A Clinical Guideline for the Management of Immunotherapy Toxicity

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A Clinical Guideline for Immunotherapy

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A Clinical Guideline for Immunotherapy

Version and Document Control:

Version No.	Date of Update	Change Description	Author
1	May 2020 18.09.20	New Document MS - + minor changes (frequency of treatment)	Dr David Maskell
2	Sep 2021	Review and update by Dr Maskell. Format changes and flowcharts updated	Dr David Maskell

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Objective/s

The aim of this document is to provide standardised recommendations for the management of immune-mediated side effects caused by immune checkpoint inhibitors (iCPIs), also known as immunotherapy. These drugs are used as systemic anti-cancer treatment (SACT) in oncology.

We hope this will ensure timely and appropriate treatment of our patients who can present with complex medical problems attributable to their cancer treatment.

Rationale

The use of iCPIs in the oncology world has rapidly increased and with this so too has the frequency of immune-mediated side effects, which are very different from the classical side effects we see with other cancer treatments such as cytotoxic chemotherapy.

These guidelines are based upon recommendations by European Society of Medical Oncology (ESMO) which are widely adopted across the UK and in Europe. There has also been trust-wide consultation with other specialities to gain their opinion on the management of specific presentations.

Scope

These guidelines cover the management of patients treated with iCPIs. These drugs include:

- CDLA-4 monoclonal antibodies – Ipilimumab
- PD-1 monoclonal antibodies – Pembrolizumab, Nivolumab and Cemiplimab
- PDL1 monoclonal antibodies – Atezolizumab, Durvalumab and Avelumab

These drugs are currently being used in the treatment of melanoma, squamous cell carcinoma of skin and head and neck, merkel cell carcinoma, renal cell carcinoma, bladder cancer and non-small cell lung cancer. The list of indications is growing rapidly and these drugs are likely to be used in other solid malignancies in the future.

Processes to be followed

Please see Pages 6-19

Background

Immune checkpoint inhibitors (ICPIs) are systemic anti-cancer drugs that can result in *immune-related* adverse effects. The most common being:

Skin rashes	Page 5
Diarrhoea and colitis	Page 6
Hepatitis	Page 7
Pneumonitis	Page 8
Endocrinopathies	Page 9,10,11,12,
Neurological toxicity	Page 13,14,15,
Renal toxicity	Page 16
Arthralgia	Page 17

These guidelines set out to assist clinicians in the management of these common immune related toxicities. It is essential that symptoms are identified early and treated appropriately to prevent excessive morbidity or mortality. The cornerstone of management is with high dose corticosteroids which suppresses T-cell activation to control the inflammatory reaction. Early involvement with the relevant specialties is also encouraged.

It is important to consider that although a lot of these side effects tend to manifest whilst patients are on treatment, others can present with symptoms weeks or months after stopping treatment.

For all iCPI associated toxicity please score using the NCI CTAE v4 adverse event grading criteria and follow guidelines outlined below.

For all patients who experience toxicity secondary to iCPIs please contact the acute oncology service (AOS) on ext 6799 for advice.

These guidelines have been based upon consensus clinical practice guidelines published by ESMO in 2017. For more comprehensive details please refer to full article found through the hyperlink below:

https://www.esmo.org/Guidelines/Supportive-and-Palliative-Care/Management-of-Toxicities-from-Immunotherapy

Monitoring compliance

All grade 3 and 4 toxicity will be recorded by the AOS. There will be yearly review of the management of these patients within an immunotherapy working group and review of the guidelines.

Summary of development and consultation process undertaken before registration and dissemination

Guidelines put together by Dr David Maskell (Consultant in Clinical Oncology) based upon ESMO guidelines and other peer reviewed resources. These guidelines were sent to relevant medical specialties and amendments made based on this feedback Amended guidelines reviewed by Dr Jenny Nobes (Consultant Clinical Oncologist) and Dr Gill Gray (Consultant Medical Oncologist).

The first Trust Document version of this document had been given Chair interim approval for six months by the Clinical Guidelines Assessment Panel during the covid-19 pandemic. Approved by Chemotherapy Review Board on 26 11 2021; waiting for approval by the Medicines Committee.

References

J. Haanen, F. Carbonnel, C. Robert, K. Kerr, S. Peters, J. Larkin and K. Jordan Management of the Toxicities from Immunotherapy : ESMO Clinical Practice Guidelines. Ann Oncol (2017) 28 (suppl 4): iv119–iv142.

C Higham, A Olsson-Brown, P Carroll. Acute management of the endocrine complications of checkpoint inhibitor therapy, *Endocrine Connections*, *7*(7), G1-G7

