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Review

The Other Side of the Checkpoint: An Emergency Physician's Guide to Immune-Related Adverse Events of Immune Checkpoint Inhibitors

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Abstract: Immune checkpoint inhibitors (ICIs) have reshaped prognosis across more than twenty malignancies, yet their mechanism of action carries the cost of a heterogeneous and potentially life-threatening spectrum of immune-related adverse events (irAEs) that may involve virtually every organ system. As indications expand and survival lengthens, a growing share of these patients reach emergency departments (EDs) before reaching their oncology team, where toxicity often masquerades as common acute pathology. This narrative review synthesises current epidemiology, pathophysiology, and management of clinically relevant irAEs from the perspective of acute care, drawing on guidelines from the American Society of Clinical Oncology, the European Society for Medical Oncology, the National Comprehensive Cancer Network, the Society for Immunotherapy of Cancer, and the European Society of Cardiology, supplemented by recent observational data and pharmacovigilance series. Organ-specific syndromes (cardiac, endocrine, pulmonary, gastrointestinal, hepatic, neurological, renal, haematological, and dermatologic) are described with diagnostic pearls, time-from-exposure patterns, key differential considerations, and graded treatment pathways. Particular attention is given to fulminant myocarditis, adrenal crisis, hyponatraemia of mixed pathogenesis, and neuromuscular emergencies, which carry disproportionate mortality. Early recognition, methodical exclusion of infection, and judicious use of high-dose corticosteroids form the backbone of emergency management of irAEs. Familiarity with this class of adverse events has become a competency of acute care, alongside sepsis recognition and stroke pathway activation.

Keywords: Immune Checkpoint Inhibitors; Immune-Related Adverse Events; Emergency Department; Myocarditis; Pneumonitis; Cancer Immunotherapy; Corticosteroids

1. Introduction

Within little more than a decade, immune checkpoint inhibitors (ICIs) have moved from experimental molecules to first-line therapy across more than twenty solid and haematological malignancies, including melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, urothelial carcinoma, gastric and oesophageal cancers, hepatocellular carcinoma, head and neck squamous cell carcinoma, and several lymphomas [1,2]. Approved agents target cytotoxic T-lymphocyte associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and lymphocyte activation gene 3 (LAG-3). Conservative estimates indicate that roughly 40% of patients with advanced cancer in high-income countries are now eligible for ICI-based therapy [3,4].

The disinhibition of T-cell responses that drives anti-tumour activity also produces a constellation of autoimmune-

like syndromes collectively termed immune-related adverse events (irAEs). Any-grade irAEs occur in 60% to 80% of patients receiving PD-1 or PD-L1 monotherapy and exceed 90% with dual CTLA-4 plus PD-1 combinations; grade 3 or higher events affect roughly 15% of monotherapy patients and over half of those on combination therapy [5–7]. Most resolve with appropriate management. Fulminant presentations, by contrast, carry case-fatality rates between 25% and 50%, with myocarditis, neurological syndromes, pneumonitis, colitis, and hepatitis accounting for most fatal cases [8].

A growing share of these patients first present to the ED rather than to their oncology team. Single-centre cohorts report that 30% to 40% of patients receiving ICIs attend an ED at least once during therapy, and roughly one in ten of those visits represents a new irAE [9,10]. Symptoms are nonspecific (fatigue, nausea, breathlessness, diarrhoea, headache) and overlap with infection, disease progression, or unrelated comorbidity. Delays between arrival and initiation of corticosteroids correlate with worse outcomes in observational data, particularly for cardiac, neurological, and severe pulmonary toxicity [11,12]. A multi-centre risk-stratification effort, the Immune-Related Emergency Disposition Index (IrEDi), is currently being developed precisely to address this gap [13–16].

The aim of this review is to provide a syndrome-based, emergency-oriented framework for the recognition and initial management of irAEs. The intent is to translate the consensus produced by oncology societies into the operational reality of acute care, where time, information, and access to subspecialty consultation are constrained.

2. Pathophysiology and Risk Patterns

CTLA-4 and PD-1 are co-inhibitory checkpoints that ordinarily restrain T-cell activation. CTLA-4 acts in lymph nodes during T-cell priming; PD-1, engaged peripherally by PD-L1, dampens cytotoxic responses at the tumour site [17,18]. Blocking either pathway amplifies anti-tumour activity at the cost of peripheral tolerance, and the toxicity signature reflects which checkpoint is hit. CTLA-4 blockade (ipilimumab, tremelimumab) drives higher rates of colitis, hypophysitis, and severe dermatitis; PD-1 or PD-L1 blockade (nivolumab, pembrolizumab, cemiplimab, atezolizumab, durvalumab, avelumab, dostarlimab) leans toward thyroiditis, pneumonitis, and arthritis [5,19]. Combination regimens roughly double the rates: grade 3 or higher toxicity rises from approximately 15% with PD-1 monotherapy to over 55% with nivolumab plus ipilimumab [6]. Relatlimab, an LAG-3 inhibitor used with nivolumab for advanced melanoma, sits between the two profiles [20].

