Endocrine & Gastrointestinal Immune-related adverse event

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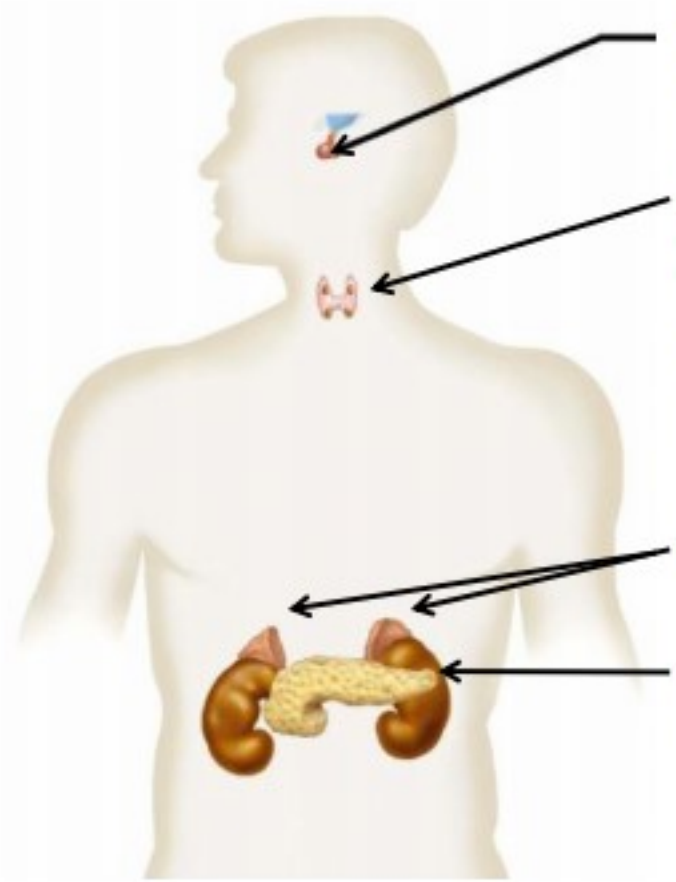
Endocrine toxicity

Endocrine toxicity: overview



Pituitary gland
- Hypophysitis
- Corticotropin (ACTH) decrease
- Secondary adrenal insufficiency[a]

Thyroid gland
- Hyperthyroidism
- Hypothyroidism
- TSH increase or decrease
- Thyroiditis
- Free thyroxine increase or decrease
- Autoimmune thyroiditis

Adrenal glands
- Primary adrenal insufficiency[b]

Pancreas
- Diabetes mellitus

Mario Sznol et.al, Endocrine-related adverse events associated with immune checkpoint blockade and expert insights on their management Canc Treat Rev 2017

Highlights

- High-grade immune-related endocrinopathies occur in ~1–2% of patients.

- Can affect thyroid, pituitary, adrenal, gonadal or islet cell function.

- Endocrinopathies are managed by hormone replacement and are often not reversible.

- Heightened awareness, routine monitoring, and management can reduce morbidity.

Mario Sznol et.al, Endocrine-related adverse events associated with immune checkpoint blockade and expert insights on their management Canc Treat Rev 2017

Endocrine Toxicities

Organ system	Presentation	
	Routinely reported events	Rare or infrequently reported events
Dermatologic	Rash (maculopapular, lichenoid), pruritus, vitiligo	Acneiform rash, alopecia, bullous pemphigoid, papulopustular rosacea, psoriasis, Stevens–Johnson syndrome, toxic epidermal necrosis, DRESS, Sweet syndrome
Gastrointestinal	Diarrhea, colitis, lichenoid mucositis	Enteritis, gastritis, pancreatitis
Endocrine	Hypothyroidism, hyperthyroidism, thyroiditis, hypophysitis	Autoimmune type 1 diabetes, primary adrenal insufficiency
Hepatic	Transaminitis, hepatitis	—
Respiratory	Pneumonitis	Pleuritis, sarcoidosis
Rheumatic	Arthralgia, inflammatory arthritis, myalgia	Dermatomyositis, myositis, polymyalgia-like syndrome, Sjögren syndrome, vasculitis
Renal	Increase in serum creatinine, nephritis	—
Ophthalmic	—	Uveitis, conjunctivitis, scleritis, episcleritis, blepharitis, retinitis
Neurologic	Sensorimotor neuropathy	Aseptic meningitis, autonomic neuropathy, encephalitis, facial nerve palsy, Guillain–Barré syndrome, myasthenia gravis, posterior reversible leukoencephalopathy, transverse myelitis
Hematologic	—	Aplastic anemia, hemolytic anemia, idiopathic thrombocytopenia purpura, lymphopenia, hemophilia
Cardiac	—	Cardiomyopathy, myocarditis, pericarditis

Myers, G. (2018). Immune-related adverse events of immune checkpoint inhibitors: a brief review. Current Oncology, 25(5)

Different ICIs

	CTLA-4 inhibitor	PD-1 inhibitor		PD-L1 inhibitor	
	Ipilimumab	Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab
Dermatological					
Pruritus	25–30%	17%	11–21%	12–14%	<1%
Rash	33–34%	15%	10–21%	15%	<1%
Vitiligo	3–4%	10–11%	9%	NR	NR
Gastrointestinal					
Diarrhoea	36–38%	8–16%	8–20%	18–20%	1–2%
Colitis	8–10%	1–3%	1–2%	<1%	<1%
Hepatic					
Increased ALT	<1%	1–2%	2–8%	2–3%	0
Increased AST	1–2%	1–2%	3–10%	2–3%	0
Hepatitis	<1%	1–2%	1–2%	1–2%	1%
Endocrine					
Hypothyroidism	1–2%	4–5%	8–10%	2–4%	<1%
Hyperthyroidism	0–2%	0–3%	3–4%	1%	<1%
Hypophysitis	2–3%	<1%	<1%	<1%	<1%
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Neurological	<1%	<1%	<1%	0	NR
NR, not reported					

Adapted from: Kumar V, Chaudhary N, Garg M, et al. Current diagnosis and management of immune related adverse events (irAEs) induced by immune checkpoint inhibitor therapy. Front Pharmacol 2017; 8:49

Endocrine toxicity

- Around 10% of patients treated with ICIs are likely to develop endocrine irAEs of any grade with variable rates of endocrine dysfunction (from 0 to 40%) in different studies.

- Endocrine dysfunctions present on average **9–11 weeks** after the first dose (range 5–36 weeks), but delayed toxicities have been reported. The time of onset of endocrine irAEs has been reported to be similar in patients receiving either anti-CTLA4 or anti-PD-1/PDL-1.

