Guidelines for Management of Immunotherapy-Related Adverse Events

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

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

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

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

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

Steroid taper guidance

Length of steroid taper is dictated by severity of the irAE.
Guidance on the recommended length of taper can be found in each pathway.
Regular monitoring during tapering is advised, as there is a risk of irAE recurrence.
For out-patients, the options are:

- to emphasise to the patient to telephone if ANY new symptom or worsening symptom, **and** to monitor in clinic at least every 2 weeks
  or
- to pro-actively monitor by telephone, once or twice weekly, throughout the taper.

Tapering guidance:

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

While on steroids, regular random blood glucose monitoring is required

- pre-existing diabetes may require escalation in oral hypoglycaemic agents or insulin
- if new hyperglycaemia is detected, manage accordingly; endocrinology advice may be sought

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

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

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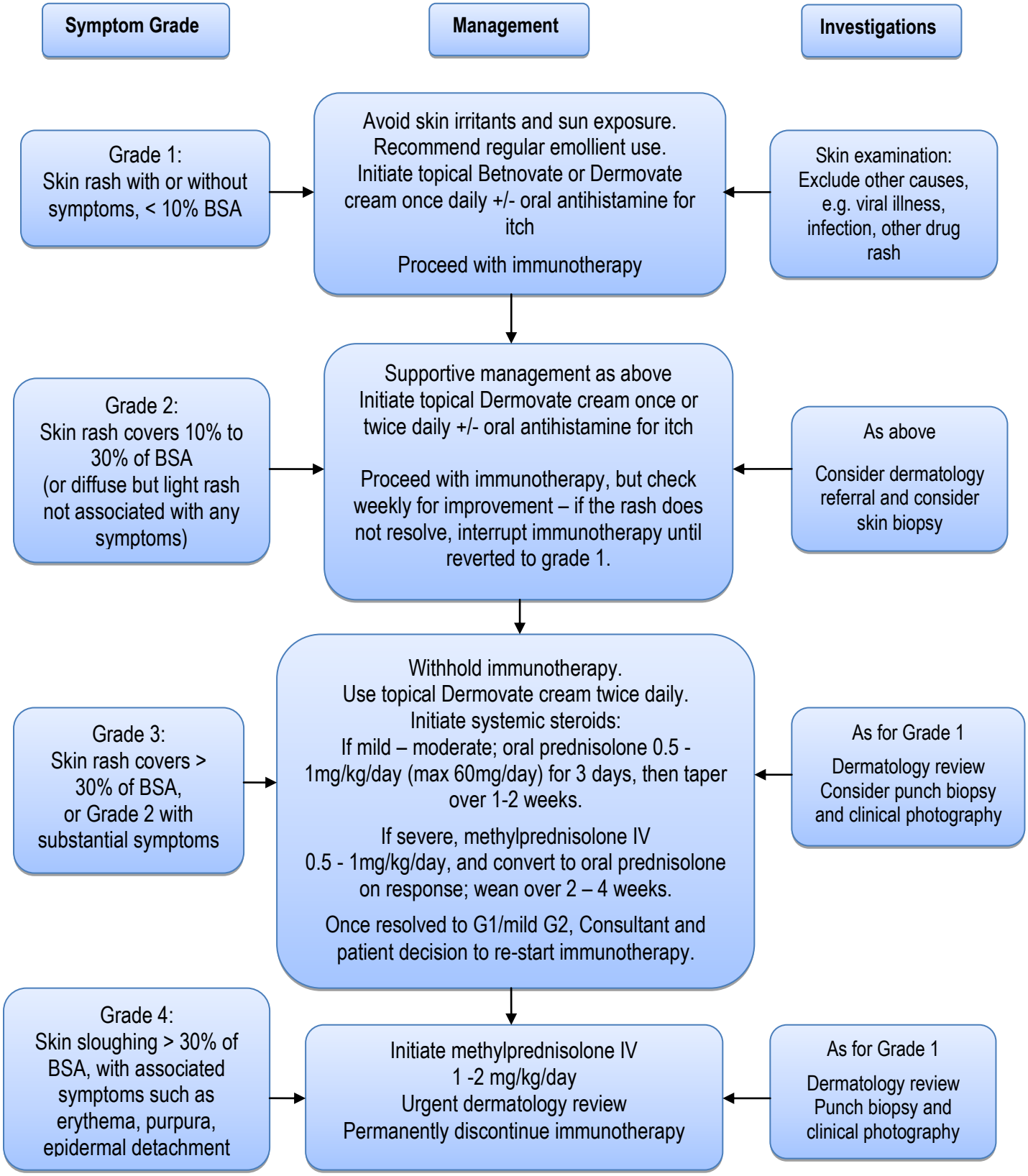
Supersedes: information included in individual immunotherapy protocols	Review Date: October 2019
Prepared by: S Taylor	Checked by: Dr M Ajaz