Onset is variable. Most events appear within the first three to six months; a substantial minority manifests later, including beyond a year and after the last infusion [21]. Each organ system follows a characteristic temporal pattern, summarised in **Table 1**. Half-lives of around three weeks for IgG4 monoclonals mean that immune effects can persist for weeks after the last dose, which matters when an irAE is suspected in a patient who has already stopped therapy. Identified risk factors include pre-existing autoimmune disease, prior radiotherapy at the affected site, concurrent infection, and certain pharmacogenetic and microbiome features [21]; older age, performance status, sex, and ethnicity have shown inconsistent associations in observational data.

Table 1. Typical onset, incidence, and emergency department features of organ-specific immune-related adverse events.

Organ System	Typical Onset	Incidence (Any Grade)	Salient ED Features
Cutaneous	2 to 6 weeks	30% to 50%	Maculopapular rash, pruritus; rare SJS/TEN or DRESS
Gastrointestinal (colitis)	5 to 10 weeks	10% to 35% (anti-CTLA-4)	Diarrhoea, abdominal pain, occasional haematochezia; perforation risk
Hepatic	6 to 14 weeks	5% to 30%	Asymptomatic transaminitis or jaundice; rule out viral and drug causes
Endocrine (hypophysitis)	8 to 12 weeks	10% (anti-CTLA-4); <1% (anti-PD-1)	Headache, fatigue, hyponatraemia, hypotension; risk of adrenal crisis
Pulmonary (pneumonitis)	Median ~2.5 months	3% to 10%	Cough, dyspnoea, hypoxia; multiple HRCT patterns; DAD worst prognosis
Cardiac (myocarditis)	Median 17 to 34 days	0.27% to 2%	Variable: chest pain, dyspnoea, arrhythmia, shock; check troponin and ECG
Neurological	5 to 7 weeks	<5%	Encephalitis, myasthenia gravis, GBS-like, aseptic meningitis

Table 1. *Cont.*

Organ System	Typical Onset	Incidence (Any Grade)	Salient ED Features
Renal	Median ~3 months	2% to 5%	Acute interstitial nephritis pattern; concurrent PPI, NSAID common
Endocrine (thyroid)	4 to 12 weeks	5% to 15%	Transient hyperthyroid phase, then hypothyroidism; rare storm

Note: Incidences are approximate and were drawn from registry, pharmacovigilance, and meta-analytical sources current to 2024 [5,7,8,18,19]. Newer regimens (including LAG-3 combinations) may shift these figures and are reflected where published data permit. Combination regimens roughly double monotherapy rates. CTLA-4, cytotoxic T-lymphocyte antigen 4; DAD, diffuse alveolar damage; DRESS, drug reaction with eosinophilia and systemic symptoms; ECG, electrocardiogram; GBS, Guillain-Barré syndrome; HRCT, high-resolution computed tomography; NSAID, non-steroidal anti-inflammatory drug; PD-1, programmed cell death protein 1; PPI, proton pump inhibitor; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

3. The Emergency Physician's Diagnostic Framework

Three habits anchor reliable recognition of irAEs in the ED.

3.1. Ask about Immunotherapy by Name

A generic question about ”chemotherapy” misses ICI exposure; many patients describe their treatment by the drug name (pembrolizumab, nivolumab) or by the proprietary name (Keytruda, Opdivo). Exposure within the preceding 12 months should prompt active consideration of irAEs, regardless of how distant the last dose appears.

3.2. Treat Nonspecific Symptoms as Suspect

Fatigue, anorexia, low-grade fever, mild dyspnoea, or new bowel habit changes may be the only presenting features of life-threatening toxicity. The differential should explicitly include irAE alongside infection and progression. Several centres have validated structured pathways that screen for irAE in any oncology patient presenting acutely [22].

3.3. Exclude Infection Methodically

Sepsis remains the leading mimicker of irAEs and the most consequential misdiagnosis. Blood cultures, urinalysis, chest imaging, and, where indicated, stool studies and lumbar puncture should be obtained early. In selected scenarios (fulminant myocarditis, adrenal crisis, severe neurological deterioration) empirical high-dose corticosteroids are warranted simultaneously with the infection work-up rather than after it.