Immune related skin reactions

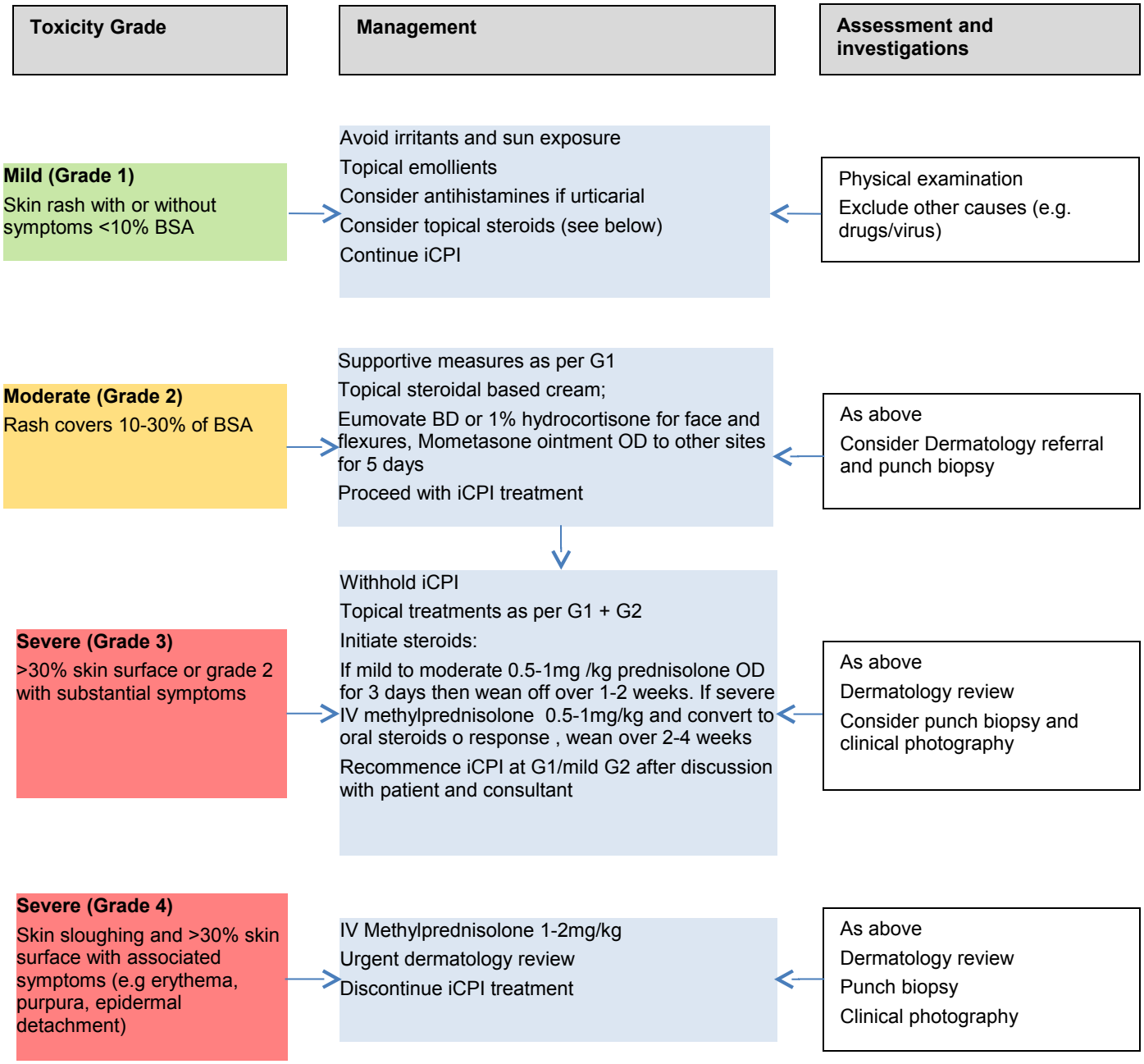


Figure 1. ICPi-related toxicity: management of skin rash/toxicity. Recognised skin AEs include: (i) most common: erythema, maculopapular and pustulopapular rash; (ii) rare: toxic epidermal necrolysis, Steven-Johnson syndrome and DRESS; (iii) vasculitis may also be present with purpuric rash.AE, adverse event; bd, twice daily; BSA, body surface area; DRESS, drug rash with eosinophilia and systemic symptoms; iCPI, immune checkpoint inhibitor; i.v., intravenous; od, once daily.

Management of immunotherapy induced diarrhoea and colitis

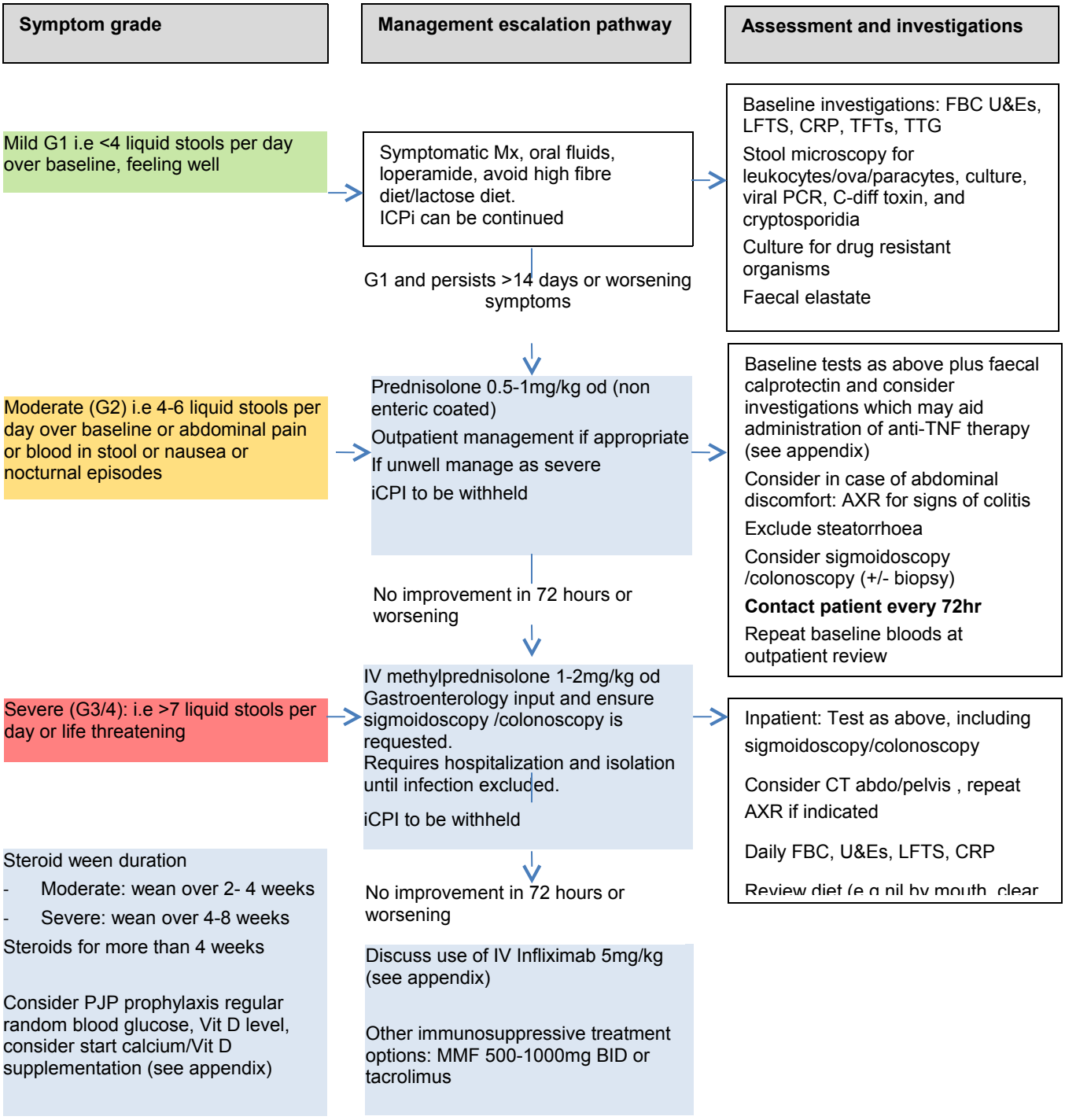


Fig 2. ICPi-related toxicity: management of diarrhoea and colitis. bd, twice daily; CHF, congestive heart failure; CRP, C-reactive protein; CT, computed tomography; FBC, full blood count; iCPI immune checkpoint inhibitor; i.v. intravenous; LFT, liver function test; MMF, mycophenolate mofetil; Mx, management;; TFT, thyroid function test; TPN, total parenteral nutrition; UEC, urea, electrolytes, creatinine; VitD, vitamin D.

