Category C (Local) GUIDELINE TEMPLATE

Guideline for the Management of Immune-Related Adverse Effects/Toxicities following Immunotherapy Treatment - CHUGGS	University Hospitals of Leicester NHS NHS Trust **Trust Reference C48/2024**

1. Introduction and application of the guideline:

This guideline refers to the management of Immunotherapy Related Adverse Effects/toxicities (irAEs). It encompasses the pathway of care to follow when a patient over the age of 25 who has received immunotherapy in adult services who in turn presents to the University Hospitals of Leicester. This applies to patients who are currently receiving immunotherapy but also those patients up to 12 months post completion of immunotherapy treatment.

This guideline refers to patients who may present to the Trust via the 24 hour Emergency Help line; the Emergency Department or any of the assessment units who are receiving immunotherapy elsewhere but who live locally to UHL.

This guideline is for use by the following staff groups:

This guideline is for utilisation by all trained medical and nursing staff who will be asked to assess and/or treat patients with irAEs of immunotherapy.

2. Guideline Standards and Procedures:

This guideline is based upon the original document developed by the Clatterbridge Cancer Centre NHS Foundation Trust and amended in accordance with UHL procedures and policies. Reference is also made to content identified within the ESMO Clinical Practice Guidelines.

The purpose of this guideline is:

- To minimise patient admissions due to irAEs
- To identify early onset of irAEs and initiate treatment in a timely manner
- To ensure that all staff managing and supporting the care of patients who have received Immunotherapy, have received relevant training and are provided with access to all relevant resources

Background

Immunotherapy agents are a relatively new class of anti-cancer drugs which activate the immune system to destroy cancer cells. The side effect profile for these agents is different from that of standard cytotoxic drugs. They can cause severe irAEs including serious immune-related

endocrine toxicities, which can be fatal, therefore, it is important to recognise and address symptoms early.

The majority of irAEs occur over the course of treatment. However, they can occur weeks to months or even years after discontinuation of treatment.

However, when managed correctly, promptly and with close monitoring, most irAEs are reversible. The exception to this are the endocrinopathies which are typically permanent.

For all immunotherapies it is necessary to grade toxicity according to the CTCAE adverse event grading criteria & follow guidelines for management of toxicities.

Toxicities can result in severe varied irAEs, the most common are fatigue, pruruitic skin rashes, diarrhoea leading to an inflammatory colitis type picture, thyroid, adrenal or pituitary dysfunction, pneumonitis, nephritis, hepatitis, uveitis, paraesthesia and neuropathy.

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 are immunosuppressive and therefore suppresses the T cell activating function of the treatment.

The majority of these side effects manifest during treatment, however some may occur up to 3 years after the last treatment cycle. Additionally, regimes are increasingly complex with longer treatment regimes, more patients being treated with combinations. These include immunotherapy with immunotherapy; Immunotherapy alone; Chemotherapy and Immunotherapy;Tyrosine Kinase Inhibitor (TKI) and immunotherapy combinations. As treatment options evolve, the variety of combinations will almost certainly increase further.

These guidelines are based on the assumption that symptoms with which patients present, are immunotherapy mediated. Other differentials exist for each toxicity so it is important that a thorough clinical assessment has been undertaken prior to reviewing and initiating these guidelines.

3. Education and Training:

PRE TREATMENT INVESTIGATIONS AND PATIENT EDUCATION

Prior to commencing treatment all patients must be informed of the potential side effects (irAEs) and what action to take should they experience these side effects. All patients must be given drug specific information and an immunotherapy alert card containing contact details for the 24 hour Emergency Help line.

Prior to commencement of immunotherapy treatment the following investigations should be taken as baseline:

- FBC,
- U&E
- LFTs
- Plasma Glucose,
- Random Cortisol,
- TSH and T4
- Bone Profile
- HBA1c
- NT-proBNP
- Virology screen to include: - HIV; HBsAg; Hep C; VCA IgG; CMV IgG; VZIgG
- ECG

If the ECG is normal and the NT-proBNP is within normal parameters, there is not the expectation to repeat these tests unless cardio toxicity is to be considered.

ECGs will be performed at: Oncology Outpatients at Osborne Centre at LRI

Coleman Centre at LGH

Cardiac Investigations Unit at GGH

It is imperative that these ECG reports are reviewed and signed off by the treating/requesting clinician prior to commencement of treatment.

These bloods should be repeated before each cycle.

- FBC,
- U&E
- LFTs
- TSH and T4
- Bone profile
- Random Cortisol

Any other blood requests can be made at the discretion of the treating clinician.

If the patient is stable on treatment the frequency of the blood test may be reduced.

Patients should have a face to face or telephone clinic review prior to each treatment cycle. If the patient is stable on treatment the frequency of review could be reduced. This will be decided following a discussion with the treating consultant.

If the patient contacts the 24 hour Emergency Help line, the triaging nurse should complete the UKONS 24 hour triage form, making reference to Immunotherapy and follow the instructions on the checklist found within this link: **https://ukons.hosting.sundownsolutions.co.uk/**
If the patient contacts the 24 hour Emergency Help line during normal working hours or presents at the Emergency Department they should be assessed and managed as appropriate.

Patients should be advised to contact the 24 hour Emergency Help line straight away if they have any of the following symptoms:

- Lung : breathing difficulties or cough
- Bowel: watery or loose stools, mucous or blood in stool, stomach pains or cramps
- Liver: eye or skin yellowing, pain on right side of abdomen
- Kidney: changes in volume of urine
- Endocrine: extreme tiredness, weight change, headache, visual disturbances
- Diabetes symptoms: excessive thirst, large volumes of urine, increased appetite with weight loss, feeling tired, drowsy, weak, depressed, irritable and generally unwell
- Skin : itching, rash, blisters, ulcers, peeling skin
- Eye : redness, pain, blurred vision
- Cardiac: Chest pain, breathlessness, tiredness, leg swelling
  Other: severe upper abdominal pain, nausea, vomiting, numbness, uncoordinated movements, paralysis, muscle weakness.

Toxicity Management

Management protocols have been developed using the The Clatterbridge NHS Trust Guidelines and have been reviewed and agreed with specialist practitioners within UHL for use.

Please find flow charts for management of toxicities within Appendix 1.

Patients who present with IO related toxicities, it may be necessary to consider the implementation of a steroid tapering programme – **Please see Appendix 2 – Steroid Tapering Guidance**

Staff Education

Educational updates will be provided for medical and nursing staff by the Immunotherapy CNS and other relevant partnerships.
Relevant staff to be included in an education programme:

- All staff who deliver SACT within the clinical areas
- Medical staff within the Emergency Department; Osborne Assessment Unit and both medical and surgical assessment units

- Junior Doctors as part of their clinical rotation induction programme
- Moving forwards, education will also be provided by the Immunotherapy team to practitioners within Primary Care to improve the patient pathway.