Severity grading follows the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0: grade 1 indicates mild symptoms not interfering with activities of daily living; grade 2, moderate symptoms limiting instrumental activities; grade 3, severe symptoms requiring hospitalisation; grade 4, life-threatening; grade 5, death [23]. Acute management follows the grade more closely than the specific organ, with notable exceptions for cardiac and neurological syndromes, and for adrenal crisis (**Table 2**). General rules are summarised below.

Table 2. General framework for emergency management of immune-related adverse events based on Common Terminology Criteria for Adverse Events version 5.0 grade [23].

Grade	Severity	ICI Status	Immunosuppression
1	Mild; not interfering with daily living	Usually continued, with monitoring	Symptomatic measures; topical agents where applicable. Note exceptions for low-grade cardiac, neurological, hepatic, or pulmonary signals (see Section 10)
2	Moderate; limits instrumental activities	Hold; reassess in 48 to 72 hours	Oral prednisone 0.5 to 1 mg/kg/day
3	Severe; warrants hospitalisation	Discontinue pending re-evaluation	Methylprednisolone 1 to 2 mg/kg/day IV; admit
4	Life-threatening	Permanent discontinuation (except controllable endocrinopathies)	Methylprednisolone 1 to 2 mg/kg/day; pulse 500 to 1,000 mg/day for cardiac, neurological, or fulminant pulmonary disease; consider second-line agents early

Note: Organ-specific exceptions apply, particularly for cardiac and neurological syndromes, which warrant pulse-dose corticosteroids regardless of haemodynamic stability, and for adrenal crisis, which requires empirical hydrocortisone before laboratory confirmation. Grade 1 disease is not always benign: asymptomatic troponin or transaminase elevation in an ICI-treated patient deserves closer observation, as detailed in Section 10. ICI, immune checkpoint inhibitor; IV, intravenous.

Oncology should be contacted whenever the diagnosis of irAE is plausible, even outside business hours. A documented exchange about the suspected diagnosis, the chosen immunosuppressive regimen, and the planned disposition is the single most informative piece of communication a referring ED can produce.

4. Cardiovascular Toxicity: Myocarditis and the Triple-M Overlap

ICI-related myocarditis (ICI-M) was once thought rare; troponin-based surveillance suggests an incidence between 0.27% and roughly 2% with monotherapy, climbing to 2% to 3% with dual checkpoint blockade [24, 25]. Despite its modest frequency, ICI-M is the most lethal irAE: case-fatality rates between 25% and 50% have been described in pharmacovigilance and registry data [26,27]. Onset is early, with a median time from first dose of 17 to 34 days; over 80% of cases present within the first 90 days [26].

The presentation is protean. Chest pain may be absent; fatigue, dyspnoea, palpitations, syncope, and arrhythmia all feature in case series. Up to a third of patients exhibit overlap with myositis and myasthenia gravis, the so-called triple-M (3M) syndrome, in which proximal weakness, ptosis, dysphagia, or respiratory failure accompany cardiac involvement and confer a markedly worse prognosis [28].

Initial work-up in the ED should be performed in every ICI-treated patient with new cardiopulmonary symptoms and includes a 12-lead electrocardiogram (looking for new conduction disease, ST-T changes, low voltage, or ventricular ectopy; new bundle branch block carries particular concern); high-sensitivity troponin (a single normal value has high negative predictive value early in presentation but should be repeated if symptoms persist); natriuretic peptides; transthoracic echocardiogram (left ventricular ejection fraction is often preserved despite severe inflammation); and continuous telemetry. The threshold for transfer to a coronary or intensive care unit should be low, because progression to high-grade atrioventricular block is rapid and unpredictable.

Cardiac magnetic resonance and endomyocardial biopsy provide definitive confirmation [29]. Two diagnostic frameworks are in use: the Bonaca criteria (definite, probable, or possible categories combining biopsy, cardiac magnetic resonance, troponin trajectory, and clinical syndrome) and the 2022 European Society of Cardiology and International Cardio-Oncology Society (ESC-ICOS) criteria [25,29]. The two frameworks show good but imperfect concordance and serve complementary purposes in current cardio-oncology practice.