Management of Hepatitis

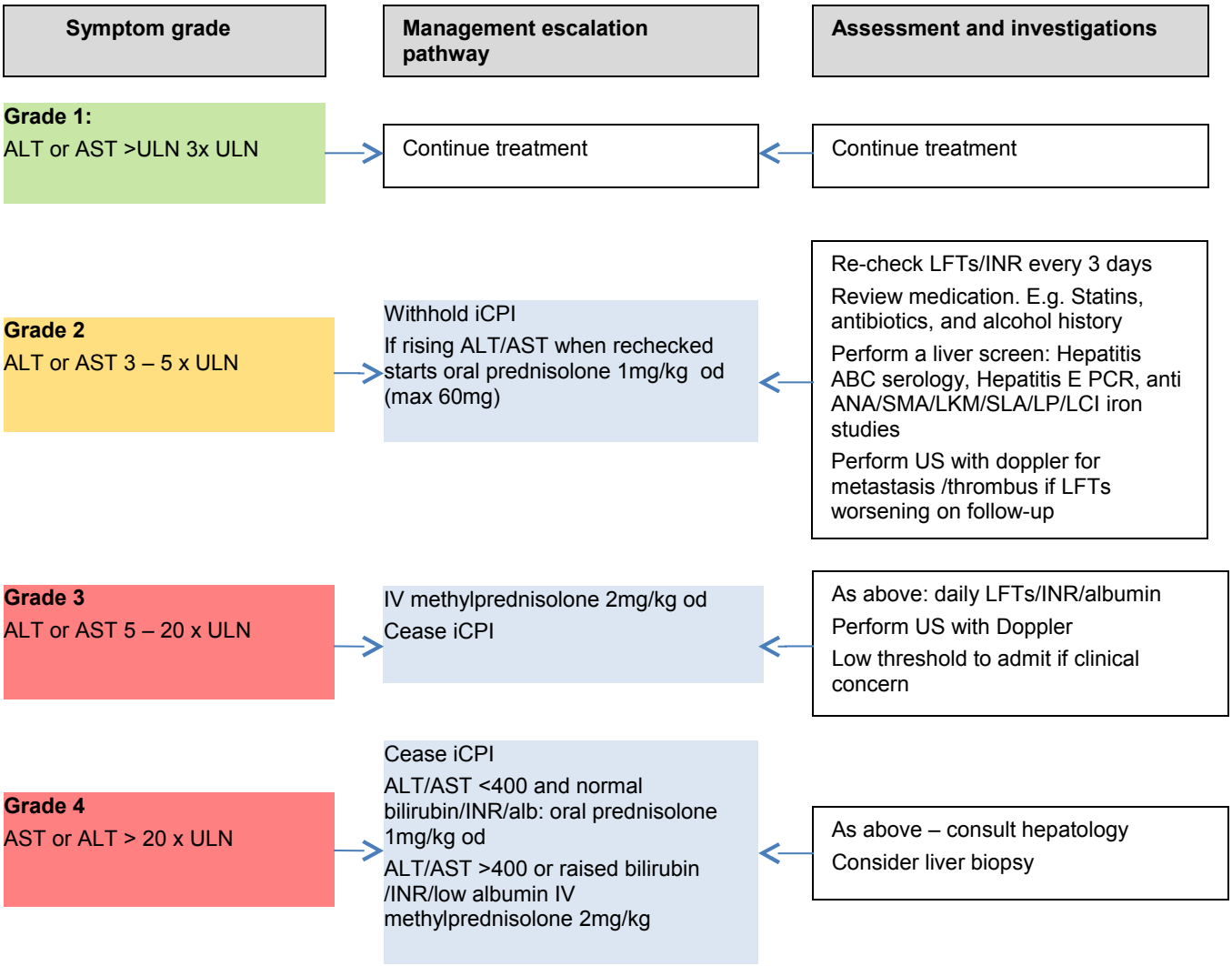


Figure 3. ICPi-related toxicity: management of hepatitis. ALT, alanine transaminase; ANA, antinuclear antibodies; AST, aspartate transaminase; bd, twice daily; iCPI, immune checkpoint inhibitor; INR, international normalised ratio of prothrombin time; i.v. intravenous; LCI, lung clearance index; LFT, liver function test; LKM, liver kidney microsomal; MMF, mycophenolate mofetil; PCR, polymerase chain reaction; SLA/LP, soluble liver antigen/liver-pancreas antibody; SMA, smooth muscle autoantibody; ULN, upper limit of normal; US, ultrasound.