- The **combined use** of anti-CTLA4 and anti-PD-1/PD1-L has been associated to ***earlier development*** of endocrine irAEs, often more than one in the same patient

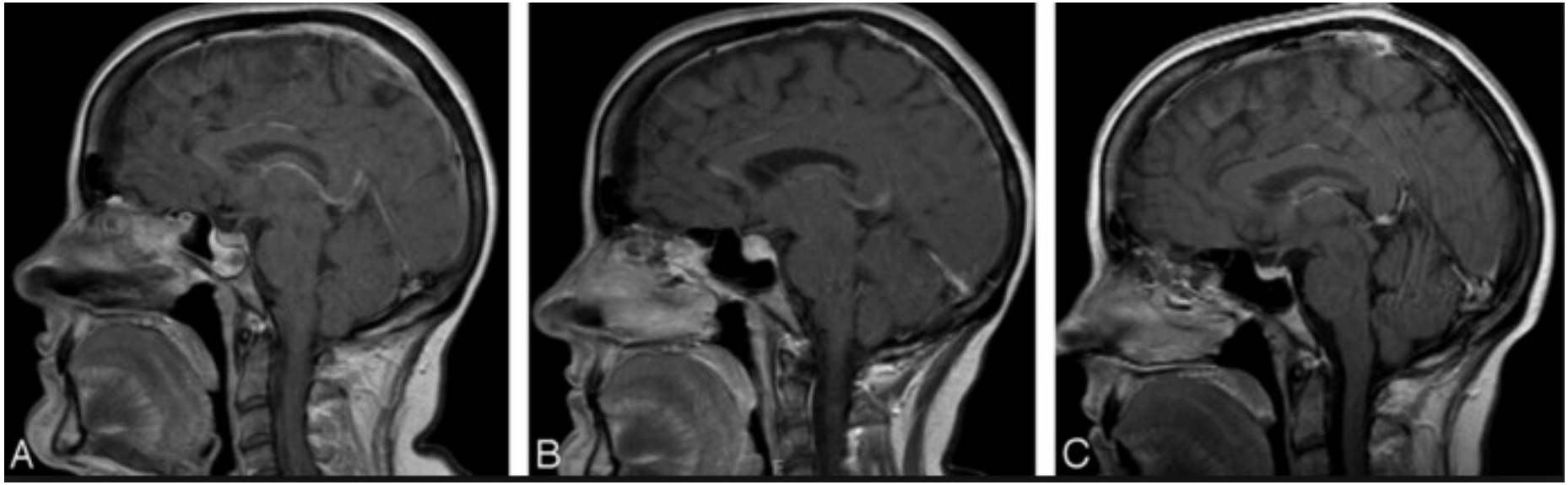
Mario Sznol et.al, Endocrine-related adverse events associated with immune checkpoint blockade and expert insights on their management Canc Treat Rev 2017

Pituitary disorders - 1

- Hypophysitis is the most peculiar endocrine side effect of **anti-CTL4 ICIs** (dose-dependent relationship)
- Onset usually **11 weeks** after start
- In most cases, involves adenohypophysis: *headache, asthenia, nausea, weakness and anorexia, hypotension, oligo-amenorrhea in females, erectile dysfunction in males, and loss of libido*
- Rare neurohypophysis (diabetes insipidus)

Pituitary disorders - 2

- No criteria to confirm the diagnosis
- Treatment: steroides (depending of Grade)



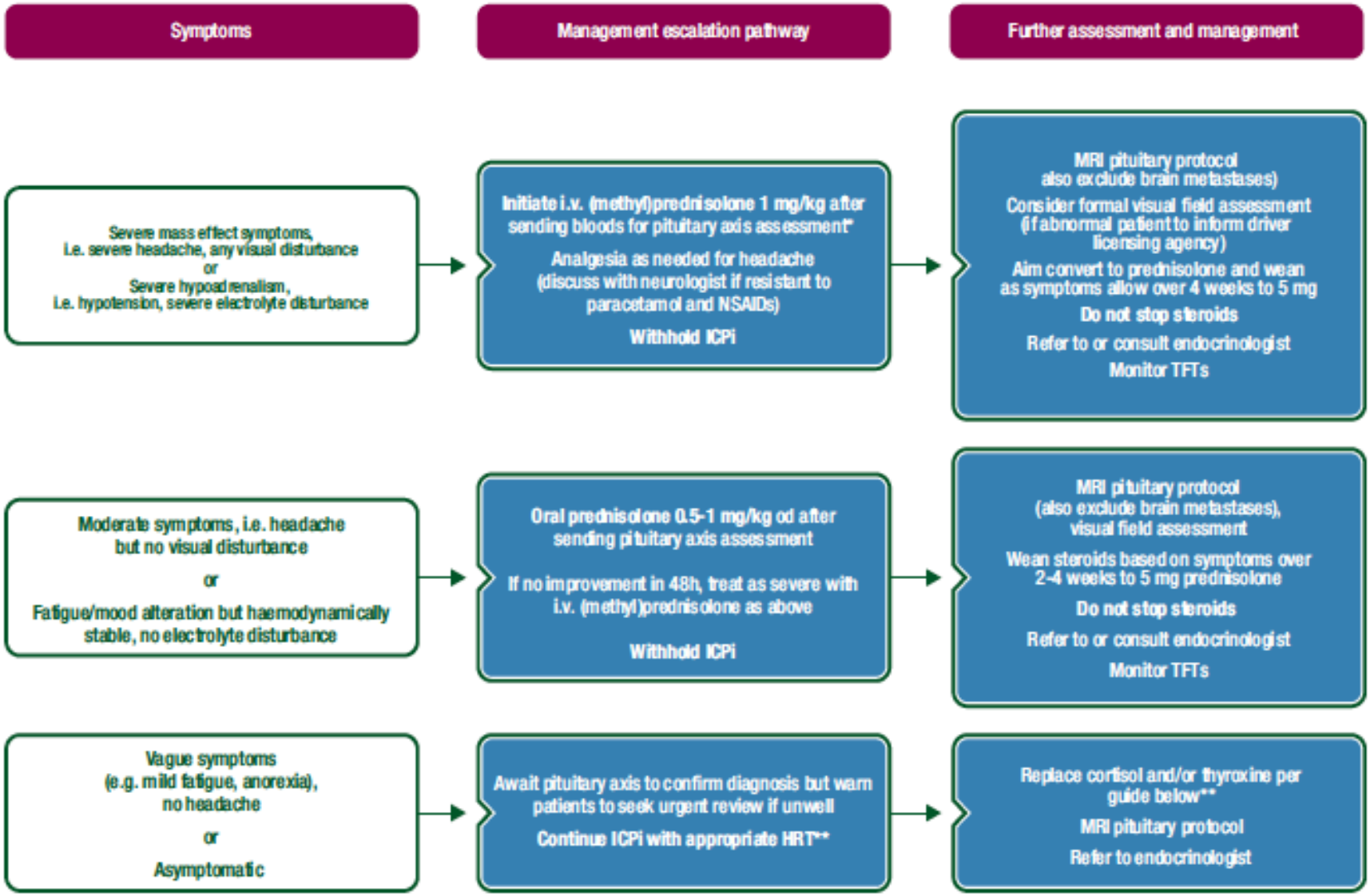
Ipilimumab-Induced Hypophysitis: MR Imaging Findings