Patient education leaflets will be developed and, once approved will be available on 'Your Health' on the UHL intranet website.

The Immunotherapy Clinical Nurse Specialist and/or SACT trained nurses will conduct a new patient case talk, providing relevant information regarding immunotherapy and potential side effects/complications.

Patient Escalation

If a patient is not responding appropriately to initial treatment plan, it may be necessary to refer the patient to an additional speciality Consultant lead:

Gastroenterology: Dr Kadri Sudarshan – contact via Switchboard

Hepatology – Dr Raj Vemala– contact via Switchboard

Respiratory: Dr Majid Muhammad – contact via Switchboard

Cardiology: Specialist Registrar – contact via Switchboard

Endocrinology: Professor Miles Levy – refer/request advice via the UHL email address

Dermatology: Dr Matthew Scorer contact via switchboard or Specialist Registrar on call via Switchboard

Rheumatology: Specialist Registrar via Switchboard

Nephrology: Dr Jorge Jesu-Silva – contact via Switchboard

Opthalmology: Specialist Registrar – contact via Switchboard

Neurology: Specialist Registrar – contact via Switchboard

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
All patients with immune-related reactions receive appropriate and timely management	Audit to monitor compliance with guidance	Immunotherapy clinical team	6 monthly	Report to clinical lead/CHUGGS Present at audit review meeting
Monitor patients number of contacts made	Snapshot audit of records documented on Somerset Cancer Record	Immunotherapy Nurses	6 monthly	Immunotherapy clinical leads Audit review meeting

To monitor potential admission avoidance	To monitor triage data throught he 24hr triage help line; from data collected from direct patient calls and external Healthcare providers	Immunotherapy Nurses	6 monthly	Immunotherapy clinical leads Present at audit review meeting
To montor average length of stay	Snapshot 1 month audit for inpatients treated for all immunotherapy toxicities			Immunotherapy clinical leads Present at Audit review meeting

5. Supporting References

Nivolumab Dosing Administration and Safety Guide (2016) Bristol-Myers Squibb

Pembrolizumab Important Safety information to Minimise the Risk of Immune-Related Adverse Reactions (2016) Merck Sharp& Dohme

http://www.ukons.org/ - UKON's Acute Oncology Initial Management Guidelines – version 4.0 (2023).

I-O immediate management guideline UKONS (2).pdf

https.//www.esmo.org/guidelines

The Clatterbridge Cancer Centre NHS Foundation Trust

6.(a) Appendix 1

Management of Immunotherapy Toxicity Flow Charts

1) Adrenal Crisis
2) Arthralgia
3) Colitis
4) Hepatoxicity
5) Hyphositis
6) Myocarditis
7) Neurotoxicity
8) Pneumonitis
9) Renal Toxicity
10) Skin Toxicity
11) Thyroid Toxicity

6.(b) Appendix 2

Steroid Tapering Guidance

7. Key Words

Immunotherapy; nurse led service; immunotherapy side effects; steroids

CONTACT AND REVIEW DETAILS	
Guideline Lead: Nursing Lead: Clair Burroughs, Macmillan Lead SACT Nurse Clinical Lead: Dr Meera Chauhan, Consultant Medical Oncologist	**Executive Lead**
Details of Changes made during review: 1st document	

University Hospitals of Leicester NHS
NHS Trust

APPENDIX ONE: TOXICITY MANAGEMENT FLOW MANAGEMENT

Please click on the relevant hyperlink:

Adrenal Crisis

Arthralgia

Colitis

Hepatoxicity

Hypophysitis

Myocarditis

Neurotoxicity

Pneumonitis

Renal Toxicity

Skin Toxicity

Thyroid dysfunction

All of the above have been discussed an approved by the relevant clinical specialities.

University Hospitals of Leicester NHS
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Adapted from The Clatterbridge Cancer Centre NHS Foundation Trust Guidelines

Immune-Related Adverse Event: 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, TSH, Free T4,, prolactin, blood glucose, ACTH, LH, FSH, cortisol (ideally 9am or earlier) and testosterone or oestradiol as appropriate.

CAUTION If the patient is on steroids then serum cortisol will likely be suppressed – please discuss with endocrinology team before commencing replacement and when interpreting cortisol results if unsure.

Asymptomatic
Identified on routine blood tests

Biochemical alteration in cortisol with early morning serum level <200nmol/L

Hypoadrenalism is likely if early morning cortisol is<100nmol/L

Symptomatic
Mild/Non-Life Threatening
Suspect endocrinopathy based on symptoms
Tiredness/fatigue, headache, weight loss, susceptibility to infection

Symptomatic
Severe/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 Failure

Investigations:
9am Cortisol and ACTH
If headache present consider MRI pituitary

Cortisol (9am) 100-200nmol/L	**Cortisol (9am) <100nmol/L**
Investigations: • Repeat cortisol at 9am ≤ 48 hours - if <200 arrange short synacthen test • If<100 see "Cortisol <100" green strand • Complete endocrine functiopanel if outstanding • **Actions** Monitor regularly (before each cycle as a minimum) and act as per algorithm if serum levels fall • Continue immunotherapy	**Investigations** • Repeat cortisol at 9am ≤ 24 hours –if <100 arrange short synacthen test • Complete endocrine panel if outstanding **Treatment** • Replace with hydrocortisone 20mg/10mg/10 mg • Reduce to 10mg/5mg/5mg after two weeks **Actions** • Consider referral to endocrinology for advice/ further investigation • Give emergency steroid advice and alert card Continue immunotherapy

Cortisol (9am) >400 nmol/L

Adrenal insufficiency unlikely

Actions
- Consider other causes of symptoms

Cortisol (9am) 100-400 nmol/L

Adrenal insufficiency possible

Actions
- Arrange short synacthen test
- Consider endocrine referral
- Complete endocrine bloods as above
- Refer to IO toxicity team
- Continue immunotherapy

Cortisol (9am) <100nmol/L
Adrenal insufficiency likely

Treatment
- Commence hydrocortisone 20mg/10mg/ 10mg
- Reduce to 10mg/5mg/5mg after 2 weeks

Actions
- Arrange short synacthen test
- Consider endocrine referral
- Complete endocrine bloods as above
- Give emergency steroid advice and alert card
- Continue immunotherapy