Immunotherapy related Pneumonitis

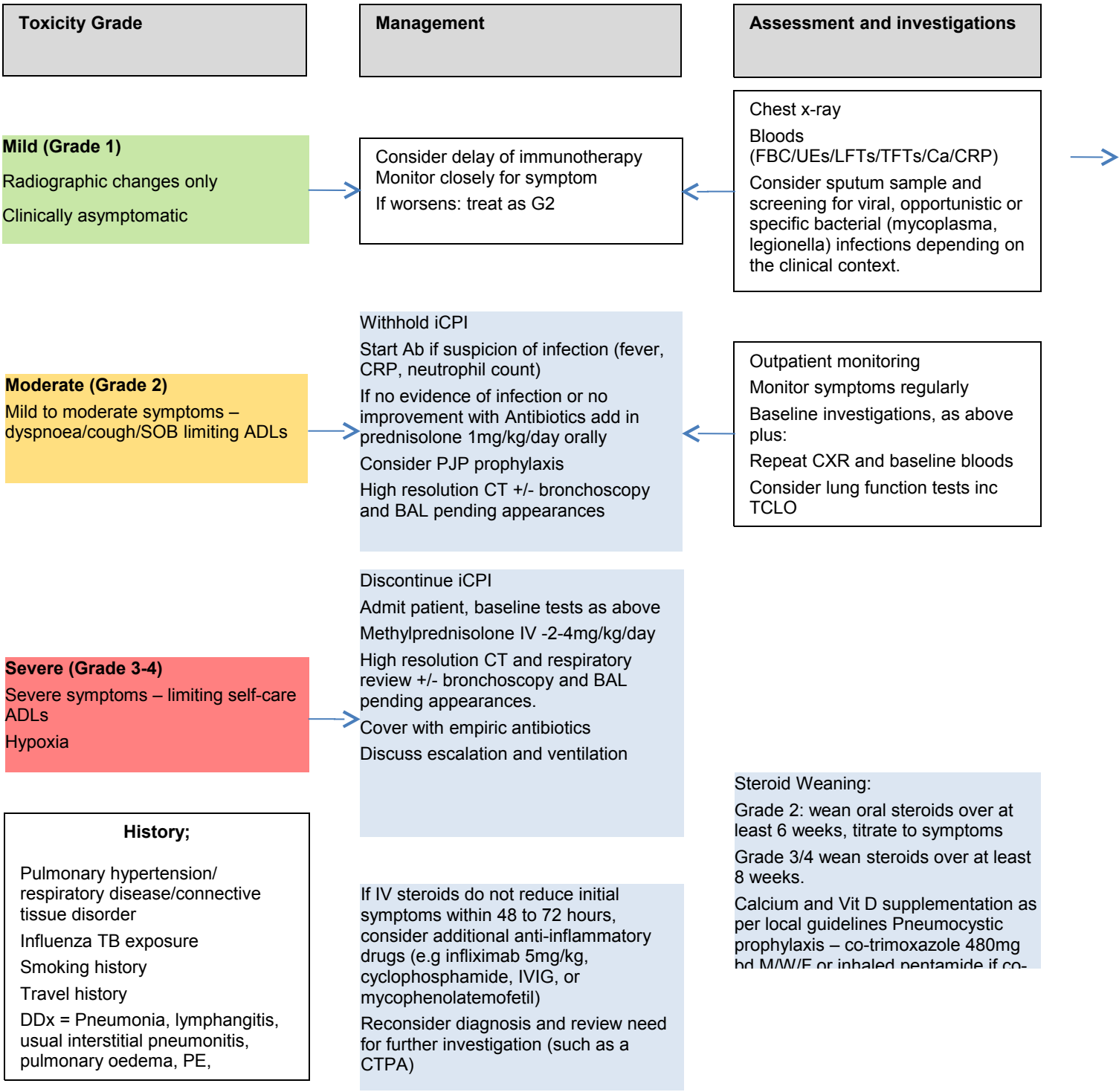


Figure 4. ICPi-related toxicity; management of pneumonitis. Ab antibiotic; ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; bd M/W/F, twice daily Monday/Wednesday Friday; Ca, calcium; CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; FBC, full blood count; iCPI, immune check-point inhibitor; i.v, intravenous; LFT, liver function test; MMF, mycophenolate mofetil; TCLO, transfer factor for carbon monoxide; TFT, thyroid function test; UEC, urea, electrolytes, creatinine; CTPA, computed tomography pulmonary angiogram.

Endocrinopathies

Checkpoint inhibitor related endocrine toxicity is complex and can present in non -specific ways. Please have a high index of suspicion for patients who are generally unwell and involve the endocrine team early in all cases aside from simple hypothyroidism. This section covers management approaching for the following:

- Adrenal insufficiency
- Life threatening adrenal insufficiency
- Thyroid disorders
- Pituitary disorders

Management of non-life threatening adrenal insufficiency

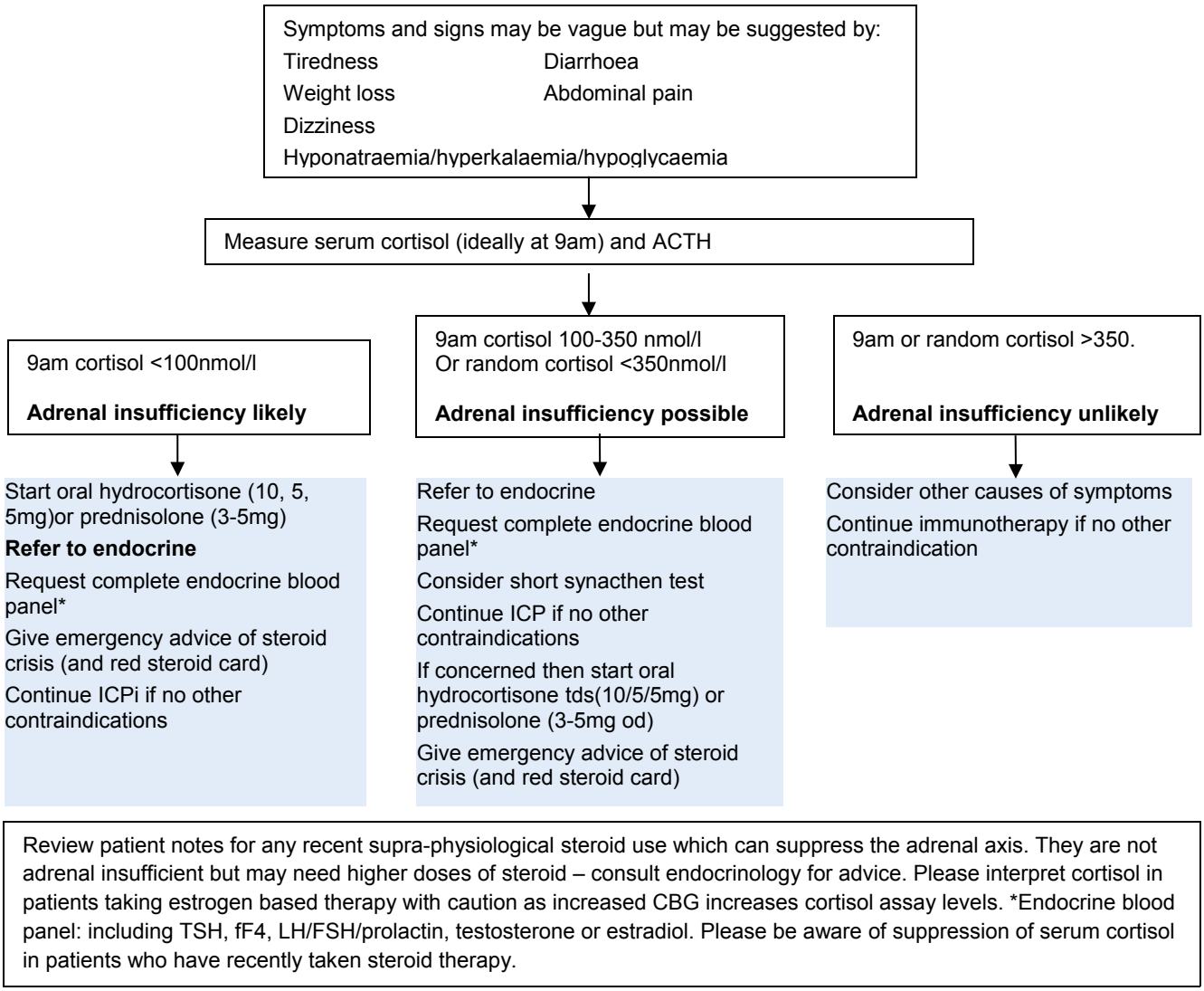


Figure 5. ICPi related adrenal insufficiency (non-life threatening). ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; FT4, free thyroxine; HRT, hormone replacement therapy; ICPi, immune checkpoint inhibitor; IGF-1, insulin-like growth factor-1; IM, LH, luteinizing hormone; TSH, thyroid-stimulating hormone; TFT, thyroid function test.

