

Review Article

Beyond the Heart and Lungs: Extrapulmonary and Treatment-Related Emergencies in Critically Ill Patients with Sarcoidosis

Semahattin Serkan Sezer¹

1. Izmir Bakırçay University

Sarcoidosis is a multisystem granulomatous disease that increasingly leads to hospital and, in a subset of patients, intensive care unit (ICU) admission. Critical care reviews have focused mainly on cardiopulmonary complications, yet critically ill patients with sarcoidosis frequently present with problems that arise outside the heart and lungs or that result from immunosuppressive treatment. This narrative review synthesises the evidence on four groups of such emergencies: hypercalcaemic crisis and renal involvement; neurosarcoidosis emergencies, including seizures, hydrocephalus and hypothalamic–pituitary involvement; infections, including opportunistic infections that are often mistaken for disease activity; and drug toxicities together with glucocorticoid-induced adrenal insufficiency.

Sarcoidosis-specific ICU data are scarce, and most recommendations rest on non-ICU sarcoidosis cohorts or are extrapolated from other populations; the evidence base for each topic is therefore stated explicitly. Recurrent pitfalls include replacing vitamin D on the basis of a low 25-hydroxyvitamin D level alone, relying on the CD4 count to exclude opportunistic infection, attributing new neurological deficits to neurosarcoidosis without excluding tuberculosis, cryptococcosis or progressive multifocal leukoencephalopathy, overlooking the interaction between methotrexate and trimethoprim–sulfamethoxazole, and omitting stress-dose glucocorticoid cover. A pragmatic, non-validated checklist for the first 24 hours is proposed; it separates routine assessments from investigations triggered by the clinical picture. Priorities for research are also identified.

Corresponding author: Semahattin Serkan Sezer, serkanzade@gmail.com

Key points

- Infection is a leading cause of emergency hospitalisation and of in-hospital death in patients with sarcoidosis. Exclude infection before escalating immunosuppression.
- Sarcoidosis-associated hypercalcaemia is independent of parathyroid hormone (PTH). Glucocorticoids are disease-specific therapy; bisphosphonates and denosumab can cause significant hypocalcaemia.
- The CD4 count is not a reliable safety threshold: cryptococcosis and progressive multifocal leukoencephalopathy (PML) can occur without severe CD4 lymphopenia.
- In patients taking methotrexate, acute kidney injury and co-prescription of trimethoprim-sulfamethoxazole are associated with severe toxicity.
- Critically ill patients with current or recent glucocorticoid exposure who are undergoing significant physiological stress should receive stress-dose cover unless adrenal insufficiency has been excluded; testing should not delay treatment.
- ICU-specific evidence is scarce: most recommendations are extrapolated from non-ICU or non-sarcoidosis populations.

1. Introduction

Sarcoidosis is a systemic inflammatory disease characterised by non-necrotising granulomas in affected organs. Granulomas form most often in the lungs, but almost any organ can be affected ^[1]. The pattern of organ involvement varies with sex, ethnicity and age. In the ACCESS cohort, women more often had ocular and neurological involvement, men were more often hypercalcaemic, and Black patients more frequently had hepatic and bone marrow involvement ^[2].

The hospital burden of sarcoidosis has grown. In the United States, hospitalisations of patients with sarcoidosis almost doubled between 1998 and 2008 ^[3], and age-adjusted sarcoidosis-related mortality rose by 50.5% in women and 30.1% in men between 1988 and 2007 ^[4]. Between 2007 and 2018, hospitalisations for respiratory failure in pulmonary sarcoidosis increased about ninefold and the need for mechanical ventilation threefold, with in-hospital mortality of 31.2% among ventilated patients ^[5]; the interpretation of these administrative trends has, however, been questioned ^[6]. In national data from 2016–2019, sepsis and pneumonia were the most common individual diagnoses leading to hospitalisation, and infections accounted for the largest share (30%) of in-hospital deaths ^[7]. A French single-centre study of 154 emergency hospitalisations found a similar pattern: lower respiratory tract infection was the

leading cause (21%), 9% of patients required ICU admission, in-hospital mortality was 3.9%, and comorbidity burden, pulmonary hypertension and oxygen requirement were associated with worse transplant-free survival [8].

Data restricted to critically ill patients remain scarce. In a Belgian single-centre series of 86 patients with systemic diseases admitted to a medical ICU, sarcoidosis was the second most frequent diagnosis. Infection was the main reason for admission (60%) across the overall systemic-disease cohort, while ICU and hospital mortality were 19% and 39%, respectively [9]. The literature search did not identify a large ICU cohort restricted to patients with sarcoidosis.

A comprehensive review has addressed the critical care of cardiopulmonary complications of sarcoidosis [10], and a recent review has proposed a practical approach to neurosarcoidosis in critical care, internal and pulmonary medicine [11]. However, the non-cardiopulmonary emergencies and treatment-related complications that intensivists encounter extend beyond the nervous system, and the relevant evidence is scattered across the endocrinology, nephrology, infectious diseases and pharmacology literature.

The diagnosis of sarcoidosis rests on a compatible clinical presentation, non-necrotising granulomatous inflammation and the exclusion of alternative causes, so it is never fully secure [12]. This caveat becomes critical when new organ dysfunction appears in an immunosuppressed patient. Glucocorticoids remain first-line therapy, but prolonged use carries substantial toxicity; the European Respiratory Society (ERS) guideline therefore includes glucocorticoid-sparing agents, such as methotrexate and the tumour necrosis factor (TNF) inhibitor infliximab, for selected patients [13].