Admit patient
Immediate Intervention
- Send endocrine panel including ACTH prior to giving steroids if able
- Immediate management with an ABCDE approach
- Commence IV hydrocortisone 100mg QDS immediately without awaiting blood tests
- Urgent Endocrinology referral
- Rule out superadded infections
- Society for Endocrinology [SfE] guidelines for adrenal crisis: www.endocrineconnections.com/content/5/5/G1

Next Steps are dependent on blood results
- Introduce steroid replacement hydrocortisone PO 20mg, 10mg, 10mg
- Reduce hydrocortisone to 10mg, 5mg, 5mg after 2 weeks
- Once stable on hydrocortisone replacement for 5-7 days if thyroid deplete then commence levothyroxine
- Arrange short synacthen test.
- Recheck testosterone after 3 weeks and replace if remains suppressed
- Give emergency steroid advice and alert card

A short synacthen test can be arranged at any time of the day. If on hydrocortisone, the dose needs to be omitted the night before and on the morning of the synathen test and dose taken after the test is complete. ACTH needs a separate sample and needs to be sent to the lab on ice within 30 minutes.

All patients with hypoadrenalism should be assessed for postural hypotension and fludrocortisone (50mcg OD) considered if persistent

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 the grade 1 hypothyriodism guidelines should be instituted)

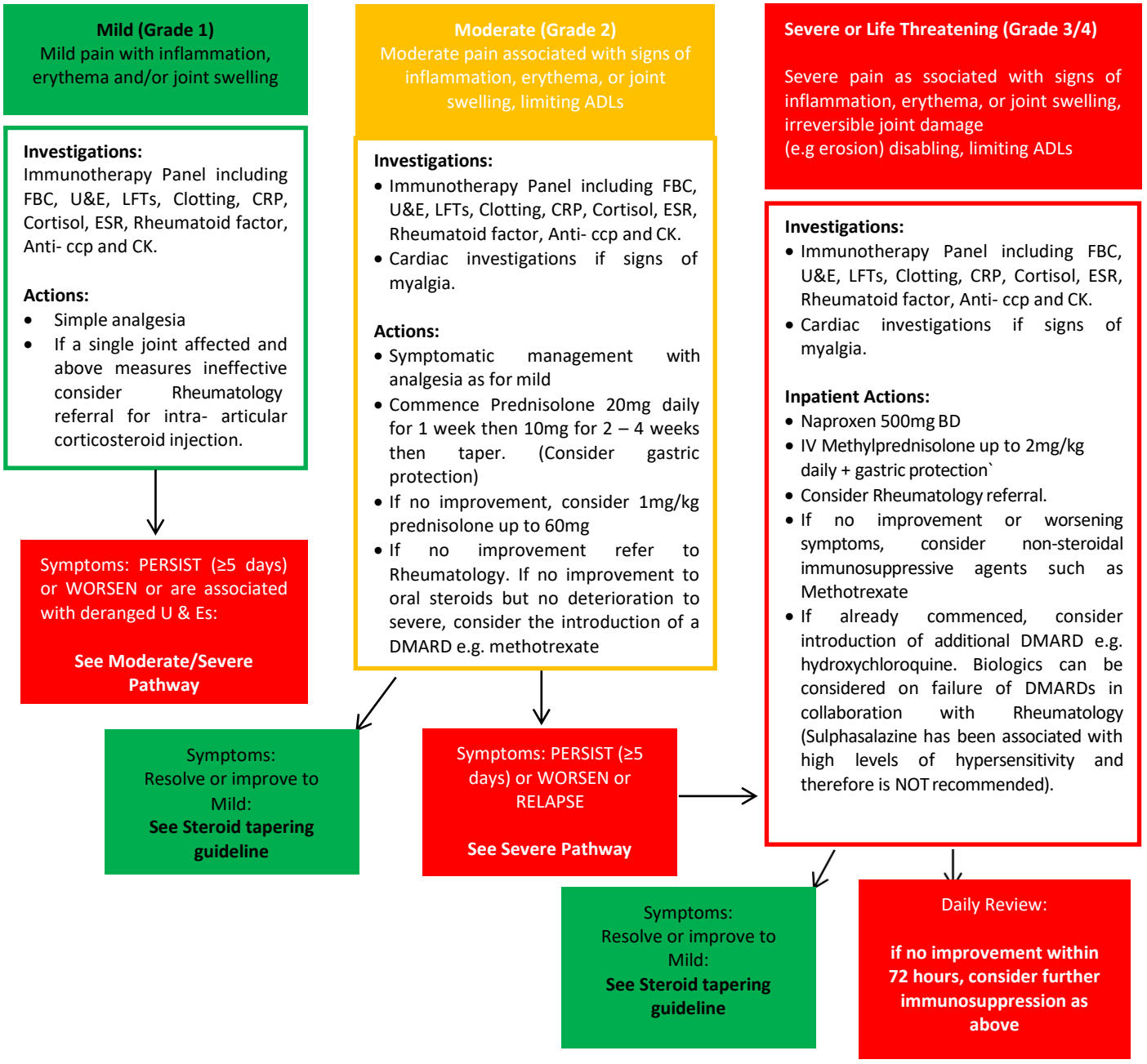
Interrupt SACT immunotherapy until discussed with Immunotherapy Team or Responsible Oncology Consultant.
Please contact these teams for further advice. Ensure that the Immunotherapy Team are informed of admission.

Adapted from The Clatterbridge Cancer Centre NHS Foundation Trust Guidelines

Immune-Related Adverse Event: Arthralgia/Myalgia

Arthralgia is an increasing recognised side effect of oncological immunotherapy. This may manifest with single joint involvement or multi-articular involvement with synovitis. Additionally, patients may develop myalgia which may go on to develop myositis. It is important to note that myositis can evolve into myocarditis and thus it is important to undertake the investigations recommended and monitor both symptomatic and biochemical responses to treatment. Patients often require non-steroid sparing agents so please implement the protocols for management of patients on these agents e.g. methotrexate and consider early referral to local rheumatology services.

NB: Myalgia can be a sign of myositis, which can transform into Myocarditis therefore cardiac involvement should be excluded



Interrupt SACT immunotherapy until discussed with Immunotherapy Team or Responsible Oncology Consultant.

Please contact these teams for further advice. Ensure that the Immunotherapy Team are informed of admission.