Immune-related Skin Toxicities

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



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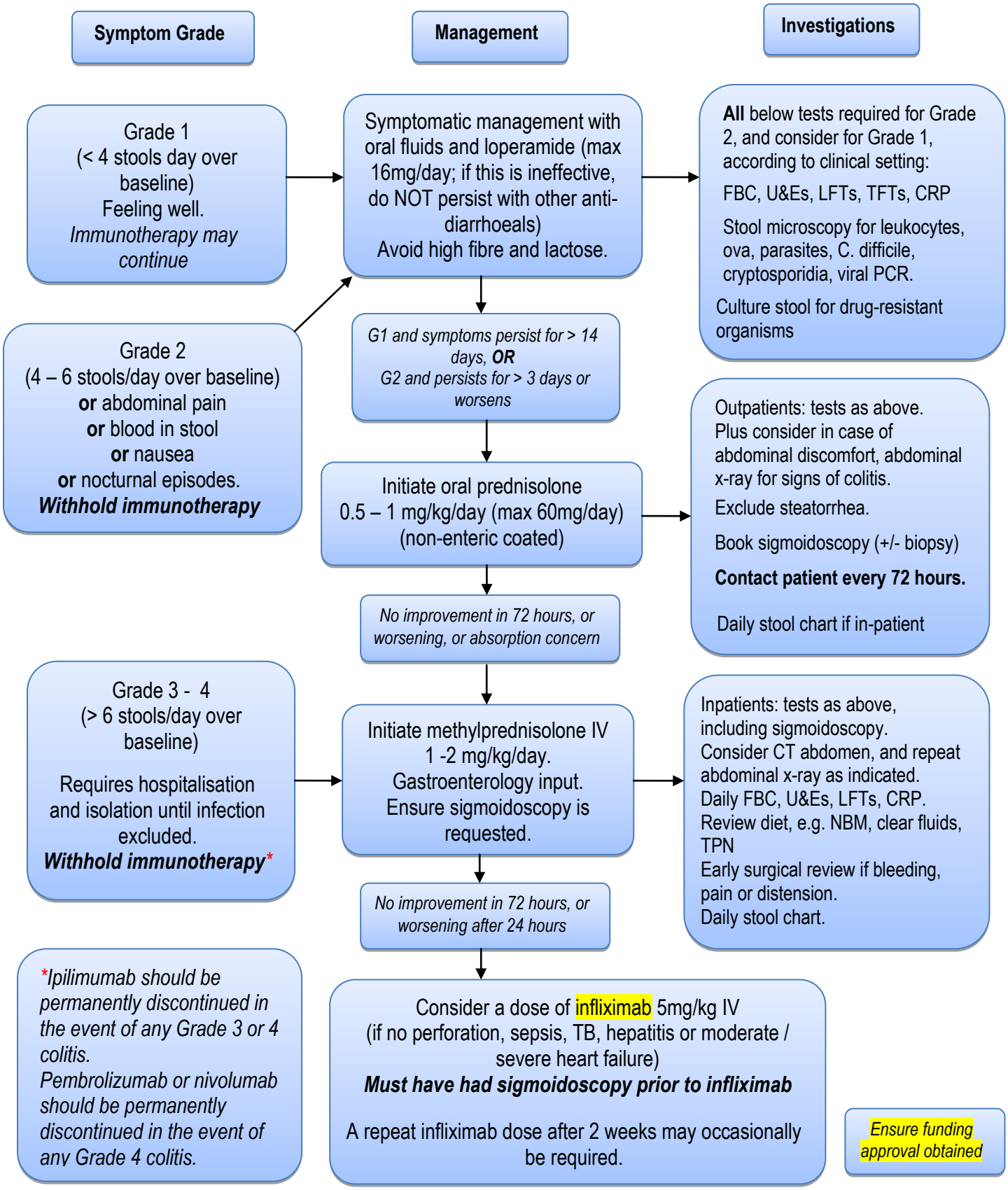
Immune-related Colitis