Pituitary disorders - 3

Endocrine irAEs	CTCAE grade[a]	CTCAE description	Corticosteroids (CCS) management
Hypophysitis	1	Asymptomatic or mild symptoms; clinical observation only; intervention not indicated	-Not indicated
	2	Moderate, minimal; local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL	-Oral prednisone 0.5–1 mg/kg/d -If IV, methylprednisolone 0.5–1 mg/kg/d -If no improvement in 2–3 days, increase to 2 mg/kg/d -Once improved to grade ≤ 1, 4–6 week taper
	3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	-Prednisone (or equivalent dose of methylprednisolone) 1–2 mg/kg/d -If no improvement in 2–3 days add additional/alternative immunosuppressant -Once improved to grade ≤ 1, 4–6 week taper
	4	Life-threatening consequences; urgent interventions indicated	-Prednisone (or equivalent dose of methylprednisolone) 1–2 mg/kg/d -If no improvement in 2–3 days add additional/alternative immunosuppressant

RM Ruggeri et.al, Endocrine and metabolic adverse effects of immune checkpoint inhibitors: an overview (what endocrinologists should know), Journal of Endocrinological Investigation

Pituitary disorders - 4



Thyroid disorders - 1

- The most common endocrine side effect of ICIs [up to 40% anti-Pd1]
- More frequent in women
- Type of thyroid disfunction:
  - Painless Thyroiditis/Hashimoto's thyroiditis
  - Primary hypothyroidism
  - Thyrotoxicosis (Grave's disease)
  - Rare case of orbitophaty

P. Chalan et al. Thyroid dysfunctions secondary to cancer immunotherapy, J Endocrinol Invest. 2018

Thyroid disorders - 2

Treatment type	Prevalence of:			
	Thyroid dysfunction not otherwise specified	Hypothyroidism	Hyperthyroidism (including transient subclinical hyperthyroidism)	Destructive thyrotoxicosis
Cytokines				
IL-2	22%	15–40%	19%	NR
IFNs	1–50%			2–3%
Anti-CTLA-4	23%	4–15%	3%	NR
Anti-PD-1	39%	9–40%	1–13%	12%
Anti-PD-L1	7–21%	7–21%	10%	NR
Combination of anti-CTLA-4 + anti-PD-1 or anti-CTLA-4 + anti-PD-L1	50%	2–27%	22–30%	NR
Oncolytic viruses	NR	NR	NR	NR
Adoptive T-cell transfer	NR	NR	NR	NR
Cancer vaccines (alone or in combination with IL-2 or adjuvant)	0–25%	4–11%	11–24%	NR

P. Chalan et al. Thyroid dysfunctions secondary to cancer immunotherapy, J Endocrinol Invest. 2018

Thyroid disorders - 3

Hypothyroidism	1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	High-dose CCS (1 mg/kg/d) are not indicated	-Continue ICIs
	2	Symptomatic; thyroid replacement indicated; limiting instrumental ADL		-Continue ICIs and start L-T4 replacement therapy with levothyroxine at an initial full dose (1.6 μg/kg) in young, healthy patients, while a reduced dose of 20–50 μg/d should be used in elderly patients with cardiovascular disease
	3	Severe symptoms; limiting self-care ADL; hospitalization indicated		-Hold ICIs with grade ≥ 3 and start L-T4 replacement therapy (see above). Restart ICIs after resolution of symptoms to grade 2 or better
	4	Life-threatening consequences; urgent intervention indicated		-Check hormonal parameters (FT4, TSH) every 6–8 weeks until maintenance dose has been reached, and then every 6 months/yearly
Hyperthyroidism	1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	High-dose CCS (1 mg/kg/d) are not routinely required	-Continue ICIs
	2	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL		-Continue ICIs. Consider standard therapy for hyperthyroidism: (a) painless/subacute thyroiditis is a self-limiting disease in two phases: in the hyperthyroid phase treatment is conservative, with beta-blockers and NSAIDs[b]/CCS (prednisone 30–40 mg/d with adequate tapering) with close monitoring of thyroid hormones; in the hypothyroid phase introduce replacement therapy (even with low FT3 and FT4 and normal TSH) (b) Graves' disease should be managed as per current guidelines
	3	Severe symptoms; limiting self-care ADL; hospitalization indicated		-Hold ICIs with grade ≥ 3. Restart ICIs after resolution of symptoms to grade 2 or better
	4	Life threatening consequences; urgent intervention indicated		

High dose steroids NOT indicated

P. Chalan et al. Thyroid dysfunctions secondary to cancer immunotherapy, J Endocrinol Invest. 2018

Thyroid disorders - 2

Baseline Endocrine Panel:
TSH, FT4, T3* TFTs

Baseline abnormal values do not preclude treatment; discuss with endocrinologist if uncertain
*when indicated

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)
- Cortisol as indicated by symptoms/falling TSH

A falling TSH across two measurements with normal or lowered T4 may also suggest pituitary dysfunction and weekly cortisol measurements should be performed (see also Figure 6)

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: Thyroxine 0.5-1.5 µg/kg (start low in elderly, if cardiac history)

Continue ICPi

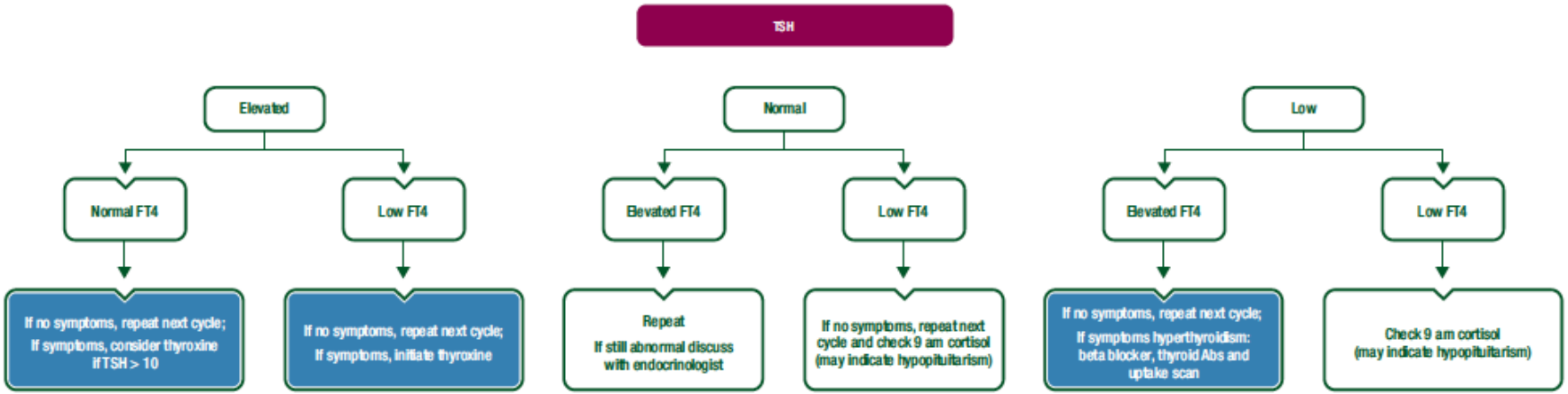
Thyrotoxicosis (DDx thyroiditis, Grave's disease):

Investigations: Anti-TSH Receptor Ab, anti-TPO Ab, nuclear medicine thyroid uptake scan

Treatment: Propranolol or atenonol for symptoms; consider carbimazole if anti-TSH Receptor Ab positive

Painful thyroiditis – consider prednisolone 0.5 mg/kg and taper

If unwell, withhold ICPi and consider restarting when symptoms controlled



Adrenal disorders - 1

- Adrenal insufficiency less common irAE (> PD1 antibodies)
- Clinical presentation nonspecific
- Adrenal crisis is the most life-threatening endocrinopathy during ICIs

  – If autoimmune adrenalitis is suspected: measure of cortisol, ACTH, aldosterone and renin!