Adapted from The Clatterbridge Cancer Centre NHS Foundation Trust Guidelines

Immune-Related Adverse Event: Diarrhoea and Colitis

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:
- Increase in oral fluids
- Loperamide if Stool culture negative
- Avoid high fibre and lactose

Actions:
- Regular monitoring
- Consider holding immunotherapy (if on combination anti-PD1/CTLA4 withhold immunotherapy)

Symptoms PERSIST >5 days or WORSENS or associated deranged U&Es
See Moderate Pathway

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
- Mucous in stool

Investigations:
- As per mild (grade 1)
- CMV viral load + PCR
- Faeces CMV
- Faecal calprotectin
- Abdominal X-Ray (consider CT abdo/pelvis if AXR abnormal or in presence of abdominal pain)
- Consider Infliximab screen as per Grade 3&4
- If recurrent, send for faecal elastase.
- Flexi sigmoidoscopy/scope via stoma/endoscopy*

Treatment:
- Prednisolone 60mg/day + gastric protection
- Fluid balance and replacement as appropriate
- Loperamide

Actions:
- Omit next dose of immunotherapy
- Taper per steroid weaning guidance
- Regular telephone monitoring
- Consider Gastroenterology advice/review

Symptoms:
Resolve or improve to Mild:
See Steroid tapering guideline

Symptoms WORSEN or PERSISTS ≥ 72 hours:

See Severe Pathway

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 ADLs

Investigations:
As per moderate (grade 2) +
Consider Admission of patient
- Investigations on day 1: Screen for Infliximab administration suitability on admission (to include- TB Quantiferon test, hepatitis screen, HIV, varicella zoster anti-bodies (IGG antibody), chest X-Ray (if chest CT not already performed)
- Refer for endoscopy with biopsies on day 1 of admission
- Daily bloods (FBC, U&E, LFTs & CRP)
- CT Abdomen/pelvis

Treatment:
- IV hydration and fluid balance
- Loperamide
- IV Methylprednisolone 2 mg/kg/day + gastric protection cover and continue for a minimum of 3 days
- Antibiotics are not required as standard
- Use analgesia with CAUTION

Actions:
- Stop Immunotherapy
- Daily stool chart
- Consider referral & potential transfer to gastroenterology

Symptoms:
Resolve or improve to Mild:
See Steroid tapering guideline

Daily Review:

If no improvement within 72 hours consider Infliximab

*If endoscopy findings in keeping with collagenous/microscopic colitis, switch from prednisolone/methylprednisolone to budesonide. Budesonide 9mg OD should be given for 10 weeks and then reduced to 6mg OD for 1 week and then to 3mg OD for 1 week then stop. The systemic dose of budesonide is equivalent to less than 10mg prednisolone.

Interrupt SACT immunotherapy until discussed with Immunotherapy Team or Responsible Oncology Consultant.

Please contact these teams for further advice. Ensure that the Immunotherapy Team are informed of admission.

Adapted from The Clatterbridge Cancer Centre NHS Foundation Trust Guidelines

Immune-Related Adverse Event: Hepatotoxicity

Hepatic transaminases (ALT/AST) and bilirubin must be evaluated before each dose of immunotherapy, as early laboratory changes may 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.

Mild (Grade 1)
AST or ALT <3 x ULN but increasing from baseline

Investigations:
- Weekly LFT check between cycles of immunotherapy and ensure remain stable prior to next cycle.
- Review Concomitant Medications

Actions:
Continue Immunotherapy Treatment

Biochemical abnormality WORSENS or RELAPSES: **See Moderate/Severe Pathway (LFT dependant)**

Moderate (Grade 2)
AST or ALT >3 to ≤5 x ULN

Clinical Assessment
- Regular LFTs, direct and direct and indirect bilirubin and clotting profile
- Thorough clinical history including recent antibiotic use
- CT scan to exclude PD & thromboembolism and evaluate if evidence of inflammation
- Hepatitis viral panel (hepatitis A, B, C, E)
- CMV, EBV and HIV and auto- antibodies, immunoglobulins

Treatment:
- Commence prednisolone 60mg/day+ PPI if liver screen negative

Actions:
- Withhold dose until the adverse reaction resolves to grade 1 (or returns to baseline).
- Review medications (e.g. statins, antibiotics)
- Re-check LFTs and INR every 3 days and review patient by phone twice weekly

Symptoms: Resolve or improve to Mild: **See Steroid tapering guideline**

Biochemical abnormality PERSISTS ≥ 3days: **See Severe Pathway**

Severe or Life Threatening (Grade 3/4)
AST or ALT >5x ULN (Grade 4 >20 x ULN)

Clinical Admission
- Daily LFTs, clotting profile and daily venous gas
- Thorough clinical history including recent antibiotic use
- CT scan to exclude PD & thromboembolism and evaluate if evidence of inflammation
- Hepatitis viral panel (hepatitis A, B, C, E)
- CMV, EBV and HIV and auto-antibodies, immunoglobulins

Treatment:
- IV methylprednisolone 2mg/kg/day
- IV hydration
- Vitamin K 10mg IV daily for 3 days if INR deranged
- Grade 4 (loss of synthetic function/ hyperbilirubinemia/abnormal INR despite Vitamin K) commence N-acetylcystine (NAC as per paracetamol overdose protocol in BNF) & discuss with hepatologist

Actions:
- Referral to hepatologist for furtheradvice
- If Grade 3 on combination therapy reduce to monotherapy; if monotherapy continue discontinuation of treatment
- If Grade 4 discontinue treatment permanently
- Establish escalation plan and ceiling of care

Symptoms: Resolve or improve to Mild: **See Steroid tapering guideline**

Daily Review: **If no improvement within 24 hours seek further hepatologist advice**

Abbreviations:
LFTs: Liver Function Tests
INR: International Normalised Ratio
ULN: Upper Limit of Normal
PD: Progressive Disease

Interrupt SACT immunotherapy until discussed with Immunotherapy Team or Responsible Oncology Consultant.

Please contact these teams for further advice. Ensure that the Immunotherapy Team are informed of admission.

Adapted from The Clatterbridge Cancer Centre NHS Foundation Trust Guidelines

Immune-Related Adverse Event: Hypophysitis

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, TSH, Free T4, prolactin, blood glucose, ACTH, LH, FSH, cortisol (ideally 9am or earlier) and testosterone or oestadiol as appropriate.
Check vision: Bitemporal visual field defect should prompt formal visual field check via ophthalmology and an urgent MRI pituitary
CAUTION If the patient is on steroids then serum cortisol will likely be suppressed – please discuss with endocrinology team before commencing replacement and then interpreting cortisol results if unsure.