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

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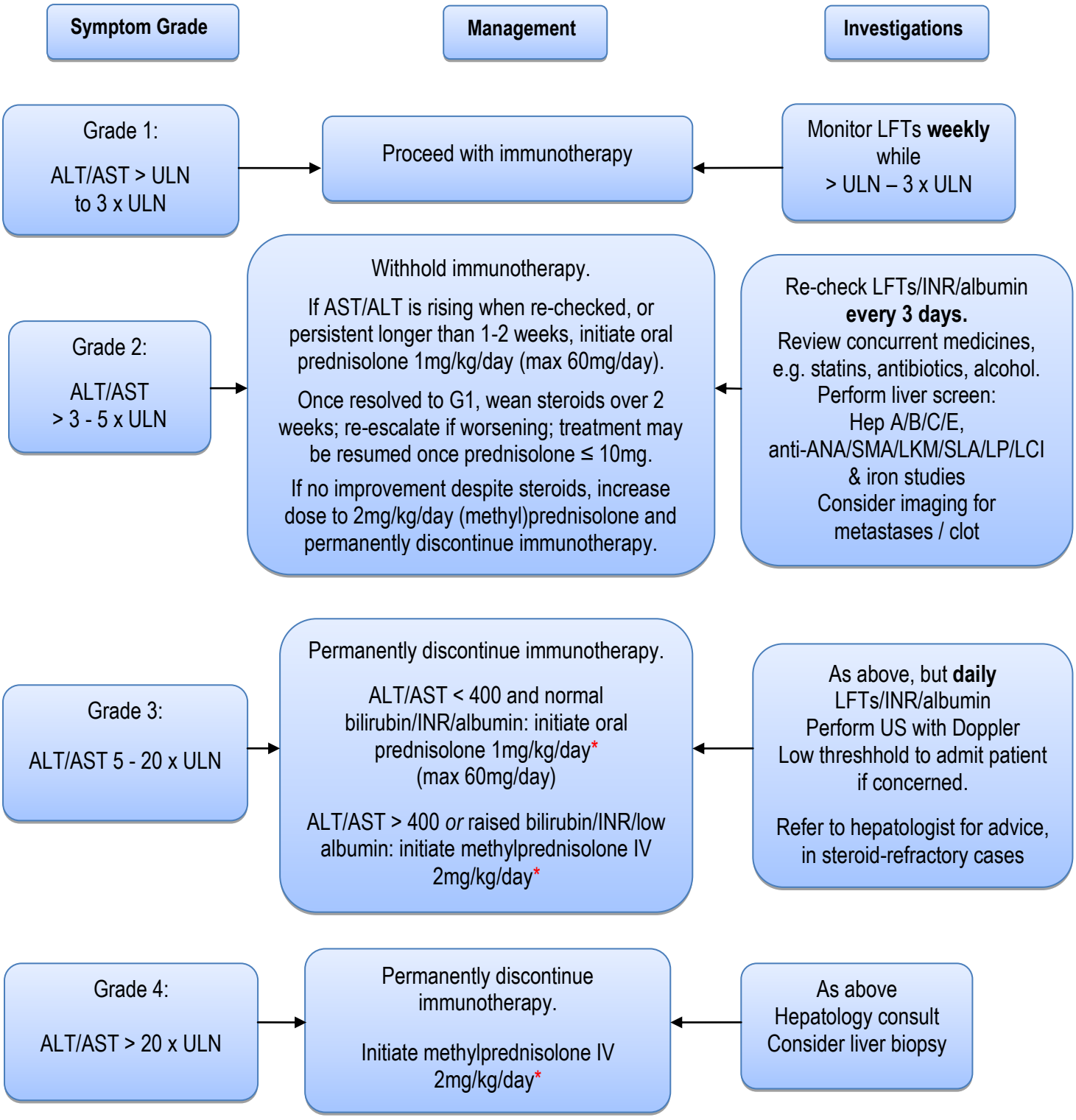
Immune-related Hepatitis