Treatment begins with intravenous methylprednisolone 500 to 1,000 mg daily for three to five days, irrespective of haemodynamic status, followed by an oral taper over four to six weeks [30]. This pulse-dose approach is stronger than that recommended by the ASCO guideline, which allows initiation at 1 to 2 mg/kg/day with rapid escalation to pulse dosing if no clinical response is observed within 24 h [31]. Three observations justify the more aggressive position adopted at high-volume cardio-oncology centres: case-fatality remains 25% to 50% despite available therapy [26,27]; the therapeutic window appears narrow, with retrospective data suggesting better outcomes the earlier methylprednisolone is given [30]; and progression to high-grade conduction disease can be abrupt and unpredictable [26,28]. The position should be understood as expert consensus, derived from referral-centre experience and supported by mechanistic and observational data, rather than as a randomised-trial standard [32].

Steroid-refractory disease may justify second-line agents such as mycophenolate mofetil, abatacept, or antithymocyte globulin. Infliximab is contraindicated because of an association with heart failure decompensation; tofacitinib and other Janus kinase inhibitors have emerging case-series evidence [33,34]. Patients must remain on telemetry until troponin trends downward and conduction has stabilised.

A practical pearl: any oncology patient with unexplained tachycardia, hypotension, or arrhythmia in whom ICI exposure is suspected should have a troponin drawn before discharge, even when the working diagnosis appears unrelated. Published case reports describe fatal ICI-M initially misdiagnosed as anxiety, gastroenteritis, or panic attack.

5. Endocrine Emergencies

Endocrine irAEs occur in 10% to 35% of patients receiving ICIs and span thyroid dysfunction, hypophysitis, primary adrenal insufficiency, and insulin-dependent diabetes [5]. Two presentations dominate the ED context by virtue of their lethality if missed: adrenal crisis and severe thyrotoxicosis [35].

5.1. Hypophysitis and Secondary Adrenal Insufficiency

CTLA-4 blockade produces clinically apparent hypophysitis in roughly 10% of recipients; PD-1 blockade does so in less than 1%, although magnetic resonance evidence of pituitary inflammation is more frequent than the clin-

ical syndrome [36]. The classic presentation comprises headache, profound fatigue, anorexia, nausea, vomiting, and hyponatraemia, often with hypotension. Visual field changes are uncommon. Median onset is 8 to 12 weeks. Critically, adrenocorticotropic hormone and thyroid-stimulating hormone deficiency may persist after pituitary inflammation has resolved, leaving the patient dependent on lifelong hormone replacement.

5.2. Adrenal Crisis

Any ICI-treated patient presenting with hypotension, electrolyte disturbance, or unexplained shock should receive empirical hydrocortisone 100 mg intravenously after blood is drawn for cortisol and adrenocorticotropic hormone, and before levothyroxine is administered if both adrenal and thyroid deficiency are suspected. Premature levothyroxine in untreated adrenal insufficiency can precipitate fatal cardiovascular collapse. Subsequent management mirrors that of classical adrenal crisis: isotonic crystalloid resuscitation, glucose correction, identification and treatment of precipitants (infection in particular), and hydrocortisone 50 mg every six hours until clinical stability.

5.3. Hyponatraemia in the ICI-Treated Patient

Hyponatraemia in the ED warrants a moment of pause whenever ICI exposure is on the chart. The reflex of fluid restriction for presumed syndrome of inappropriate antidiuretic hormone secretion (SIADH), or of hypertonic saline for severe hyponatraemia, can be actively harmful if undiagnosed adrenal insufficiency is the underlying mechanism. Both SIADH and adrenal insufficiency present with euvolaemic, hypotonic hyponatraemia, and the two may coexist [37,38]. Discriminating clues at the bedside include hypotension, hyperkalaemia, hypoglycaemia, hyperpigmentation in primary adrenal insufficiency, and a history of high-dose corticosteroid use suggesting tertiary insufficiency. None is fully sensitive. A practical rule, supported by case-series and case-report literature, is to obtain cortisol and ACTH at presentation and to give hydrocortisone 100 mg intravenously empirically when hyponatraemia is accompanied by hypotension, hyperkalaemia, hypoglycaemia, or unexplained vomiting in an ICI-treated patient, before any decision on fluid restriction or hypertonic saline is taken [37,38]. Sodium correction in confirmed SIADH should otherwise follow standard rate limits to avoid osmotic demyelination.

5.4. Thyroid Dysfunction

Anti-PD-1 agents trigger thyroiditis in 5% to 15% of patients, typically with a transient hyperthyroid phase (usually three to six weeks) followed by permanent hypothyroidism in the majority [39]. The hyperthyroid phase is usually mild but may cause tachycardia, atrial fibrillation, or weight loss; symptomatic patients respond to beta-blockade. True thyroid storm is rare but reported and should be managed with conventional Burch-Wartofsky-guided therapy. Antithyroid drugs are seldom needed, because the pathology is destructive rather than synthetic.