Asymptomatic
Identified on routine blood tests

Biochemical alteration in cortisol with early morning serum level <200nmol/L

Hypoadrenalism is likely if early morning cortisol is <100nmol/L

Cortisol (9am) 100-200nmol/L

Investigations:
- Repeat cortisol at 9am ≤ 48 hours - if <200 arrange short synacthen test
- If <100 see "Cortisol <100" green strand
- 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 immunotherapy

Cortisol (9am) <100nmol/L

Investigations
- Repeat cortisol at 9am ≤ 24 hours – if <100 arrange short synacthen test
- Complete endocrine panel if outstanding

Treatment
- Replace with hydrocortisone 20mg/10mg/10 mg
- Reduce to 10mg/5mg/5mg after two weeks

Actions
- Consider referral to endocrinology for advice/ further investigation
- Give emergency steroid advice and alert card
- Continue immunotherapy

Symptomatic
Mild/Non-Life Threatening

Suspect endocrinopathy based on symptoms
Tiredness/fatigue, headache, weight loss, susceptibility to infection

Investigations:
9am Cortisol and ACTH
MRI pituitary

Cortisol (9am) >400 nmol/L

Adrenal insufficiency unlikely

Actions
- Consider other causes of symptoms

Cortisol (9am) 100-400 nmol/L

Adrenal insufficiency possible

Actions
- Arrange short synacthen test
- Consider endocrine referral
- Complete endocrine bloods as above
- Refer to IO toxicity team
- Continue immunotherapy

Cortisol (9am) <100nmol/L
Adrenal insufficiency likely

Treatment
- Commence hydrocortisone 20mg/10mg/ 10mg
- Reduce to 10mg/5mg/5mg after 2 weeks

Actions
- Endocrine referral
- Complete endocrine bloods including prolactin, testosterone and ACTH
  Emergency steroid advice and alert card
- Continue immunotherapy

Symptomatic
Severe/Life Threatening

Severe headache, visual disturbance, evidence of focal neurology
Combination of mild/moderate symptoms and pituitary inflammation on MRI
If severe symptoms/signs of hormonal insufficiency with no headache/visual disturbance/pituitary inflammation then follow adrenal crisis algorithim

Admit patient
Immediate Intervention
- Send endocrine panel including ACTH prior to giving steroids if able
- MRI pituitary
- Commence IV hydrocortisone 100mg QDS
- If clinically improved with mild/resolved symptoms switch to hydrocortisone 20mg, 10mg, 10mg
- Reduce hydrocortisone to 10mg, 5mg, 5mg after 2 weeks
- Once stable on hydrocortisone replacement for 5-7 days commence thyroxine if needed
- Recheck testosterone after 3 weeks and replace if remains suppressed
- Endocrinology referral
- Give emergency steroid advice and card

A short synacthen test can be arranged at any time of the day. If on hydrocortisone, the dose needs to be omitted the night before and on the morning of the synathen test and dose taken after the test is complete. ACTH needs a separate sample and needs to be sent to the lab on ice within 30 minutes.

All patients should be monitored for polyuria and polydipsia after administration of steroids as steroid replacement can unmask AVP deficiency in hypophysitis.

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

Interrupt SACT immunotherapy until discussed with Immunotherapy Team or Responsible Oncology Consultant. Please contact these teams for further advice. Ensure that the Immunotherapy Team are informed of admission.

Adapted from The Clatterbridge Cancer Centre NHS Foundation Trust Guidelines

Immune-Related Adverse Event: Myocarditis

Myocarditis is a recognised complication of immune checkpoint inhibitors. The majority of reported cases have occurred within the first month of therapy. Approximately 1% of patients treated with checkpoint inhibitors develop cardio-toxicity. Myocarditis is associated with a high mortality rate if not treated. It is common for patients to be asymptomatic/ have minimal symptoms and abnormal cardiac tests are significant.

Mild (Grade 1)

Clinically asymptomatic or presenting with fatigue/new pedal oedema

Cardiac enzymes:
Trop I is >5 and <40 ng/L
OR
any rise above baseline by <20 ng/L
NT-Pro-BNP is >500 <1000 ng/L

Investigations:
- ECG
- Bloods (Troponin, NT-pro-BNP, Creatinine Kinase, FBC, U&Es
- Chest X-ray

Actions:
- Consider delay of immunotherapy
- Repeat ECG and bloods in 2 weeks
- Consider echocardiogram in the presence of pedal oedema

Moderate (Grade 2)

New onset of symptoms with moderate exertion (e.g. Dyspnoea, chest pain, palpitations, peripheral oedema, pre-syncope, syncope) OR evidence of elevated cardiac enzymes/ECG changes even in the absence of symptoms.

Cardiac Enzymes:
Trop I is >40 and <100 ng/L
OR elevated above baseline by >20 ng/L
NT-Pro-BNP is ≥1000 <3000 ng/L OR increased from baseline

Investigations:

As per mild (grade 1) plus:

- Echocardiogram
- Cardiac Magnetic Resonance Scan
- Infliximab screen
- TPMT Levels
- Whilst on IV steroids for Daily ECG and repeat cardiac markers.

Treatment:
- IV Methylprednisolone 4mg/kg/day + PPI for 5/7. Taper to 2mg/kg/day for 3/7. Step down to Oral Prednisolone 1mg/kg. Review response and oral steroid taper
- Consider ACEi +/- beta-blocker
- If evidence of overload consider diuretics.
- If evidence of cardiac impairment refer for heart failure optimisation.

Actions:
Hold immunotherapy
- Consider hospital admission
- Refer to cardiology

Severe/Life-Threatening (Grade 3 & 4)

New onset of severe symptoms at rest or with minimal exertion; intervention indicated

Cardiac Enzymes:
Trop I is ≥100 ng/L
NT-Pro-BNP is ≥3000 ng/L

Investigations:

As per moderate (grade 2)

Treatment:
- IV Methylprednisolone 1g + PPI for 3/7. Taper to 4mg/kg/day for 3/7. Taper to 2mg/kg/day for 3/7. Step down to Oral Prednisolone 1mg/kg.
- Review response and oral steroid taper
- Supportive therapy (inotropes, anti-arrhythmics*) and as for grade 2

Actions:
- Stop immunotherapy
- Consider whether patient requires admission to CCU/HDU and their ceilings of care
- Refer to cardiology and IO Clinician
- Consider Mycophenolate or Tacrolimus, in patients not responding optimally to high dose steroids.
- If limited response consider adding in further steroid sparing immunosuppression - e.g. infliximab or azathioprine

**If anti-arrhythmics are required amiodarone should be avoided if possible and only used on discussion with immunotherapy specialist due to the risk of pneumonitis.*

