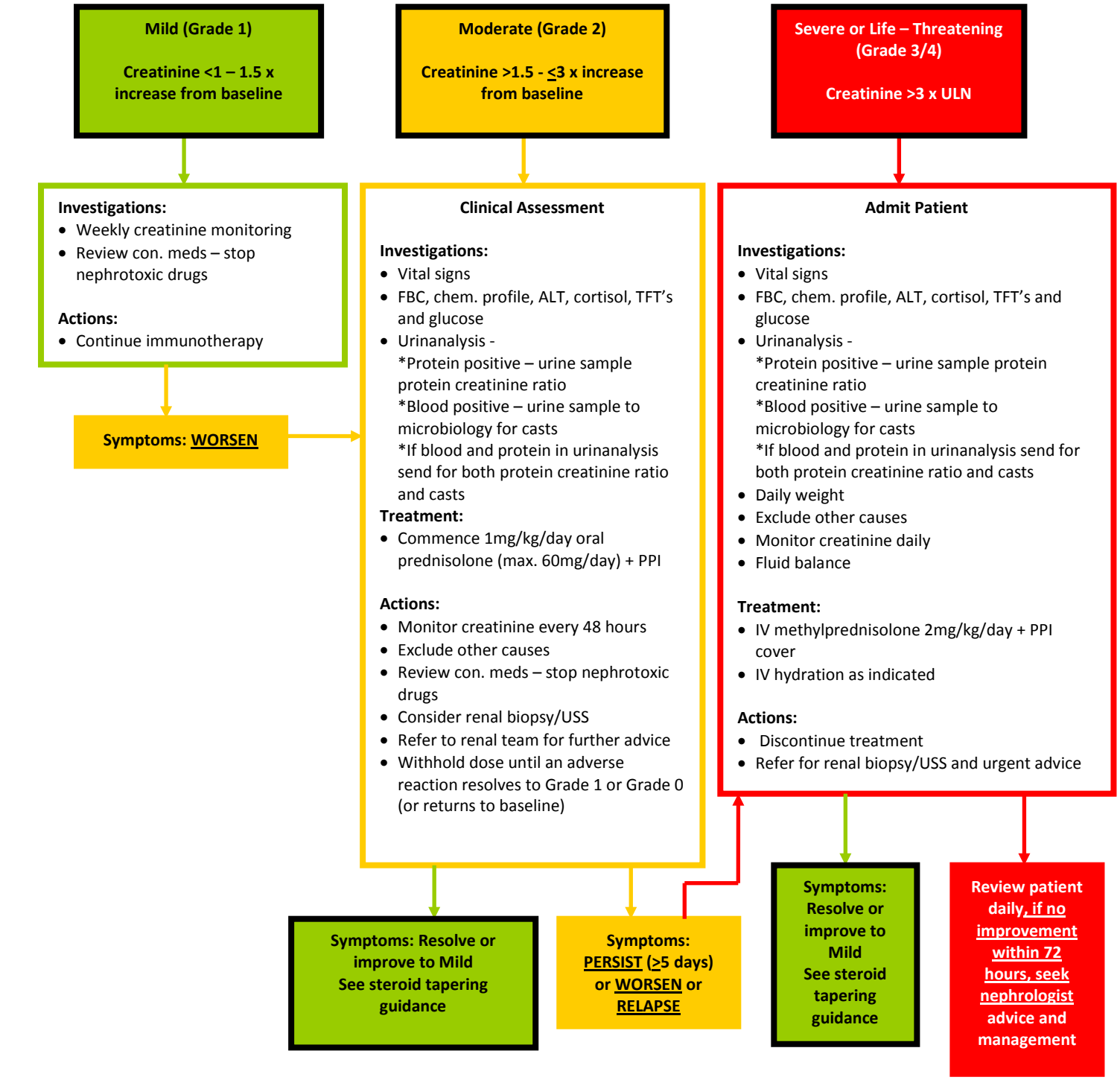
Abbreviations

LFTs = Liver function tests
INR = International **normalised ratio**
ULN = Upper limit of normal
PD = Progressive disease