This review aims to provide intensivists and consulting pulmonologists with a practical synthesis of non-cardiopulmonary and treatment-related emergencies in sarcoidosis. Because ICU-specific data are scarce, each section states whether the supporting evidence derives from patients with sarcoidosis, from critically ill patients, or from other populations.

2. Methods

Design. This is a narrative review. Its planning and reporting were guided by the Scale for the Assessment of Narrative Review Articles (SANRA) [14].

Search strategy. PubMed/MEDLINE was searched from inception to 20 August 2026. The term "sarcoidosis" was combined with topic-specific terms, including "intensive care", "critically ill",

"hypercalcaemia", "renal sarcoidosis", "neurosarcoidosis", "hypothalamic-pituitary", "opportunistic infection", "tuberculosis", "cryptococcosis", "progressive multifocal leukoencephalopathy", "aspergillosis", "methotrexate", "azathioprine", "infliximab", "hydroxychloroquine" and "adrenal insufficiency". Where sarcoidosis-specific evidence was lacking, targeted searches without the term "sarcoidosis" were performed for Pneumocystis prophylaxis, methotrexate toxicity, stress-dose glucocorticoids and the management of hypercalcaemia. Reference lists of key reviews and guidelines were screened for additional sources.

Eligibility. English-language, peer-reviewed publications concerning adults were considered. Clinical practice guidelines, systematic reviews and meta-analyses, multicentre cohorts and case series were prioritised. Case reports were cited only when no other evidence was available for a clinically important question (for example, denosumab for sarcoidosis-associated hypercalcaemia). Conference abstracts were not included.

Selection and synthesis. Literature was identified, selected and synthesised by the author; study selection was therefore not performed in duplicate. For each topic, the study design, the population studied and whether the evidence was specific to sarcoidosis and to critically ill patients were recorded; this information is summarised in Section 10. Where cited guidelines graded their recommendations, their grading is reported. No formal risk-of-bias assessment, GRADE rating or quantitative synthesis was performed, and the conclusions should be interpreted accordingly. Bibliographic details of all references were checked against PubMed records.

3. Hypercalcaemic Crisis and Renal Involvement

3.1. Pathophysiology

Hypercalcaemia in sarcoidosis is driven by extrarenal production of calcitriol [1,25(OH)₂D]; classic evidence came from an anephric patient with sarcoidosis who developed hypercalcaemia [15]. Macrophages within granulomas convert 25-hydroxyvitamin D [25(OH)D] into calcitriol through autonomous 1 α -hydroxylase activity. The resulting disturbance of calcium metabolism produces hypercalciuria in 40–62% of patients and hypercalcaemia in 5–10% [16][17]. In a cohort of 1,606 patients, sarcoidosis-associated hypercalcaemia was identified in 6%, and renal insufficiency was documented in 42% of affected patients [17].

3.2. Presentation in the ICU

Clinical features of hypercalcaemia include polyuria and thirst, confusion or coma, renal impairment including acute kidney injury (AKI), nephrolithiasis, pancreatitis, and a shortened QT interval with dysrhythmias; levels above 3.5 mmol/L require urgent correction ^[18]. Renal sarcoidosis contributes independently. In 47 patients with renal sarcoidosis, median estimated glomerular filtration rate (eGFR) at presentation was 20.5 mL/min/1.73 m², granulomatous interstitial nephritis was found in 37, and 32% were hypercalcaemic ^[19]. Hypercalcaemia was markedly more frequent in cases diagnosed between June and September (50% vs 16%), a seasonal pattern clinicians should recognise ^[19].

3.3. Management

Initial management follows the general principles for acute hypercalcaemia ^[18]:

- Intravenous isotonic saline to restore circulating volume. UK emergency guidance suggests 4–6 L over 24 hours; in critically ill patients, particularly those with cardiac or renal dysfunction, the volume should be individualised to haemodynamic status and fluid tolerance.
- Loop diuretics only if fluid overload develops; they are not effective for lowering serum calcium.
- Renal replacement therapy for severe hypercalcaemia with advanced renal failure.

Glucocorticoids, which inhibit calcitriol production, are disease-specific therapy in granulomatous disease; the same guidance lists prednisolone 40 mg/day, which is usually effective within 2–4 days ^[18]. Intravenous bisphosphonates can be added but may precipitate hypocalcaemia when PTH is suppressed or vitamin D is deficient ^[18], both of which are typical of sarcoidosis-associated hypercalcaemia.

Evidence for other agents in sarcoidosis is limited to case reports. Denosumab lowered calcium and creatinine and allowed glucocorticoid reduction in one patient with relapsing hypercalcaemia ^[20], whereas a single 60 mg dose caused prolonged, severe hypocalcaemia with tetany in another patient with renal impairment ^[21]. Denosumab should generally be reserved for refractory cases and used under specialist supervision, particularly in patients with renal impairment; calcitonin may be considered as a short-term adjunct in severe hypercalcaemia ^{[18][20][21]}.