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

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Immune-related Endocrinopathies

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

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

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

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

Note that subclinical hyperthyroidism (low TSH, normal T_4) often precedes overt hyp**o**thyroidism.

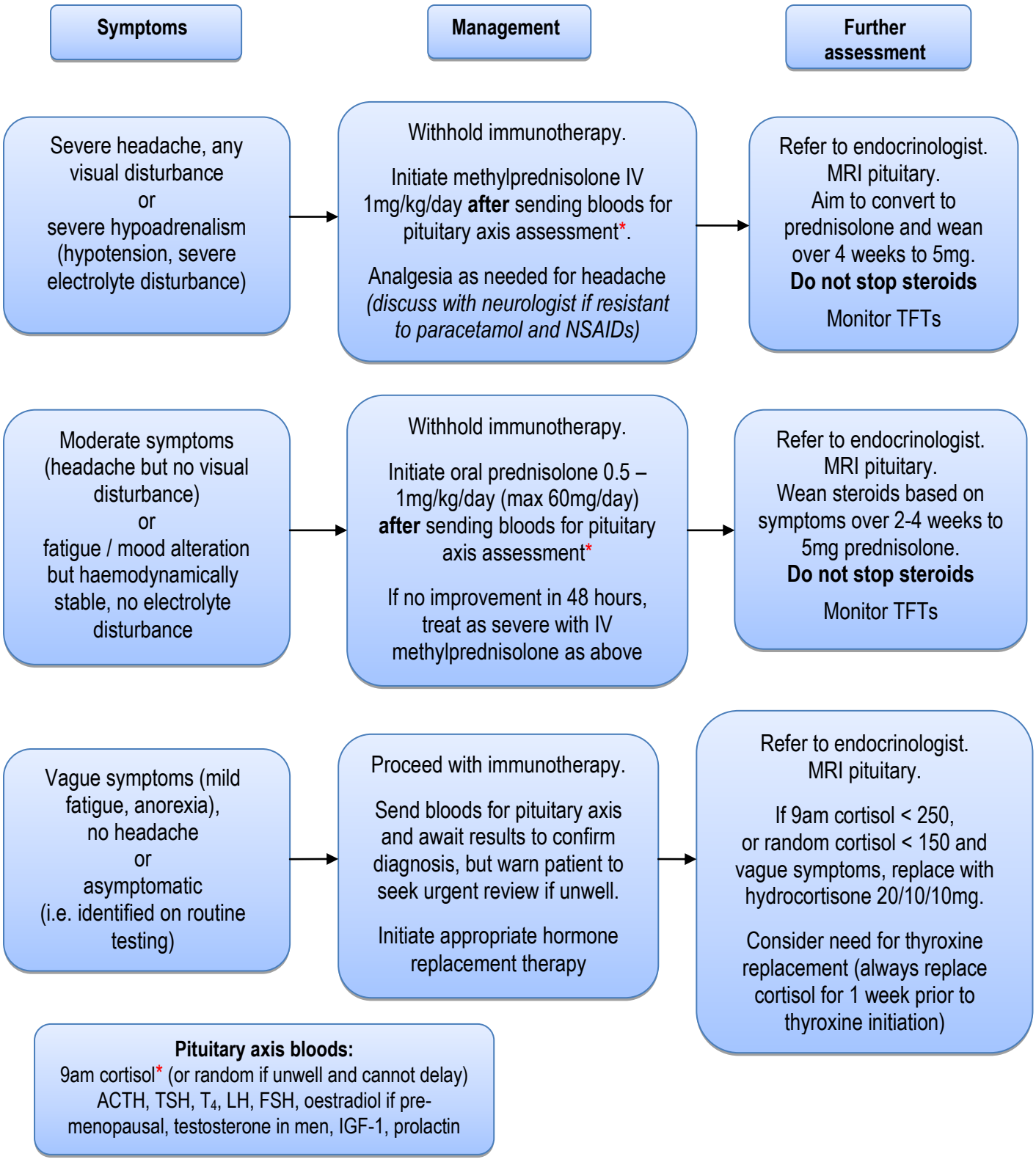
Withhold immunotherapy if patient is unwell with symptomatic hyperthyroidism.
Refer to endocrinologist.
If painful thyroiditis, consider prednisolone 0.5mg/kg/day (max 60mg/day) and then taper.