Interrupt SACT immunotherapy until discussed with Acute Oncology team. Please contact on-call oncology/haematology team for advice. Ensure that Acute Oncology/Haematology team are informed of admission

Immune-Related Adverse Event: Renal Toxicities

Elevated creatinine and biopsy confirmed tubulointerstitial nephritis and allergic nephritis have been infrequently observed following treatment with immunotherapy agents. The frequency of renal AEs may be greater with combination therapies than with monotherapy. Most cases were Grade 2 or Grade 3 and based on creatinine elevation. Patients with a history of RCC or prior nephrectomy do not appear to be at higher risk. Events were managed with corticosteroids and in all cases renal function partially or fully improved.



Interrupt SACT immunotherapy until discussed with Acute Oncology team. Please contact on-call oncology/haematology team for advice. Ensure that Acute Oncology/Haematology team are informed of admission

Luton & Dunstable University Hospital

Immune-Related Adverse Event: Skin Toxicities

Immunotherapy administration is associated with immune-related adverse events (irAEs) Dermatological irAEs are common and although they are typically mild to moderate in severity, if they are left unrecognised or untreated, they can become life – threatening. These toxicities can be managed effectively in almost all patients by using established guidelines that stress vigilance and the use of corticosteroids and other immunosuppressive agents when necessary.

Mild (Grade 1)

- Localised macular/papular eruption
- Asymptomatic

Investigations:

- Emollient with paraffin content (eg 50:50 ointment)
- Consider anti-histamines – regular chlorpheniramine 4mg qds tablet.

Actions:

- Regular monitoring
- Continue immunotherapy

Symptoms: WORSEN

Symptoms: Resolve or improve to Mild
See steroid tapering guidance

Moderate (Grade 2)

- Rash affecting ≤ 50% skin surface
- Itchy
- Affecting ADL's/sleep

Clinical Assessment

Investigations:

- Vital signs
- FBC, chem. profile, ALT, cortisol, TFT's and glucose
- Photograph rash
- Measure lesions

Treatment:

- Anti-histamines – chlorpheniramine 4mg tables qds
- Betamethasone valerate 0.1% bd
- Emollient with paraffin content (eg 50:50 ointment)

Extensive rash:

- Prednisolone – commence at 30mg OD and can be increased to 1mg/kg/day (max. 60mg/day) + PPI
- Emollient with paraffin content (eg 50:50 ointment)
- Betamethasone valerate 0.1% cream bd

Actions:

- Withhold treatment until ≤ Grade 1
- Consider referral to local dermatology team
- Monitor daily

Symptoms: PERSIST (≥5 days) or WORSEN or RELAPSE

Severe or Life – Threatening (Grade 3/4)

Is defined as **any** of the following:

- > 50% skin surface
- Generalised
- Exfoliative
- Ulcerative
- Bullous dermatitis

Admit Patient

Investigations:

- Vital signs
- FBC, chem. profile, ALT, cortisol, TFT's and glucose
- Photograph rash
- Measure lesions
- Antibiotics are not indicated unless there is a concern of recurrent infections and/or recommended by treating clinician

Treatment:

- Commence IV hydration
- IV methylprednisolone 2mg/kg/day + PPI
- Regular vital signs and fluid balance
- Anti-histamines – chlorpheniramine 4mg QDS. Can add in cetirizine/loratadine
- Emollient to 50:50 white soft paraffin (liquid paraffin)

Actions:

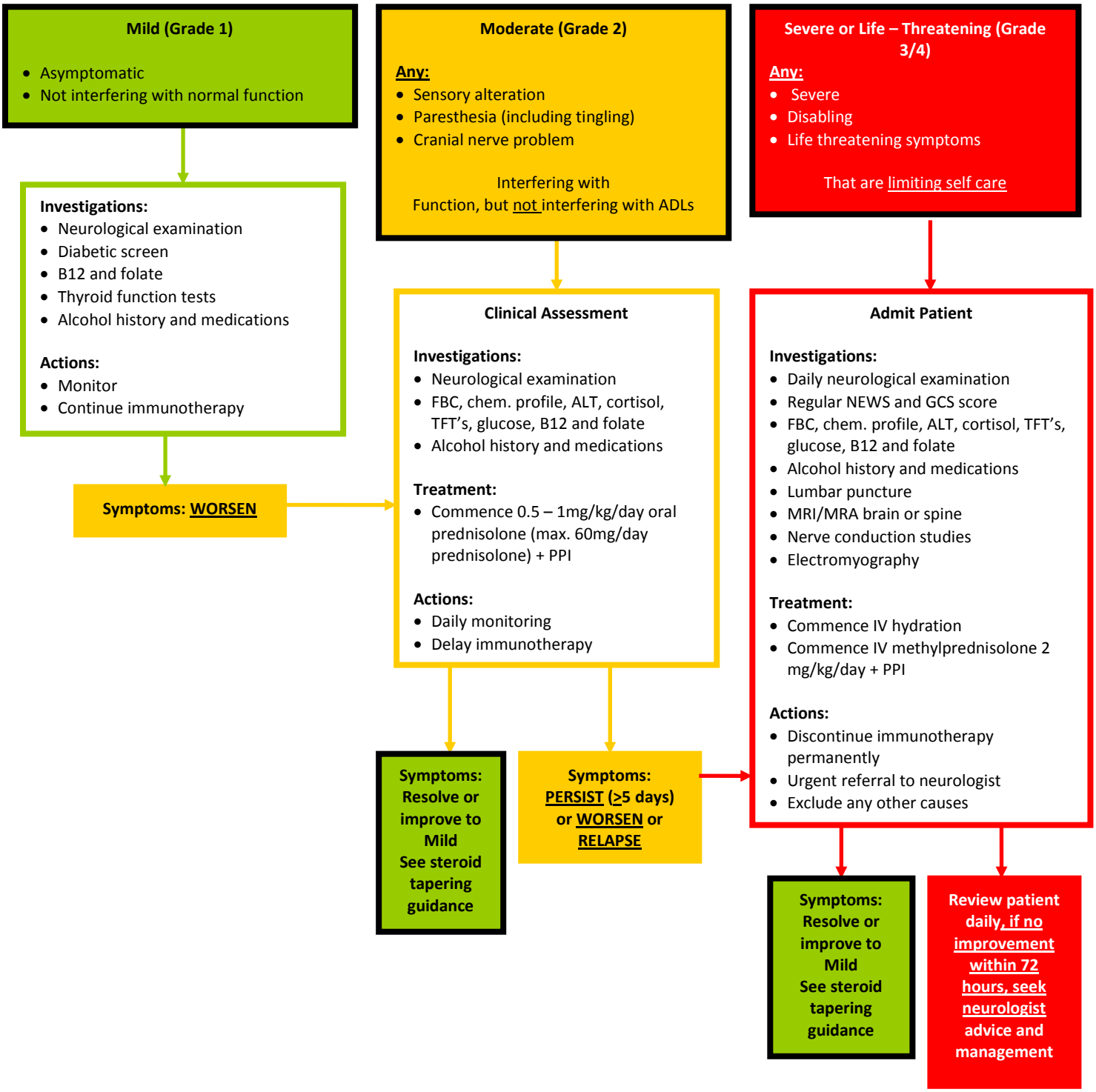
- Discontinue immunotherapy permanently
- Urgent referral to local dermatology team for advice +/- biopsy
- Monitor daily