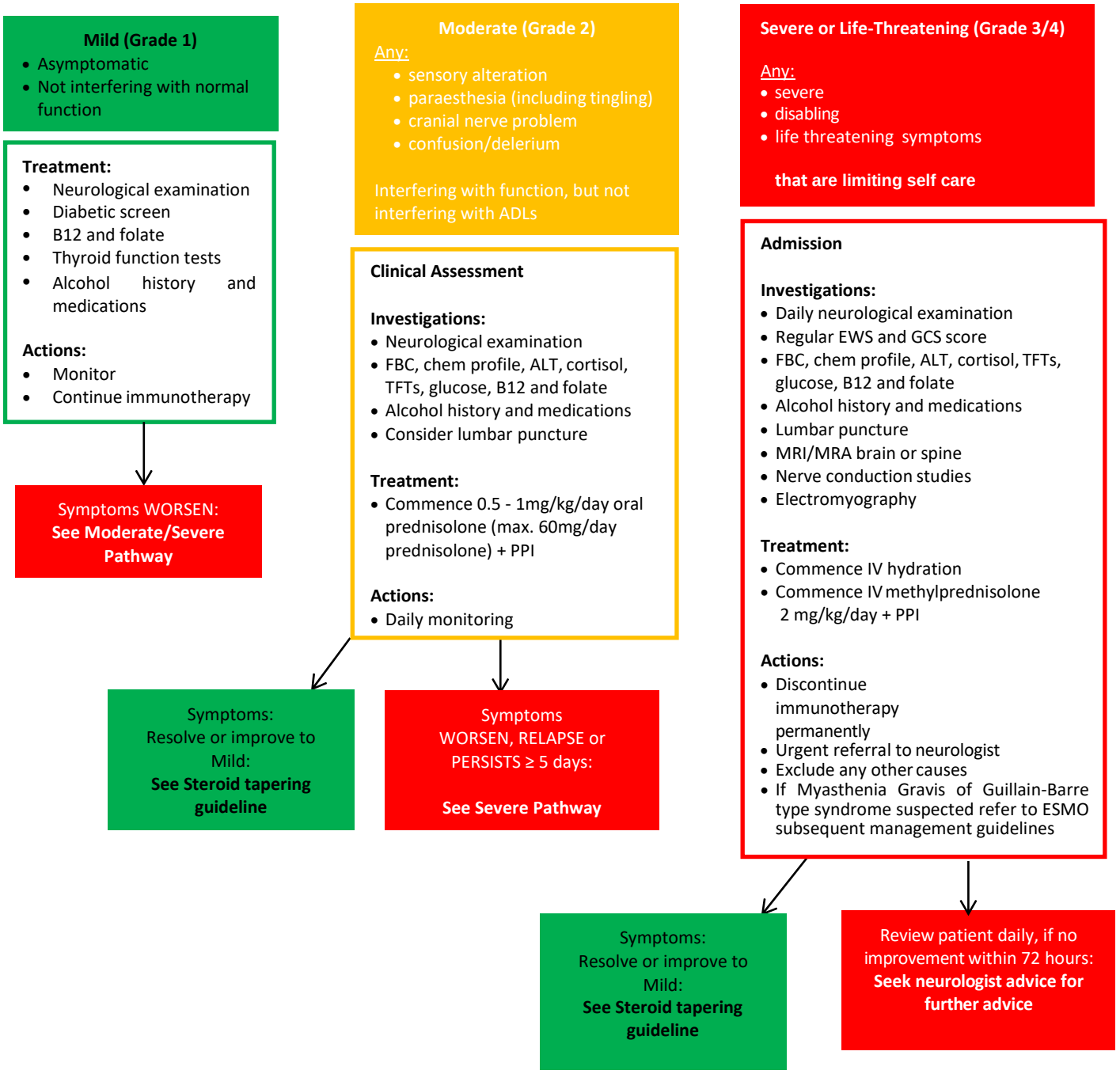
Interrupt SACT immunotherapy until discussed with Immunotherapy Team or Responsible Oncology Consultant.

Please contact these teams for further advice. Ensure that the Immunotherapy Team are informed of admission.

Adapted from The Clatterbridge Cancer Centre NHS Foundation Trust Guidelines

Immune-Related Adverse Event: Neurological Toxicities

Neurologic immune related adverse events can manifest as central abnormalities (e.g. aseptic meningitis, encephalitis) or peripheral sensory/motor neuropathies (e.g. Guillain-Barre Syndrome). Early recognition and treatment of neurologic AEs are critical to their management. As neurologic symptoms can be common in patients with cancer, it is important that an evaluation/work-up distinguishes 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 Immunotherapy Team or Responsible Oncology Consultant.

Please contact these teams for further advice. Ensure that the Immunotherapy Team are informed of admission.

Adapted from The Clatterbridge Cancer Centre NHS Foundation Trust Guidelines

Immune-Related Adverse Event: Pneumonitis

Pulmonary immune related adverse events 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 (eg, 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.

Mild (Grade 1)
Clinically asymptomatic *with* Radiographic changes only (focal ground glass opacities, patchy infiltrates)

Clinical Assessment & O2 sats

Investigations:
- Sputum sample for MC& S
- Baseline bloods
- Procalcitonin

To exclude a-typical infections:
- Beta-D-Glucan/Galactomanan
- A-typical Viral Screen
- Covid Swab
- Urine legionella and pneumococcal antigen
- Mycoplasma Serology
- CT Imaging and baseline X-Ray

Actions:
- Monitor symptoms weekly and re- image if worsening
- Consider delay of Immunotherapy
- Consider 30mg of Prednisolone with a weaning course

Symptoms WORSEN:
See Moderate Pathway

Moderate (Grade 2)
Mild to moderate new onset of symptoms limiting instrumental ADL (e.g dyspnoea, cough, fever, chest pain)

Clinical Assessment & O2 sats

Investigations:
- Sputum sample for MC&S
- Baseline bloods (FBC, U&Es, LFTs, calcium, CRP)
- Procalcitonin
- CT imaging as symptomatic for CTPA to exclude PE as a differential (if CTPA –ve for pathology but suspicion of Pneumonitis remains complete HRCT

To exclude a-typical infections:
- Beta-D-Glucan/Galactomanan
- A-typical Viral Screen
- Covid Swab
- Urine legionella and pneumococcal antigen
- Mycoplasma Serology
- Sputum for PGP

Treatment:
- Prednisolone 1mg/kg/day (max. 60mg/day prednisolone) + PPI
- If evidence of infection consider ABX as per local protocol