Adrenal disorders - 2

Adrenal insufficiency	1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-Continue ICIs
	2	Moderate symptoms; medical intervention indicated	-Start replacement with hydrocortisone 15–20 mg/d until patient is stable under treatment, before resuming immunotherapy
	3	Severe symptoms; hospitalization indicated	-Hold ICIs with grade ≥ 3
	4	Life-threatening conditions; urgent intervention indicated	-If in adrenal crisis start with stress dose CCS (and iv fluids), as per current guidelines; rule out sepsis

RM Ruggeri et.al, Endocrine and metabolic adverse effects of immune checkpoint inhibitors: an overview (what endocrinologists should know), Journal of Endocrinological Investigation

Metabolic adverse events - 1

- Type 1 diabetes mellitus occurs at low frequency (<1%).
- Diabetes mellitus (DM) appears to be more common with PD-1 and PD-L1 blockade than with anti-CTLA4.
- It is recommended that blood glucose levels are regularly monitored in order to detect the emergence of DM.
- Role of highdose steroids is unclear. Steroids will most likely negatively influence diabetes control in these patients.

Metabolic adverse events - 2

Endocrine irAEs	CTCAE grade[a]	CTCAE description	Corticosteroids (CCS) management	Clinical management
Type 1 diabetes mellitus	1	Fasting glucose > ULN—160 mg/dl (8.9 mmol/l)	High-dose corticosteroids (1 mg/kg/d) are not indicated	-Continue ICIs -Provide patient education on diet and lifestyle modification, and blood glucose testing
	2	Fasting glucose > 160–250 mg/dl (> 8.9–13.9 mmol/l)		-Therapy as per guidelines
	3	Fasting glucose > 250–500 mg/dl (> 13.9–27.8 mmol/l); hospitalization indicated		-T1DM with ketoacidosis: hold ICIs, hospitalize and treat as per standard guidelines
	4	Fasting glucose > 500 mg/dl (> 27.8 mmol/l); life-threatening consequences		-T1DM without ketoacidosis: hold ICIs for hyperglycaemia ≥ 3, treat with insulin and continue ICIs when patient recovers to grade 1

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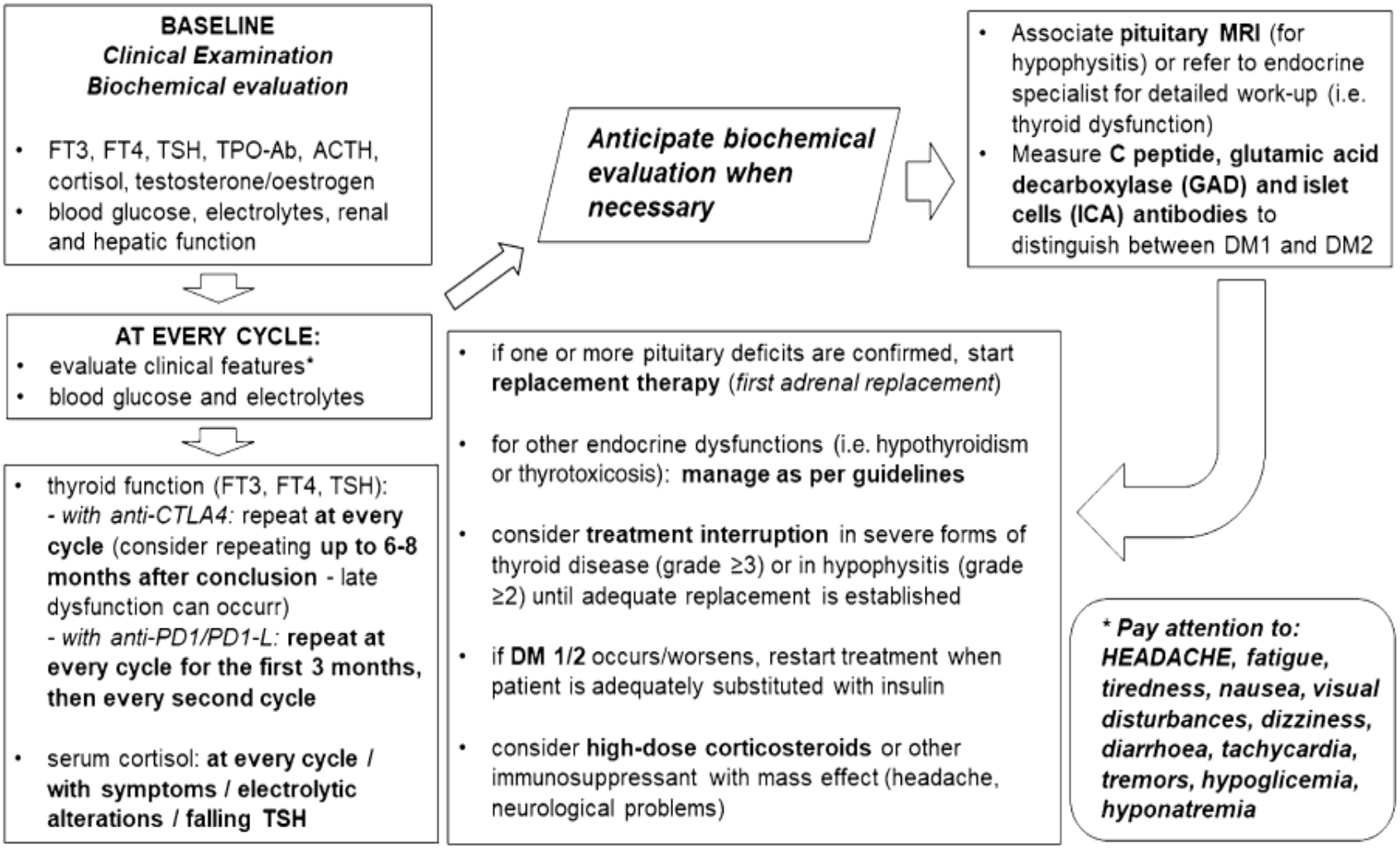
Proposed flowchart for the detection and clinical management of endocrine immune-related adverse effects (irAEs) of ICIS



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Gastrointestinal and hepatic toxicity