All calcium and vitamin D supplements should be stopped. In one cohort, eight patients improved with vitamin D withdrawal alone, and hypercalcaemia improved in more than 90% of treated patients, with parallel improvement in renal function ^[17]. In renal sarcoidosis, prednisone rapidly improved eGFR, from

about 20 to 44 mL/min/1.73 m² at one month, and complete response at one month correlated strongly with long-term response [19].

3.4. Pitfalls

Low 25(OH)D is common in sarcoidosis (80% in one cohort) and does not by itself justify replacement [17]. The American Thoracic Society (ATS) guideline strongly recommends baseline serum calcium testing in all patients (very low-quality evidence) and suggests measuring both 25(OH)D and 1,25(OH)₂D before any vitamin D replacement [12].

Sarcoidosis also does not exclude a second cause of hypercalcaemia: primary hyperparathyroidism coexisted in 0.6% of patients in a large cohort [17]. The expected profile is hypercalcaemia with low PTH [18]; a non-suppressed PTH should prompt further evaluation.

Evidence base. Sarcoidosis-specific cohorts and a guideline recommendation graded on very low-quality evidence support the diagnostic approach. Acute management is extrapolated from general hypercalcaemia guidance, and evidence for denosumab is limited to case reports. No ICU-specific data were identified.

4. Neurosarcoidosis Emergencies

4.1. Epidemiology and Diagnosis

Clinically apparent neurosarcoidosis occurred in about 5% of patients with systemic sarcoidosis in a meta-analysis of 1,088 patients [22], and in 5–15% according to a recent review [23]. In about half of cases, neurological symptoms are the first manifestation of the disease [22]. Cranial neuropathy (55%, most often facial or optic) and headache (32%) are the most common features; cerebrospinal fluid (CSF) pleocytosis and elevated protein are found in 58% and 63% of patients, respectively [22].

The Neurosarcoidosis Consortium criteria classify disease as possible, probable or definite. They emphasise exclusion of infection and malignancy and, where feasible, biopsy of non-neural tissue to document systemic sarcoidosis [24]. About 75% of patients with systemic sarcoidosis who develop neurosarcoidosis do so within two years of diagnosis [25].

4.2. Syndromes Relevant to the ICU

Acute neurosarcoidosis syndromes encountered in emergency and critical care include seizures, stroke, neuroendocrinopathy, hydrocephalus, meningeal disease, myelopathy and infectious complications [11]. Leptomeningeal disease may be complicated by cranial nerve dysfunction, seizures and communicating hydrocephalus, the latter usually resulting from chronic meningitis; intraparenchymal mass-like lesions occur in about 15% of cases [25]. Acute hydrocephalus requires urgent neurosurgical assessment, and seizures are managed with standard protocols while the underlying inflammation is treated.

Hypothalamic–pituitary involvement comprises two distinct problems. Anterior pituitary dysfunction was present in all but two of 24 patients in a multicentre series; although MRI abnormalities improved or resolved in half of the patients with glucocorticoids, hormonal deficiencies recovered in only two [26]. Arginine vasopressin deficiency (AVP-D; formerly central diabetes insipidus [27]) was present in half of that series [26]. In a more recent cohort, hypothalamic–pituitary involvement affected 12.6% of patients with neurosarcoidosis. Symptomatic presentations were usually chronic, often with polyuria and polydipsia; nearly all treated patients responded acutely to glucocorticoids, yet almost all symptomatic patients still required glucocorticoid and/or hormonal therapy after a median follow-up of 55 months [28]. In the ICU, unrecognised AVP-D can cause severe hypernatraemia once the patient loses free access to water, for example after sedation or intubation. In a patient with pituitary involvement, secondary adrenal insufficiency should be assumed until excluded.

4.3. Mimics: Infection Before Inflammation

The most consequential pitfall is attributing new neurological deterioration to neurosarcoidosis without excluding infection, and no single CSF finding reliably distinguishes the two. Neurosarcoidosis is one of the few non-infectious causes of low CSF glucose (hypoglycorrhachia), but a CSF glucose below 20 mg/dL should raise concern for fungal, mycobacterial or malignant disease [25]. Neurosarcoidosis and tuberculosis can also coexist, and thorough screening for tuberculosis before treatment has been emphasised [29].

Two French series illustrate the risk. Cryptococcosis complicating sarcoidosis presented as meningitis in 72% of 18 cases [30]. In a series of PML complicating sarcoidosis, eight of ten cases were first attributed to neurosarcoidosis; immunosuppression was intensified, and the diagnosis was delayed by a mean of 4.5 months [31].

In settings with a substantial tuberculosis burden, and whenever the presentation is atypical, investigations guided by the clinical and radiological picture should precede escalation of immunosuppression [25][30][31].

- In patients with meningeal involvement or an unexplained new neurological deficit, microbiological investigations should be guided by the clinical and radiological presentation and may include CSF mycobacterial culture and nucleic acid amplification testing, fungal studies and cryptococcal antigen testing.
- White-matter lesions suggestive of PML: CSF JC virus PCR.

4.4. Treatment

The ERS guideline recommends glucocorticoids for clinically significant neurosarcoidosis (strong recommendation, very low-quality evidence). It suggests adding methotrexate for continued disease despite glucocorticoids, and adding infliximab for continued disease despite glucocorticoids and a second-line agent (both conditional recommendations, very low-quality evidence) [13]. Randomised trials are lacking, and treatment strategies rest on cohort studies and expert consensus [23]. In severe presentations, intravenous pulse methylprednisolone is widely used in practice.

