

Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.



South East Wales

Immunotherapy Toxicity Guidelines (v3)

Intranet Quick Reference and Full Management Pathways

This information is issued by the Medicines Management Committee on the understanding that it contains the best available evidence from the resources available at the time of preparation. It is an interactive document which will be regularly reviewed.

These guidelines are intended to support clinical judgment. The clinician must use his discretion when following them.

Approved by:	Medicines Management Group
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Reviewed by	Medic	Loretta Sweeney
	Nurse	Rosie Roberts
	Pharmacist	Usman Malik
Original document		

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Scope of guidelines

These guidelines provide advice for all healthcare professionals in the recognition and management of checkpoint inhibitor immunotherapy induced toxicities. There are some quick reference guides for toxicities but if you need more information please see the full management guidelines.

Background

Immune checkpoints are responsible for “switching off” the T-cell. Inhibition of these checkpoints allows for over-activation of the immune system.

This immune system over-activation may result in side effects in healthy body tissues. These side effects are referred to as immune-related adverse events (irAEs).

The overall incidence of grade 3 or 4 irAEs is higher with CTLA-4 blockers (Ipilimumab), compared to PD-1 and PDL-1 inhibitors, which are better tolerated. The combination of PD-1 inhibitor with a CTLA-4 inhibitor is associated with more adverse reactions, especially grade 3 or 4 irAEs. 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 please grade toxicity according to the [NCI CTCAE v5.0 \(link\)](#) adverse event grading criteria & follow guidelines for management of toxicities.

Toxicities can result in severe immune mediated adverse reactions, the most common are fatigue, pruritic skin rashes, diarrhoea leading to an inflammatory colitis type picture, thyroid, adrenal or pituitary dysfunction, pneumonitis, nephritis, hepatitis, uveitis, paraesthesia 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 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 18months after the last cycle. Additionally, regimes are increasingly complex with longer treatment regimes, more patients being treated with combinations. These include IO-IO IO-Chemotherapy and IO-TKI combinations. As treatment options evolve, the variety of combinations will almost certainly increase further.

These guidelines are based on the assumption that symptoms 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.

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The Immunotherapy team

In November 2021, Velindre were successful in their bid for funding from the Welsh Government SDEC Ambulatory Care fund to create a new Immunotherapy Service. This resides under the existing umbrella of Ambulatory Care and is a South East Wales service aligned closely with acute oncology. The IO team will manage immunotherapy toxicities in consultation with the treating team and provide information, education and resources to patients and staff. Additionally they will develop partnerships to develop pathways with specialist teams from other health-boards to promote consistent, patient care across South East Wales. For any further information please follow this link to the Immunotherapy page: https://nhs.wales365.sharepoint.com/sites/VEL_cc_intranet/SitePages/Immunotherapy.aspx

Pre treatment

Pre-treatment blood tests:

Pre-treatment bloods are as follows:

- FBC
- U&Es
- LFTs & bone profile, glucose
- Thyroid function tests
- Baseline Vitamin D

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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 toxicity severity. Regular monitoring during tapering is strongly advised as there is an increased risk of toxicity re-flare. **Consider only giving a PPI if steroid dose is >40mgs. If pre-existing co-morbidities consider H2-receptor antagonist Famotidine as alternative.**

INTRAVENOUS STEROID TAPERING

Tapering guidance:

· Continue IV methylprednisolone 1-2mg/kg/day for a total of 3 days and **if responding** switch to oral Prednisolone max 60mg/day.

ORAL STEROID TAPERING

Ensure patient has a blue National steroid card

Tapering guidance: Corticosteroid taper over at least 3 – 6 weeks:

- Monitor patient by telephone twice weekly - weekly during taper. Blood tests as needed specific to toxicity.
- Reduce Prednisolone dose by 10mg every 5 days (as toxicity allows) until dose is 10mg/day.
- Once steroid dose is 10mg/day, reduce by 5mg for 5 days then stop

If relapse on steroid taper, then increase corticosteroids back to lowest effective dose, and increase duration of taper. If re-flare again then discuss in IO SST.

ALL PATIENTS SHOULD HAVE A 9AM CORTISOL CHECKED WITHIN 5-7 DAYS FOLLOWING COMPLETION OF THEIR STEROID TAPER

Special Considerations

HYPERGLYCAEMIA: Check blood sugar, if raised check HbA1c. If known Diabetic, ensure blood sugar is being monitored whilst on steroid taper and ensure patient is aware of safety netting support – pre-existing diabetics may require escalation in oral hypoglycemic agents or insulin and review from diabetic nurses. Random blood sugar monitoring (BM) should be undertaken whilst on treatment. If new hyperglycemia is detected, Endocrinology advice should be sought through MDT.

INSOMNIA: This is the most common steroid-related side effect. Advise patients to take prednisolone early morning after breakfast. Sleep hygiene counselling is important. Patients may require short-term use of Zopiclone.

BONE HEALTH: Vitamin D and calcium levels should be taken at baseline and if low, replace as appropriate. In patients on steroids for >3 months, or with pre-existing osteopenia or osteoporosis, a bone density scan, Calcichew D3 Forte & a bisphosphonate should be considered.

INFECTION:

Bacterial: In patients receiving the equivalent of prednisolone 25mg for > 6 weeks PCP prophylaxis with Co-trimoxazole (80/400mg Mon/Wed/Fri) should be considered.

Fungal: The oropharynx should be monitored for candidiasis and may require topical therapy such as Nystatin or oral fluconazole.

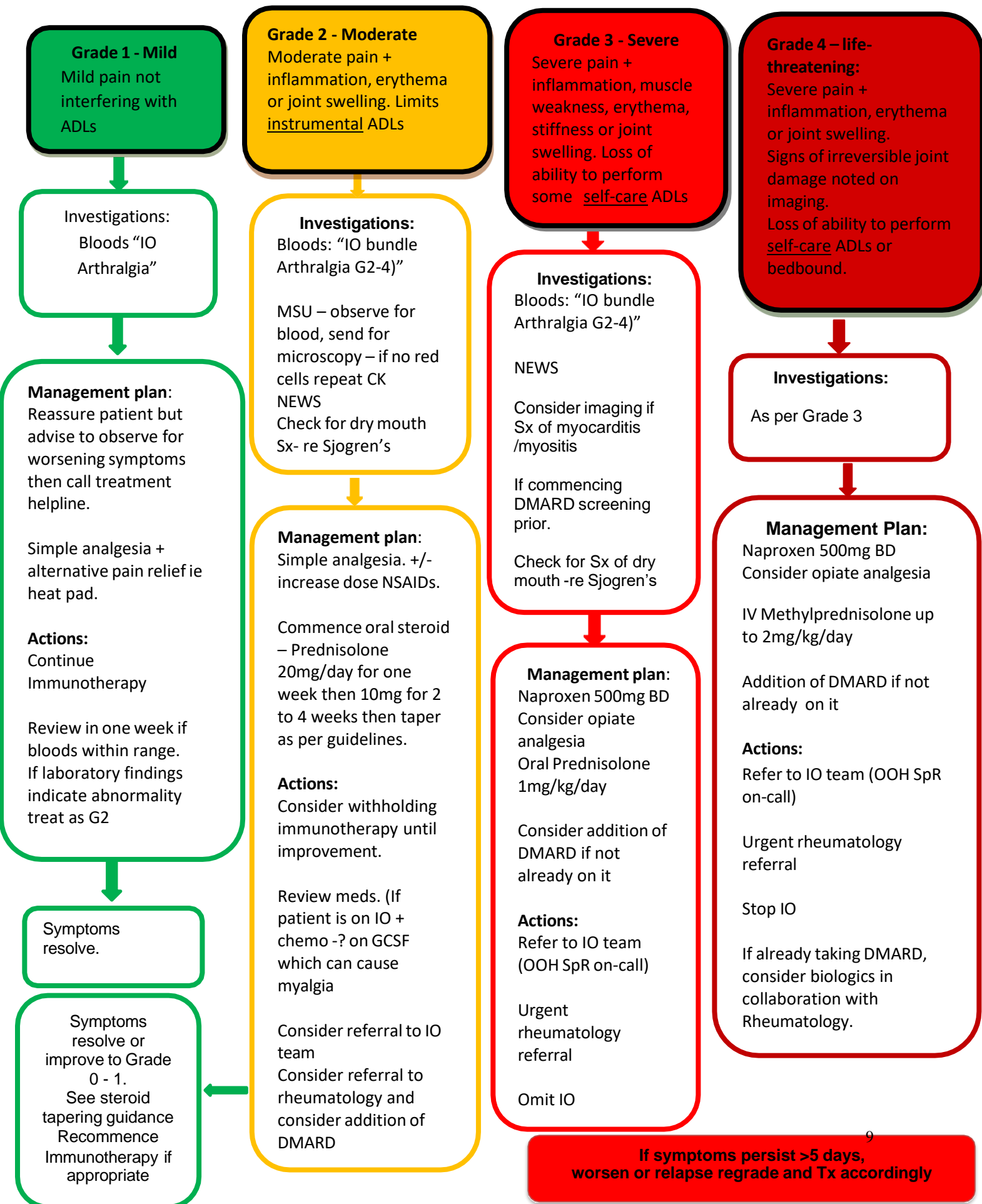
Viral: If patients are on other immuno-modulatory agents e.g. Mycophenylate mofetil (MMF), consideration may be given to CMV prophylaxis with Gancyclovir, especially if CMV IgG negative and lymphopenic.

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Full Management Guidelines

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Immune-Related Adverse Event: Arthralgia/Myalgia



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WCP Bundles:

“IO bundle Arthralgia G1”

FBC, U&E, LFT, Clotting, CRP, Cortisol, CRP. ESR, ANA, ENA, Rheumatoid factor, CK, Vitamin D

“IO bundle Arthralgia G2 - 4”

FBC, U&E, LFT, Clotting, CRP, Cortisol, CRP. ESR, ANA, ENA, Rheumatoid factor, CK, Vitamin D

Plus

Random glucose, Troponin, Cortisol
And MSU for microscopy

Consider Anti CCP antibodies

DMARD Screening bloods:

Hep B and Hep C
*Risk assess for TB

In presence of associated Sx of Sjogren’s refer to Rheumatology

ASCO recommend consideration introduction of steroid-sparing agents earlier than other IrAEs to avoid erosive joint damage.

Rheumatology referral to exclude autoimmune disorder, consideration of intra-articular steroid. If presence of dry mouth? Sjogren’s -? +/- labial biopsy.

Co-morbidities: Rheumatoid conditions, Arthritis, Systemic Lupus Erythematosus, Myasthenia Gravis, Myocarditis.

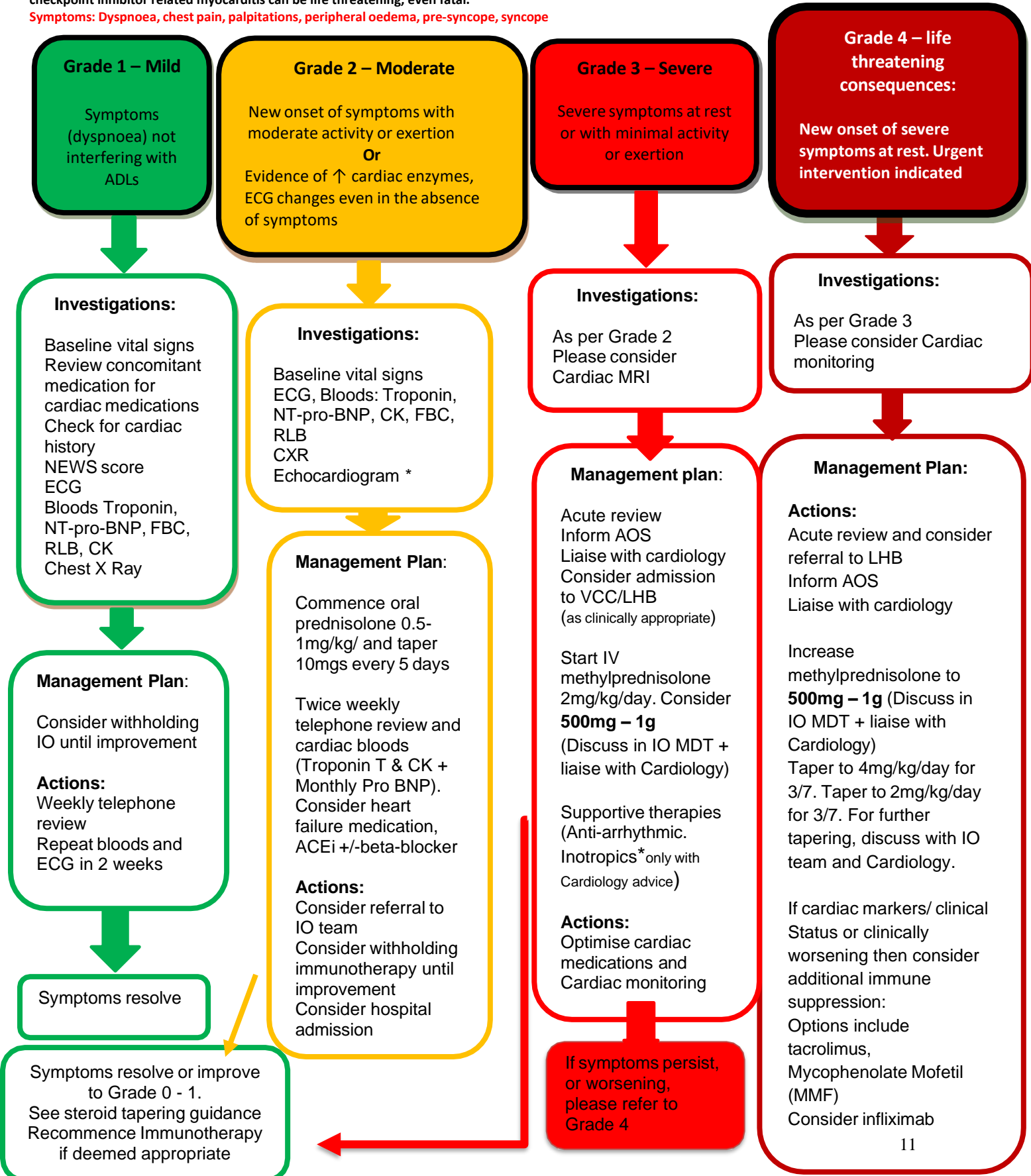
Reviewed by Dr Jo Ocen September 2022 and Ricky Frazer October 2022

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Immune Related Adverse Event: Cardiac/Myocarditis

Myocarditis is a recognised complication of checkpoint inhibitors. 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 or to have minimal symptoms and abnormal cardiac tests are significant. In practice, if a patient has unremitting respiratory symptoms, despite intervention, then need to exclude cardiac toxicity. Although rare, immune checkpoint inhibitor related myocarditis can be life threatening, even fatal.

Symptoms: Dyspnoea, chest pain, palpitations, peripheral oedema, pre-syncope, syncope



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*Echocardiogram – ECHOs are done weekly on a Tuesday as an outpatient service at VCC.

Please email mark.jones@wales.nhs.uk

WCP PATHOLOGY TEST BUNDLES:

IO Myocarditis bundle:

FBC
RLB
CK
Troponin
NT-pro-BNP
Vitamin D

See separate guidance
for second line
immunosuppression

*add appropriate monitoring bloods for MMF (eg FBC) and Tacrolimus (drug levels)

IO BIOLOGICS: If considering biologic/second line immunosuppression.

FBC,
RLB
CMV PCR (blood - listed as viral opportunistic infection),
HBV, HCV, HIV (blood – listed as virology routine screen BBV)
Herpes Simplex (blood – listed as Virology routine screen)
Add Varicella Zoster (VZV) on handwritten purple virology form if patient has not had chicken pox or if status unknown.