Gastrointestinal toxicity: highlights

- GI toxicity well decribed for **anti-CTLA4** antibodies (less for anti-PD1/anti-PD-L1 or for combined anti-CTLA4 and anti-PD1 antibodies)
- Shares certain clinicopathological features with **IBD**
- **Endoscopic and histological** investigation should be arranged to confirm diagnosis
- Steroids first instance, Infliximab in patients steroids-refractory

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Gastrointestinal Toxicities

Organ system	Presentation	
	Routinely reported events	Rare or infrequently reported events
Dermatologic	Rash (maculopapular, lichenoid), pruritus, vitiligo	Acneiform rash, alopecia, bullous pemphigoid, papulopustular rosacea, psoriasis, Stevens–Johnson syndrome, toxic epidermal necrosis, DRESS, Sweet syndrome
Gastrointestinal	Diarrhea, colitis, lichenoid mucositis	Enteritis, gastritis, pancreatitis
Endocrine	Hypothyroidism, hyperthyroidism, thyroiditis, hypophysitis	Autoimmune type 1 diabetes, primary adrenal insufficiency
Hepatic	Transaminitis, hepatitis	—
Respiratory	Pneumonitis	Pleuritis, sarcoidosis
Rheumatic	Arthralgia, inflammatory arthritis, myalgia	Dermatomyositis, myositis, polymyalgia-like syndrome, Sjögren syndrome, vasculitis
Renal	Increase in serum creatinine, nephritis	—
Ophthalmic	—	Uveitis, conjunctivitis, scleritis, episcleritis, blepharitis, retinitis
Neurologic	Sensorimotor neuropathy	Aseptic meningitis, autonomic neuropathy, encephalitis, facial nerve palsy, Guillain–Barré syndrome, myasthenia gravis, posterior reversible leukoencephalopathy, transverse myelitis
Hematologic	—	Aplastic anemia, hemolytic anemia, idiopathic thrombocytopenia purpura, lymphopenia, hemophilia
Cardiac	—	Cardiomyopathy, myocarditis, pericarditis

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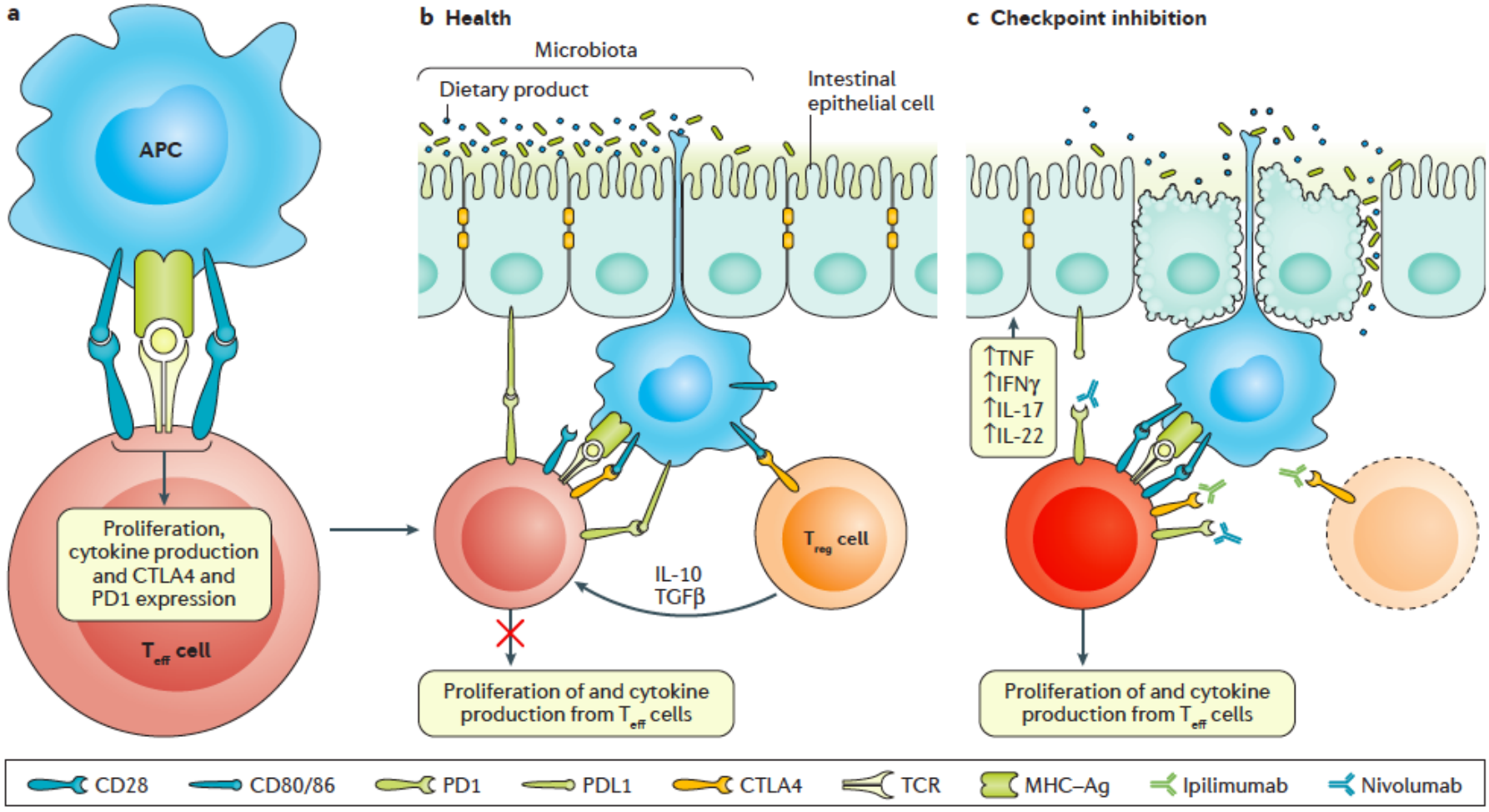
Different ICIs

	CTLA-4 inhibitor	PD-1 inhibitor		PD-L1 inhibitor	
	Ipilimumab	Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab
Dermatological					
Pruritus	25–30%	17%	11–21%	12–14%	<1%
Rash	33–34%	15%	10–21%	15%	<1%
Vitiligo	3–4%	10–11%	9%	NR	NR
Gastrointestinal					
Diarrhoea	36–38%	8–16%	8–20%	18–20%	1–2%
Colitis	8–10%	1–3%	1–2%	<1%	<1%
Hepatic					
Increased ALT	<1%	1–2%	2–8%	2–3%	0
Increased AST	1–2%	1–2%	3–10%	2–3%	0
Hepatitis	<1%	1–2%	1–2%	1–2%	1%
Endocrine					
Hypothyroidism	1–2%	4–5%	8–10%	2–4%	<1%
Hyperthyroidism	0–2%	0–3%	3–4%	1%	<1%
Hypophysitis	2–3%	<1%	<1%	<1%	<1%
Renal failure	1%	1–3%	<1%	0	NR
Pneumonitis	<1%	1–5%	4–6%	2.6%	<1%
Neurological	<1%	<1%	<1%	0	NR
NR, not reported					