In a multi-institutional series of 66 patients with central nervous system sarcoidosis treated with infliximab, a favourable MRI response was seen in 82% of those with follow-up imaging and clinical improvement in 77%, but disease recurred in 9 of 16 patients (56%) whose infliximab was stopped during remission [32]. TNF-inhibitor regimens were also the most frequently successful maintenance therapy in hypothalamic–pituitary disease [28]. Overall, about one-third of patients do not respond to treatment, and mortality in pooled series is about 5% [22].

Evidence base. A sarcoidosis-specific meta-analysis, retrospective series and guideline recommendations graded on very low-quality evidence. ICU-oriented guidance is limited to a narrative review [11], and no ICU cohorts were identified.

5. Infections in the Immunosuppressed Patient

5.1. *An Immune Paradox*

Sarcoidosis combines peripheral immune anergy with exuberant granuloma formation. Opportunistic infections have been reported even in untreated patients, although glucocorticoids are the major risk factor ^[33]. In a study of 28 patients, more than half had low CD4, CD8 or CD19 counts, and lymphopenia correlated with severe organ involvement ^[34].

The CD4 count is nevertheless not a reliable safety threshold. In the respective French series, cryptococcosis and PML in sarcoidosis were not associated with severe CD4 lymphocytopenia ^{[30][31]}. Opportunistic infections with extrapulmonary features are also frequently misdiagnosed as new localisations of sarcoidosis ^[33].

5.2. *Bacterial Sepsis and Pneumonia*

Common bacterial infections predominate. Lower respiratory tract infection was the leading cause of emergency hospitalisation in one cohort ^[8], and sepsis and pneumonia were the most frequent individual causes of hospitalisation in national data ^[7]. Standard sepsis management applies; in immunosuppressed patients, the threshold for microbiological sampling, including bronchoalveolar lavage (BAL) when pulmonary infiltrates are present, should be low.

5.3. *Tuberculosis and TNF Inhibition*

Tuberculosis reactivation is the prototypical complication of TNF inhibition. Among 70 cases reported after infliximab, tuberculosis developed after a median of 12 weeks, 48 cases occurred after three or fewer infusions, and 40 were extrapulmonary, including 17 disseminated cases ^[35]. TNF inhibitors also predispose to fungal infections such as histoplasmosis, herpes zoster reactivation and, rarely, PML ^[25].

The 2022 EULAR recommendations advise screening for latent tuberculosis before biologic or targeted synthetic agents, state that screening may also be considered before conventional immunosuppressants and glucocorticoids, and prefer interferon-gamma release assays where available ^[36]; these recommendations were developed for autoimmune inflammatory rheumatic diseases. Because the diagnosis of sarcoidosis requires exclusion of mycobacterial infection ^[12] and extrapulmonary infection

may be mistaken for disease activity [33], mycobacterial evaluation should be part of the work-up of febrile or deteriorating patients receiving TNF inhibitors.

5.4. *Pneumocystis Pneumonia and the Methotrexate Interaction*

No sarcoidosis-specific data define when prophylaxis against *Pneumocystis jirovecii* pneumonia (PJP) is indicated. In patients with rheumatic diseases receiving prolonged (≥ 4 weeks) high-dose (≥ 30 mg/day prednisone) glucocorticoids, PJP mortality was 36.7%, and trimethoprim–sulfamethoxazole (TMP-SMX) prophylaxis reduced one-year PJP incidence (adjusted HR 0.07) and related mortality [37]. The 2022 EULAR recommendations state that prophylaxis appears beneficial in patients receiving more than 15–30 mg/day of prednisolone or equivalent for more than 2–4 weeks [36]. These thresholds are extrapolated from autoimmune inflammatory rheumatic disease populations and have not been specifically validated in sarcoidosis. Concomitant immunosuppression, lymphopenia and structural lung disease may influence the individual risk–benefit assessment.

Prophylaxis must be weighed against the interaction with methotrexate. Reviews and case reports describe severe, sometimes fatal, pancytopenia with the combination [38]; a population-based cohort of older adults found no increase in 30-day mortality but higher rates of all-cause hospitalisation and hospital admission with infection [39]. When both drugs are required, blood counts and renal function should be monitored closely. Pentamidine, atovaquone and dapsone are second-line alternatives when TMP-SMX is contraindicated or poorly tolerated [40]; this guidance was developed for haematological patients.

5.5. *Cryptococcosis and Progressive Multifocal Leukoencephalopathy*

In the French cryptOsarc study of 18 patients, extrathoracic sarcoidosis and glucocorticoid therapy were independent risk factors for cryptococcosis. One-third of cases occurred in untreated patients, and prognosis with antifungal therapy was good [30].

PML carries a much worse prognosis. In the French series, 6 of 10 patients died, and case fatality was 57% when these cases were pooled with 20 published cases; this pooled estimate may be affected by publication bias. Interrupting immunosuppression remains the mainstay of treatment [31].