Actions:
- Hold immunotherapy
- Consider hospital admission
- Monitor symptoms daily with clinical examination review if symptoms worsening (with repeat imaging)
- Assess response to treatment within 72 hours

Symptoms:
Resolve or improve to Mild:
See Steroid tapering guideline

Symptoms
WORSEN, RELAPSE or PERSISTS:

See Severe Pathway

Severe or Life-Threatening (Grade 3/4)
Severe new onset of symptoms limiting self-care ADL; *or* Hypoxia (new or worsening); *or*ARDS

Admission
Clinical Assessment & O2 sats

Investigations:
As per moderate (grade 2)
+/- Pulmonary function test

Treatment:
- IV Methylprednisolone 2mg/kg/day + PPI
- Oxygen therapy
- Consider *increasing* to 4mg/kg/day *if* clinical improvement is unsatisfactory
- If evidence of infection consider ABX as per local protocol

Actions:
- Consider discontinuing Immunotherapy
- Refer to a chest physician
- Monitor symptoms daily with clinical examination and repeat imaging as indicated, if symptoms worsening, repeat imaging is required
- Consider Second line Immunosuppression with Tacrolimus (MMF and Infliximab can be considered as alternative)
- Referral to Interstitial Lung MDT

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

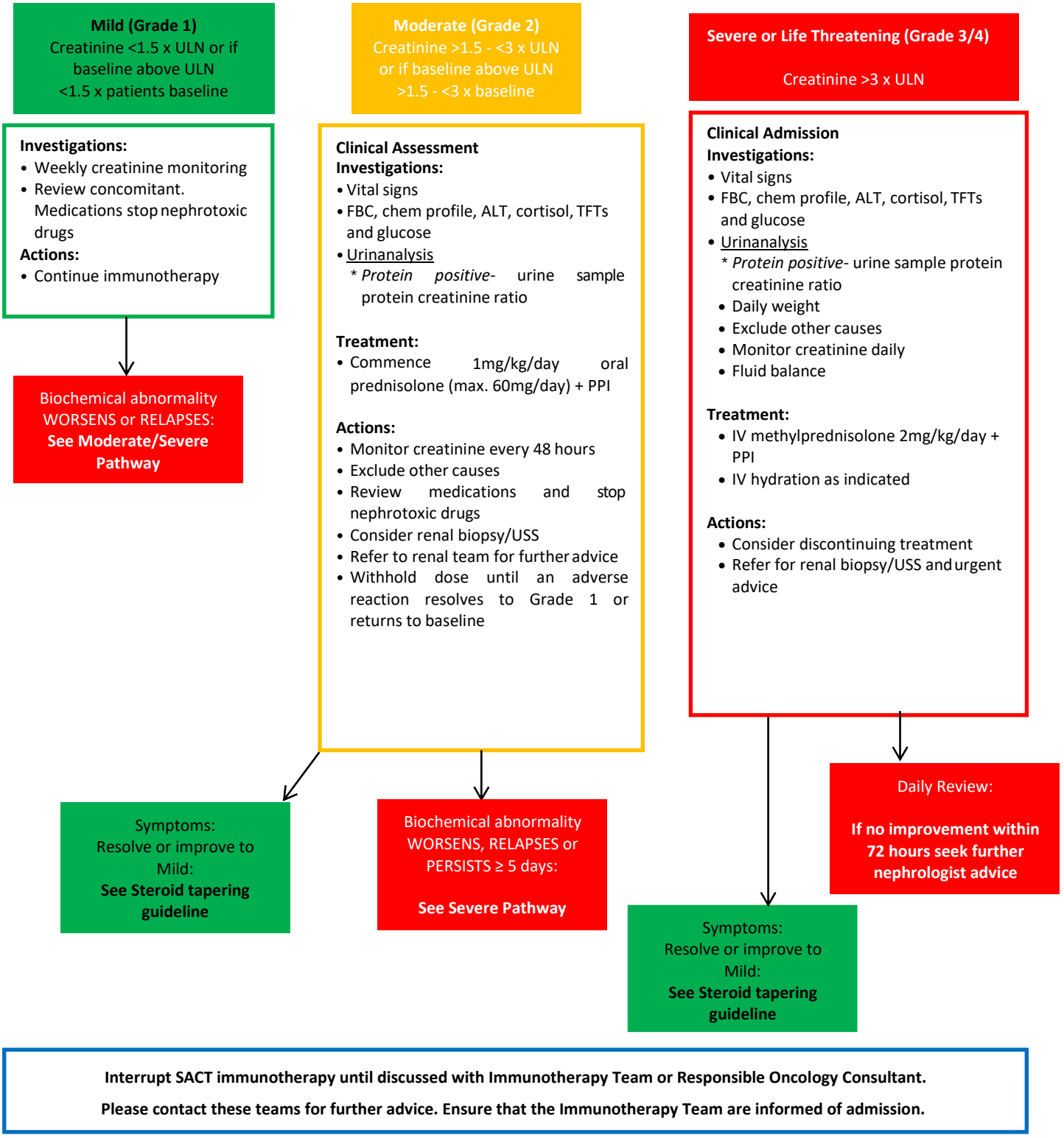
Interrupt SACT immunotherapy until discussed with Immunotherapy Team or Responsible Oncology Consultant.

Please contact these teams for further advice. Ensure that the Immunotherapy Team are informed of admission.

Adapted from The Clatterbridge Cancer Centre NHS Foundation Trust Guidelines

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 Immunotherapy Team or Responsible Oncology Consultant.

Please contact these teams for further advice. Ensure that the Immunotherapy Team are informed of admission.

Adapted from The Clatterbridge Cancer Centre NHS Foundation Trust Guidelines

Immune-Related Adverse Event: Skin Toxicities

Immunotherapy administration is associated with immune-related adverse events (irAEs). Dermatological irAEs 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

Treatment:
- Formulary Emollient with paraffin content
- Consider anti-histamines- eg Cetrizine 10mg OD

Actions:
- Regular monitoring
- Continue immunotherapy

Symptoms WORSEN:
See Moderate/Severe Pathway

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:
- Consider anti-histamines- eg Cetrizine 10mg OD

Localised rash:
- Betamethasone cream (eg Betnovate® cream bd)
- Formulary Emollient with paraffin content

Extensive rash:
- Prednisolone - commence at 30mg OD and can be increased to 1mg/kg/day (max. 60mg/day) +PPI
- Formulary Emollient with paraffin content
- Betamethasone cream (eg Betnovate® cream bd)

Actions:
- Consider withholding immunotherapy treatment until ≤ grade 1
- Consider referral to local dermatology team
- Monitor

Symptoms:
Resolve or improve to Mild:
See Steroid tapering guideline

Symptoms
WORSEN< RELAPSE or PERSISTS ≥ 5 days:

See Severe Pathway

Severe or Life-Threatening (Grade 3/4)
Is defined as any of the following:
- >50% skin surface
- generalised
- ulcerative
- widespread bullous dermatitis

Admission

Investigations:
- Vital signs
- FBC, chem profile, ALT, cortisol, TFTs 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 2 mg/kg/day + PPI
- Anti-histamines- eg Cetrizine 10mg OD
- Regular vital signs and fluidbalance
- Emollient 50:50 white soft paraffin (liquid paraffin)

Actions:
- Consider discontinuing immunotherapy permanently
- Urgent referral to local dermatology team for advice +/- biopsy
- Monitor daily

Symptoms:
Resolve or improve to Mild:
See Steroid tapering guideline

Interrupt SACT immunotherapy until discussed with Immunotherapy Team or Responsible Oncology Consultant.