Adapted from: Kumar V, Chaudhary N, Garg M, et al. Current diagnosis and management of immune related adverse events (irAEs) induced by immune checkpoint inhibitor therapy. Front Pharmacol 2017; 8:49

Colitis: damage mechanism



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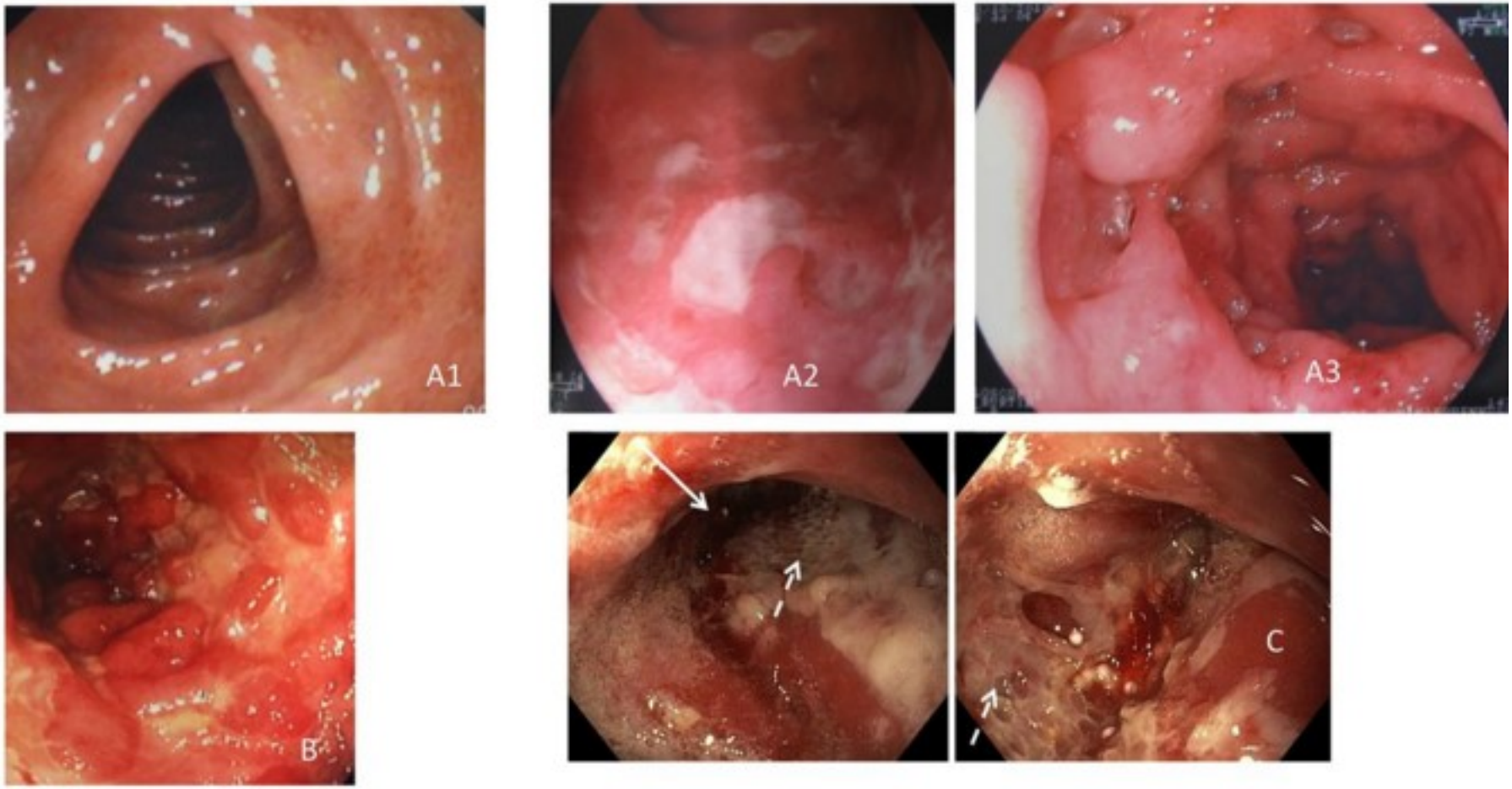
GI toxicity: anti-CTLA4

- **Diarrhoea** occurs in 27-54% of cases treated with anti-CTLA4 abs, median time of onset 11 mo
- GI toxicity is the *most severe* (grade 3 or higher) irAEs associated with anti-CTLA4.
- Concomitant FANS increased risk
- Most frequent symptom is diarrhoea (then abdominal pain and fever), with anemia e increased of PCR
- Need of **endoscopy** for differantial diagnosis

GI toxicity: anti-CTLA4



IPILIMUMAB-INDUCED ENTEROCOLITIS

Prediction of ipilimumab-related colitis

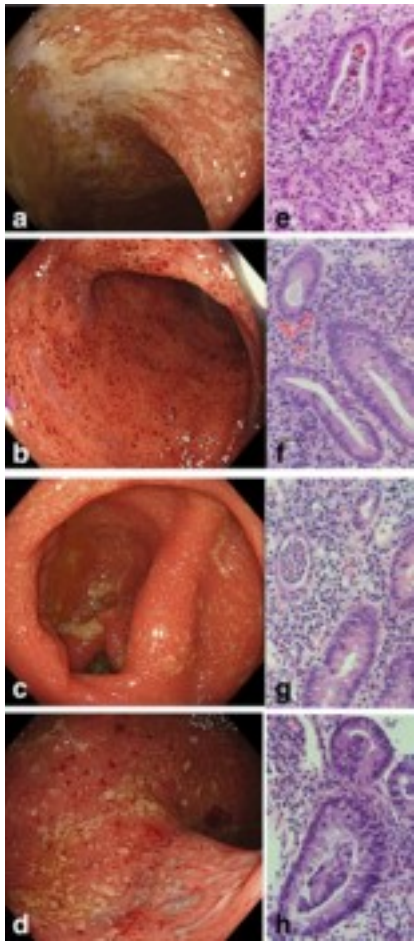
Baseline microbiota composition may predict ipilimumab-induced colitis.