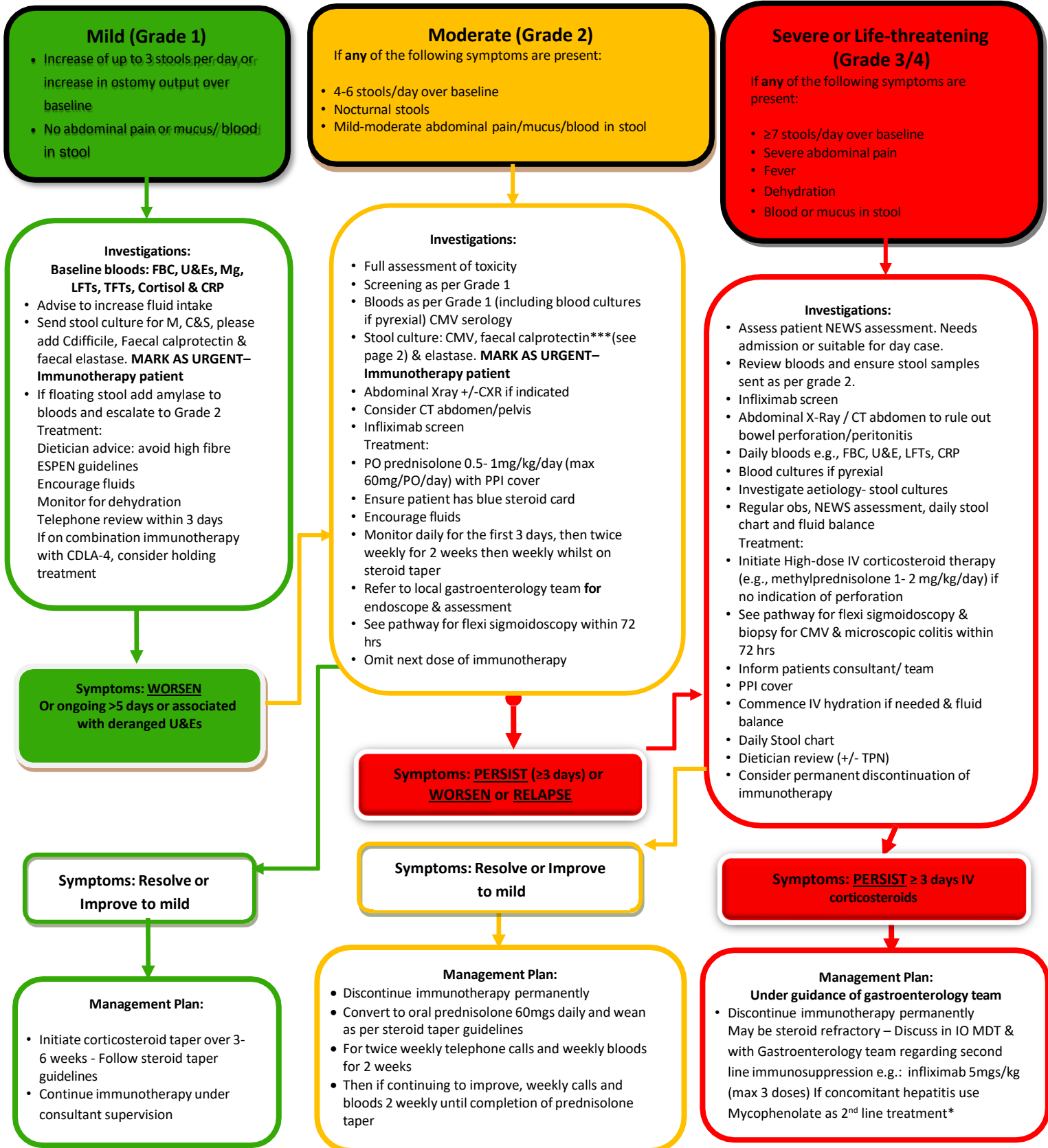
*Risk assess for TB – see full management guidelines.

Reviewed by Dr Jo Ocen September 2022 and Ricky Frazer October 2022

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Immune Related Adverse Event: Diarrhoea/Colitis

Unless alternative aetiology identified signs & symptoms should be considered immune-related. Gastrointestinal immune related adverse events are a common side effect of immunotherapies. It is generally reported as diarrhoea, defined by frequent and watery bowel movements, and/or colitis, defined by inflammation of the colon.



If patient is receiving treatment with immunotherapy and a TKI

Monitor diarrhoea for grade 1. For grade 2 stop the TKI and start loperamide for 3 days only and monitor. If the diarrhoea persists when loperamide has been stopped, the diarrhoea is more likely IO related and then follow pathway above

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***Colitis second line immunosuppression / Steroid refractory guidelines**

If concomitant hepatitis use Mycophenolate as second line treatment option, **NOT** Infliximab.

Discuss in IO MDT: You may need to start infliximab whilst waiting for colonic biopsy result

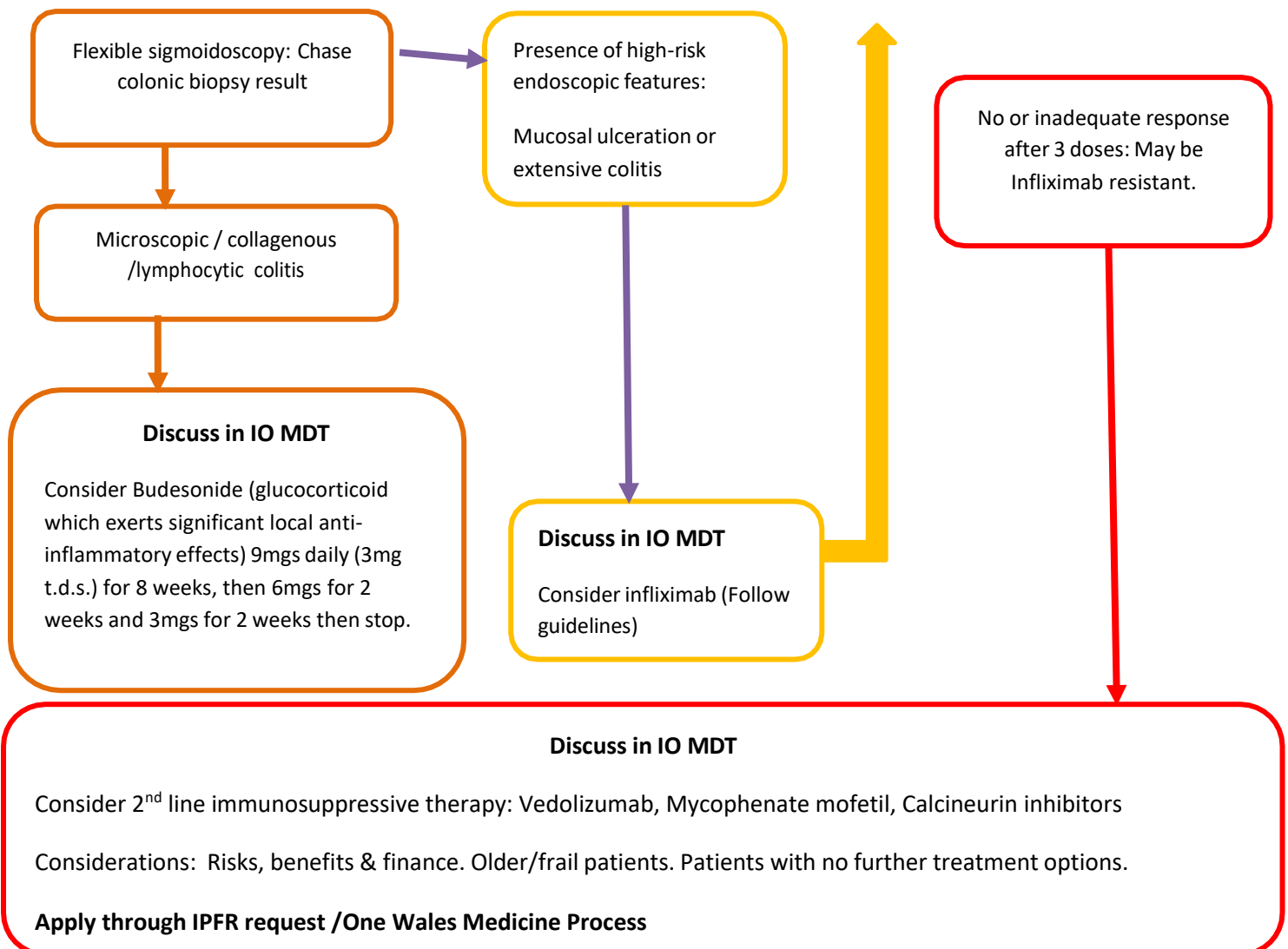
Infliximab: Follow Infliximab screening checklist & pathway

WEEK 0: 5mg/kg IV

WEEK 2: Second dose to be given 2 weeks later if symptoms remain
May be given 1 week after original dose if clinical symptoms indicate this)

WEEK 6: Third dose may be given a further 2 weeks later

Once infliximab given switch to oral Prednisolone (60mg OD) and wean as per steroid taper guidelines



***** Faecal calprotectin should be marked "Urgent – FAO Metabolic Lab". Please send an email to lesley.heirene@wales.nhs.uk, Shella.Soodharry@wales.nhs.uk, Moniek.hut@wales.nhs.uk to notify that the sample has been sent, and it will be extracted from the batch. The lab team will then aim to assay within 72 hours. If an emergency sample needs to be expedited please contact the UHW metabolic**

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Flexible sigmoidoscopy referral pathway

Scope within 72 hours of onset of colitis symptoms

If known IBD/Colitis

In patients with any pre-existing immune-mediated inflammatory disease, there is an increased risk of disease exacerbation. Baseline assessment of disease activity should include ileocolonoscopy, oesophago-gastro-duodenoscopy, faecal calprotectin & CRP. Vigilant monitoring for relapse e.g. regular faecal calprotectin measurement (Powell et al 2020).

Seek advice from IBD team within their LHB (Local Health Board). Start recovery pack e.g.: Budesonide and Salofalk. If no improvement in symptoms, then change to prednisolone 60mg/day and titrate as per steroid taper guidelines.

If patient is receiving treatment with immunotherapy and a TKI:

Monitor diarrhoea for grade 1. For grade 2 stop the TKI and start loperamide for 3 days only and monitor. If the diarrhoea persists when Loperamide has been stopped, the diarrhoea is more likely IO related therefore then follow pathway as above.

WCP PATHOLOGY TEST BUNDLES:

IO COLITIS:

FBC,

RLB,

TFT,

CORTISOL,

CRP,

Mg

Stool culture MC&S (Request inclusion of C. Diff), faecal calprotectin and Elastase.

PLEASE ADD CMV IF NOT SCREENING FOR BIOLOGICS

Vitamin D

For Grade 2 and above, consider Anti tTG

IO BIOLOGICS:

FBC,

RLB

CMV PCR (blood - listed as viral opportunistic infection),

HBV, HCV, HIV (blood – listed as virology routine screen BBV)

Herpes Simples (blood – listed as Virology routine screen)

Varicella Zoster (VZV)

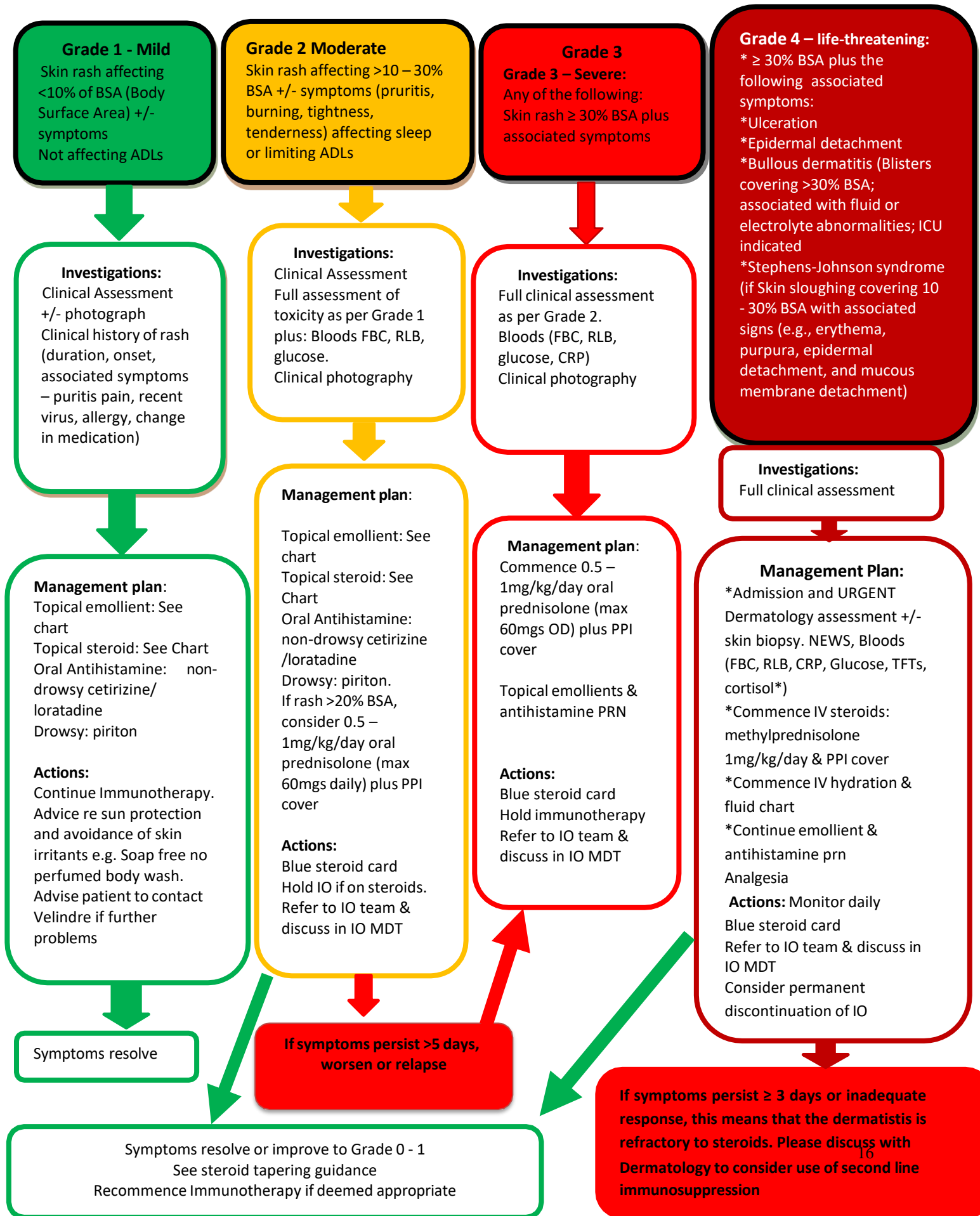
Rubella IgG - ** Select "Virology, clinical, other" use red or yellow topped bottle and write reason for test request on clinical details.

Please refer patient to LHB TB services for TB screening

Reviewed by Dr Jo Ocen August 2022 and Ricky Frazer October 2022

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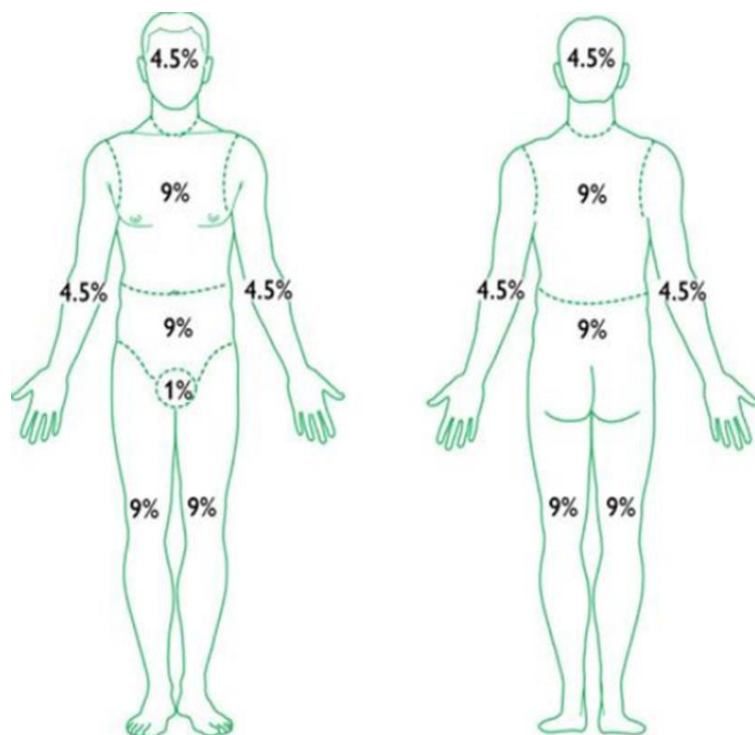
Immune Related Averse Event: Dermatological Toxicity



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WCP PATHOLOGY TEST BUNDLES: IO Skin: FBC, RLB, Glucose (random).

For Grade 3 - IO skin bundle plus CRP. For Grade 4: As per Grade 3 plus TFT & cortisol* if NOT on steroids.