Symptoms: Resolve or improve to Mild
See steroid tapering guidance

Interrupt SACT immunotherapy until discussed with Acute Oncology team. Please contact on-call oncology/haematology team for advice. Ensure that Acute Oncology/Haematology team are informed of admission

Immune-Related Adverse Event: Neurological Toxicities

Immunotherapy administration is associated with immune-related adverse events (irAEs) Neurological irAEs can manifest as central abnormalities (eg, asceptic meningitis, encephalitis) or peripheral sensory/motor neuropathies (e.g, Guillain-Barre syndrome) early recognition and treatment of neurologic AEs is critical to its management. As neurologic symptoms can be common in patients with cancer, it is important that an evalutation/work-up distinguish between non-drug-related causes (e.g, progression of disease, concomitant medications, infection) and a possible drug-related AE as the management can be quite different.



Interrupt SACT immunotherapy until discussed with Acute Oncology team. Please contact on-call oncology/haematology team for advice. Ensure that Acute Oncology/Haematology team are informed of admission

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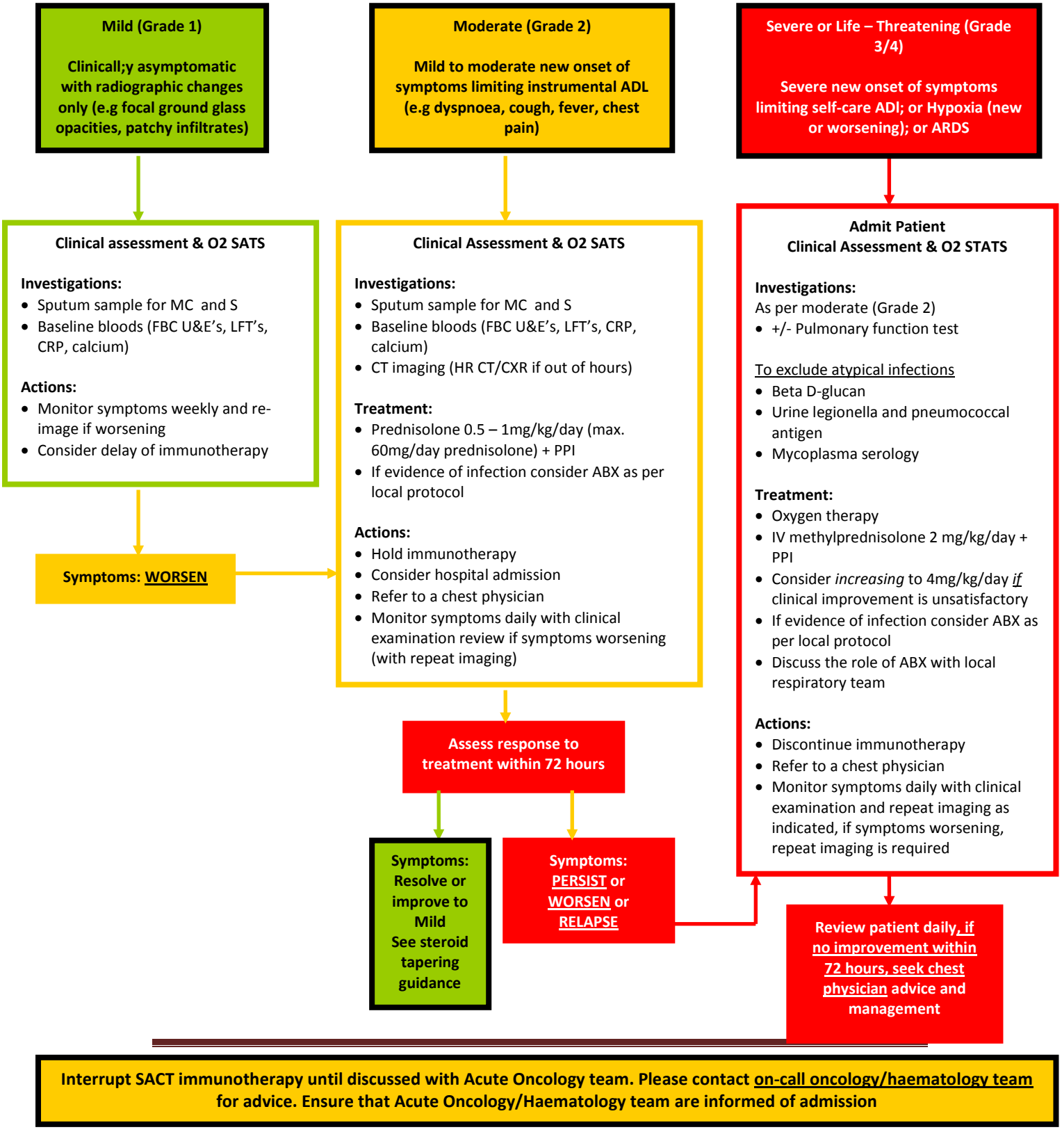
Immune-Related Adverse Event: Pneumonitis