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

Diabetes: The emergence of either Type 1 or Type 2 diabetes occurs in < 1% of patients treated with immune checkpoint inhibitors.
Steroids will negatively influence diabetic control, and it is unclear whether they will prevent total loss of beta cells in the islands of Langerhans, so they are not routinely recommended in this setting.
Withhold immunotherapy until diabetic control has been achieved.

Immune-related Hypophysitis

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



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

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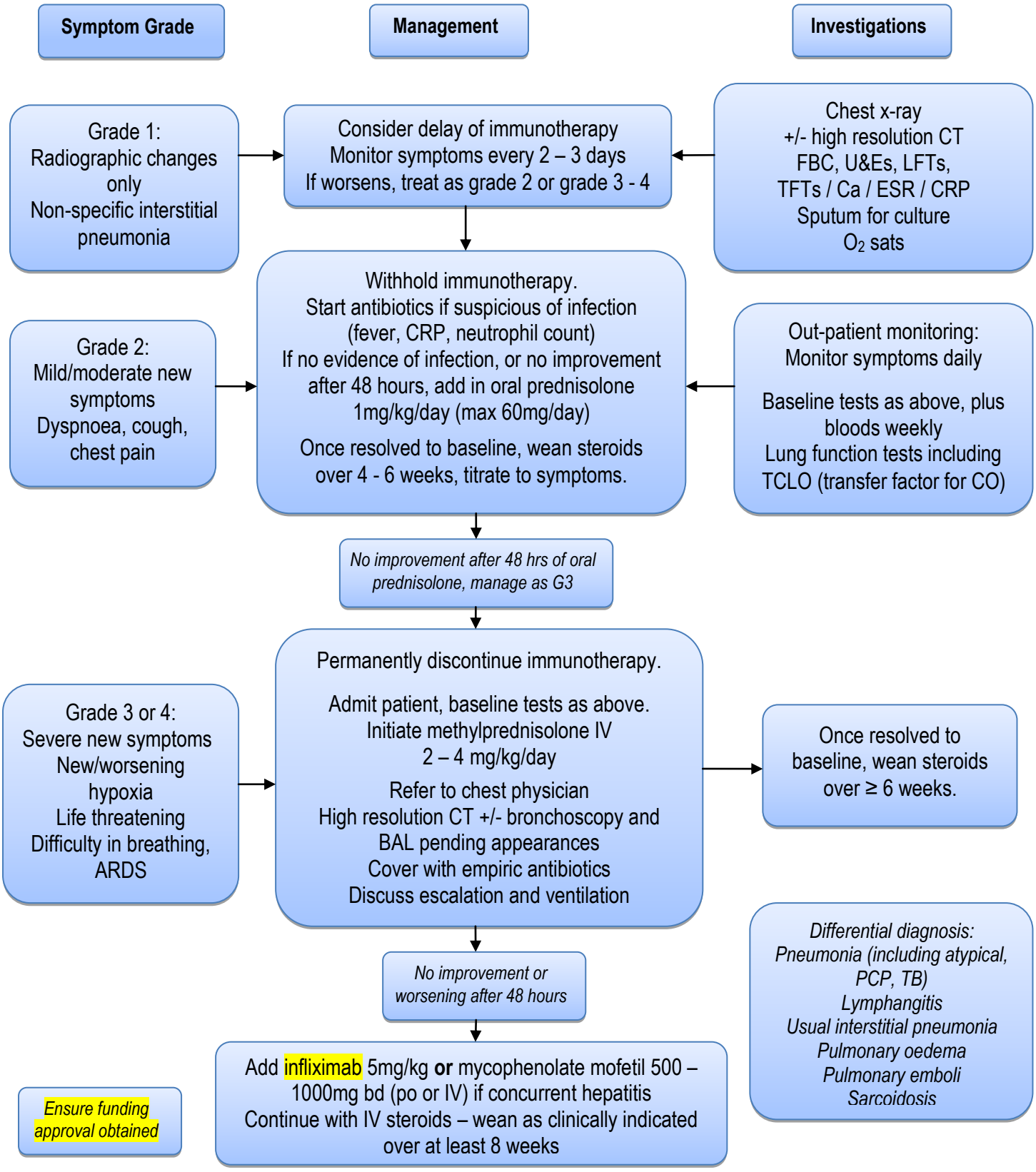
Immune-related Pneumonitis