An increased presence of bacteria belonging to the *Bacteroidetes* phylum species was found in patients who remained free of colitis after ipilimumab

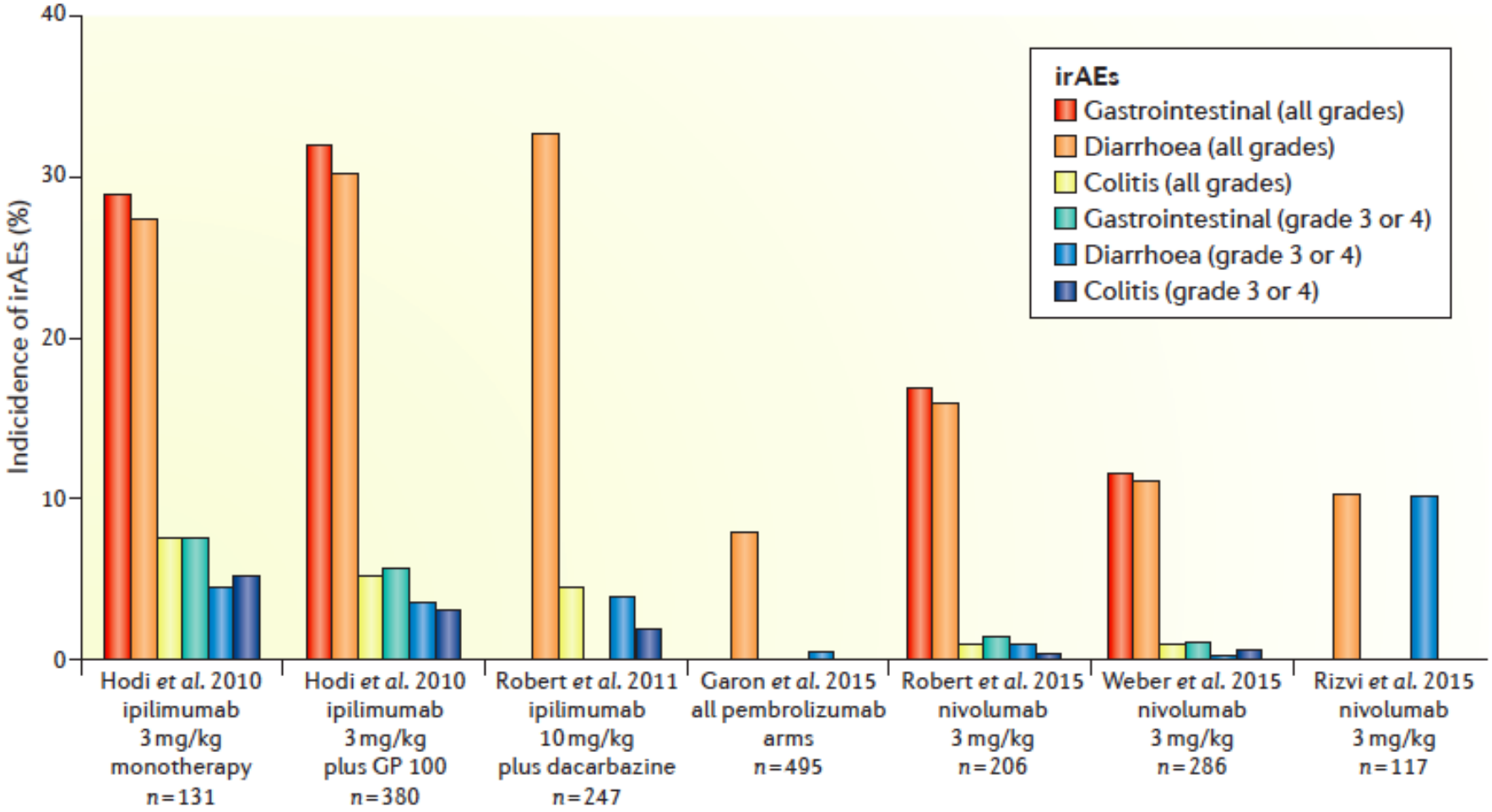
Mark A. Samaan et al. Nature Reviews Gastroenterology & Hepatology 2018

GI toxicity: anti-PD1 or anti-PD-L1

- Few data for anti-PD1 or anti-PD-L1
- Median time 3 months
- Four diffent patterns:
  - Acute colitis (= anti-CTLA4)
  - Microscopic colitis
  - Upper GI involvement
  - Pseudo-obstruction



GI toxicity observed among selected randomized controlled trials of ICIs



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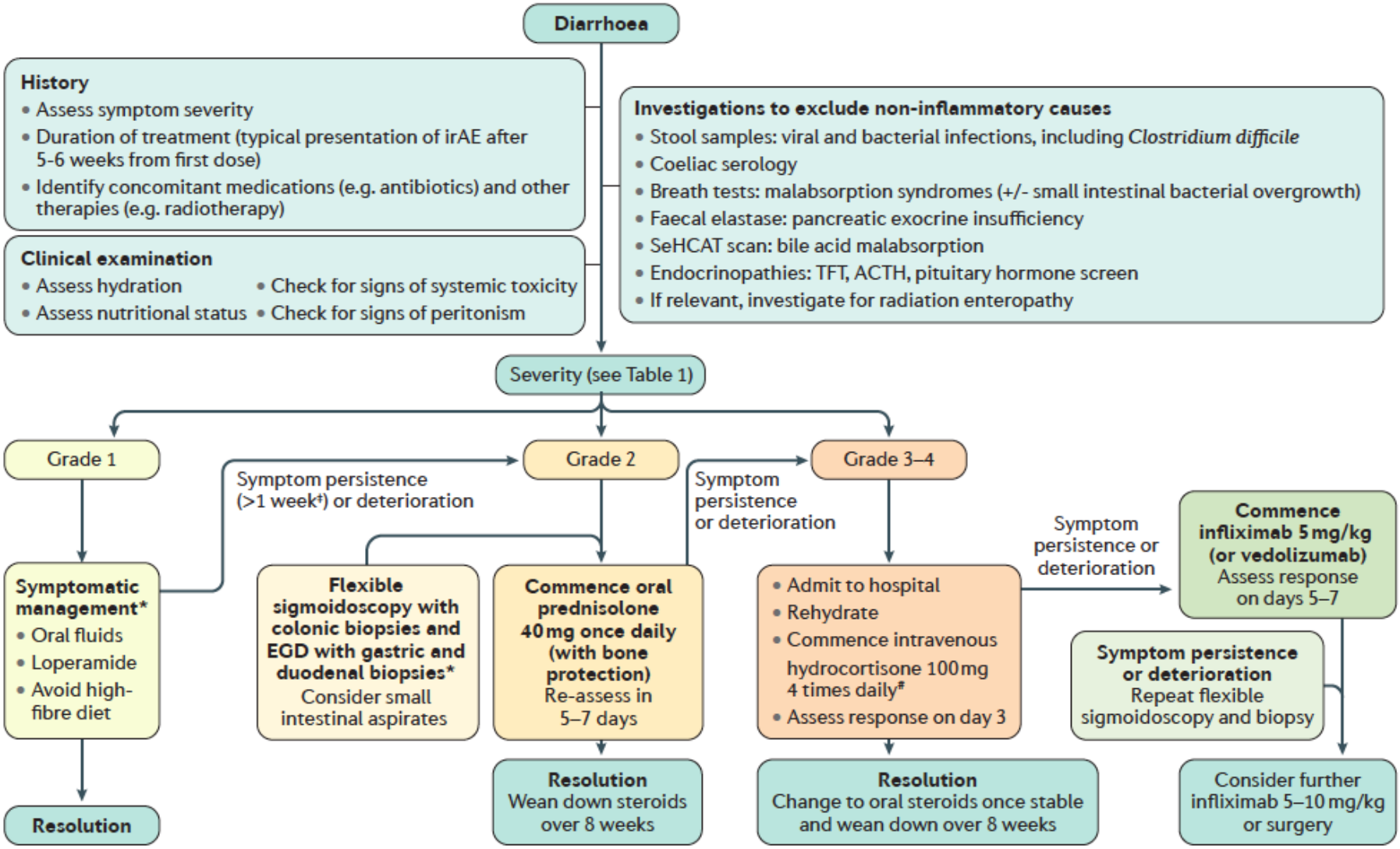
Suggested algorithm for the management of ICI-associated GI toxicity