Skin grading body graph

GRADE 1

<10%

GRADE 2

>10% to 30%

GRADE 3/4

≥ 30% BSA

Reviewed by Ricky Frazer October 2022

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Guidance for topical steroid creams & emollients:

SCALP	Treatment	Preparation
ITCHY SCALP (no rash)	ALPHOSYL 2 in 1 medicated shampoo	250mls
SCALP RASH (Skin intact)	BETNOVATE cream 0.122%. Potent topical corticosteroid	Apply thinly once or twice daily. Available in 15gm, 30gm and 100gm tubes
SCALP RASH (Skin intact)	DERMOVATE 0.05% scalp application is a potent topical corticosteroid	Apply thinly once or twice a day. Available in 25g, 30g or 100g tubes
SCALP RASH (broken skin)	SYNALAR 0.025% cream	Available in 30grm & 100grm tubes
THICK SCALY ITCHY SCALP	COCOIS_(Coconut Oil Compound Ointment)	Descaling ointment: Cociois has mild, antipruritic, antiseptic and keratolytic properties. Available in 5g, 15g, 40g and 100g tubes
THICK SCALY ITCHY SCALP	CAPASAL Therapeutic Shampoo	For use as a shampoo in the treatment of dry, scaly scalp conditions. Available in 100, 200, 300, 500 ml bottles

FACE	Treatment	Preparation	Advice
GENERAL FACE RASH	HYDROCORTISONE Mild topical corticosteroid	1% cream	Use sparingly over a small area once/twice a day Pack Size: 15g
PERI-ORBITAL RASH	PROTOPIC (Tacrolimus)	0.03% ointment. (Also available in 0.1% ointment if indicated by Dermatology)	In consultation with Dermatology. Available in 30 & 60grm tubes. Emollients should not be applied to the same area within 2 hours of applying Protopic ointment

TRUNK AND LIMBS	Treatment	Preparation	Advice
ANY PART TRUNK OR LIMBS	ELOCON 0.1%: Mometasone furoate 0.1% is a potent corticosteroid	Available in cream or ointment	Use sparingly once daily. Do not use on face. Available in 15, 30 & 100grm tubes. Add emollient

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LIGHT EMOLIENT	Treatment	Preparation	Advice for patients
AVEENO	Cream or lotion	Cream available in 100, 300 & 500mls. Lotion available in 500mls	Light and absorbs quickly. May need repeated application
DOUBLEBASE	gel, shower-gel, wash or bath additive	Double base gel available in 100, 500 & 1000grm Double base emollient wash gel 200grms & shower gel 200grms	Light and absorbs quickly. May need repeated application
ZEROBASE	Cream	Available in 50 & 500grms	Light and absorbs quickly. May need repeated application
CETOMACROGOL	Cream	500grms	

EMOLIENT GREASY	OTHER USES	WARNINGS	Advice to patients
HYDROMOL OINTMENT	Can also be used as a hydrating soap substitute: Available in 125, 500 & 1000grms	Regularly change clothing and bedding impregnated with product and keep away from naked flame	Can feel heavy and greasy when used as emollient but gentle soothing hydrating soap substitute. Use with warm water Stays on skin all day
EPADERM OINTMENT	Can also be used as a hydrating soap substitute: Available in 125, 500 & 1000grms	Regularly change clothing and bedding impregnated with product and keep away from naked flame	Can feel heavy and greasy when used as emollient but gentle soothing hydrating soap substitute. Use with warm water. Stays on skin all day

EMOLIENTS WITH ADDITIONAL PROPERTIES	Treatment	Preparation	Advice for patients
DERMOL	SOAP SUBSTITUTE	Cream or lotion	Antimicrobial
ARJUN 1% cream	For itchy irritated skin	Cream available in 100 & 500grms	Cooling cream Apply 1-2 times a day

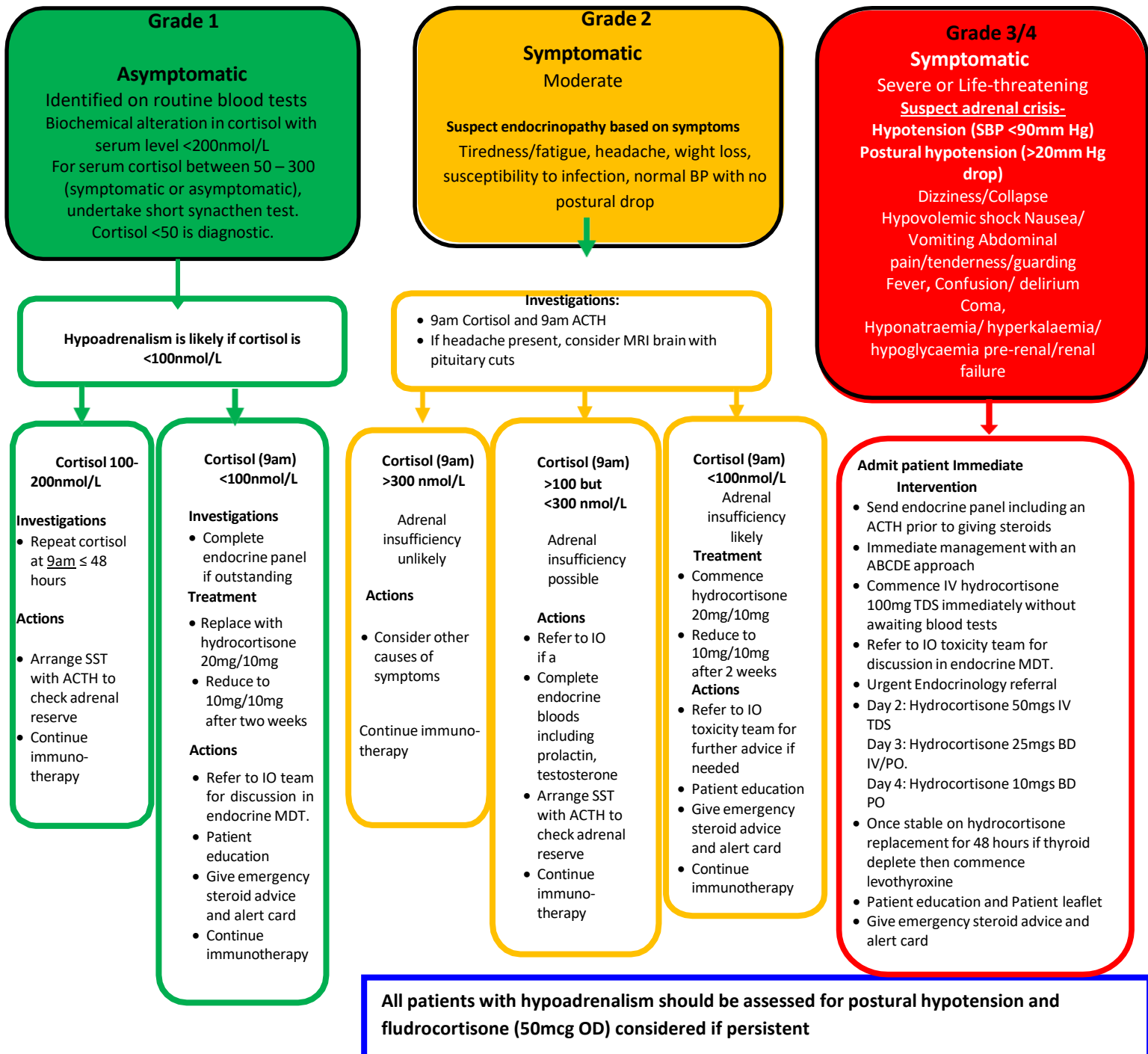
Guideline reviewed by Dr Jo Ocen August 2022 and Ricky Frazer October 2022

Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

Immune-Related Adverse Event: Endocrinopathies- Adrenal Crisis

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

Please do not order a 9am cortisol if patient is on steroids (prednisolone/dexamethasone) as serum cortisol will be suppressed



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 hypothyroidism guidelines should be instituted)



Priority is adrenal replacement

Please do not order a 9am cortisol if patient is on steroids (prednisolone/dexamethasone) as serum cortisol will be suppressed

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WCP PATHOLOGY TEST BUNDLES:

IO Adrenal G1:

FBC,
RLB,
TFT,
Cortisol,
CRP,
Glucose (Random)
Mg
Vit D

IO Adrenal G2-4:

FBC,
RLB,
TFT,
Cortisol,
CRP,
Glucose (Random)
Mg
Vit D
ACTH
LH
FSH
Prolactin
+/- Testosterone/Oestrodial

Subsequent management will be undertaken by the IO team in the event of hypoadrenalism. On referral to the IO service patient will be discussed at the endocrinology MDT, and an SST will be arranged if needed. Patients will be issued an emergency steroid card and enrolled in the adrenal insufficiency education workshop. Please follow guidelines for SST.

Dose omission prior to SST: Dexamethasone - omit 72 hours before and switch to hydrocortisone.
Hydrocortisone – omit afternoon dose the day before and the morning dose the day of the SST.
Prednisolone: omit morning dose day of SST test

Note to consider: If patient is taking oestrogen replacement therapy, cortisol levels may be falsely elevated. Maintain low threshold of suspicion of adrenal insufficiency.

Reviewed by Dr Andrew Lansdown September 2022 and Ricky Frazer October 2022

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Immune-Related Adverse Event: Endocrinopathies Hypophysitis

The pituitary gland can become inflamed as a side effect of the immunotherapy, as a result cortisol, thyroxine and sex hormones can become low.

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, ACTH, LH, FSH & cortisol (between 9-11am if possible), prolactin, blood glucose +/- testosterone/oestrogen

Please do not order a 9am cortisol if patient is on steroids (prednisolone/dexamethasone) as serum cortisol will be suppressed

Grade 1 Asymptomatic

Identified on routine blood tests
Biochemical alteration in cortisol with serum level <200nmol

For serum cortisol between 50 – 300 (symptomatic or asymptomatic), undertake short synacthen test. Cortisol <50 is diagnostic.

Hypoadrenalism is likely if cortisol is <100nmol/L

Cortisol <100nmol/L

Investigations

- Complete endocrine panel if outstanding

Treatment

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

Actions

- Refer to IO Team for discussion in endocrine MDT.
- Patient education
- Give emergency steroid advice and alert card
- Continue immunotherapy

Cortisol 100-200nmol/L

Investigations

- Repeat cortisol at 9am ≤ 48 hours

Actions

- Arrange SST with ACTH to check adrenal reserve if symptomatic
- Continue immunotherapy

Grade 2

Symptomatic

Moderate threatening

Suspect endocrinopathy based on symptom

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

Investigations:

- 9am Cortisol and ACTH
- If headache present, consider MRI brain with pituitary cuts

Cortisol (9am) >300 nmol/L

Adrenal insufficiency unlikely

Actions

- Consider other causes of symptoms
- Continue immunotherapy

Cortisol (9am) >100 but <300 nmol/L

Adrenal insufficiency possible:

Actions

- Refer to IO Team if any concerns.
- Complete endocrine bloods including prolactin, testosterone
- Arrange SST with ACTH to check adrenal reserve if symptomatic.
- Continue immunotherapy

Cortisol (9am) <100nmol/L

Adrenal insufficiency likely

Treatment

- Commence hydrocortisone 20mg/10mg.
- Reduce down to 10mg/10mg after 2 weeks

Actions

- Refer to IO Team for discussion in Endocrine MDT
- Patient education
- Give emergency steroid advice and alert card
- Continue immunotherapy

Grade 3/4 Symptomatic

Severe headache, visual disturbance, evidence of focal neurology

Combination of moderate/severe symptoms and pituitary inflammation on MRI

If severe symptoms/signs of hormonal insufficiency with no headache/visual disturbance/pituitary inflammation then follow adrenal crisis algorithm

Investigations:

Endocrine panel inc ACTH
MRI brain with pituitary cuts

Admit Patient - Immediate Intervention

- Send endocrine panel including an ACTH prior to giving steroids with an ABCDE approach.
- Commence IV hydrocortisone 100mg TDS immediately without waiting for blood tests in unwell patients.
- Refer to IO Toxicity team and discuss in endocrine MDT.
- Follow hydrocortisone taper:
Day 2 Hydrocortisone 50mg IV TDS
Day 3 Hydrocortisone 25mg, IV/PO, BD
Day 4 Hydrocortisone 10mg, PO BD
- Maintenance dose is Hydrocortisone 10mg BD
- Thyroid function tests may show secondary hypothyroidism.
- Thyroxine 50 micrograms od can be commenced once the patient is safely established on steroids for > 48hours.
- Recheck testosterone after 3 weeks and replace if remains suppressed Patient education
- Give emergency steroid advice and card

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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 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.

Asymptomatic with biochemical changes

Investigations
TSH, 9am cortisol, random glucose

Hyperthyroidism

TSH <0.30 mU/L and Free T4 > 22pmol/L

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

Actions:

- Recheck TFT's and cortisol within 3 weeks and then 3-6 weekly thereafter. N.B. the majority of cases become hypothyroid within a matter of weeks
- Discuss with Endocrinology if symptomatic

Once hypothyroid-manage as per hypothyroidism algorithm

Hypothyroidism

Treatment: Levothyroxine 50mcg/day

Caution: Check cortisol before replacing thyroxine

Actions:

- Recheck TFT's cycles of treatment
- Check cortisol only if clinically indicated
- Increase Levothyroxine in 25mcg increments
- Discuss with endocrine team in MDT if unable to stabilise thyroid function

Continue Immunotherapy

Symptomatic or severe biochemical disturbance

Investigations (if cortisol is low)
TSH, ACTH, LH, FSH, prolactin, random glucose +/- testosterone

Hyperthyroidism

TSH <0.30 mU/L and Free T4 > 22pmol/L

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

Treatment (only if symptomatic):

- B-blocker- Propranolol 40-80mg daily (start at 40mg)
- Carbimazole-rarely indicated due to the transient nature of hyperthyroidism. If concerned discuss in endocrine MDT
- TSI ** see next page
- Add anti-TPO antibodies

Continue Immunotherapy
Once hypothyroid-manage as per hypothyroidism algorithm

Hypothyroidism

TSH of >10mU/L and Free T4 < 8.9 pmol/L (check local parameters)

Treatment:

Actions (only if symptomatic):

- Recheck TFT's cycles of treatment
- Check 9am Cortisol
- Increase Levothyroxine in 25mcg increments
- Discuss with endocrine team in MDT if unable to stabilise thyroid function

Continue Immunotherapy



If 9am cortisol is less than 100, initiate hydrocortisone replacement for 48 hours prior to commencing thyroid replacement. In the case of adrenal insufficiency, if thyroid deficiency is replaced **before** addressing low cortisol levels it can be fatal.

Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

WCP PATHOLOGY TEST BUNDLES:

NB: Check thyroid function acceptable range, as they vary in LHBs

IO Thyroid:

TFT

9am Cortisol

Random Glucose

(T4 will be assayed as part of the TFT. If TSH abnormal, biochem will automatically assay

Free T3)

Vit D

** Thyroid Stimulating Antibodies (TSI) - add if personal or family Hx of thyroid disease, if if features suggest Grave's disease.

Anti TPO antibodies.

IO Adrenal:

FBC

U&E

LFT

Bone Profile

TFT

Blood glucose random

9am ACTH

LH

FSH

Prolactin

9am Cortisol

Testosterone

Oestrodiol

Vit D

Add TSI (thyroid stimulating immunoglobulins) if personal or family history of thyroid disease, or if features suggestive of Graves' disease e.g. eye signs or goitre.