Please contact these teams for further advice. Ensure that the Immunotherapy Team are informed of admission.

Adapted from The Clatterbridge Cancer Centre NHS Foundation Trust Guidelines

Immune-Related Adverse Event: 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 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, ACTH, 9am cortisol, prolactin, blood glucose +/- LH, FSH and testosterone/oestradiol

Hyperthyroidism

TSH <0.55 miU/L and Free T4 > 22.7pmol/L

(If TSH low and T4 normal or low, check Free T3 and need to exclude pituitary dysfunction)

Actions:
- Recheck TFTs and 9am cortisol within 3 weeks and then 3 weekly thereafter.
- N.B. the majority of cases become hypothyroid within a matter of weeks.
- Once hypothyroid- manage as per hypothyroidism algorithm
- Continue Immunotherapy

Hypothyroidism

TSH of >10mU/L and Free T4 < 11.5pmol/L

Treatment:
Levothyroxine 50-100mcg/day

Actions:
- Recheck TFTs and 9am cortisol with next cycle of treatment
- Increase Levothyroxine in 25mcg increments
- Long term hypothyroidism management can usually take place in primary care.
- Refer to endocrinologist if unable to stabilise thyroid function
- Continue Immunotherapy

Moderate (Grade 2)

- Symptomatic or severe biochemical disturbance

Investigations
TSH, Free T4, ACTH, 9am cortisol, prolactin, blood glucose +/- LH, FSH and testosterone/oestradiol

Hyperthyroidism

TSH <0.55 mU/L and Free T4 > 22.7pmol/L

(If TSH low and T4 normal or low, check Free T3 and need to exclude pituitary dysfunction)

Treatment:
- 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 TFTs and 9am 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
- Continue Immunotherapy

Hypothyroidism

TSH of >10mU/L and Free T4 < 11.5pmol/L

Treatment:
Levothyroxine 50-100mcg/day

Actions:
- Recheck TFTs and 9am cortisol with next cycle of treatment
- Long term hypothyroidism management can usually take place in primary care.
- Increase Levothyroxine in 25mcg increments
- Refer to endocrinologist if unable to stabilise thyroid function
- Continue Immunotherapy

Interrupt SACT immunotherapy until discussed with Immunotherapy Team or Responsible Oncology Consultant.

Please contact these teams for further advice. Ensure that the Immunotherapy Team are informed of admission.

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Appendix 2 – Steroid Tapering Guidance

Oral steroid tapering

- Initiate corticosteroid taper over 3-6 weeks

Tapering Guidance

- Monitor patient by telephone consultation a minimum twice weekly during taper process
- Reduce Prednisolone dose by 10mg every 3/7 (as toxicity allows) until dose is 10mg/day
- Once steroid dose is 10mg/day, further reduce by 5mg for 5 days then discontinue
- If clinicians wish to adjust the steroid tapering process in accordance with their clinical judgement, please ensure this is clearly communicated with the Immunotherapy Clinical Nurse Specialists

Escalation

- If a patients symptoms do not resolve or recur when dose is reduced, refer back to oncology team to advise on management plan.
- If unwell when reviewed in clinic, they will be referred to OAU in the first instance for admission for IV steroid +/- immune suppressant therapy

Intravenous Steroid Tapering

- Corticosteroid taper over at least 3-6 weeks

Tapering Guidance

- Continue IV Methylprednisolone 2mg/kg/day for a total of 5 days then switch to **oral** prednisolone of 1mg/kg/day
- If following a re-flare and re introduction of IV steroids, reduce to 1mg/kg/day of oral prednisolone for 3 days then commence steroid taper

Upon discharge home

- Monitor patient by telephone consultation a minimum twice weekly during taper process
- Reduce Prednisolone dose by 10mg every 3/7 (as toxicity allows) until dose is 10mg/day
- Once steroid dose is 10mg/day, further reduce by 5mg for 5 days then discontinue

ALL PATIENTS SHOULD HAVE A CORTISOL SAMPLE AT 09:00 WITHIN THE 5-7 DAYS FOLLOWING THE COMPLETION OF THEIR STEROID TAPER

If the patient does not respond to steroid management – discuss with the treating clinician and refer to: **Infliximab and Biosimilar Prescribing and Administration for Day Case Adult Patients – UHL Guideline (This is not currently licensed for treatment of Immunotherapy Related AE's)**

Supportive measures:

Hyperglycaemia

A baseline HbA1c should be requested prior to initiation of steroids and random blood sugar monitoring should be undertaken throughout the duration of the steroid treatment. If a new hyperglycaemia is identified, it is necessary that advice is sought fro the Endocrinology team – it may be that the patient will require short term insulin administration. Pre-existing diabetes may require immediate escalation in oral hypoglycaemic agents or insulin

Insomnia

This is the most common steroid-related side effect which can be quite distressing for patients. Sleep counselling is important. Patients may require short term prescription of Zopiclone – these should only be considered in extreme circumstances for a maximum of 3-5 days

Osteoporosis

It is necessary to ensure that baseline Vitamin D and Calcium levels are taken prior to initiation, and if low, to be replaced as appropriate. Patients who are receiving steroids for >3 months, or with pre existing osteoporosis, it would be recommended that a bone density scan is conducted and a Bisphosphonate such as AdCal be considered.

Infection

Patients who are receiving the dose equivalent of 25mg of Prednisolone for >6 weeks, PCP Prophylaxis should be considered, with one option being Co-Trimoxazole 80/400mg administered 3 times weekly – Mon/Weds and Fri.

If there are any visual signs of candida, it may be necessary to consider Nystatin oral drops or oral Fluconazole