5.6. Chronic Pulmonary Aspergillosis

Chronic pulmonary aspergillosis (CPA) affects about 2% of patients with sarcoidosis in tertiary cohorts and develops mainly in advanced fibrocystic disease ^[41]. In a series of 65 patients, 31% had pulmonary hypertension and 41.5% died during follow-up; death most often resulted from advanced sarcoidosis and rarely from haemoptysis, although 14 patients required interventional radiology and 11 underwent surgical resection ^[42]. Diagnosis follows the ERS/ESCMID criteria, which require compatible imaging and evidence of *Aspergillus* infection or immune response (typically *Aspergillus* IgG) for at least three months, with alternative diagnoses excluded ^[43]. Management of haemoptysis relies on bronchial artery embolisation ^[41].

Evidence base. Opportunistic infections in sarcoidosis are described in retrospective case series. Prophylaxis thresholds and tuberculosis screening recommendations are extrapolated from rheumatic and haematological populations. No ICU-specific data were identified.

6. Drug Toxicities Relevant to Critical Care

6.1. Glucocorticoids

Beyond infection, glucocorticoids may contribute to hyperglycaemia, gastrointestinal bleeding, delirium and myopathy. A meta-analysis of predominantly observational studies found an association between corticosteroid use and ICU-acquired weakness (OR 1.84; 95% CI 1.26-2.67) ^[44]; confounding by indication cannot be excluded.

6.2. Methotrexate

Methotrexate pneumonitis is usually subacute. In a combined cohort of patients with rheumatoid arthritis, dyspnoea (93%), cough (83%) and fever (69%) had typically been present for several weeks before diagnosis; mortality was about 17%, and rechallenge frequently caused recurrence ^[45]. Distinguishing methotrexate pneumonitis from progression of pulmonary sarcoidosis and from opportunistic infection, particularly PJP, requires BAL with appropriate microbiological testing.

Low-dose methotrexate toxicity can be life-threatening. Among 28 hospitalised patients, pancytopenia was the most common manifestation (78.5%); risk factors included acute renal failure,

hypoalbuminaemia, interacting drugs and dosing errors, and 25% of patients died, all from pancytopenia followed by sepsis ^[46]. AKI in the ICU can therefore turn a stable weekly regimen into a toxic exposure.

Management includes withholding methotrexate and giving folinic acid (leucovorin). In a randomised trial of 38 patients with severe low-dose methotrexate toxicity, leucovorin 25 mg every 6 hours was not superior to 15 mg every 6 hours; 30-day mortality was 42–47%, and serum albumin was the only independent predictor of survival ^[47]. No trial has defined leucovorin dosing during renal replacement therapy. Glucarpidase is established for delayed clearance during high-dose therapy, where high-dose leucovorin and glucarpidase usually allow renal recovery without dialysis ^[48]; evidence for glucarpidase in low-dose toxicity is limited.

6.3. Azathioprine

Azathioprine-associated myelosuppression is strongly influenced by thiopurine methyltransferase (TPMT) and NUDT15 genotypes, and genotype-guided dosing is recommended ^[49].

6.4. TNF Inhibitors

Cardiac sarcoidosis may coexist with extracardiac disease, so the cardiac safety of TNF inhibitors matters. In the ATTACH trial of patients with NYHA class III–IV heart failure, infliximab 10 mg/kg increased the combined risk of death or heart-failure hospitalisation (HR 2.84) ^[50]. Although this evidence comes from a non-sarcoidosis heart-failure population, it is relevant when considering TNF inhibition in patients with coexisting or suspected cardiac dysfunction.

TNF inhibitors can also paradoxically induce sarcoid-like granulomatosis, which usually improves after the drug is stopped ^[51]; this has been reported particularly with etanercept ^[51]. Neurosarcoidosis-like reactions during TNF-inhibitor therapy are rare, with seven cases identified in a recent literature review ^[52]. A new granulomatous process in a patient receiving a TNF inhibitor should therefore be interpreted with caution.

6.5. Hydroxychloroquine

In a systematic review of 127 published patients with cardiac toxicity attributed to chloroquine or hydroxychloroquine, 85% had conduction disorders and 26.8% had heart failure, usually after prolonged exposure ^[53]. These proportions describe reported cases, not the incidence among users. ECG monitoring is nevertheless advisable when other drugs affecting cardiac conduction are given in the ICU.

Evidence base. Largely derived from non-sarcoidosis populations (rheumatic diseases, haematology, heart-failure trials). Only the leucovorin trial and the corticosteroid–weakness meta-analysis involved hospitalised or critically ill patients.

7. Glucocorticoid-Induced Adrenal Insufficiency and Stress Dosing

At least 1% of the population receives chronic glucocorticoid therapy. The risk of glucocorticoid-induced adrenal insufficiency depends on dose, duration, potency, route and individual susceptibility ^[54]. Daily prednisolone doses of 5 mg or more for one month or longer may suppress the hypothalamic–pituitary–adrenal axis ^[55].

Critical illness constitutes major physiological stress. The 2024 European Society of Endocrinology/Endocrine Society guideline recommends that patients with current or recent glucocorticoid use who have not undergone testing to exclude adrenal insufficiency receive stress-dose cover when exposed to stress (a good clinical practice statement) ^[54]. For patients requiring hospital admission, it specifies:

- Hydrocortisone 100 mg intravenously, followed immediately by 200 mg over 24 hours as a continuous infusion.
- If an infusion is not feasible, hydrocortisone 50 mg intravenously every 6 hours.