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



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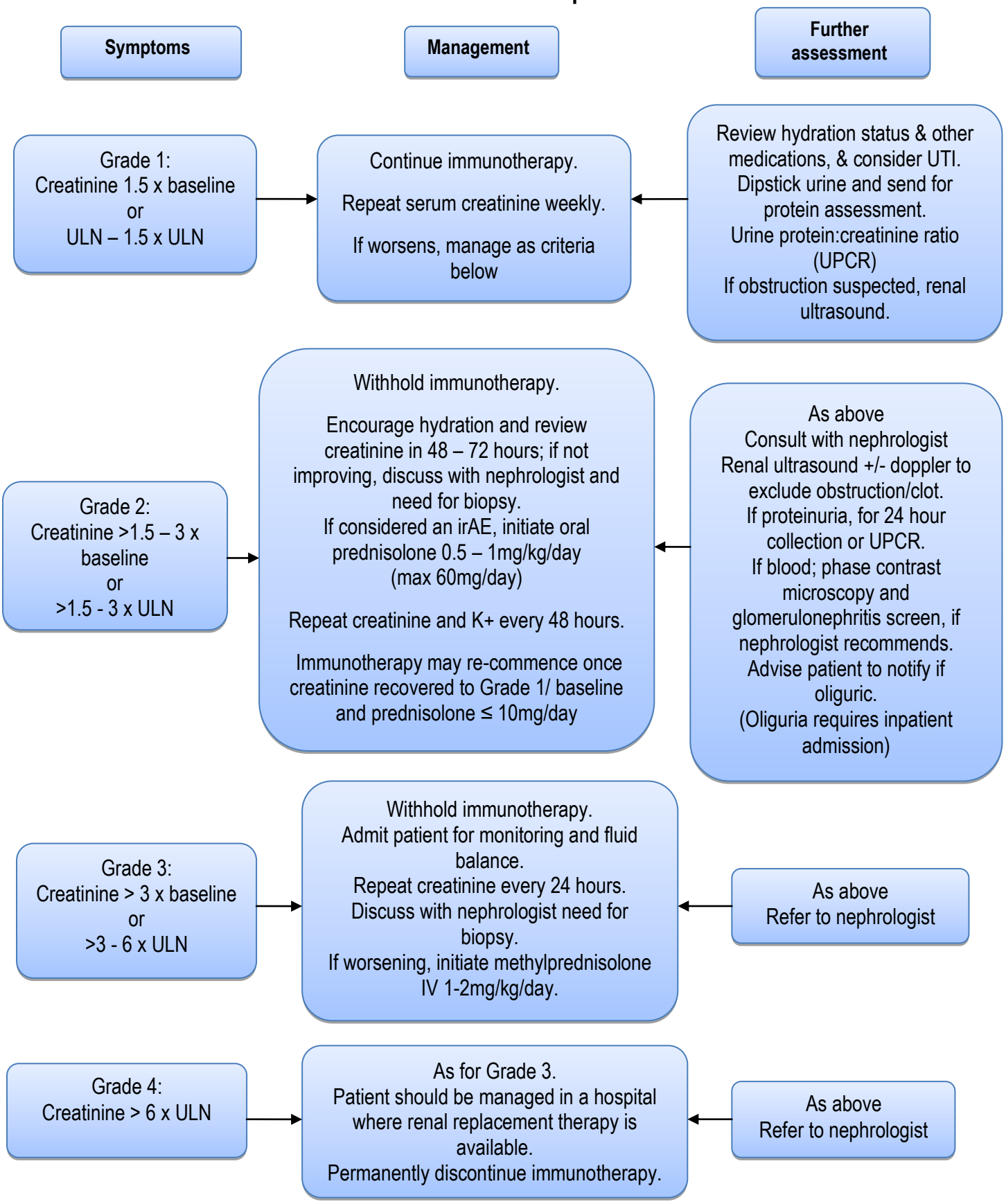
Immune-related Nephritis