Management of life threatening adrenal insufficiency

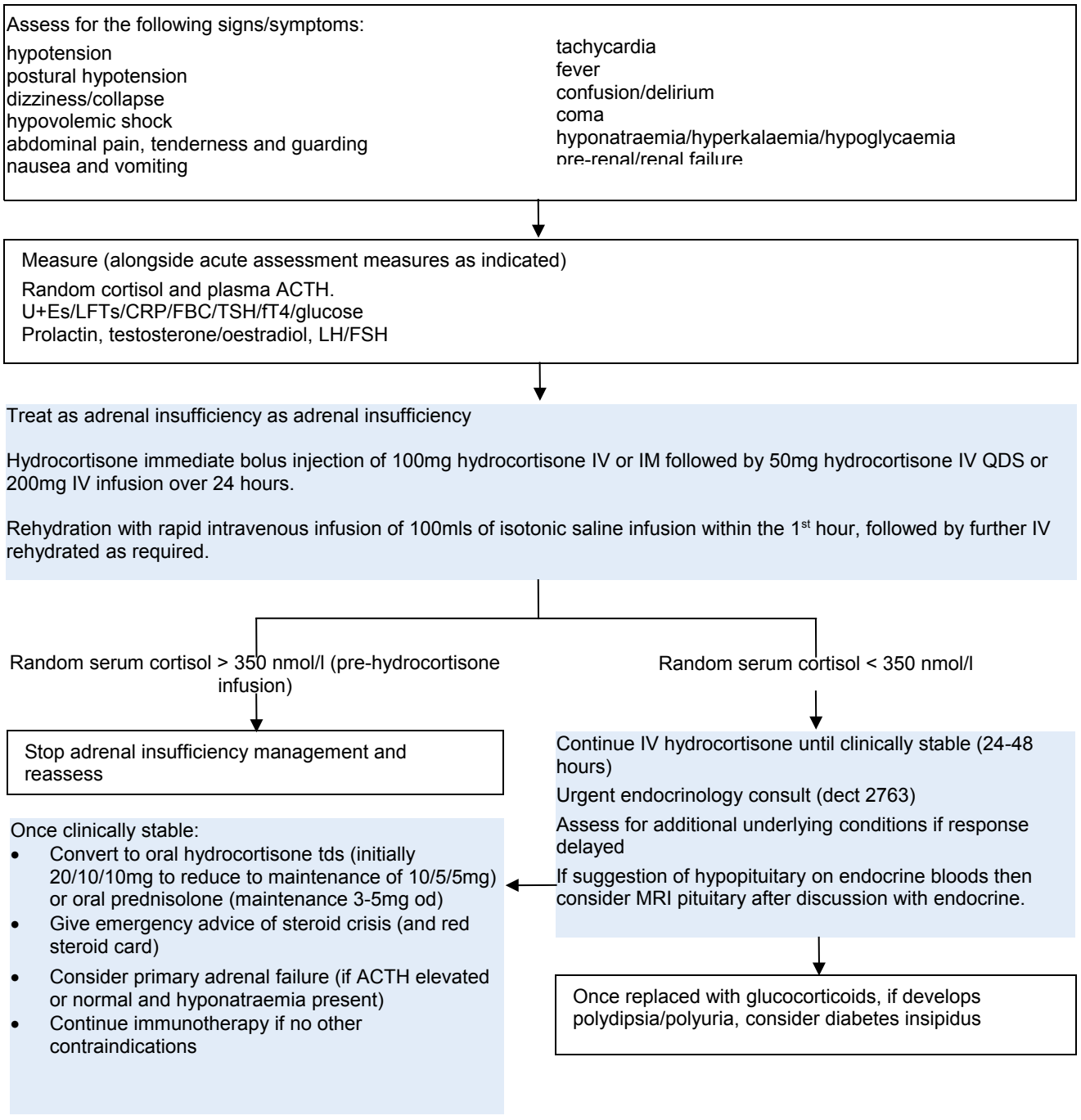


Figure 6. ICPi related adrenal insufficiency (non-life threatening). ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; FT4, free thyroxine; HRT, hormone replacement therapy; ICPi, immune checkpoint inhibitor; IGF-1, insulin-like growth factor-1; IM, intramuscular; i.v. intravenous; LH, luteinizing hormone; MRI, magnetic resonance imaging; od, once daily; QDS four times daily, TSH, thyroid-stimulating hormone; TFT, thyroid function test.

Thyroid dysfunction

Baseline thyroid bloods: TSH, FT4, T3* TFTs Baseline abnormal values do not preclude treatment; discuss with endocrinologist if uncertainty

Monitoring during treatment: Anti-CTLA4 (including combination with anti-PD-1) · TFTs every cycle · TFTs 4-6 weeks after cycle 4 (i.e. with restaging CT) Late endocrine dysfunction can occur

Anti-PD-1/Anti-PD-L1 · TFTs every cycle for first 3 months, every second cycle thereafter (in case of 2-weekly schedule)

A falling TSH across two measurements with normal or lowered T4 may also suggest pituitary dysfunction and weekly cortisol measurements should be performed

If TSH is abnormal, refer to algorithm below. Iodine from CT scans may impact TFTs

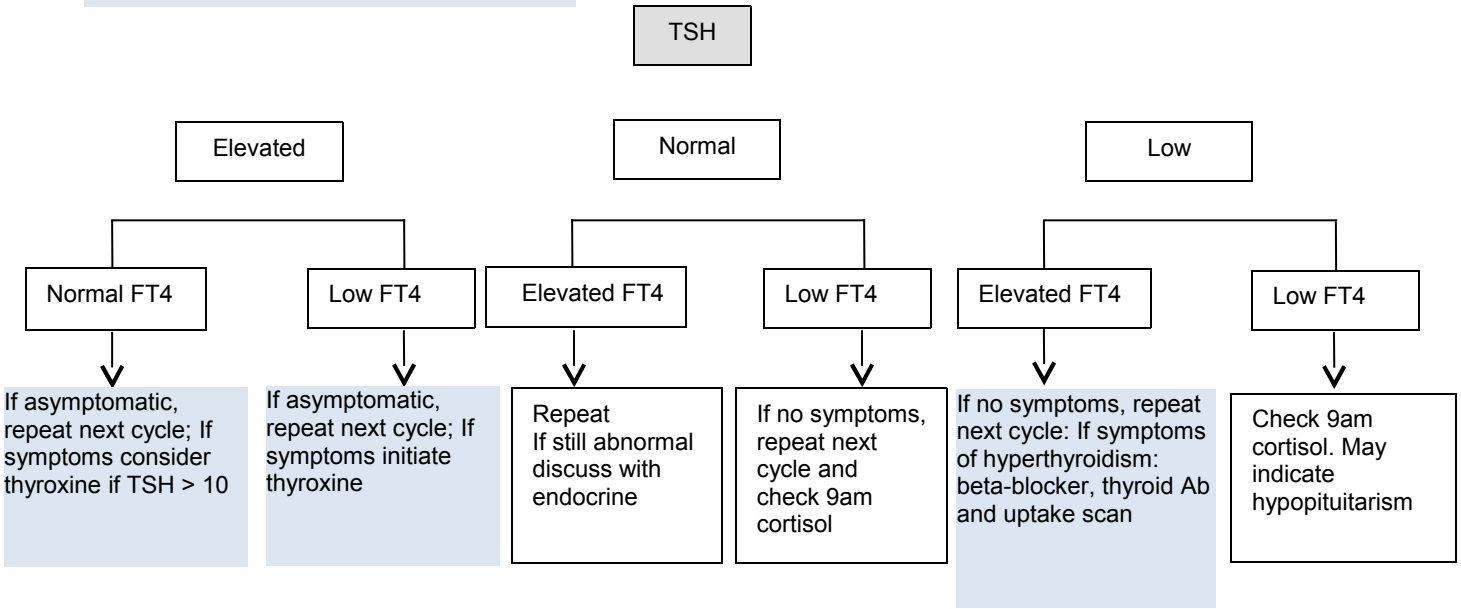
Hypothyroidism: Low FT4 with elevated TSH or TSH > 10 with normal FT4

Treatment: Levothyroxine 75microgram PO OD and titrate every 6 weeks by 25-50microgram until TSH<1mU/l (start at low dose e.g. 25-50microgream if elderly, cardiac history or low BMI)

Continue ICPi

Thyrotoxicosis (DDx thyroiditis, Grave's disease): Refer to endocrinology. Suggested investigations: Thyroid stimulating Immunoglobulin (TSI), anti-TPO Antibody Treatment: Propranolol for symptoms; consider carbimazole particularly if TSI positive

Painful thyroiditis – consider prednisolone 0.5 mg/kg od and taper If unwell, withhold ICPi and consider restarting when symptoms controlled



Withhold ICPi if patient is unwell with symptomatic hyperthyroidism

Subclinical hyperthyroidism (low TSH, normal FT4) often precedes overt hypothyroidism

Figure 7. ICPi monitoring and management: thyroid function. Ab, antibody; CT, computed tomography; CTLA4, cytotoxic T-lymphocyte associated antigen 4; DDx, differential diagnosis; FT4, free thyroxine; ICPi, immune checkpoint inhibitor; PD-1, programmed death 1; PD-L1, programmed death ligand 1; T3, triiodothyronine; T4, thyroxine; TFT, thyroid function test; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone.