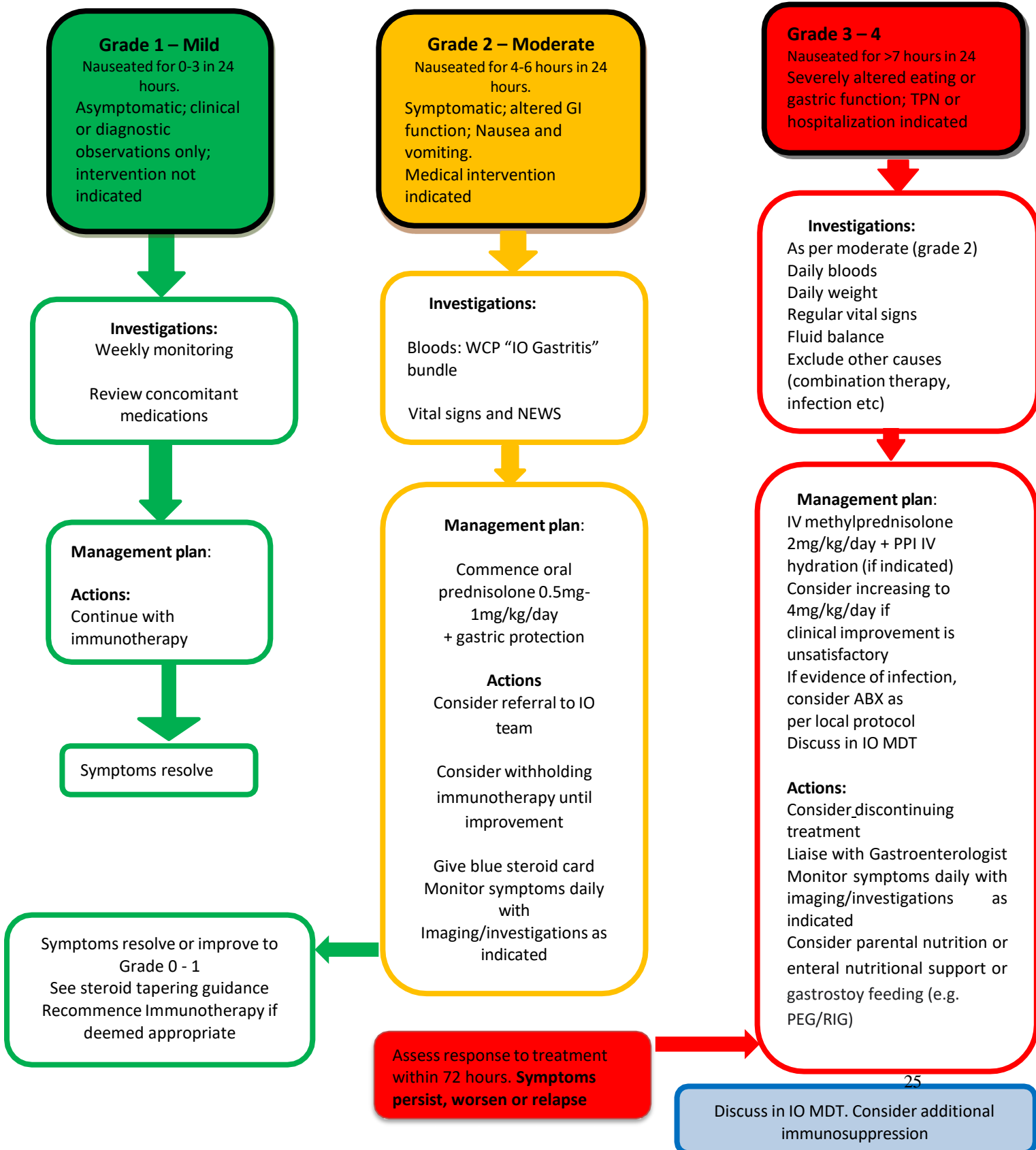
If thyroid function is also compromised within a hypopituitary picture ensure cortisol is replaced prior to commencement of thyroid replacement (see grade 1 hypothyroidism guidelines) priority is adrenal replacement

Reviewed by Andrew Lansdown September 2022 and Ricky Frazer October 2022

Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

Immune Related Adverse Event: Gastritis/Oesophagitis

Upper-GI toxicity is much less common and characterized by dysphagia, nausea or vomiting, and epigastric pain. Patchy chronic duodenitis or chronic gastritis with rare granulomas may be identified on biopsies. It can coexist with lower-GI toxicity or as an isolated condition. The treatment strategy is similar to colitis: corticosteroid followed by infliximab or vedolizumab for refractory cases based on case studies (ASCO 2021).



Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

WCP PATHOLOGY TEST BUNDLES:

“IO Gastritis”:

FBC

U & E’s

LFT’s

Blood glucose

Cortisol and TFT if clinically indicated

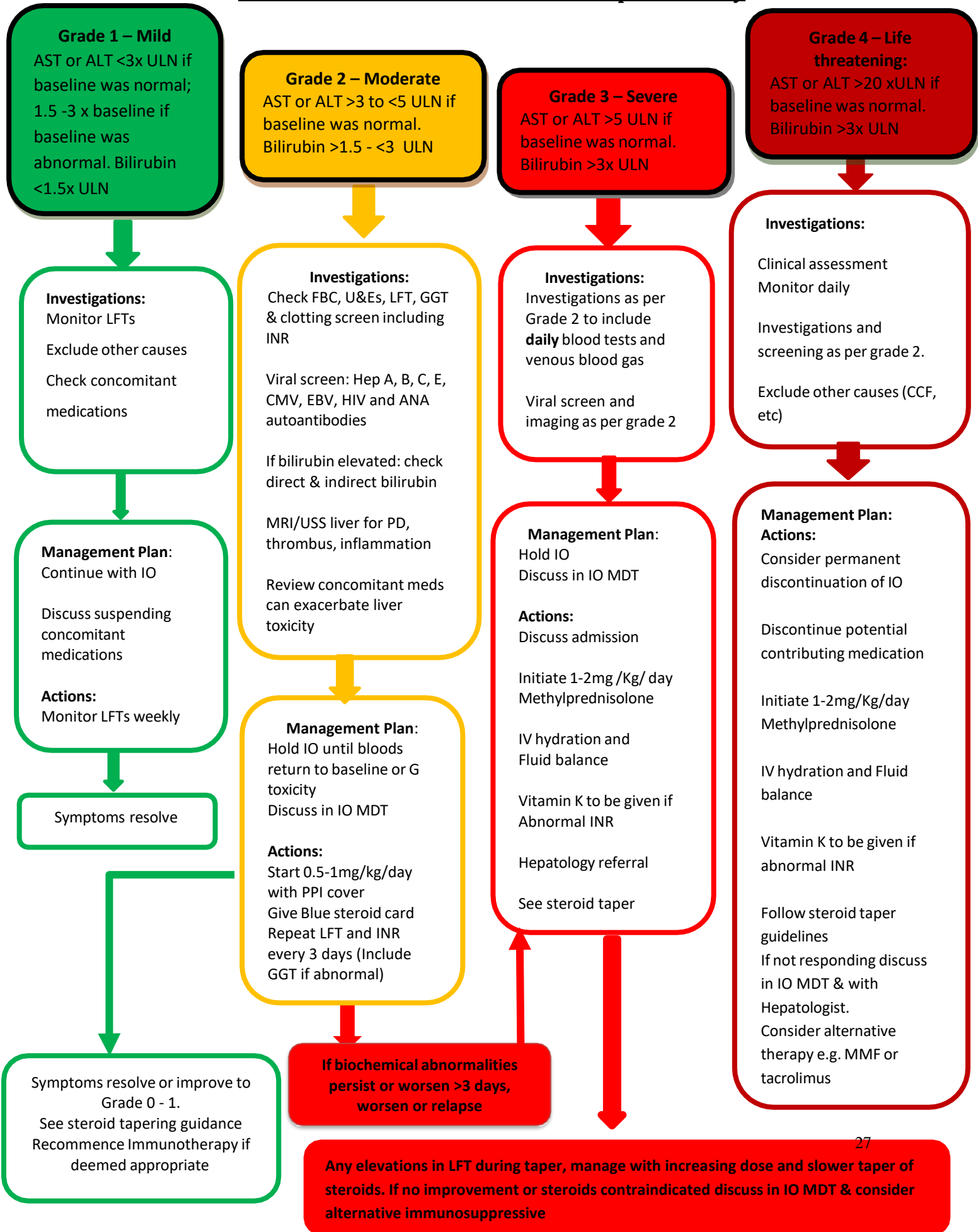
TFT’s

Vit D

Reviewed by Ricky Frazer October 2022

Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

Immune Related Adverse Event: Hepatotoxicity



Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

WCP PATHOLOGY TEST BUNDLES:

IO Liver toxicity G1:

RLB

FBC

AST

IO Liver toxicity bundle G2, G3 & G4:

FBC

LFTs

AST

U&Es

Hepatitis A,B,C,E.

CMV, EBV, HIV and ANA auto antibodies

GGT

INR

Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

Immune Related Adverse Event: Mucositis and Stomatitis

Grade 1 – Mild

Mild oral soreness, normal oral., No dry mouth noted, erythema possible. Mild symptoms

Investigations:

Clinical assessment to determine severity
Advice regarding general oral care.
No further investigations indicated.
Baseline weight

Management plan:

0.9% sodium chloride mouthwashes, use of ice cubes to alleviate feeling of dry mouth
Difflam oral solution 10mls QDS
Gelclair or Caphasol mouthwash

Actions: Review within 1 week, advice re:

Encourage fluid intake and diet. Avoid spicy foods, rough or crunchy textures. Avoid alcohol/tobacco

Symptoms resolve or improve to Grade 0 - 1.
See steroid tapering guidance
Recommence Immunotherapy

Grade 2 – Moderate

Moderately Painful. Pain on swallowing, mild oral ulceration and erythema, somewhat dry mouth – scant moisture.
Solid diet tolerated
Limiting instrumental

Investigations:

NEWS, FBC, RLB, LFT, CRP, blood cultures if febrile or clinically indicated
Fungal mouth swab
Weight

Consider differential diagnosis
Viral /bacterial infection, candidiasis.
Radiotherapy reaction

Management plan:

Nystatin or miconazole oral gel if fungal cause.
Local anaesthetic (Benzylamine hydrochloride) and corticosteroid
Prednisolone 5mg soluble prednisolone as mouthwash QDS +/- oral prednisolone 0.5mg/kg/day.
Dispersible paracetamol 1g 4 hourly
Oral lubricants: Gelclair or Caphasol mouthwash

Actions:

Review weekly
Refer to dietician, SLT team if concerns about dysphagia
Encourage oral fluids
Defer IO
Consider referral to IO service

Grade 3 – Severe

Severely painful, oral ulceration +/- blistering able to tolerate liquid diet only. Likely weight loss. Absence of moisture – sticky, viscous saliva.
Limiting self-care ADLs

Investigations:

As per grade 2

Management plan:

Consider admission
Refer to IO service
I/V methylprednisolone 1mg/kg/day
IV fluids/fluid balance.
Consider stronger analgesia in line with WHO pain ladder (be aware that oromorph may sting as it has an alcohol base)

Actions:

Refer to dietician, SLT team if concerned about dysphagia. Withhold immunotherapy Review daily

Grade 4 – life-threatening:

Oral alimantation not possible. Weight loss. Life-threatening.
Absence of moisture. Coated mucosa

Investigations:

As per Grade 2 and ? Endoscopy +/- Biopsy:
Establish presence of oedema/oesophageal or small intestine ulceration and to rule out infection or malignancy/pre- colitis

Management Plan:

If nil fungal or infective cause isolated.
Mucositis may be steroid refractory
Consider second line immunosuppression. As per steroid refractory protocol.
Pre biologic screening as per protocol

Actions:

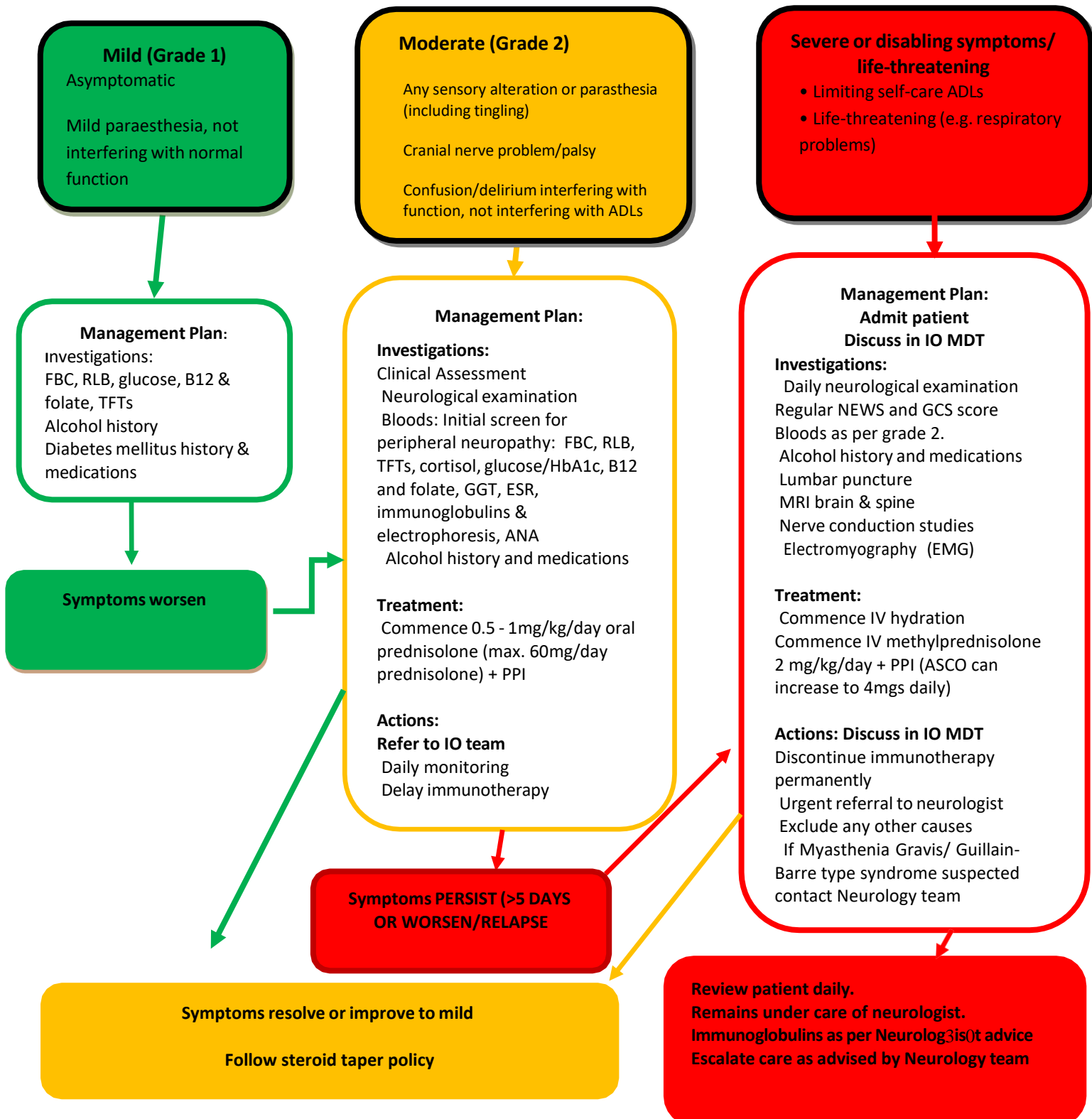
Admit to hospital for parental nutrition or enteral nutritional support or gastrostomy feeding (e.g. PEG/RIG)

Stop Immunotherapy

Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

Immune Related Adverse Event: Neurological Toxicity - Peripheral

Immune checkpoint inhibitors (ICI) can cause various neurological side effects. This can manifest as radiculopathies, neuropathies, myopathies as well as myasthenic syndromes. The majority of neurological side effects involve the peripheral nerves which can affect the nerve root, peripheral nerve, neuromuscular junction or muscle. Toxicity involving the central nervous system (eg aseptic meningitis, encephalitis) are less frequent but can result in severe clinical symptoms. Close clinical monitoring is key for early recognition of neurological immune related side effects (Roth et al 2021).



Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

Suggested bloods as per initial screen for peripheral neuropathy. Other tests such as HIV, ACE, ANCA, ENA, antiganglioside abs etc. might be considered depending on the clinical presentation.