The same regimen is advised at anaesthetic induction for surgery ^[54]. Patients already receiving hydrocortisone ≥ 200 mg/day, prednisone ≥ 50 mg/day or dexamethasone ≥ 6 –8 mg/day typically need no increase ^[54]. UK perioperative guidance likewise emphasises identifying at-risk patients and providing stress-dose cover ^[55].

Biochemical diagnosis during critical illness is unreliable. The SCCM/ESICM task force could not agree on a single reliable test, although a delta cortisol <9 $\mu\text{g/dL}$ after 250 μg cosyntropin or a random cortisol <10 $\mu\text{g/dL}$ may be used ^[56]. In critically ill patients with ongoing or recent glucocorticoid exposure, empirical stress dosing should not be delayed for testing. Hypothalamic–pituitary neurosarcoidosis adds a further, often permanent, cause of secondary adrenal insufficiency ^{[26][28]}.

Evidence base. Endocrine guideline statements based on good clinical practice and applicable to all glucocorticoid users; the SCCM/ESICM guideline addresses critically ill adults in general. No sarcoidosis-specific data were identified.

8. Selected Less Common Emergencies

Hepatic involvement occurs in up to 70% of patients and is usually asymptomatic, but long-standing disease can lead to portal hypertension and cirrhosis and, rarely, to liver transplantation ^[57]. An elevated alkaline phosphatase is the most common sign ^[58], and the ATS guideline suggests baseline alkaline phosphatase testing ^[12]. Variceal bleeding in a patient with sarcoidosis should raise suspicion of portal hypertension related to hepatic sarcoidosis.

Laryngeal sarcoidosis is rare but matters for airway management. In a series of ten patients, the supraglottis and arytenoids were affected in all, and two required emergency tracheostomy ^[59]. Known or suspected upper-airway involvement should prompt difficult-airway planning, including awake techniques and early otolaryngology input.

Haematological abnormalities may reflect bone marrow involvement, which is more common in Black patients ^[2]. In the ICU, however, drug toxicity (methotrexate, azathioprine) and infection should be excluded first ^{[46][49]}.

9. A Proposed Approach to the First 24 Hours

Tables 1–3 summarise organ-specific emergencies, drug toxicities and opportunistic infections. Box 1 presents a checklist for the first 24 hours of ICU admission. It is a pragmatic synthesis of the evidence reviewed here, has not been validated, and is not intended to replace clinical judgement or local protocols. To avoid indiscriminate testing, it separates assessments recommended for every patient from investigations that should be triggered by the clinical picture.

Emergency	ICU presentation	Key investigations	Initial management	Ref.
Hypercalcaemic crisis	Confusion, polyuria, dehydration, AKI, short QT/dysrhythmia	Ca, PTH (low), 25(OH)D, 1,25(OH) ₂ D, creatinine	Isotonic saline (volume individualised); glucocorticoid; stop vitamin D/Ca; bisphosphonate with caution	[17] [18] [20] [21]
Renal sarcoidosis (GIN)	AKI, often with hypercalcaemia	Urinalysis; renal biopsy if feasible	Glucocorticoid; early response predicts outcome	[19]
Seizures / hydrocephalus	Reduced consciousness, focal deficits	Gadolinium MRI; CSF with infection work-up	Standard seizure care; neurosurgical consultation; glucocorticoid once infection is reasonably excluded	[11] [25]
AVP deficiency (formerly central diabetes insipidus)	Polyuria; hypernatraemia, especially when sedated	Na, plasma and urine osmolality	Desmopressin; free-water replacement	[26] [27] [28]
Anterior pituitary deficiency	Hypotension (secondary adrenal insufficiency)	Cortisol, TSH/ft4	Hydrocortisone; other hormone replacement as needed	[26] [28]
Laryngeal obstruction	Stridor, dysphonia	Nasendoscopy	Difficult-airway plan; tracheostomy may be required	[59]
Portal hypertension (hepatic)	Variceal bleeding	ALP, imaging, biopsy if needed	Standard variceal bleeding care	[57] [58]

Table 1. Non-cardiopulmonary emergencies in sarcoidosis

AKI, acute kidney injury; ALP, alkaline phosphatase; AVP, arginine vasopressin; CSF, cerebrospinal fluid; GIN, granulomatous interstitial nephritis; PTH, parathyroid hormone.

Agent	Key toxicities	Risk modifiers / interactions	Practical action	Ref.
Glucocorticoids	Infection, hyperglycaemia, ICU-acquired weakness (association), adrenal suppression	Prednisolone ≥ 5 mg/day for ≥ 1 month (HPA suppression)	Stress-dose cover when critically ill; consider PJP prophylaxis with prolonged high doses (thresholds extrapolated)	[36] [37] [44] [54] [55]
Methotrexate	Pancytopenia, pneumonitis	AKI, hypoalbuminaemia, TMP-SMX, dosing errors	Withhold; folinic acid; BAL if pneumonitis suspected	[38] [39] [45] [46] [47]
Azathioprine	Myelosuppression	TPMT/NUDT15 variants	Withhold; consider TPMT/NUDT15 testing	[49]
TNF inhibitors	Tuberculosis (often extrapulmonary), fungi, zoster, rarely PML; worsening heart failure; paradoxical granulomatous reactions	High-dose infliximab in NYHA III–IV heart failure	Mycobacterial and fungal work-up if febrile; avoid high-dose infliximab in advanced heart failure	[25] [35] [50] [51] [52]
Hydroxychloroquine	Conduction disorders, cardiomyopathy (reported cases)	Long exposure, high cumulative dose	ECG monitoring	[53]

Table 2. Immunosuppressive agents: ICU-relevant toxicities

BAL, bronchoalveolar lavage; HPA, hypothalamic–pituitary–adrenal; PJP, *Pneumocystis jirovecii* pneumonia; PML, progressive multifocal leukoencephalopathy; TMP-SMX, trimethoprim–sulfamethoxazole.