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Studies of infliximab use and response ICI-induced enterocolitis

Study	Year of publication	Immune checkpoint inhibitor	Diarrhoea or enterocolitis (*n*)	Patients treated with infliximab *n* (%)	Infliximab doses (dose: *n* (%))	Patients who had response or remission *n* (%)
Horvat et al.[133]	2015	Ipilimumab	50	29 (58)	• 1: 21 (72) • 2: 3 (28)	21 (72)
Hillock et al.[136]	2017	Ipilimumab	Only patients treated with infliximab reported	13	• 1: 8 (62) • >1: 5 (28)	6 (46)
Marthey et al.[96]	2016	Ipilimumab or tremelimumab	39	12 (38)	Not reported	10 (83)
Verschuren et al.[135]	2016	Ipilimumab	27	12 (44)	• 1: 7 (58) • 2: 4 (33) • 3: 1 (9)	12 (100)
Jain et al.[95]	2017	Ipilimumab	16	9 (56)	1: 9 (100)	8 (89)
O'Connor et al.[134]	2016	Ipilimumab	16	5 (31)	• 1: 3 (60) • 2: 2 (40)	5 (100)

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Hepatotoxicity: Highlights

- **Acute hepatitis** resulting from treatment with immune checkpoint inhibitors is **rare**.
- Immune-mediated hepatitis diagnosis requires exclusion of all causes of hepatitis.
- **Liver histology** is paramount for the diagnosis and severity evaluation of liver damage (*in steroids and immunosuppresive refractory cases)*
- Management should be based on biological and histological severity of liver injury.

EleonoraDe Martin et al, Journal of Hepatology 2018

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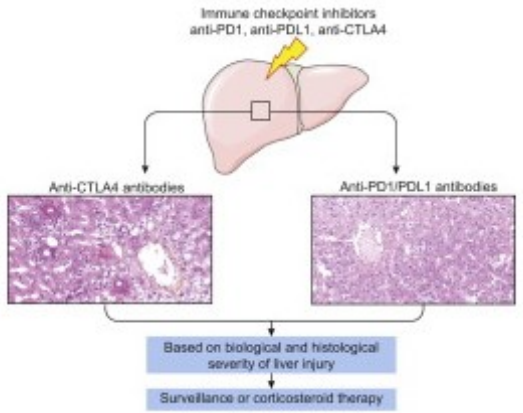
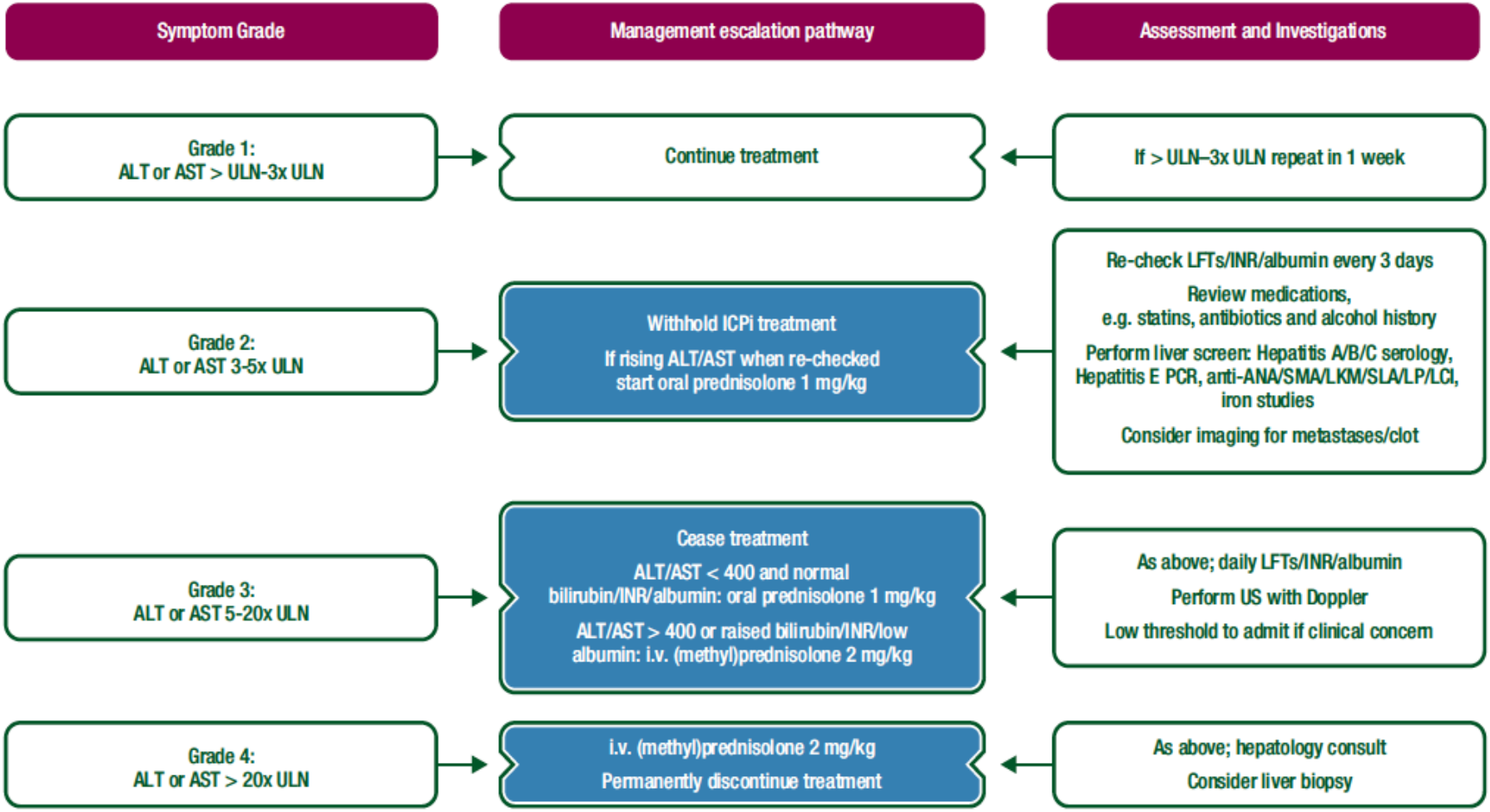
Hepatotoxicity

- Hepatitis occurs in 5-10% (1-2% G3) in ICIs monotherapy, 25-30% in combination (IPI+NIVO)
- All patients shoul be assessed with serum ALT/AST and bilirubin every cycle.
- Different patterns:
  - Lobular autoimmune haepatitis
  - Panlobular haepatitis



Hepatotoxicity: management



Hepatitis usually resolves within 4-6 weeks with appropriate treatment

ESMO 2017