5.5. Insulin-Dependent Diabetes Mellitus

ICI-induced diabetes occurs in less than 1% of recipients but presents abruptly, often in diabetic ketoacidosis, with rapid pancreatic beta-cell failure [40]. C-peptide is typically low or undetectable. Diabetic ketoacidosis management follows standard protocols. Corticosteroids do not reverse the pancreatic injury and are not indicated; lifelong insulin is required, and ICI is typically resumed after metabolic stabilisation.

6. Pulmonary Toxicity: Checkpoint Inhibitor Pneumonitis

Checkpoint inhibitor pneumonitis (CIP) occurs in 3% to 5% of patients on monotherapy and 7% to 10% on combination regimens; rates in NSCLC populations are higher, partly reflecting baseline lung pathology [41, 42]. Although grade 3 or higher events occur in only 1% to 2% of recipients, CIP accounts for a disproportionate share of treatment-related mortality, with reported case-fatality rates between 10% and 17% in historical series [43]. Median onset sits around 2.5 months from initiation, with wide individual variability [44].

Symptoms (cough, dyspnoea, fatigue, hypoxia, fever in roughly a third of cases) are nonspecific. The ED differential should always include infection (community-acquired pneumonia, Pneumocystis jirovecii pneumonia, viral pneumonia including influenza and respiratory syncytial virus, atypical bacteria), pulmonary embolism, lymphangitic carcinomatosis, radiation pneumonitis recall, and pulmonary oedema. High-resolution computed tomography

of the chest is the key investigation. Five radiological patterns are described: cryptogenic organising pneumonia-like, non-specific interstitial pneumonia-like, hypersensitivity pneumonitis-like, diffuse alveolar damage-like, and bronchiolitis-predominant disease. Diffuse alveolar damage carries the worst prognosis [45].

Initial work-up includes pulse oximetry on room air and on exertion, arterial blood gas if hypoxia is present, complete blood count, basic chemistry, lactate, blood cultures, respiratory viral panel, and, where local protocols allow, urinary Legionella and Streptococcus pneumoniae antigens. Sputum analysis or bronchoalveolar lavage may be required when infection cannot be excluded; bronchoscopy is rarely feasible in the ED itself, although it should be discussed early with the admitting team.

Treatment escalates with grade. Grade 2 disease (symptoms not requiring oxygen, with only one lobe involved on imaging) is treated with oral prednisone 1 to 2 mg/kg/day. Grade 3 to 4 disease (oxygen requirement, multilobar involvement, or respiratory failure) warrants intravenous methylprednisolone 2 to 4 mg/kg/day and hospital admission, with intensive care for hypoxic respiratory failure. Empirical broad-spectrum antibiotic cover is reasonable until infection is excluded. Steroid-refractory disease (no improvement at 48 to 72 h) prompts second-line therapy with infliximab, mycophenolate mofetil, intravenous immunoglobulin, or cyclophosphamide, ideally guided by a multidisciplinary discussion [46].

A practical caution applies to patients on tyrosine kinase inhibitors plus ICIs. The combination of osimertinib with durvalumab in early studies produced interstitial lung disease rates of around 22%, prompting termination of the TATTON arm; hybrid pneumonitis can also develop when a tyrosine kinase inhibitor is sequenced after an ICI, given the prolonged immune effects of checkpoint blockade [47].

7. Gastrointestinal Toxicities

7.1. Immune-Related Enterocolitis

Diarrhoea and colitis are among the most common irAEs. With CTLA-4 blockade, all-grade diarrhoea and colitis occur in approximately 35% and 10% of patients, respectively; rates fall to about 10% and 1% with PD-1 monotherapy and rise to 32% and 15% with combination therapy [48]. The median time to onset is five to ten weeks. Diarrhoea, abdominal pain, and, less frequently, haematochezia and fever dominate; severe disease may progress to dehydration, toxic megacolon, perforation (reported in 1% to 6.6% of cases), and death [49].

The ED evaluation begins with vital signs, abdominal examination for peritoneal signs, stool culture, Clostridioides difficile testing, and, where refractory or at risk, cytomegalovirus polymerase chain reaction. Cross-sectional imaging is indicated when perforation, ileus, or megacolon is suspected. Endoscopic confirmation with biopsy is recommended for grade 2 or higher disease and is increasingly performed early, since rectosigmoidoscopic findings predict response to escalation of therapy.