Hypophysitis

Hypophysitis can present with either hormone defects or mass effect (including visual disturbance such as a bitemporal hemianopia). It is an immune-mediated inflammation of the pituitary gland, the exact mechanism of this in relation to iCPIs is not fully elucidated, but it almost inevitably results in permanent hypopituitarism, of one or more pituitary axis.

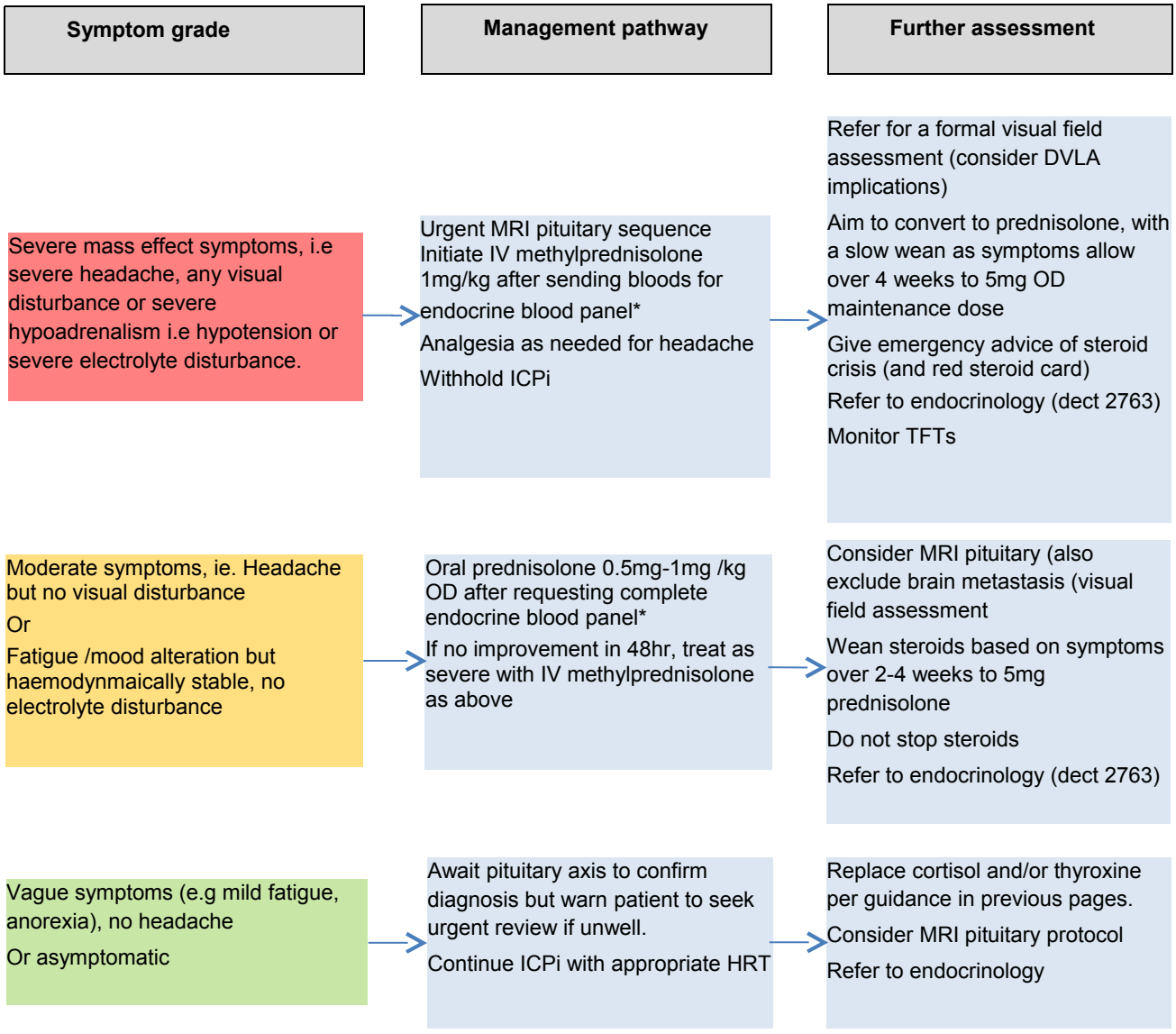


Fig 8. **ICPi-related toxicity: management of hypophysitis**. * Pituitary axis bloods: 9am cortisol (or random if unwell and treatment cannot be delayed), ACTH, TSH/FT4, LH, FSH, oestradiol if premenopausal, testosterone in men, IGF-1, prolactin. Mineralocorticoids replacement is rarely necessary in hypopituitarism. ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; FT4, free thyroxine; HRT, hormone replacement therapy; ICPi, immune checkpoint inhibitor; IGF-1, insulin-like growth factor-1; IM, intramuscular; i.v. intravenous; LH, luteinizing hormone; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs; od, once daily; TSH, thyroid-stimulating hormone; TFT, thyroid function test.