Infection	Main risk factors	Clues and pitfalls	Diagnosis	Ref.
Tuberculosis	TNF inhibitors, glucocorticoids	Early after infliximab (median 12 weeks); often extrapulmonary or disseminated; may coexist with or mimic sarcoidosis	IGRA for latent infection; culture, NAAT, histology	[29] [35] [36]
PJP	Prolonged high-dose glucocorticoids (thresholds extrapolated from rheumatic diseases)	Mortality 36.7% in a rheumatic disease cohort	BAL PCR/staining	[36] [37]
Cryptococcosis	Extrathoracic sarcoidosis, glucocorticoids; one-third untreated	Meningitis in 72%; not linked to severe CD4 lymphopenia	Cryptococcal antigen, CSF culture	[30]
PML	Immunosuppression	Misdiagnosed as neurosarcoidosis; 57% fatality in 30 pooled cases	MRI, CSF JC virus PCR	[31]
CPA	Advanced fibrocystic disease (about 2% in tertiary cohorts)	Haemoptysis; death mostly from advanced sarcoidosis	Compatible imaging for ≥ 3 months plus <i>Aspergillus</i> IgG	[41] [42] [43]

Table 3. Opportunistic infections complicating sarcoidosis

CPA, chronic pulmonary aspergillosis; IGRA, interferon- γ release assay; NAAT, nucleic acid amplification test.

A. Assess in every patient

1. **Map the disease.** Review biopsy history and known organ involvement; obtain an ECG ^{[10][12]}.
2. **Reconcile medications.** Record glucocorticoid dose and duration, methotrexate (weekly dose, day of intake, renal function), azathioprine, the last TNF-inhibitor dose, hydroxychloroquine and PJP prophylaxis ^{[37][38][49]}.
3. **Assess adrenal risk.** In patients with current or recent glucocorticoid exposure who are undergoing significant physiological stress, provide stress-dose hydrocortisone unless adrenal insufficiency has been excluded ^[54].
4. **Check calcium and renal function.** Measure serum calcium and creatinine; stop vitamin D and calcium supplements if calcium is raised ^{[12][18]}.
5. **Monitor sodium, fluid balance and urine output,** particularly with neurological or pituitary involvement ^[26].
6. **Check blood count and liver tests** in patients receiving methotrexate or azathioprine ^{[46][49]}.
7. **Ask about stridor or dysphonia** before airway instrumentation ^[59].
8. **Involve other specialties early** according to the organs involved.

B. Investigations triggered by the clinical picture

- **Hypercalcaemia:** PTH, 25(OH)D and 1,25(OH)₂D ^{[12][17]}.
- **Fever or deterioration on a TNF inhibitor:** mycobacterial and fungal work-up ^{[25][35]}.
- **New pulmonary infiltrates with hypoxaemia:** BAL with cultures and Pneumocystis PCR; consider methotrexate pneumonitis ^{[37][45]}.
- **New neurological deficit or meningeal signs:** gadolinium-enhanced MRI and CSF analysis, including mycobacterial and fungal studies and cryptococcal antigen ^{[25][30]}.
- **White-matter lesions:** CSF JC virus PCR ^[31].
- **Cytopenia on methotrexate:** withhold the drug and give folinic acid ^{[46][47]}.
- **Haemoptysis in fibrocystic disease:** chest imaging and *Aspergillus* IgG; plan bronchial artery embolisation ^{[41][43]}.

Box 1. Proposed (non-validated) checklist for the first 24 hours of ICU admission in patients with sarcoidosis

10. Evidence Base and Limitations

Table 4 summarises the evidence underlying the main recommendations. Most derive from sarcoidosis cohorts outside the ICU or from other populations. Only the association between corticosteroids and ICU-acquired weakness and the SCCM/ESICM guidance on corticosteroid insufficiency were derived from critically ill patients, and neither is specific to sarcoidosis.

Topic	Main evidence (design)	Population	Sarcoidosis-specific	ICU-specific	Ref.
Hypercalcaemia: frequency and mechanism	Cohorts; narrative review; ATS guideline (very low-quality evidence)	Sarcoidosis	Yes	No	[12] [16] [17]
Acute hypercalcaemia management	Society emergency guidance (expert-based)	General adult hypercalcaemia	No	No	[18]
Denosumab	Case reports	Sarcoidosis	Yes	No	[20] [21]
Renal sarcoidosis	Retrospective multicentre series (n = 47)	Sarcoidosis	Yes	No	[19]
Neurosarcoidosis treatment	ERS guideline (very low-quality evidence); meta-analysis; retrospective series	Sarcoidosis	Yes	No	[13] [22] [32]
Neurosarcoidosis in critical care	Narrative review	Sarcoidosis	Yes	Partly	[11]
Hypothalamic–pituitary disease	Retrospective series (n = 24; n = 31)	Sarcoidosis	Yes	No	[26] [28]
Cryptococcosis, PML, CPA	Retrospective case series	Sarcoidosis	Yes	No	[30] [31] [42]
Tuberculosis with TNF inhibitors; screening	Pharmacovigilance reports; EULAR recommendations	Rheumatic and inflammatory bowel diseases	No	No	[35] [36]
PJP prophylaxis	Retrospective cohort; EULAR and ECIL recommendations	Rheumatic diseases; haematology	No	No	[36] [37] [40]
Methotrexate–TMP–SMX interaction	Review of case reports; population cohort	Mixed; older adults	No	No	[38] [39]