Pulmonary irAEs have been observed following treatment with immunotherapy and have occurred after a single dose and after as many as 48 treatments. The frequency of pulmonary AEs may be greater with immunotherapy combination therapies than with monotherapy. The majority of cases reported were Grade 1 or Grade 2 and subjects presented with either asymptomatic radiographic changes (e.g focal ground glass opacities, patchy infiltrates) or with symptoms of dyspnoea, cough or fever. Subjects with reported Grade 3 or Grade 4 pulmonary AEs were noted to have more severe symptoms, more extensive radiographic findings and hypoxia.



Interrupt SACT immunotherapy until discussed with Acute Oncology team. Please contact on-call oncology/haematology team for advice. Ensure that Acute Oncology/Haematology team are informed of admission

Luton & Dunstable University Hospital

Steroid tapering Guidance

Many patients will receive moderate – to high-dose steroid therapy for their immune-related toxicity for several weeks. Length of tapering is usually dictated by the severity of the irAE. Regular monitoring during tapering is strongly advised as there is an increased risk of irAE recurrence.

Oral steroid tapering:

- Initiate corticosteroid taper over 3-6 weeks

Tapering guidance

- Monitor patient by telephone twice weekly during taper.
- 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.

Intravenous steroid tapering:

- Corticosteroid taper over at least 6 weeks

Tapering guidance

- Continue IV methyprednisolone 2mg/kg/day for a total of 5 days then switch to oral prednisolone 1mg/kg/day x 3 days, then reduce to 60mg/day Prednisolone.

Upon discharge:

- Monitor patient by telephone twice weekly during taper.
- 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 7 days then stop.

Supportive measures:

Hyperglycaemia:

A baseline HbA1c should be requested at steroid initiation and random afternoon blood sugar monitoring (BM) should be undertaken whilst on treatment. If new hyperglycaemia is detected, Endocrinology advice should be sought (many patients will require short term insulin in this setting) Pre-existing diabetes may require escalation in oral hypoglycaemic agents or insulin.

Insomnia:

This is the most common steroid-related side effect. Sleep hygiene counselling is important. Patients may require short-term use of zopiclone or benzodiazepines such as temazepam.

Osteoporosis:

Vitamin D and calcium levels should be taken at baseline and if low, replaced as appropriate. In patients on steroids for >3 months, or with pre-existing osteoporosis, alendronate should be considered.

Infection:

In patients receiving the equivalent of prednisolone 25mg for ≥ 6 weeks we suggest PCP prophylaxis with co-trimoxazole (480mg bd Mon/Wed/Fri)
The oropharynx should be monitored for candidiasis and may require topical therapy such as Nystatin or even oral fluconazole.

If patients are on other immuno-modulatory agents e.g Mycophenolate mofetil, consideration may be given to CMV prophylaxis with valganciclovir, especially if CMV IgG negative and lymphopenic after seeking approval from microbiology.