Treatment escalates by grade. Grade 1: continue ICI, supportive measures, careful hydration. Grade 2: hold ICI; oral prednisone or intravenous methylprednisolone 1 mg/kg/day. Grade 3 to 4: hospital admission and methylprednisolone 2 mg/kg/day intravenously. Disease refractory at 72 to 96 hours warrants infliximab 5 mg/kg or vedolizumab 300 mg, ideally after endoscopic evaluation [50]. Antimotility agents such as loperamide should be avoided because of perforation risk, and opiates are best avoided for the same reason [51,52].

7.2. Immune-Related Hepatitis

Liver involvement, usually clinically silent, occurs in roughly 5% to 10% of patients on monotherapy and up to 30% on combination therapy [53]. Most cases manifest as asymptomatic transaminase elevation detected on routine bloods; the ED encounter is more often driven by jaundice, fatigue, abdominal discomfort, or coagulopathy. Median onset is 6 to 14 weeks.

The differential demands rigorous exclusion of viral aetiology (hepatitis A, B, C, E, Epstein-Barr virus, cytomegalovirus, herpes simplex virus), drug-induced liver injury from concurrent medications, autoimmune hepatitis (antinuclear antibodies, anti-smooth muscle antibodies, immunoglobulin G subclasses), biliary obstruction (with abdominal ultrasound), and metastatic infiltration. Acetaminophen co-exposure is easily missed and should be specifically queried.

Treatment is grade-dependent. Asymptomatic transaminase elevation up to 3 times the upper limit of normal usually does not require steroids if hepatitis B or other contributors are excluded. Grade 2 (alanine aminotrans-

ferase 3 to 5 times the upper limit of normal): methylprednisolone 0.5 to 1 mg/kg/day. Grade 3 (5 to 20 times): 1 to 2 mg/kg/day, hospital admission. Grade 4 (>20 times) or any synthetic dysfunction (international normalised ratio >1.5, encephalopathy): 2 mg/kg/day intravenously, intensive care. Mycophenolate mofetil is the preferred second-line agent for steroid-refractory cases. Infliximab should not be used in immune-related hepatitis, owing to its inherent hepatotoxicity [54].

8. Neurological Toxicities

Neurological irAEs occur in less than 5% of ICI recipients, yet account for a disproportionate share of fatalities, with up to 15% of all ICI deaths attributable to neurological causes in pharmacovigilance series despite their rarity [8,55]. The phenotype range is wide and includes encephalitis, aseptic meningitis, myasthenia gravis, Guillain-Barré-like polyradiculoneuropathy, myositis, demyelinating disease, and cranial neuropathies. Median onset is 5 to 7 weeks, although later presentations are well described [56].

Five clinical pictures deserve special mention in the ED.

8.1. Encephalitis

Subacute confusion, behavioural change, seizures, or focal deficits in a patient on ICIs should be considered encephalitis until proven otherwise. Lumbar puncture typically shows a mild lymphocytic pleocytosis with elevated protein; magnetic resonance imaging may reveal limbic enhancement or be unremarkable. Empirical acyclovir is reasonable while herpes simplex encephalitis is excluded. Methylprednisolone 1 to 2 mg/kg/day is initiated as soon as central nervous system infection has been excluded or treated empirically; pulse therapy is reserved for severe disease, with addition of intravenous immunoglobulin (2 g/kg over 2 to 5 days) or plasmapheresis when there is no response or when severe disability is evolving [57].

8.2. Myasthenia Gravis

ICI-related myasthenia behaves more aggressively than classical autoimmune myasthenia. Up to 30% of reported cases develop respiratory failure requiring mechanical ventilation, and case fatality has been reported between 20% and 30% [58]. Bulbar features (dysphagia, dysarthria), ptosis, and proximal weakness should be specifically sought; fluctuation is less pronounced than in classical disease. Bedside forced vital capacity and negative inspiratory force, even when imperfect, are more informative than oxygen saturation, which is preserved until catastrophic decompensation. Overlap with myositis and myocarditis is frequent; troponin and creatine kinase should therefore be checked in every suspected case. Treatment combines high-dose corticosteroids with early intravenous immunoglobulin or plasmapheresis. Drugs that exacerbate neuromuscular transmission (aminoglycosides, fluoroquinolones, beta-blockers, magnesium, neuromuscular blockers) must be avoided.

8.3. Guillain-Barré-like Syndrome

Ascending weakness, areflexia, and autonomic involvement form the picture. Albuminocytological dissociation in cerebrospinal fluid may be present. Treatment with intravenous immunoglobulin or plasmapheresis is preferred to corticosteroids alone in classical Guillain-Barré syndrome; in the ICI-related variant, both are typically combined, given the autoimmune mechanism.