Steroid wean: Begin to wean once resolved to Grade 1. For G2 severity, wean over 2-4 weeks. For G3/4 episode, wean over ≥4 weeks.

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Immune-related Neurological Toxicities

A range of neurological events have been described, including polyneuropathy, facial nerve palsy, myasthenia gravis, Guillain Barré syndrome, encephalitis and aseptic meningitis.
It is important to rule out progression of the cancer, infection, or other medications as the cause of the symptoms.

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Guillian-Barré Syndrome

Progressive symmetrical muscle weakness with absent or reduced tendon reflexes.
Refer to neurologists for specialist input.

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

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

Myasthenia Gravis

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

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

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

Aseptic meningitis

Exclusion of infective causes paramount.

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

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

Encephalitis

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

Exclude bacterial and ideally viral infections prior to high-dose steroids.
Oral prednisolone 0.5 – 1mg/kg/day (max 60mg/day) or methylprednisolone IV 1-2mg/kg if very unwell.
Concurrent IV aciclovir suggested until PCR result obtained.

Transverse myelitis

Acute or subacute neurological symptoms/signs of motor/sensory/autonomic origin.
Refer to neurologists for specialist input.

Suggested investigations:
MRI brain and spine; lumbar puncture; serum B_{12}/HIV/syphilis/ANA/anti-Ro and anti-La Abs; TSH; anti-aquaporin-4 IgG

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

Other Immune-related toxicities

a) Cardiac

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

b) Rheumatology

Mild or moderate myalgia and/or arthralgia occurs in 2-12% of patients.
For mild or moderate symptoms, analgesia with paracetamol and/or NSAIDs is recommended.
Continue immunotherapy.

If moderate symptoms are inadequately controlled with NSAIDs and/or paracetamol, initiate prednisolone 10-20mg once daily, and withhold immunotherapy until prednisolone ≤ 10mg /day.

If severe symptoms, refer to a rheumatologist, withhold immunotherapy and consider high dose corticosteroids.

c) Ocular

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

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

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