Immunotherapy induced peripheral neurotoxicity

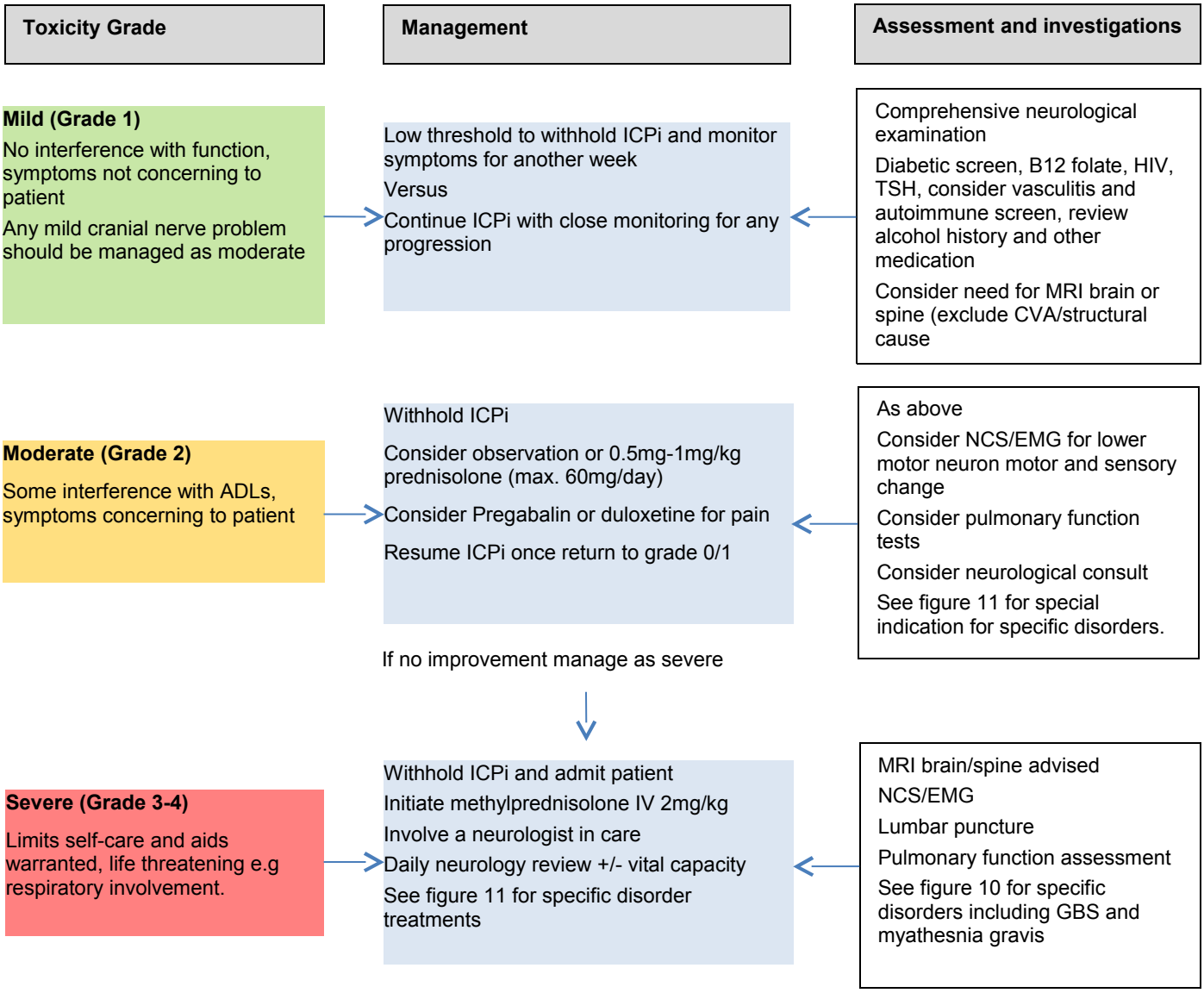


Fig 9. ICPi-related toxicity: management of suspected peripheral neurological toxicity. ADL, activities of daily living; CVA, cerebrovascular accident; HIV, human immunodeficiency virus; ICPi, immune checkpoint inhibitor; i.v. intravenous; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging; NCS/EMG, nerve conduction studies/electromyography;PJP, Pneumocystis jiroveci pneumonia; TSH, thyroid-stimulating hormone.

Management of suspected immunotherapy related peripheral neurological Toxicity

Suspected syndrome	Suggested investigations	Management approach
Guillain Barre Syndrome: Progressive symmetrical muscle weakness with absent or reduced tendon reflexes -involves extremities , facial, respiratory and bulbar and ocular motor muscles, dysregulation of autonomic nerves.	Nerve conduction studies (acute polyneuropathy) Lumbar puncture (elevated protein with normal WBC count) Pulmonary function tests with vital capacity and max inspiratory/expiration pressures Antibody testing for GBS variants e.g GQ1b in Miller Fisher syndrome	Use of steroids not recommended in idiopathic GBS, however trial of steroids reasonable methylprednisolone 1-2mg/kg Neurology consult If no improvement or worsening, plasmapheresis or IVIG indicated Consider location of care where ventilatory support available (required in 15-30% of idiopathic cases)
Myasthenia Gravis: Fluctuating muscle weakness (proximal limb, trunk, ocular, e.g ptosis/diplopia or bulbar) with fatigability, respiratory muscles may also be involved	Check for ocular muscle and proximal muscle fatigability AChR and antiMuSK antibodies Bedside tests: Tensilon test or icepack test with neurological input	Steroids indicated (oral or iv depending on symptoms) Pyridostigmine initial dose 30mg TDS Neurology review If no improvement or worsening; plasmapheresis
Other syndromes reported: Motor and sensory peripheral neuropathy, multifocal radicular neuropathy/plexopathy , autonomic neuropathy, phrenic nerve palsy, cranial nerve palsies, (e.g facial nerve, optic nerve, hypoglossal nerve) Steroids suggested as initial management where indicated with neurology specialist input and close attention to potential for respiratory or visual compromise.		

Figure 10. ICPi-related toxicity: management of suspected peripheral neurological toxicity. AChR, acetylcholine receptor; EMG, electromyography; GBS, Guillain-Barre´ syndrome; ICPi, immune checkpoint inhibitor; i.v., intravenous; IVIG, intravenous immunoglobulin; MuSK, muscle specific kinase; tds, three times a day; WBC, white blood cell.

Management of suspected immunotherapy related central neurological toxicity

Suspected syndrome	Suggested investigations	Management approach
Aseptic meningitis Exclusion of infective causes paramount Headache, photophobia, neck stiffness with fever or may be afebrile, vomiting, normal cognition, /cerebral function (distinguishes from encephalitis)	Lumbar puncture – M/C/S (normal gram stain, WBCs <500ul, normal glucose, PCR for HSV, cytology CNS imaging to exclude brain metastases and leptomeningeal disease	Exclude bacterial and ideally viral infections prior to high dose steroids Oral prednisolone 0.5mg/kg or IV methylprednisolone 1-2mg/kg if very unwell Consider concurrent empirical antiviral (acyclovir) and antibacterial therapy
Encephalitis: Exclusion of infective and metabolic causes paramount Confusion or altered behavior, headaches, alteration in GCS, motor or sensory deficits, speech abnormality, may or may not be febrile	Lumbar puncture – M/C/S (normal gram stain, WBC , usually <250mm2 with lymphocyte predominance, elevated protein but < 150mg/dl, usually normal glucose but can be elevated), PCR for HSV and consider viral culture, cytology CNS imaging Consider viral serology	As above for aseptic meningitis Suggest concurrent IV acyclovir until PCR result obtained.
Transverse myelitis: Acute or subacute neurological signs/symptoms of motor/sensory /autonomic origin; most have sensory level, often bilateral symptoms	MRI brain and spine Lumbar puncture – may be normal but lymphocytosism elevated protein may be noticed. Oligoclonal bands usually absent, cytology. Serum B12/folate/HIV/syphilis/ANA/anti-Ro and anti-La Abs, TSH, anti-aquaporin-4 IgG	Methylprednisolone 2mg/kg (or consider 1g/day) Neurology review Plasmapheresis may be required if non steroid responsive
Other syndromes reported: Neurosarcoidosis, Posterior Reversible Leucoencephalopathy (PRES), Volt-Harada-Koyanagi syndrome, demyelination, vasculitic encephalopathy, generalized seizures.		