8.4. Aseptic Meningitis

Headache, neck stiffness, photophobia, and fever in the absence of bacterial growth on cerebrospinal fluid culture characterise this entity. Leptomeningeal enhancement may be visible on contrast-enhanced magnetic resonance imaging. Prompt corticosteroids are typically curative, although progression to encephalitis is a recognised risk [59].

8.5. Myositis

Proximal weakness, myalgia, and elevated creatine kinase are the cardinal features. The overlap with myocarditis and myasthenia (the 3M syndrome described in Section 4) demands cardiac and respiratory monitoring in every case.

9. Renal, Dermatological, Haematological and Rheumatological Manifestations

9.1. Renal

Acute kidney injury attributed to ICIs occurs in 2% to 5% of recipients; acute tubulointerstitial nephritis is the predominant histological pattern, often in patients on concurrent proton pump inhibitors, non-steroidal anti-inflammatory drugs, or beta-lactam antibiotics [60]. Urinalysis often shows sterile pyuria and modest proteinuria; urine eosinophils have limited sensitivity. Suspected medications should be stopped and methylprednisolone 0.5 to 2 mg/kg/day should be initiated for grade 2 or higher injury. Renal biopsy may be considered if recovery is slow or the diagnosis remains uncertain [61].

9.2. Dermatological

Rash, pruritus, and lichenoid eruptions are common (around 40%) and rarely require ED management. The serious exceptions, all true dermatological emergencies, are Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), and bullous pemphigoid [62]. Mucosal involvement, full-thickness desquamation, dusky erythema, or systemic features should prompt immediate dermatology consultation, intravenous fluids and analgesia, methylprednisolone (with adjunctive intravenous immunoglobulin or cyclosporine for Stevens-Johnson syndrome and toxic epidermal necrolysis as per institutional protocol), and consideration of transfer to a burn unit when surface involvement is extensive [63].

9.3. Haematological

Immune thrombocytopenia, autoimmune haemolytic anaemia, pure red cell aplasia, aplastic anaemia, and haemophagocytic lymphohistiocytosis have all been reported [64]. Any cytopenia in an ICI-treated patient deserves a peripheral blood smear, reticulocyte count, haptoglobin, direct antiglobulin test, lactate dehydrogenase, ferritin, and triglycerides. Haemophagocytic lymphohistiocytosis may present as fever of unknown origin with bicytopenia or pancytopenia and warrants urgent haematology input.

9.4. Rheumatological

Inflammatory arthritis, polymyalgia-like syndromes, sicca symptoms, and vasculitis have all been described. Most are not ED emergencies, although acute polyarthritis may present to acute care and benefit from a clear referral pathway to rheumatology [65].

10. Pitfalls in the Use of Corticosteroids

A persistent misconception holds that any suspected irAE deserves empirical high-dose corticosteroids in the ED. The reality is more nuanced. Premature corticosteroid administration in undifferentiated illness can mask infection, blunt diagnostic yield (particularly for atypical pneumonia, occult abscess, or fungal disease), worsen latent tuberculosis or hepatitis B, and complicate subsequent endoscopic, cytological, or microbiological evaluation [66,67].

A pragmatic approach distinguishes three tiers, listed explicitly here for cross-reference with the organ-specific sections. First-tier (empirical) therapy is reserved for syndromes in which the diagnosis is unambiguous on clinical grounds and delay would be life-threatening. These are: suspected ICI myocarditis with troponin rise and conduction disease (Section 4); adrenal crisis (Section 5.2); severe encephalitis or ICI-related myasthenia with respiratory compromise (Sections 8.1 and 8.2); fulminant pneumonitis with hypoxia (Section 6); and Stevens-Johnson syndrome or toxic epidermal necrolysis (Section 9.2). In these scenarios, methylprednisolone 1 g intravenously (cardiac, neurological) or 1 to 2 mg/kg/day (other) should be given alongside the diagnostic work-up, after blood for cultures and relevant assays has been drawn. The cardiac recommendation in Section 4 is an instance of this first-tier logic, not a departure from it. Second-tier (targeted) therapy, after exclusion of infection, is appropriate for the broader range of grade 2 to 3 syndromes that allow a brief, focused diagnostic window measured in hours rather than days. Third-tier (watchful waiting) is acceptable for most grade 1 disease and for some grade 2 dermatological or endocrine events, where the risks of unnecessary immunosuppression outweigh the marginal benefit of early therapy [68].