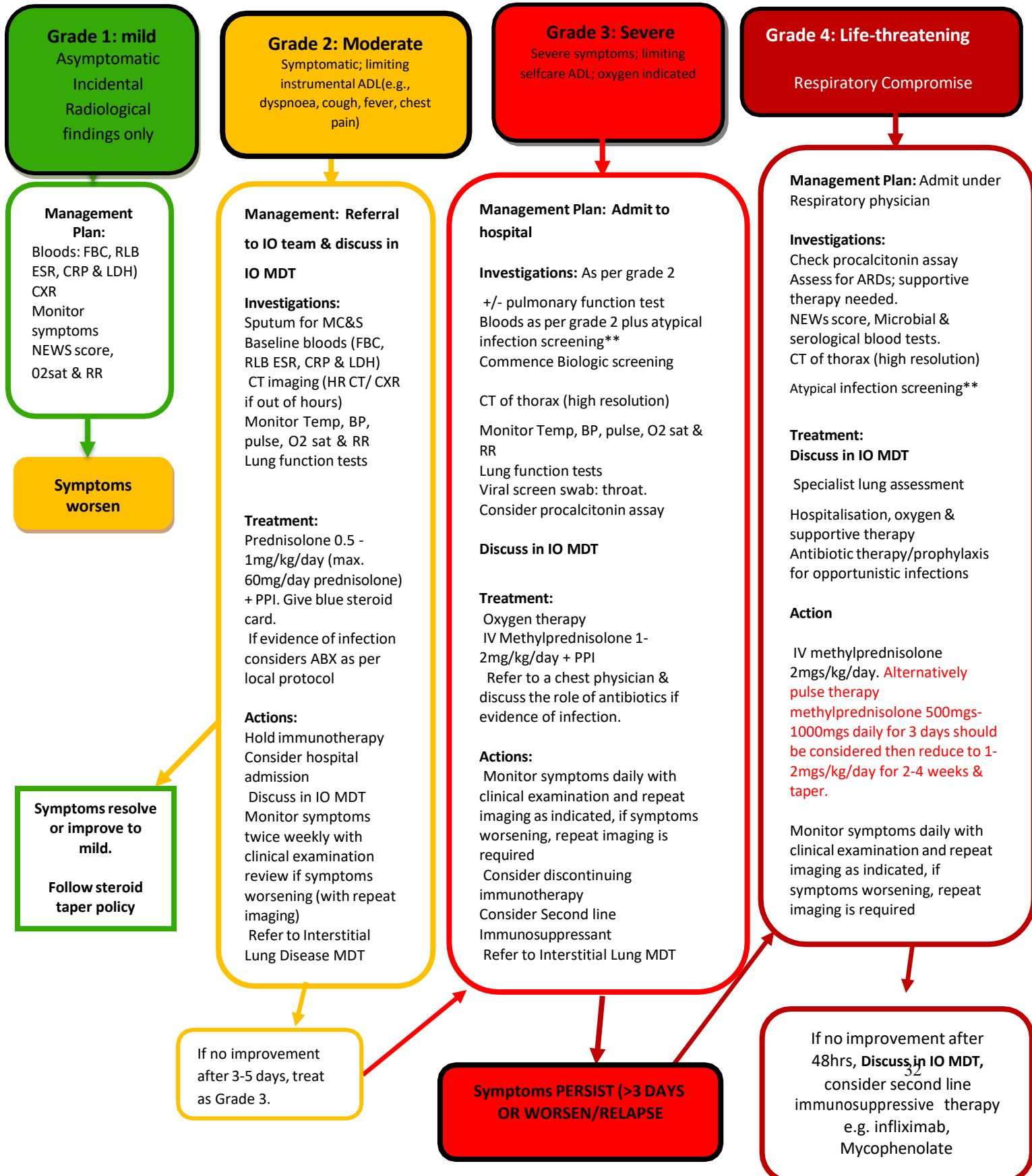
Central neurological symptoms can be varied and insidious to acute onset. Should there be any concerns of CNS symptoms, please refer directly to Neurology team.

**Reviewed by Dr Mark Willis Consultant Neurologist UHW July 2022 and Ricky Frazer
October 2022**

Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

Immune Related Adverse Event: Pneumonitis

Pneumonitis is defined as focal or diffuse inflammation of the lung parenchyma, typically identified on CT imaging. Ground-glass opacities or patchy nodular infiltrates, predominantly in the lower lobes, are common findings on chest imaging. Presenting symptoms related to immune therapy-induced pneumonitis may include new or worsening cough, shortness of breath, increased oxygen requirement, chest pain, and/or fever. The median time to onset of pneumonitis is 34 weeks but can range from 1.5 to 127 weeks



Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

WCP PATHOLOGY TEST BUNDLES:

IO Pneum G1:

FBC
RLB
ESR
CRP
LDH
Vit D

IO Pneum G2:

FBC
RLB
ESR
CRP
LDH
Vit D
Microbial Investigation (respiratory)

IO Pneum G3 + 4:

FBC
RLB
ESR
CRP
LDH
Vit D
Microbial Investigation (respiratory)
Viral throat swab. Add Procalcitonin assay if clinically indicated.

****IO Atypical infection (resp).**

B-D-Glucan Serum
Microbiology legionella (Urine)
IgG Antibodies to pneumococcus (serum)
Microbial investigation – fungal/mycology (serum) includes galactomannan
Virology Respiratory symptoms swab

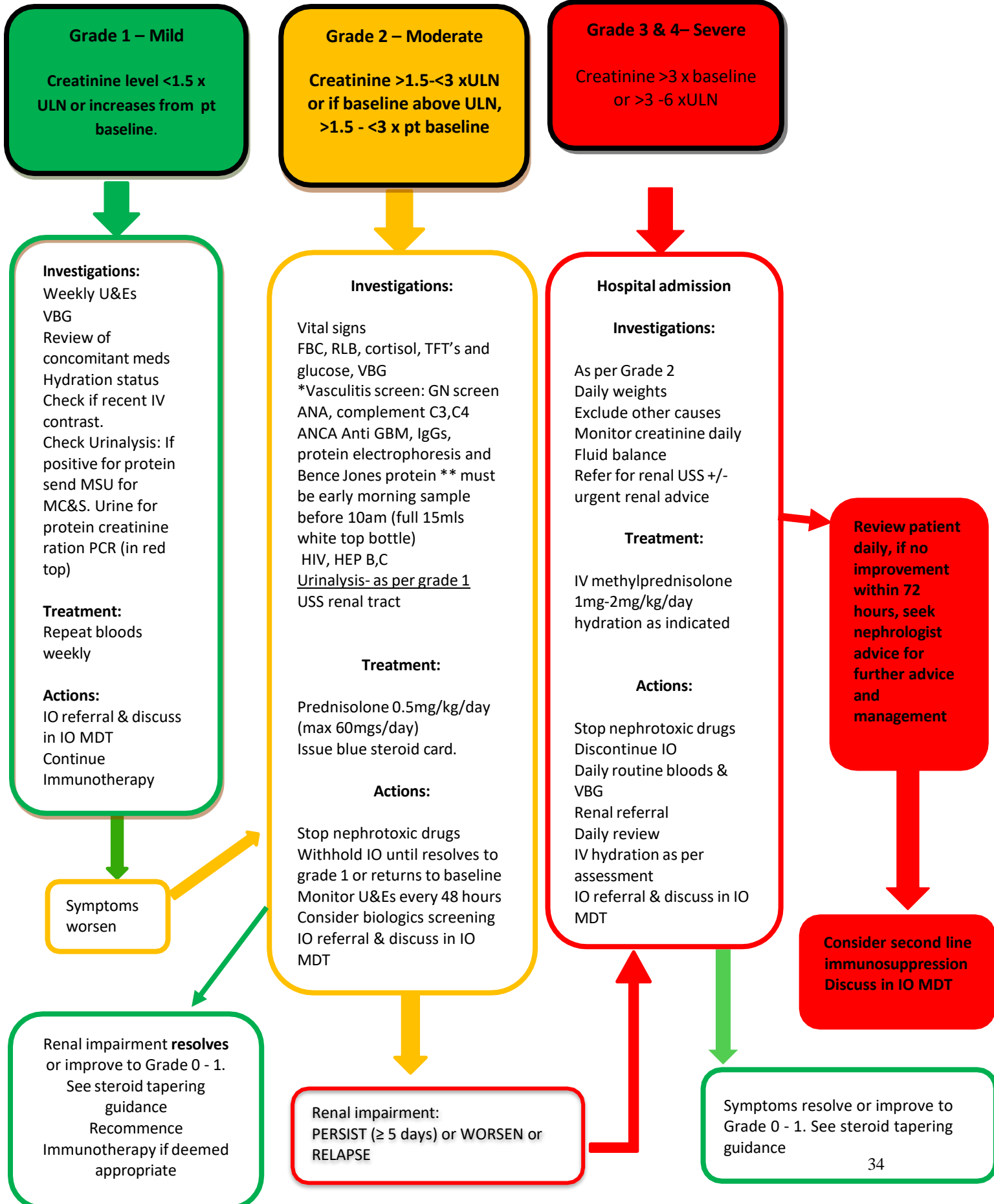
ADDITIONAL IMMUNOSUPPRESSION ONLY COMMENCE FOLLOWING DISCUSSION WITH THE IMMUNOTHERAPY TEAM +/- RESPIRATORY TEAM

Mycophenolate Mofetil (MMF) starting dose is 500mg BD increasing to 1g BD after a week. In certain cases, MMF can be increased to 1.5g BD. Regular full blood count blood monitoring required as MMF is an immunosuppressant. Stopping immunosuppression once respiratory picture is stable/ back to baseline for 2 weeks MMF can be reduced by 500mg BD and reduced by 500mg every 2 weeks until complete. Points to consider Prompt referral to ILD team

Reviewed by Dr Jo Ocen August and Ricky Frazer October 2022

Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

Immune Related Adverse Event: Renal



Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

Uveitis Full Management Guidelines

Signs and symptoms: Blurred vision, miosis, photophobia, visual distortion, tenderness, pain on eye movement, eyelid swelling, redness, dryness, Blepharitis, conjunctivitis, itching, burning, increased tear production, mucoid discharge, thickening of tarsal border

Grade 1 – Mild
Anterior Uveitis visible with penlight
Or asymptomatic Episcleritis

Investigations:

Clinical assessment of other symptoms & review bloods incl TFT
Check vision in each eye separately
Inspection of anterior aspect of eye with pen-torch
Check PEARL & pupil size & shape

Management plan:

Artificial tears Rx.
Application of warm compress to eyes. Eyelid hygiene. Topical antibacterial if infection suspected

Actions:

Optician/optometrist review within one week for fundoscopy, slit-lamp examination, eye pressures

Symptoms resolve

Grade 2 – Moderate
Anterior Uveitis
Episcleritis with visual acuity 6/12 or better
Mild visual disturbance

Symptomatic Episcleritis (see symptoms above)

As per grade 1

Investigations:

Clinical assessment of other symptoms. Routine bloods including TFT + ANA.
Check vision in each eye separately.
Inspection of anterior aspect of eye with pen-torch
Check PEARL and pupil size and shape.

Management plan: Refer to IO team

Consider Topical corticosteroids 1% prednisolone acetate suspension (Pred Forte 1% eye drops)
Consider systemic steroids following discussion with IO team
Actions: Consider holding Immunotherapy temporarily until improvement/review by ophthalmology

Grade 3 – Severe

Anterior uveitis: intermediate, posterior or pan-uveitis
Symptomatic Scleritis, episcleritis and vision worse than 6/12
Moderate visual disturbance

As per grade 1 plus:
Nocturnal eye pain – wakes patient - feels like pain boring into the eyeball. Colour desaturation

Investigations:

As per Grade 2

Management plan:

Systemic corticosteroids +/- topical corticosteroids

Actions: Refer to IO team

Urgent ophthalmology referral for review and assessment for biologics if steroid refractory + cycloplegics (atropine)

Stop Immunotherapy

Grade 4 – sight-threatening:

Symptomatic Scleritis.
Best corrected visual acuity of 6/60 or worse in the effected eye
Severe visual disturbance

As per grade 1 plus:
Nocturnal eye pain – wakes patient - feels like pain boring into the eyeball. Colour desaturation

Investigations:

As per Grade 2

Management Plan:

Refer to IO team

Systemic corticosteroids 1 – 2 mg/kg/day Or methylprednisolone 0.8 – 1.6mg/kg/day +/- topical corticosteroids

Actions: Emergency Ophthalmology referral for review and assessment for intravitreal, periocular, or topical steroids and for assessment for biologics if steroid refractory + cycloplegics (atropine)

Discontinue Immunotherapy

Symptoms resolve or improve to Grade 0 - 1. See steroid tapering guidance if on oral steroids.
Recommence Immunotherapy if deemed appropriate and if ocular toxicity is only irAE

Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

Distance Visual Acuity Conversion Chart

UK	Decimal	5m	US
6/3	2.0	5/3	20/10
6/4	1.5		20/13
6/5	1.2		20/17
6/6	1.0	5/5	20/20
6/9	0.7	5/7.5	20/30
6/12	0.5	5/10	20/40
6/18	0.3	5/15	20/60
6/24	0.25	5/20	20/80
6/36	0.2	5/30	20/120
6/60	0.1	5/50	20/200

Care Step Pathway - Ocular Toxicity

Nursing Assessment

<p>Look:</p> <ul style="list-style-type: none"> - Does the patient look unwell (or ill)? - Does the patient look uncomfortable? - Does the patient look jaundiced? - Is there any eye redness? Drainage? Tearing? - Is the patient sensitive to light? - Is there lid or periocular edema? - Are there skin lesions surrounding the eye(s)? - Are pupils reactive? 	<p>Listen:</p> <ul style="list-style-type: none"> - Patient and family descriptions of ocular health and any current or prior history of eye problems (e.g., glaucoma, retinal issues, eye inflammation) - Reports of specific eye complaints: redness, watering, drainage, change in acuity, diplopia (double vision), floaters, photophobia? - When did symptoms start? - Any recent eye injury, new medications, or exposure to toxic chemicals? - Does the patient wear contact lenses? - Is the patient diabetic? - Associated symptoms: headache, vomiting, nausea? 	<p>Recognize:</p> <ul style="list-style-type: none"> - Patients at risk for ocular issues (history of glaucoma, dry eyes, uveitis, retinal disease, macular degeneration, or diabetes) - The specific ocular complaint (if possible) and determine grade - Other treatment-related symptoms
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Grading Toxicity (Overall, Eye Disorders)

<p>Grade 1 (Mild) Asymptomatic; clinical or diagnostic observations only</p>	<p>Grade 2 (Moderate) Symptomatic (pain, irritation, photosensitivity, etc.); visual acuity falls to 20/40 or better in affected eye(s); limiting instrumental ADLs</p>	<p>Grade 3 (Severe) Highly symptomatic (pain, irritation, photosensitivity, etc.), marked decrease in visual acuity (worse than 20/40) in affected eye(s); limiting self-care ADLs</p>	<p>Grade 4 (Potentially sight-threatening) Blindness (20/200 or worse) in affected eye(s)</p>
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WCP Test Bundles:

FBC

RLB

Random glucose

LFTs

TFT

ANA

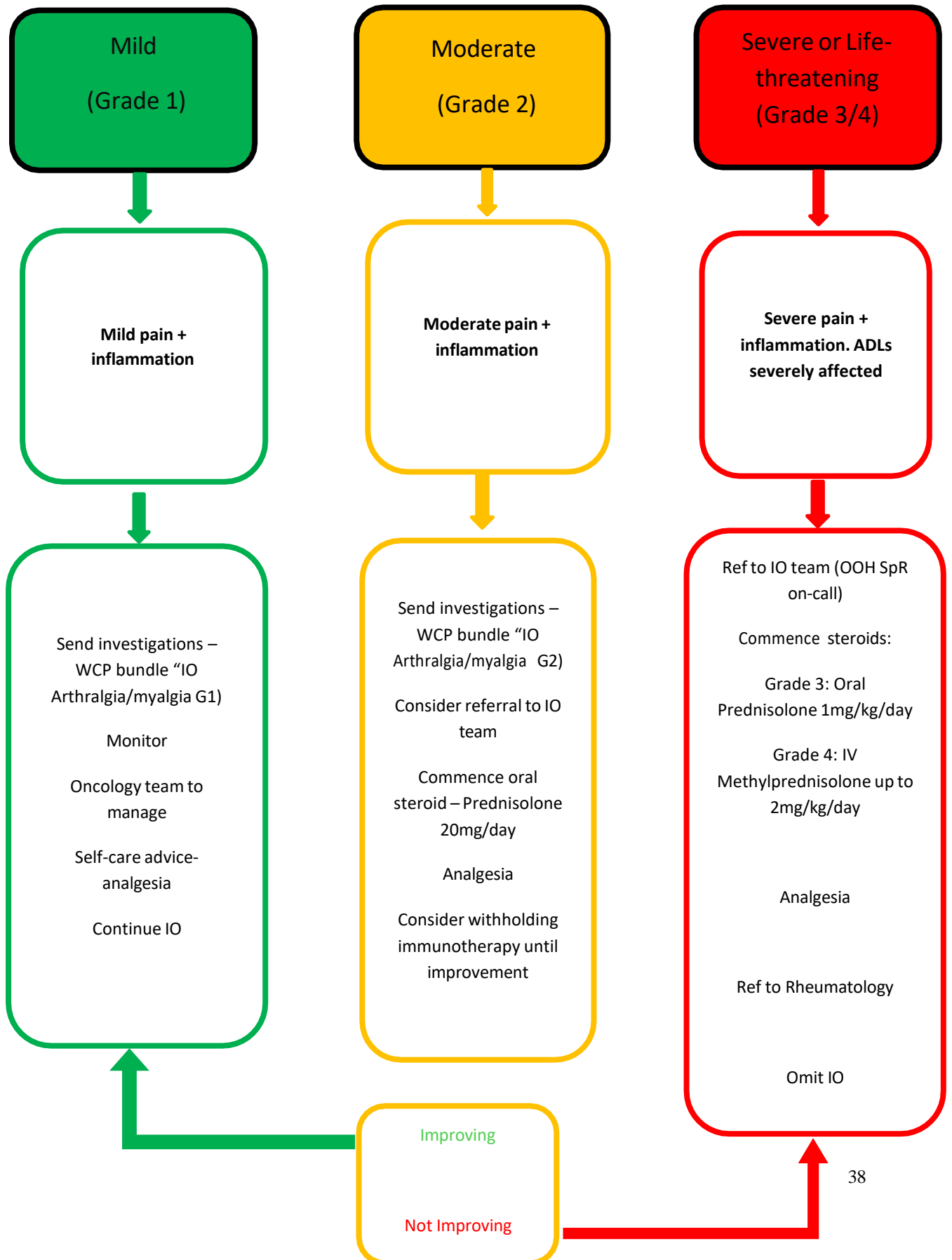
Reviewed by Ricky Frazer October 2022

Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

Quick Reference Guidelines

Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

Arthralgia Myalgia Quick Reference Pathway



Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

WCP PATHOLOGY TEST BUNDLES:

“IO Arthralgia/myalgia G1”

FBC
U&E
LFT
Clotting
CRP
Cortisol (if not on steroids)
CRP, ESR
ANA
ENA
Rheumatoid factor
Anti CCP
CK
Vit D

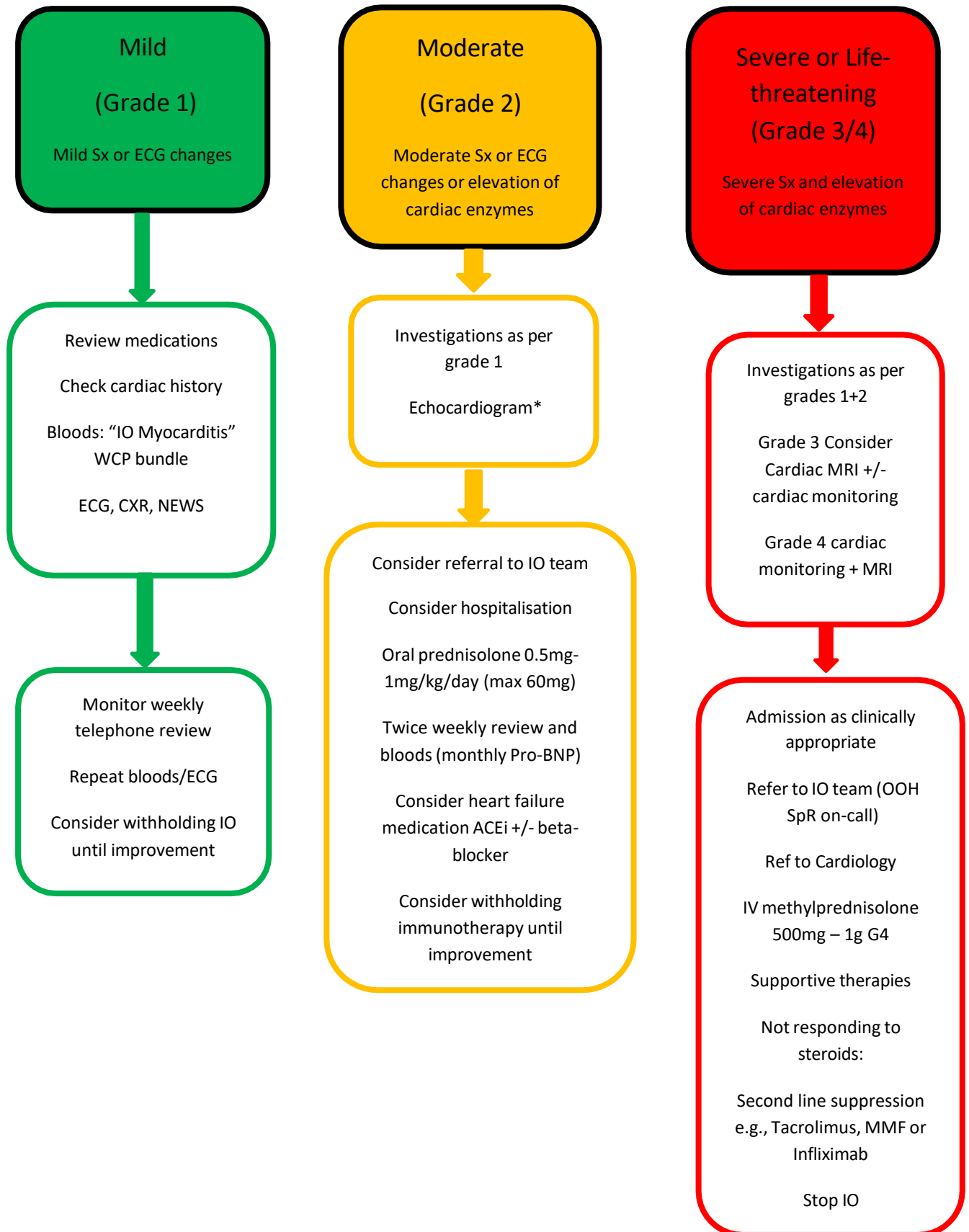
“IO Arthralgia/myalgia G2”

As per grade 1 plus:
Random Glucose
AST
Troponin
TFT
Cortisol
Plus MSU for Microscopy

Reviewed by Dr Ricky Frazer October 2022.

Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

Cardiac Quick Reference Pathway



Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

*Echocardiogram – ECHOs are done weekly on a Tuesday as an outpatient service at VCC.
Please email mark.jones@wales.nhs.uk

WCP PATHOLOGY TEST BUNDLES:

IO Myocarditis bundle:

FBC

RLB

CK

Troponin

NT-pro-BNP

*Add appropriate monitoring bloods for MMF (e.g., FBC) and Tacrolimus (drug levels)

IO BIOLOGICS: If considering biologic/second line immunosuppression.

FBC,

RLB

CMV PCR (blood - listed as viral opportunistic infection),

HBV, HCV, HIV (blood – listed as virology routine screen BBV)

Herpes Simples (blood – listed as Virology routine screen)

Varicella Zoster (VZV).

Rubella IgG

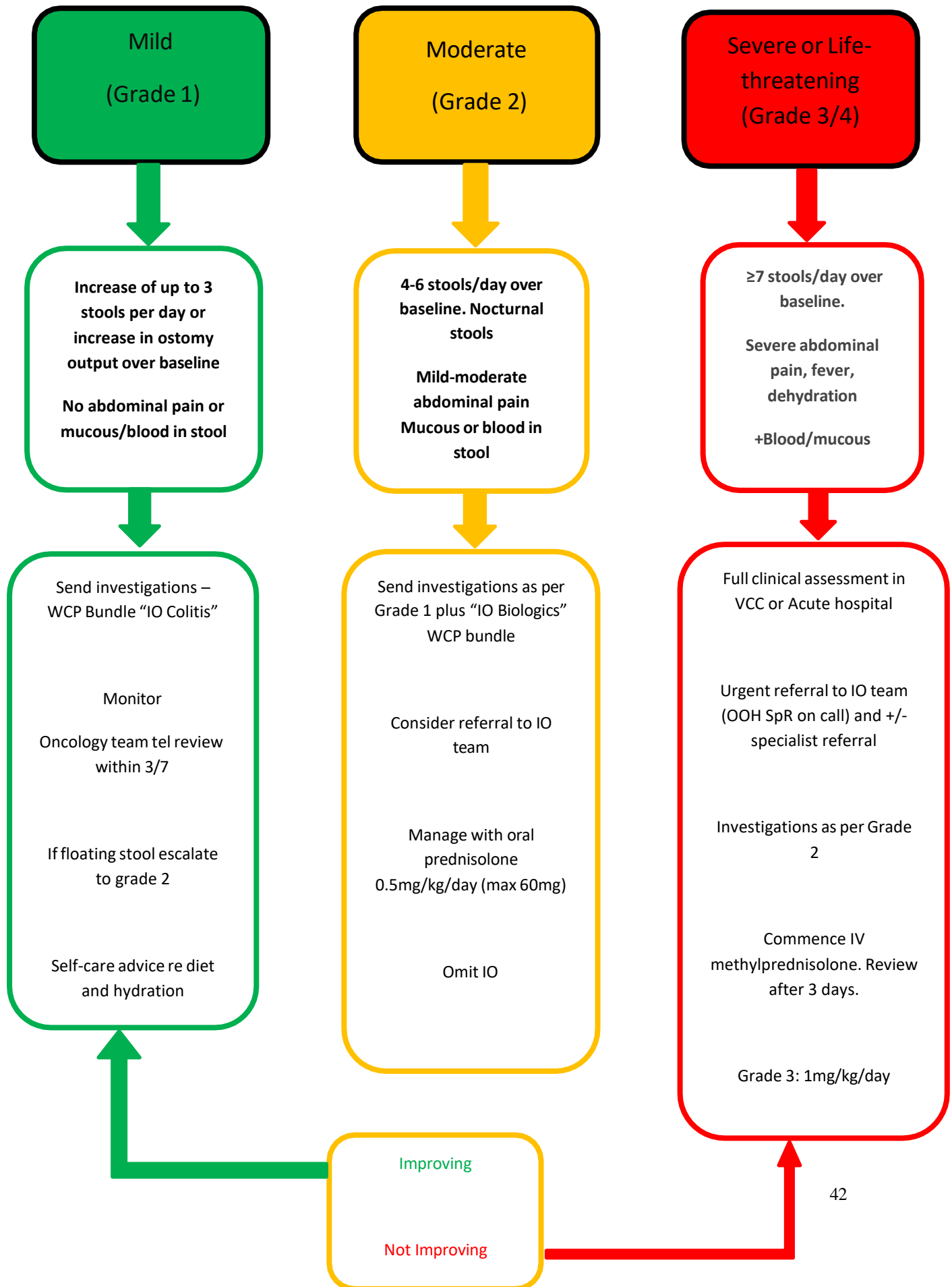
*Risk assess for TB – see full management guidelines.

Please refer patient to local LHB TB services for TB screening.

Reviewed by Ricky Frazer October 2022

Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

Diarrhoea and Colitis Quick Reference Pathway



Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

WCP PATHOLOGY TEST BUNDLES:

IO COLITIS:

FBC,

RLB,

TFT,

CORTISOL,

CRP,

Mg

Vit D

Stool culture MC&S (Request inclusion of C. Diff), faecal calprotectin and Elastase.

Consider Anti tTG antibodies for Grade 2 and above

PLEASE ADD CMV IF NOT SCREENING FOR BIOLOGICS

IO BIOLOGICS:

FBC,

RLB

CMV PCR (blood - listed as viral opportunistic infection),

HBV, HCV, HIV (blood – listed as virology routine screen BBV)

Herpes Simplex (blood – listed as Virology routine screen)

Varicella Zoster (VZV)

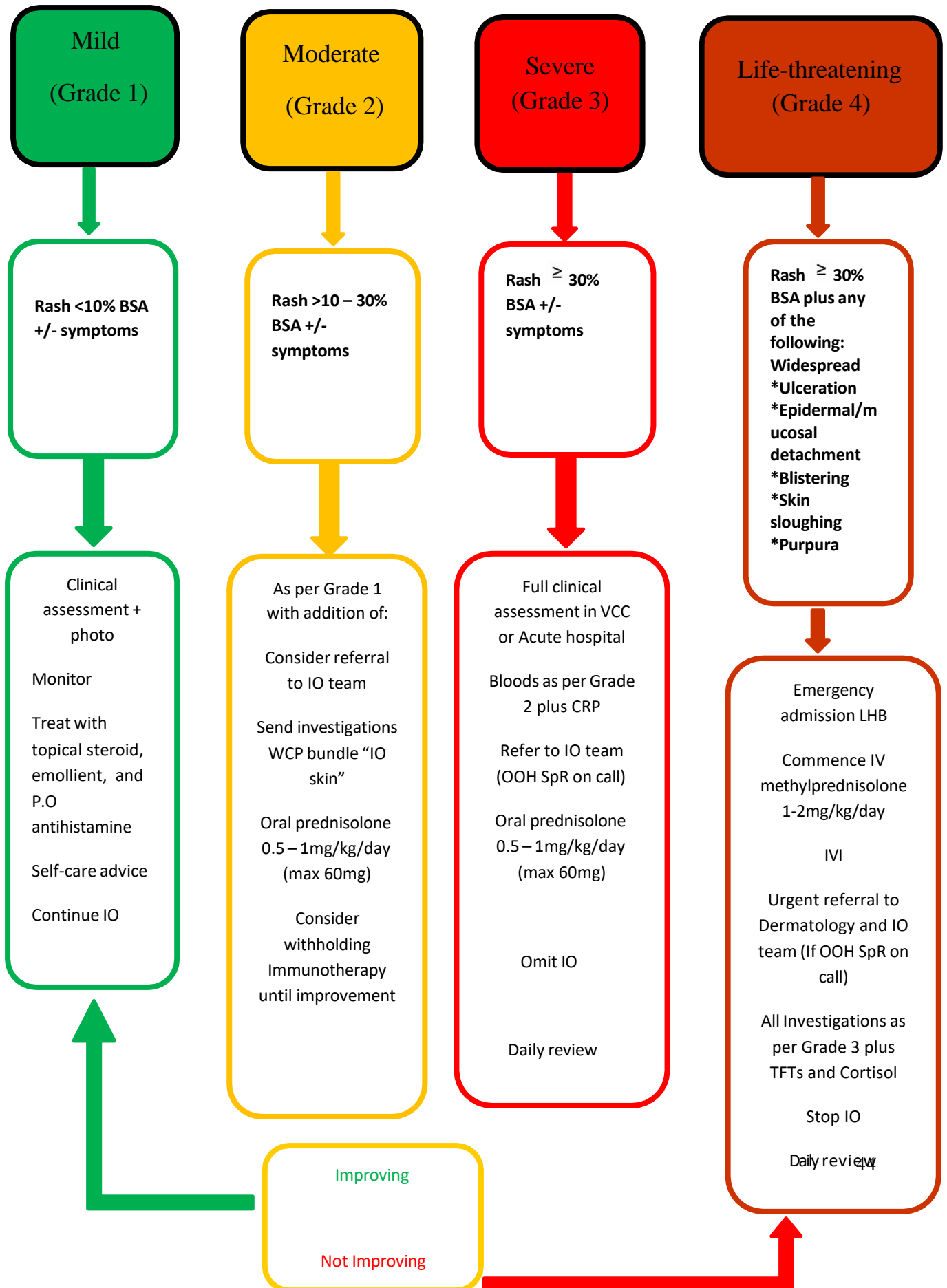
Rubella IgG

*Risk assess for TB – see full management guidelines.