Topic	Main evidence (design)	Population	Sarcoidosis-specific	ICU-specific	Ref.
Low-dose methotrexate toxicity	Case series; randomised trial (n = 38)	Mainly rheumatic diseases; hospitalised	No	No	[46] [47]
Stress-dose glucocorticoids	ESE/ES guideline (good clinical practice); SCCM/ESICM guideline	Glucocorticoid users; critically ill adults	No	Partly	[54] [56]
Corticosteroids and ICU-acquired weakness	Meta-analysis (mainly observational)	Critically ill adults	No	Yes	[44]

Table 4. Evidence base of the main recommendations

CPA, chronic pulmonary aspergillosis; ECIL, European Conference on Infections in Leukaemia; ESE/ES, European Society of Endocrinology/Endocrine Society; PJP, *Pneumocystis jirovecii* pneumonia; PML, progressive multifocal leukoencephalopathy; TMP-SMX, trimethoprim–sulfamethoxazole.

This review has limitations. It is a narrative rather than a systematic review. The search was restricted to PubMed/MEDLINE and to English-language publications, and study selection was performed by a single author. No formal risk-of-bias or GRADE assessment was undertaken. Much of the sarcoidosis-specific evidence comes from small retrospective series and case reports, which are prone to selection and publication bias; the high PML fatality in pooled cases is one example. Several recommendations are extrapolated from rheumatic, haematological or general populations, and their applicability to critically ill patients with sarcoidosis is uncertain. Finally, the checklist in Box 1 reflects the author's synthesis and requires prospective evaluation.

11. Knowledge Gaps and Future Directions

There are no dedicated ICU cohorts of patients with sarcoidosis. It is unknown whether ICU outcomes differ from those of matched controls, and no prognostic score has been validated. Thresholds for PJP prophylaxis, tuberculosis screening strategies and leucovorin dosing are extrapolated from other

populations. The management of refractory hypercalcaemia and the safe timing of resuming immunosuppression after serious infection lack prospective evidence.

Multicentre registries of critically ill patients with sarcoidosis, including centres in regions with a higher tuberculosis incidence, would allow outcome estimation, evaluation of the proposed checklist and development of prognostic tools.

12. Conclusion

In critically ill patients with sarcoidosis, life-threatening problems frequently arise outside the heart and lungs, from disordered calcium metabolism, hypothalamic–pituitary involvement, opportunistic infection and treatment toxicity. Although the evidence is largely indirect, three pragmatic principles emerge:

- Actively evaluate for infection before escalating immunosuppression when clinically feasible.
- Provide stress-dose glucocorticoid cover when adrenal insufficiency has not been excluded.
- Identify and treat hypercalcaemia and kidney injury early.

A structured, phenotype-guided approach during the first day of admission may help avoid preventable harm, but it requires prospective validation.

Abbreviations

25(OH)D, 25-hydroxyvitamin D; 1,25(OH)₂D, 1,25-dihydroxyvitamin D (calcitriol); AKI, acute kidney injury; ALP, alkaline phosphatase; ATS, American Thoracic Society; AVP-D, arginine vasopressin deficiency; BAL, bronchoalveolar lavage; CI, confidence interval; CPA, chronic pulmonary aspergillosis; CSF, cerebrospinal fluid; ECG, electrocardiogram; ECIL, European Conference on Infections in Leukaemia; eGFR, estimated glomerular filtration rate; ERS, European Respiratory Society; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; ESE/ES, European Society of Endocrinology/Endocrine Society; ESICM, European Society of Intensive Care Medicine; EULAR, European Alliance of Associations for Rheumatology; GIN, granulomatous interstitial nephritis; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; HPA, hypothalamic–pituitary–adrenal; HR, hazard ratio; ICU, intensive care unit; IGRA, interferon-gamma release assay; MRI, magnetic resonance imaging; NAAT, nucleic acid amplification test; NYHA, New York Heart Association; OR, odds ratio; PCR, polymerase chain reaction; PJP, *Pneumocystis jirovecii* pneumonia; PML, progressive multifocal leukoencephalopathy;

PTH, parathyroid hormone; SANRA, Scale for the Assessment of Narrative Review Articles; SCCM, Society of Critical Care Medicine; TMP-SMX, trimethoprim–sulfamethoxazole; TNF, tumour necrosis factor; TPMT, thiopurine methyltransferase.

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Ethics

Not applicable; this review is based on published literature and involved no human participants or patient data.

Data Availability

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Author Contributions

The author conceived the review, performed the literature search and synthesis, and wrote and revised the manuscript.

Use of Generative AI

The author used Claude (Anthropic) to improve text fluency and for spelling and grammar corrections. The author reviewed and edited all content and takes full responsibility for the final text.

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