Grade 1 disease is not, however, uniformly benign. Several scenarios warrant closer observation despite the apparent mildness of the presentation. Asymptomatic troponin elevation in an ICI-treated patient may herald evolving myocarditis and should prompt serial troponin measurement, electrocardiographic monitoring, and early cardio-oncology contact rather than discharge [26,30]. Asymptomatic transaminase elevation requires the same viral and drug-induced workup as higher grades, and trends, not absolute values, often drive the next step [54]. A mildly elevated thyroid-stimulating hormone in the absence of symptoms is usually safe to observe, but a euvolaemic hyponatraemia in the same patient is not, as outlined in Section 5.3. The general principle is that any grade 1 finding in a cardiac, hepatic, neurological, or pulmonary system, or any electrolyte disturbance, deserves a low threshold for repeat testing and explicit communication with the treating oncology service before discharge.

Prophylaxis for opportunistic infection should be considered for any patient anticipated to receive a prednisone-equivalent dose of 20 mg or more per day for four weeks or longer. Pneumocystis jirovecii prophylaxis with trimethoprim-sulfamethoxazole, antiviral prophylaxis where herpes reactivation is a concern, and screening for latent hepatitis B (with antiviral cover before infliximab) are standard considerations [69]. The taper of corticosteroids extends over four to six weeks for most syndromes and longer for pneumonitis, hepatitis, and neurological toxicities, where rebound is common with abrupt withdrawal.

After resolution, the question of ICI rechallenge frequently reaches the oncology clinic and indirectly the ED, since the recurrence of an irAE within days of restarting therapy is a recognised pattern. Updated pharmacovigilance data from VigiBase identify recurrence of the same irAE in approximately 32% of rechallenges overall, with the highest rates for nephritis (50%), dermatological events (44%), and colitis (39%), and the lowest for adrenal events [70]. The figures are not directly actionable in the ED, but knowing them allows the emergency physician to take a recurrence seriously when a patient on rechallenge returns with apparently mild symptoms.

11. Disposition, Handoff and the Immunotherapy Passport

Disposition decisions in the ED hinge on grade and on the affected organ. As a general rule, every grade 3 or 4 irAE warrants admission, with critical care reserved for cardiac, neurological, severe pulmonary, or haematological involvement. Grade 2 events may be discharged with rapid follow-up (within 24 to 72 h) by oncology, a clear oral corticosteroid plan, written safety-netting (specifically: which symptoms mandate return), and verified contact with the oncology team. Grade 1 disease usually requires only symptomatic management and outpatient communication, with the caveats discussed in Section 10.

Several centres now issue patients an "immunotherapy passport", a wallet-sized card identifying the patient as an ICI recipient, listing the agent and date of last dose, recording known toxicities, and providing direct contact for the treating oncology service. The card is a low-cost intervention shown to shorten the diagnostic process in ED encounters; structured emergency-department disposition tools, such as the Immune-Related Emergency Disposition Index currently under multi-centre validation, complement this approach by stratifying patients on arrival [13]. Adoption of patient identification tools remains patchy, and institutional standardisation is a clear opportunity, particularly in healthcare systems where ICI use is expanding faster than the cellular therapy infrastructure that historically supported its safe deployment.

Handoff to the admitting team should specify the working diagnosis (with grade), the immunosuppressive regimen already initiated, the status of the infection work-up, and the planned monitoring (telemetry, neurological observation, hourly urine output, repeat troponin). A succinct, structured note saves hours of subsequent confusion.

12. Conclusions

Immune checkpoint inhibitors are no longer a niche oncology therapy; their toxicity is therefore no longer a niche concern. The emergency physician encounters ICI recipients across the full clinical spectrum, from mild dermatitis to cardiogenic shock. Three principles travel reliably across that spectrum: ask about immunotherapy by name in any cancer patient; exclude infection methodically rather than reflexively; and reserve high-dose corticosteroids for situations where the diagnostic balance and the time sensitivity together justify their use. Institutional pathways, easy access to oncology consultation, and patient-facing identification tools close the loop. Practical familiarity with this class of adverse events has become a competency of acute care alongside sepsis recognition and

stroke pathway activation, and prompt recognition is the principal factor that determines whether the syndrome remains manageable.

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AI Use Statement

During the preparation of this manuscript, the authors used Claude (Anthropic) solely for language refinement, including grammar checking, sentence-level rewording, and consistency of terminology. No artificial intelligence tools were used for data analysis, interpretation of clinical evidence, or generation of scientific content. All recommendations, references, and clinical positions were independently developed, verified, and approved by the authors, who critically reviewed and edited all outputs. The authors take full responsibility for the integrity and accuracy of the work.

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