Reviewed by Ricky Frazer October 2022

Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

Dermatitis Quick Reference Pathway



Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

WCP PATHOLOGY TEST BUNDLES:

IO Skin

FBC

U&E

LFT

Bone profile

Glucose (random)

For Grade 3 - IO skin bundle plus CRP

For Grade 4 – As per Grade 3 plus TFT

Reviewed by Dr Jo Ocen 03.08.2022 and Sharon Hulley Dermatology CNS UHW, September 2022. Reviewed by Ricky Frazer October 2022

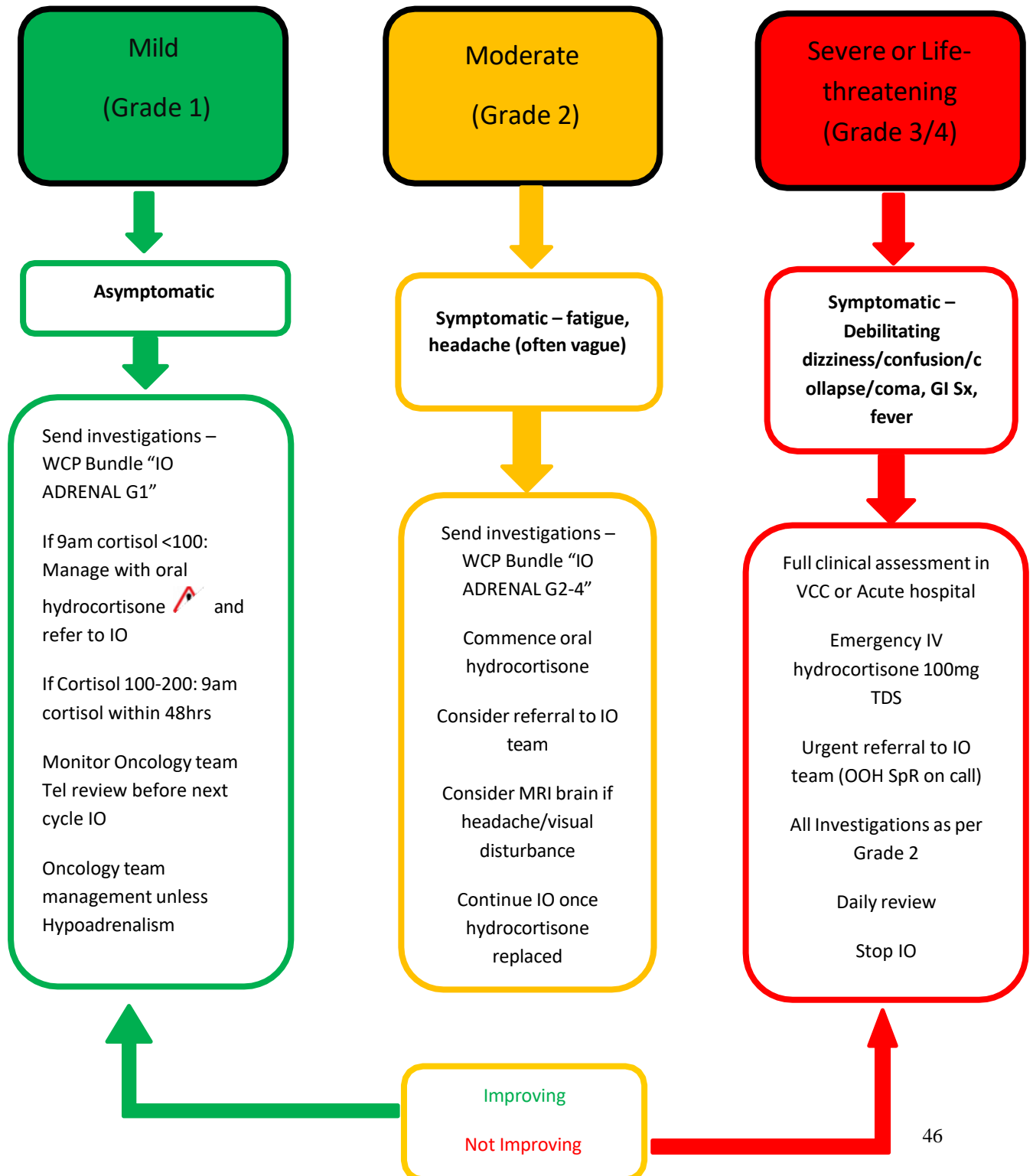
Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

Adrenal Crisis Quick Reference Pathway

Immunotherapy can cause several endocrinopathies that may present with nonspecific symptoms and may resemble other causes such as brain metastasis or underlying disease.



****CHECK CORTISOL prior to commencing thyroxine. If cortisol <100, initiate hydrocortisone for 48 hours then commence thyroid replacement**** Can be fatal if thyroid deficiency treated before treating low cortisol level.



Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

WCP PATHOLOGY TEST BUNDLES:

Please do not order a 9am cortisol if patient is on steroids (prednisolone/dexamethasone) as serum cortisol will be suppressed

IO Adrenal G1:

FBC,
RLB,
TFT,
Cortisol,
CRP,
Glucose (Random)
Mg
ACTH

IO Adrenal G2-4:

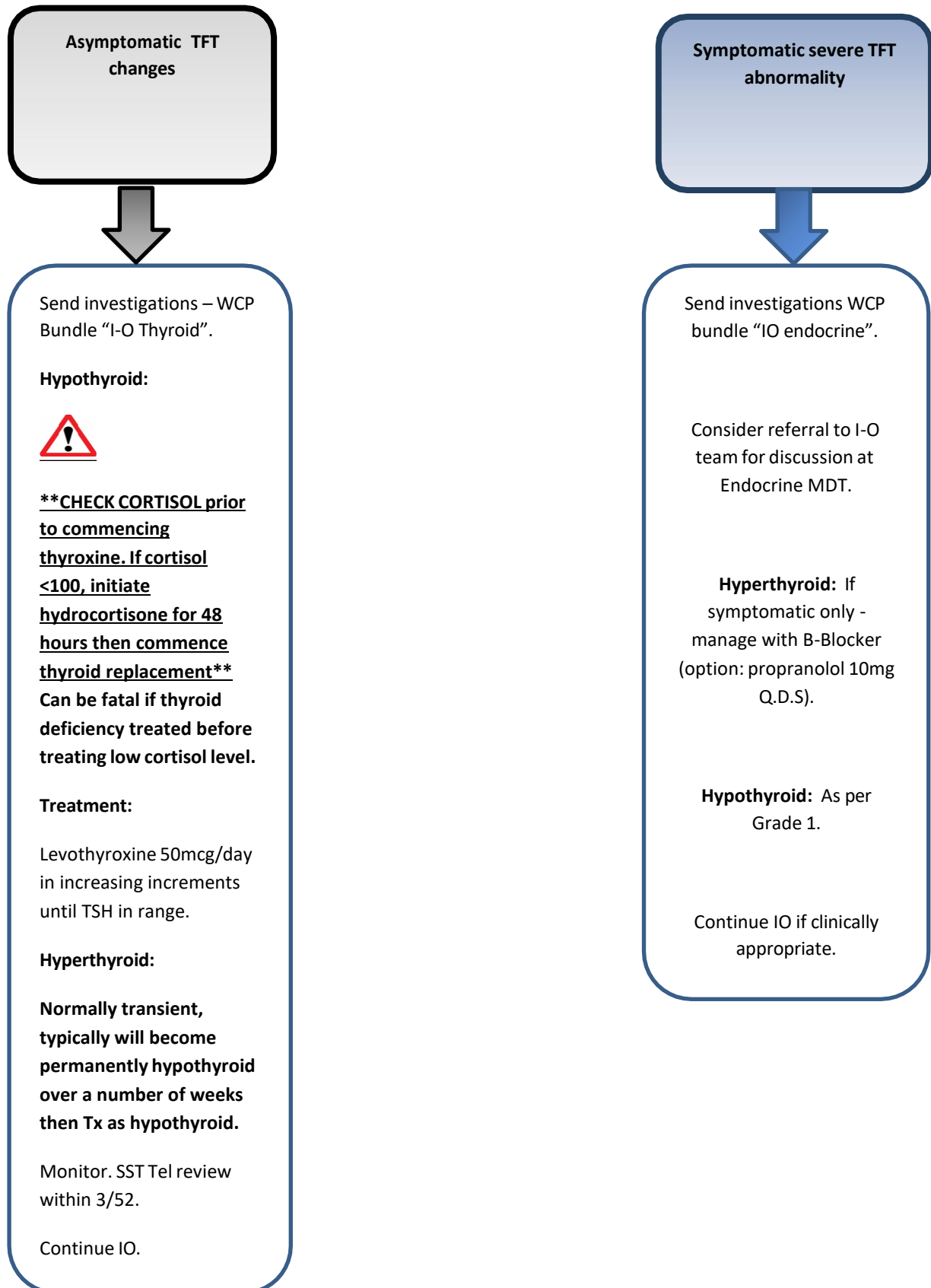
FBC,
RLB,
TFT,
Cortisol,
CRP,
Glucose (Random)
Mg
ACTH
LH
FSH
Prolactin
+/- Testosterone/Oestrodiol

Subsequent management will be undertaken by the IO team in the event of hypoadrenalism. On referral to the IO service patient will be discussed at the endocrinology MDT, and an SST will be arranged. Patients will be issued an emergency steroid card and enrolled in the adrenal insufficiency education workshop. In IO team correspondence back to site specific team, we will advise regarding ongoing endocrinology input.

Reviewed by Dr Andrew Lansdown September 2022 and Ricky Frazer October 2022

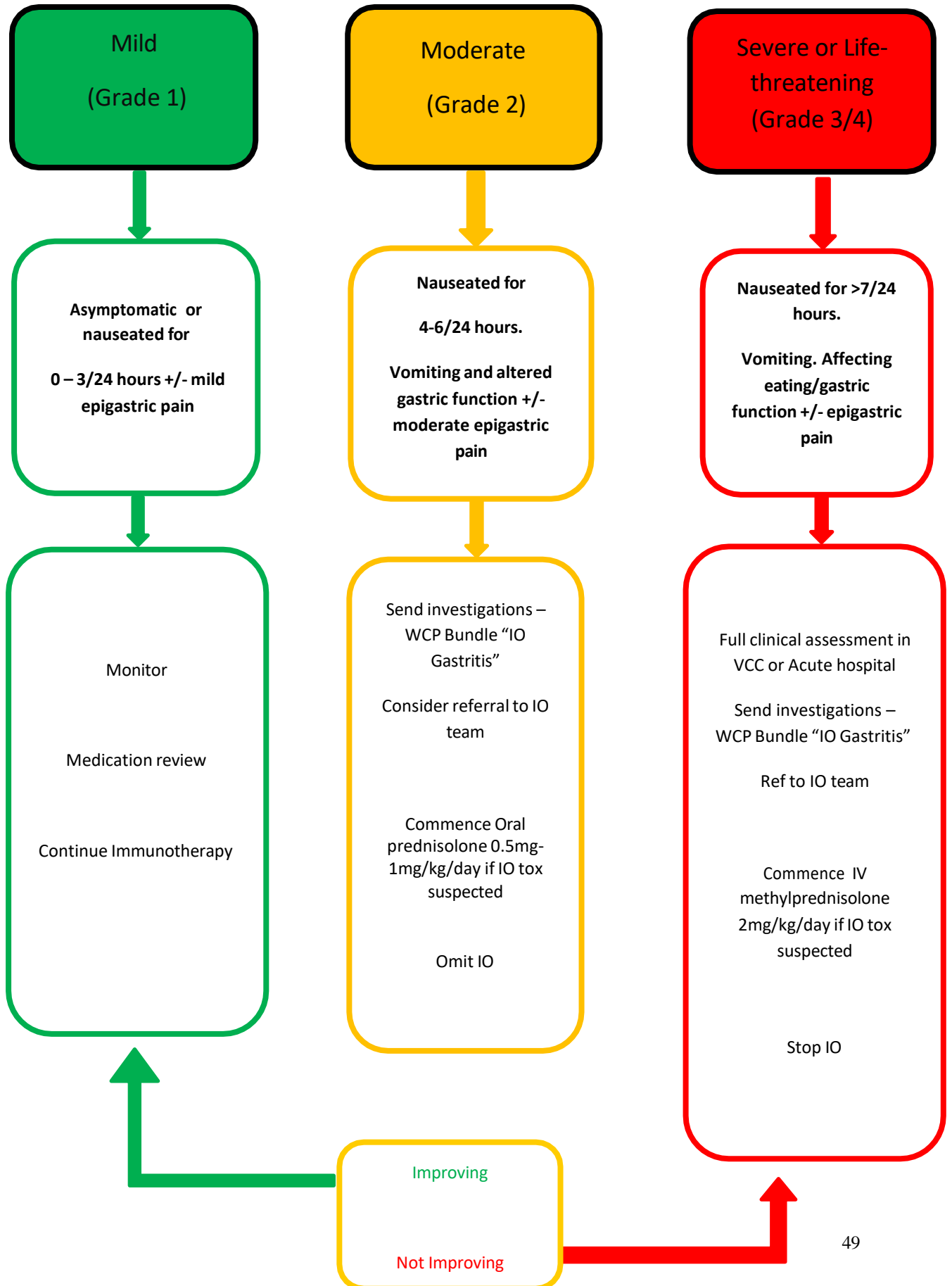
Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

Immune-Related Adverse Event: Endocrinopathies-Thyroid Dysfunction



Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

Gastritis Quick Reference Pathway



Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

WCP PATHOLOGY TEST BUNDLES:

“IO Gastritis”:

FBC

U & E’s

LFT’s

Blood glucose

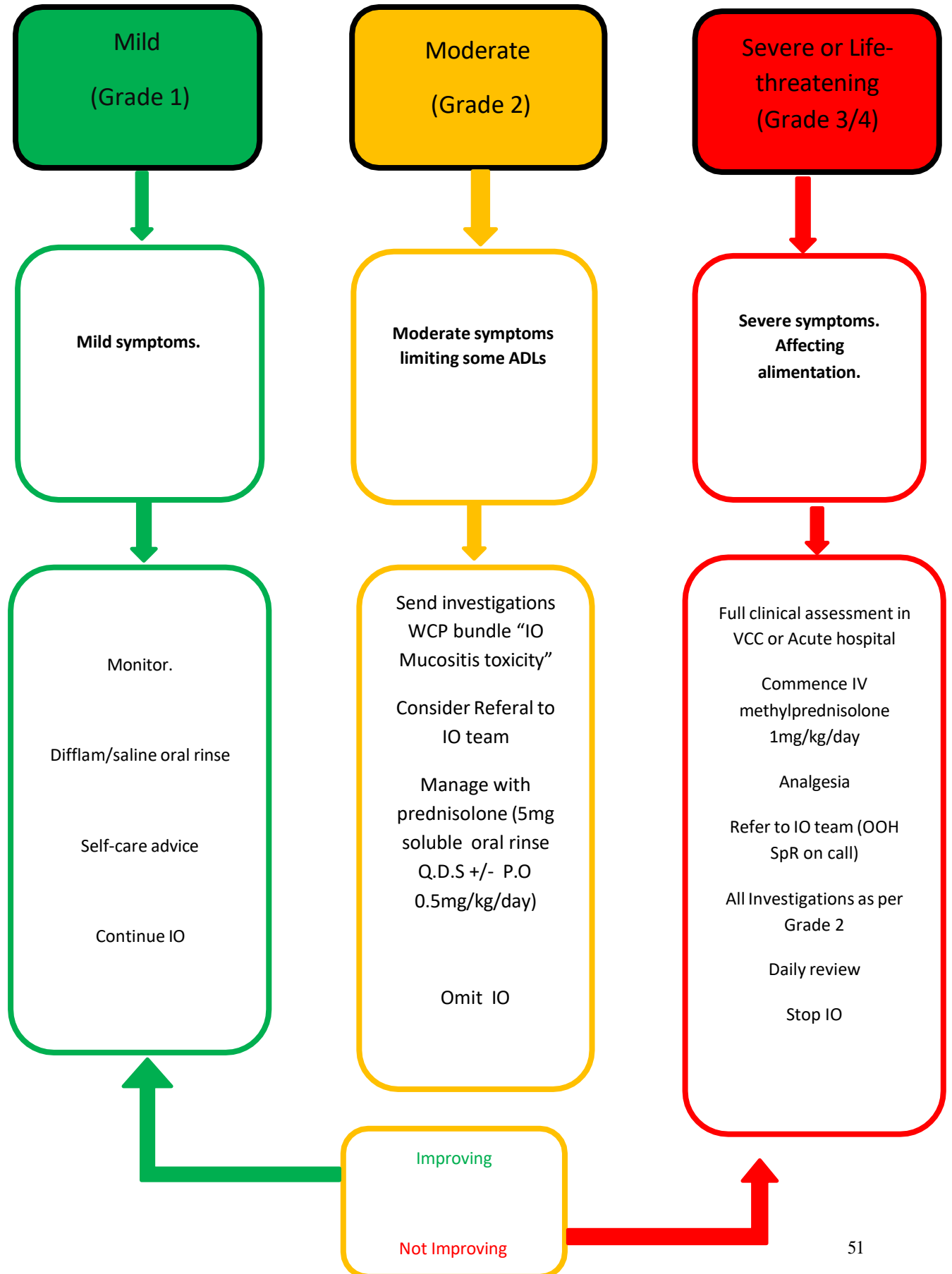
Cortisol if clinically indicated

TFT’s

Reviewed by Ricky Frazer October 2022

Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

Mucositis Quick Reference Pathway



Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

WCP PATHOLOGY TEST BUNDLES:

FBC

U&E

LFT

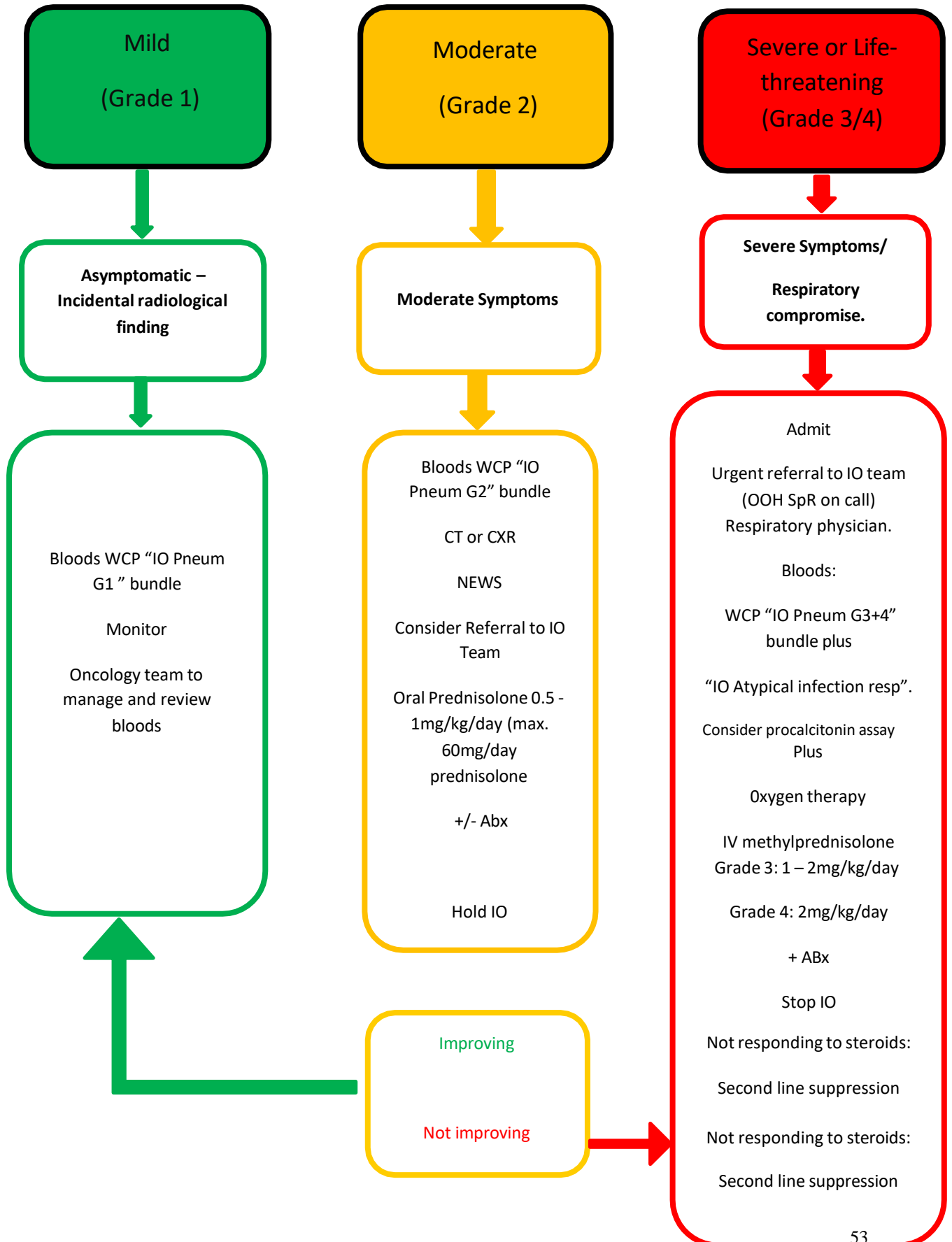
Bone profile

CRP

Reviewed by Ricky Frazer October 2022

Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

Pneumonitis Quick Reference Pathway



Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

WCP PATHOLOGY TEST BUNDLES:

IO Pneum G1:

FBC
RLB
ESR
CRP
LDH

IO Pneum G2:

FBC
RLB
ESR
CRP
LDH
Microbial Investigation (respiratory)

IO Pneum G3 + 4:

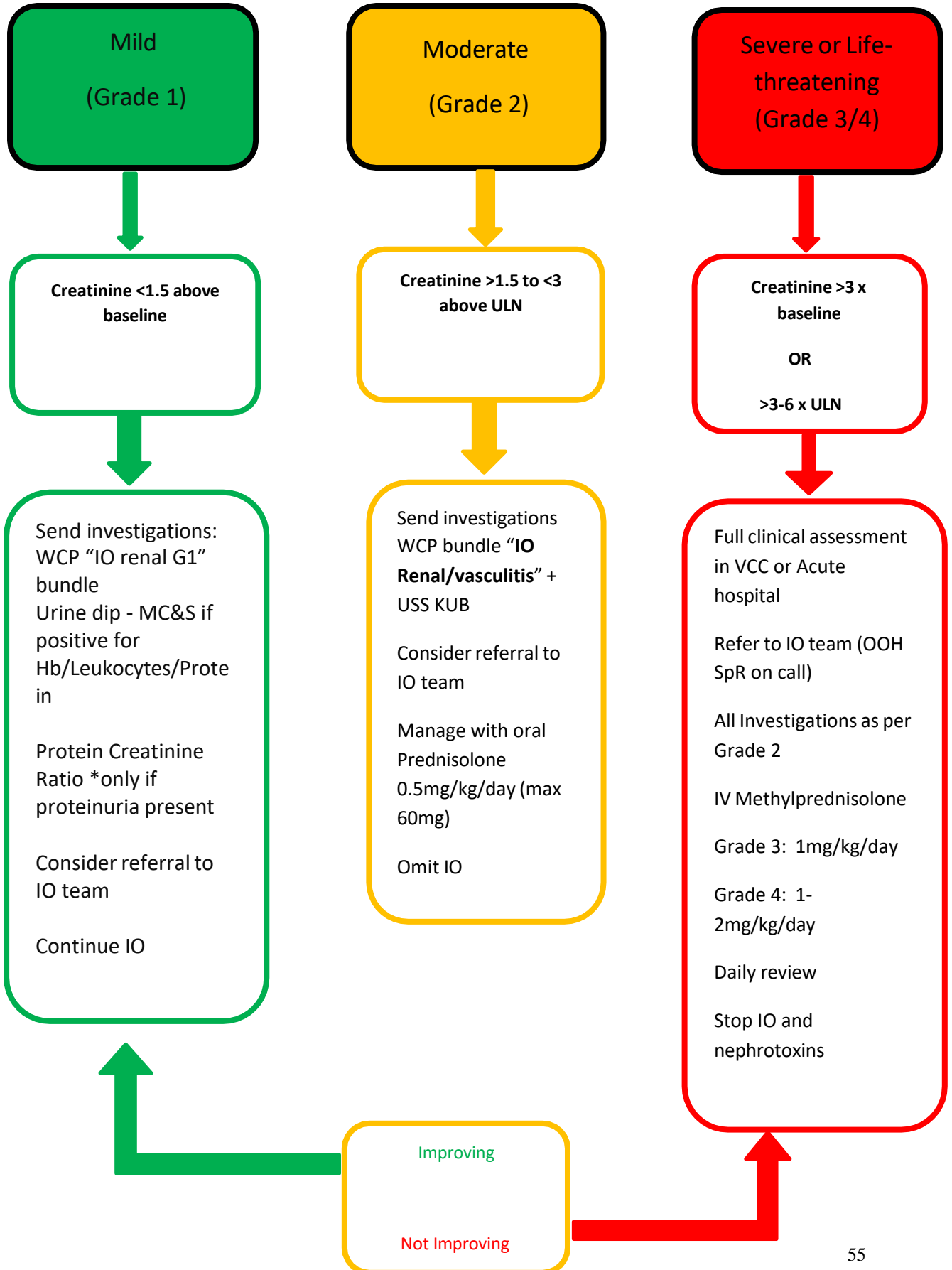
FBC
RLB
ESR
CRP
LDH
Microbial Investigation (respiratory)
Faecal microbial investigation
Virology routine screen HBV, HCV, HIV
Virology routine screen (Immunosuppression HSV)
If no PMHx of chicken pox or status unknown please add VZV virology (Handwritten virology form)

IO Atypical infection (resp). B-D-Glucan Serum
Microbiology legionella (Urine)
IgG Antibodies to pneumococcus (serum)
Microbial investigation – fungal/mycology (serum)
Virology Respiratory symptoms swab

Reviewed by Dr Jo Ocen September 2022 and Ricky Frazer October 2022

Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

Renal Quick Reference Pathway



Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

WCP PATHOLOGY TEST BUNDLES:

WCP Bundle “**IO Renal G1**”

U&E

VBG

If proteinuria, send PCR (Protein Creatinine Ratio)

Send MC&S urine if dipstick positive for blood, leukocytes, protein.

For Grade 2 and above:

IO renal/vasculitis

GFR

ANA,

Complement C3, C4

ANCA

Anti GBM,

IgGs,

Protein electrophoresis

Bence Jones protein

HIV, HEP B, C

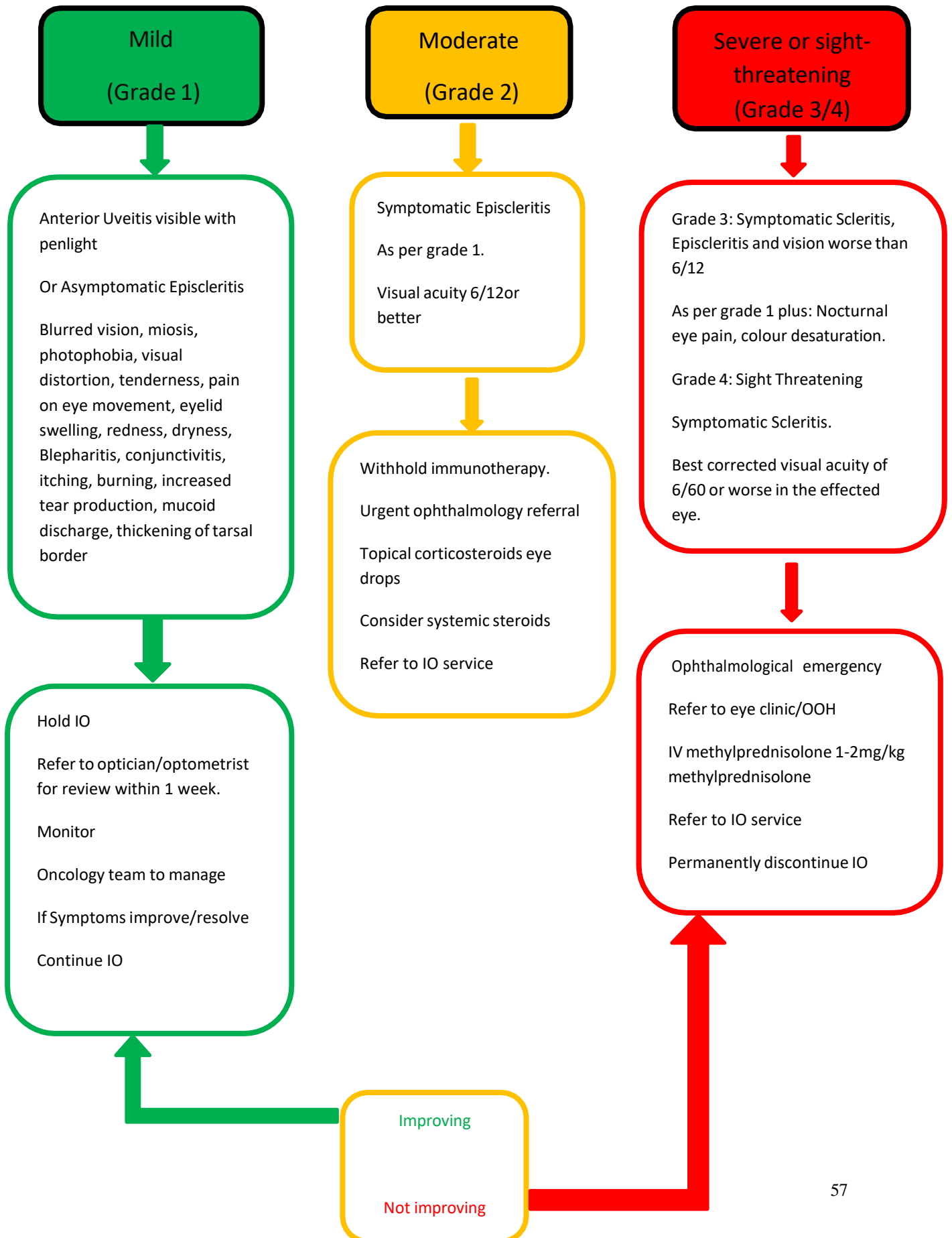
Urine MC&S

Protein Creatinine Ratio

Reviewed by Ricky Frazer October 2022

Guidance is on the assumption that symptoms are immunotherapy mediated. Other differentials exist for each toxicity therefore causation is based on clinical assessment.

Uveitis Quick Reference Pathway



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WCP PATHOLOGY TEST BUNDLES:

FBC
RLB
Random glucose
LFTs
TFT
ANA

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Infusion Reaction

There were isolated reports of severe infusion reactions in clinical trials. In case of a severe infusion reaction, treatment must be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive treatment with close monitoring. Premedication with antipyretic and antihistamine may be considered.

Drug Interactions

Corticosteroids

The use of systemic corticosteroids at baseline, before starting immunotherapy, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of treatment. However, systemic corticosteroids or other immunosuppressants can be used after starting immunotherapy to treat immune-related adverse reactions. The use of systemic corticosteroids after starting treatment does not appear to impair the overall efficacy.

Anticoagulants

The use of anticoagulants is known to increase the risk of gastrointestinal haemorrhage. Since gastrointestinal haemorrhage is an adverse reaction with immunotherapy, patients who require concomitant anticoagulant therapy should be monitored closely.

ECOG performance status

0	Fully active, able to carry out all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature
2	Ambulatory and capable of self care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair

Eastern Cooperative Oncology Group (ECOG)

	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhoea	Increase of up to 3 stools per day over baseline. (Mild increase in ostomy output)	Increase of 4-6 stools per day over baseline (moderate increase in ostomy output)	Increase of 7 or more stools per day over baseline, or incontinence or need for parenteral rehydration (severe increase in ostomy output)	Dehydration and collapse
Colitis	Asymptomatic; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	
Nausea	Nausea but able to eat almost as normal	Unable to eat normal amount but no significant weight loss	Eating and drinking almost nothing. Weight loss noticeable	Eating and drinking nothing.
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	6 or more episodes in 24 hours or need for parenteral rehydration	Dehydration and collapse or requiring parenteral nutrition
Rash	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 -30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL	-
Toxic epidermal necrosis		-	-	Skin sloughing covering $\geq 30\%$ BSA with associated symptoms (e.g., erythema, purpura, or epidermal detachment)

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	Grade 1	Grade 2	Grade 3	Grade 4
Stephens-Johnson syndrome		-	Skin sloughing covering <10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Skin sloughing covering 10 -30% BSA with associated signs (eg.erythema,purpura, epidermal detachment & mucous membrane detachment)
Dry skin	Covering <10% BSA and no associated erythema or pruritus	Covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Covering >30% BSA and associated with pruritus; limiting self care ADL	
Pruritis	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g.edema,papulation, excoriations,lichenification , oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self care ADL or sleep; oralcorticosteroid or immunosuppressive therapy indicated.	
Adrenal insufficiency	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Paraesthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting selfcare ADL	

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	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 selfcare ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
Hepatitis	ALT <3.0 x ULN Bilirubin: <1.5 x ULN	AST or ALT >3-<5x ULN Bilirubin >1.5-<3 xULN	AST or ALT >5x ULN Bilirubin >3 xULN	ALT: >20.0 x ULN Bilirubin: >10.0 x ULN
Acute kidney injury	Creatinine level creatinine 1.5 - 2.0 x above baseline	Creatinine 2 - 3 x above Baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated

Based on NCI-CTCAE v5

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