Figure 11. ICPi-related toxicity: management of suspected central neurological toxicity. Abs, antibodies; ANA, antinuclear antibody; CNS, central nervous system; HIV, human immunodeficiency virus; HSV, Herpes simplex virus; ICPi, immune checkpoint inhibitor; IgG, immunoglobulin G; i.v., intravenous; M/C/S, microscopy, culture and susceptibility; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; TSH, thyroid-stimulating hormone; WBC, white blood cell

Management of suspected renal toxicity

Toxicity Grade	Management	Assessment and investigations
Mild (Grade 1) Creatinine ULN and > than baseline but < 1.5 x ULN	Weekly creatinine monitoring Exclude other causes of renal impairment. Continue immunotherapy	Review hydration status, medication Dipstick urine +/- culture If obstruction suspected: renal ultrasound +/- Doppler to exclude obstruction/clot
Moderate (Grade 2) Creatinine >1.5 – 3 x baseline or >1.5 – 3 x ULN	Withhold dose until reaction resolves to grade 1 or grade 0 Monitor creatinine and K+ every 2-3 days If not improving discuss with renal team and consider biopsy. If attributable to irAE, initiate steroids (oral prednisolone 0.5mg-1mg/kg) If returns to G1/baseline – recommence ICPi If not attributable irAE – may continue ICPi	As above Renal ultrasound +/- Doppler to exclude obstruction/clot If proteinurea; for 24h collection or UPCR If blood: phase contrast microscopy and GN screen if nephrology recommends Advise patient to notify if oliguric
Severe (Grade 3) Creatinine > 3 x baseline or >3-6 x ULN	Withhold ICPi; admit patient for monitoring and fluid balance; repeat creat every 24hr; early discussion with renal and consider need for biopsy Initiate IV methylprednisolone 1-2mg/kg	As above
Severe (Grade 4) Creatinine > 6 x ULN	As per G3; patient should be managed in a hospital where renal replacement therapy is available.	As above

Figure 12. ICPi-related toxicity: management of nephritis. Renal injury occurs in around 1 %–4 % of patients treated with ICPi, usually in a pattern of acute tubulo-interstitial nephritis with a lymphocytic infiltrate [80]. Attention needs to be paid to the patient's baseline creatinine, not just abnormal results per biochemistry ULN. Confounding diagnoses include dehydration, recent i.v. contrast, urinary tract infection, medications, hypotension, or hypertension. Early consideration for renal biopsy is helpful which may negate the need for steroids and determine whether renal deterioration is related to ICPis or other pathology. Oliguria should prompt inpatient admission for careful fluid balance and plan for access to renal replacement therapy. Steroid wean: begin to wean once creatinine G1; G2 severity episode—wean steroids over 2–4 weeks; G3/4 episode—wean over 4 weeks. If on steroids for > 4 weeks—PJP prophylaxis, calcium/vitamin D supplementation, gastric protection and check afternoon glucose for hyperglycaemia. *GN screen: ANA, complement C3, C4, ANCA, anti-GBM, hepatitis B and C, HIV, immunoglobulins and protein electrophoresis. ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibody; GBM; glomerular basement membrane; GN, glomerulonephritis; HIV, human immunodeficiency virus; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; i.v., intravenous; K, potassium; PJP, Pneumocystis jiroveci pneumonia; ULN, upper limit of normal; UPCR, urine protein to creatinine

ICPi related toxicity – Management of arthralgia

Arthralgia: Pain in the joints without associated swelling; may be found in conjunction with myalgia (muscle pain), a common AE

DDx to consider: ·

- Arthritis (see Figure 14 for further tests and management) ·
- Polymyalgia rheumatica (see arthritis as may present with small joint synovitis) ·
- Myositis (characterised by tenderness to palpation of muscle)

Due to the paucity of literature on management of this AE, this algorithm serves as a general guide only; seek rheumatology advice if severe symptoms not responding to steroids

Symptom grade	Management escalation pathway	Assessment and investigations
Grade 1 Mild pain with inflammation erythema or joint swelling	Initiate analgesia with paracetamol and ibuprofen Continue ICPi	Complete rheumatological history regarding DDx above and examination of all joints and skin Consider plain X ray/imaging to exclude metastases if appropriate Autoimmune blood panel (as above)
Grade 2 Moderate pain associated with above, limits instrumental ADLs	Escalate analgesia and use diclofenac or naproxen or etoricoxib If inadequately controlled, initiate prednisolone 10-20 mg or consider intra-articular steroid injections for large joints Consider withholding ICPi and resuming upon symptom control, prednisolone < 10 mg; if worsens treat as per Grade 3	Complete history and examination as above; autoimmune blood panel US +/- MRI imaging of affected joints Consider early referral to a rheumatologist
Grade 3 Severe pain; irreversible joint damage; disabling; limits self-care ADLs	Withhold ICPi Initiate prednisolone 0.5-1 mg/kg If failure of improvement after 4 weeks or worsening in meantime – refer patient to rheumatologist (consider anti-TNFα therapy)	As for Grade 2 Seek rheumatology advice and review

Figure 13. ICPi-related toxicity: management of arthralgia. ADL, activities of daily living; AE, adverse event; DDx, differential diagnosis; ICPi, immune checkpoint inhibitor; MRI, magnetic resonance imaging; TNFa, tumour necrosis factor alpha; US, ultrasound

Appendix

1. Monitoring of patients on high dose steroids

Any patient on high dose steroids (> 20mg prednisolone or 3mg dexamethasone) for more than 2 weeks should undergo regular blood sugar self-monitoring.

Patients not known to have diabetes should test blood glucose once daily before evening meals for the first 2 weeks of steroid use and record results

- If results are more than 12 mmol/L on 2 consecutive occasions, increase testing to 4 times daily pre meals and consider commencing treatment as per guidance.
- If results are all less than 10mmol/L after 2 weeks, change frequency of testing to once per week while taking steroids.

Patients known to have diabetes should test 4 times daily pre –meals. The need to continue blood glucose monitoring should be individually assessed once steroid course is complete.

Management of diabetes should be in conjunction with the local diabetic service.

2. Bone protection

Consider bone protection in the form of a bisphosphate (e.g alendronic acid) for all patients taking steroids for more than 3 months and at risk of fracture. Calcium and vitamin D supplementation should be added to ensure patients are replete. Patients should be encouraged to maintain weight bearing exercise and reduce alcohol consumption and stop smoking.

3. PJP prophylaxis

Consider PJP prophylaxis if on prolonged steroids (e.g. >20mg of prednisolone for anticipated duration of >3months).

AMENDMENT HISTORY

A record of changes in this document

Date	Updated version number	Previous version number	Page Number /Section (updated version)	Details
21 07 20 18 09 20	1	New		New Treatment Protocol. MS - + minor changes (frequency of treatment)
29.09.21	2	1		DM review.