

EVIDENCE REVIEW

Propofol-Related Infusion Syndrome (PRIS) in Children

July 2026



Executive summary

Propofol is an intravenous anaesthetic agent with potent sedative and hypnotic properties. Its rapid onset of action and short half-life enable precise titration and prompt neurological recovery, rendering it a highly effective option for managing critically ill patients within paediatric intensive care units (PICUs). Despite this highly favourable pharmacological profile, the use of propofol via continuous infusion in intensive care patients under the age of 16 is contraindicated and lacks approval from the MHRA, EMA, or FDA. This regulatory restriction is driven by concerns regarding the risk of Propofol-Related Infusion Syndrome (PRIS), a rare but potentially fatal complication characterised by refractory metabolic acidosis, rhabdomyolysis, hyperlipidaemia, and progressive cardiac failure.

Determining the true incidence of PRIS remains challenging due to confounding clinical variables and the lack of universally accepted diagnostic criteria. However, the overall incidence in paediatric cohorts is generally considered to be low, occurring in $\leq 1\%$ of patients maintained within recommended propofol dosing thresholds. Crucially, once PRIS manifests, it is associated with a high mortality rate, with literature reporting mortality figures exceeding 50% in paediatric populations.

The influence of propofol infusion parameters on the development of PRIS has been extensively investigated in paediatric patients. Robust clinical evidence shows a strong correlation between the onset of the syndrome and propofol doses exceeding 4 mg/kg/h or infusion durations exceeding 48 hours. Furthermore, large-scale studies have confirmed that adhering to these stringent infusion thresholds significantly mitigates the risk of PRIS in paediatric patients.

Nevertheless, it is apparent that not all patients exposed to high-dose, prolonged infusion develop PRIS, and isolated cases have also been documented at lower doses and shorter durations. This suggests that additional factors could contribute to PRIS pathogenesis. The literature identifies several secondary predisposing and triggering factors that may amplify risk, particularly in critically ill children. These include, severe ongoing critical illness, concomitant administration of catecholamines and corticosteroids, low carbohydrate and high fat intake, and subclinical or pre-existing inborn errors of metabolism. However, it remains to be definitively established whether these factors play a direct, causal role in the development of PRIS, or merely represent a marker for severe underlying illness.

Optimising patient safety during propofol administration within the PICU requires a rigorous, individualised risk–benefit assessment alongside comprehensive clinical and laboratory monitoring. Maintaining a high index of clinical suspicion is paramount. All patients receiving propofol must be closely monitored for early indicators of PRIS, including rising serum lactate, hypertriglyceridaemia, elevated creatine kinase (CK), acute ECG changes, and deteriorating renal dysfunction. Therapeutic management relies on early recognition, immediate cessation of the propofol, initiation of alternative sedative regimens, and rapid correction of the associated metabolic and cardiovascular derangements.

Although PRIS represents a rare and potentially fatal complication, systematic risk stratification, strict compliance with established dosing thresholds, and routine metabolic surveillance can effectively mitigate its occurrence, thus ensuring safer short-term use of propofol in paediatric critical care.

Background

Propofol (2,6-diisopropylphenol) is a short-acting intravenous hypnotic agent widely used for induction and maintenance of general anaesthesia, procedural sedation, and the sedation of mechanically ventilated patients in intensive care (ICU).¹ It is formulated as a lipid emulsion and is administered via intravenous bolus, continuous infusion, or a combined regimen.² Whilst the exact mechanism of action is poorly understood, it produces its sedative and anaesthetic effects primarily through potentiating the inhibitory function of the neurotransmitter gamma-aminobutyric acid (GABA) through GABAA receptors, decreasing glutamate activity, and causing central nervous system depression.^{2,3}

Propofol's pharmacological characteristics make it a desirable option for sedation in critically ill children. Its rapid onset of action and brief half-life allows for rapid induction of sedation and quick recovery after discontinuation.¹⁻⁵ These properties enable precise titration, allowing clinicians to perform frequent, immediate neurological assessments and efficiently evaluate patients for extubation readiness. In addition, propofol has potent anticonvulsive properties, is free of dependence, suppresses nausea, and at standard infusion doses has minimal cardiorespiratory impact.³

Despite propofol's distinct sedative advantages and established safety profile, its application within the paediatric intensive care units remains the subject of debate. This is largely driven by concerns regarding the risk of Propofol-Related Infusion Syndrome (PRIS), a rare and often fatal complication characterized by severe metabolic acidosis, rhabdomyolysis, hyperkalaemia and progressive cardiovascular collapse.⁶⁻⁸ Due to these safety concerns and a lack of robust efficacy data in this population, the use of propofol via continuous infusion in intensive care patients under the age of 16 is contraindicated.^{2,9}

This review aims to synthesise the current clinical evidence regarding PRIS in paediatric patients to clarify incidence rates, mortality risk, demographics predictors, and primary risk factors, to inform the safer use of propofol in paediatric intensive care settings.

Search strategy

A systematic literature search was conducted in Medline and PubMed using the following search terms 'propofol' OR 'propofol.mp' AND 'infusion*' OR 'infusion.mp' AND 'Syndrome*' OR "Adverse Effects". The titles and abstracts of all articles were screened to identify other potentially relevant articles. All relevant articles were retrieved and reviewed, and the reference list and citing articles of included studies were screened to identify any other potentially relevant data.

Summary of evidence

The evidence base considered in this review is based on the best available published literature which largely comprises of case reports, case series, observational studies, and reviews. The review primarily focussed on identifying risk factors associated with PRIS in children (<18 years). Where relevant, important adult studies were included to better characterise the epidemiology of PRIS, and those risk factors poorly reported in children.

Propofol-Related Infusion Syndrome (PRIS)

Propofol infusion syndrome is a rare and potentially fatal complication of propofol administration. The clinical manifestations that have come to define PRIS are wide ranging and include progressive and refractory metabolic acidosis, arrhythmias, cardiac failure, rhabdomyolysis, hyperlipidaemia, and enlarged or fatty liver.^{6-8,10-12} The clinical features of PRIS can overlap with underlying disease processes in critically ill patients making it challenging to distinguish the syndrome from primary illness.⁶

The syndrome was initially described in children in the early 1990's, and since this report numerous cases of PRIS in critically ill children and adults have been published. The pathophysiological mechanisms responsible for PRIS are complex and beyond the scope of this review, but it is widely reported to involve impairment of mitochondrial beta-oxidation of fatty acids, disruption of the electron transport chain and blockage of beta adrenoreceptors, and cardiac calcium channels.^{6,13,14}

Incidence of PRIS

While PRIS was first described in the paediatric population, it has subsequently been more widely reported in adult patients. Determining the true incidence of PRIS remains challenging because no universally accepted diagnostic criteria exist, and many of its features overlap with underlying disease processes in critically ill patients, leading to potential misclassification, and under recognition of early or incomplete presentations. Furthermore, much of the available evidence is derived from case reports, small case series, and observational studies, which are inherently limited by reporting bias and heterogeneity in clinical practice.

Despite these limitations, the overall incidence of PRIS in paediatric patients is generally accepted to be low, occurring in $\leq 1\%$ of patients receiving propofol infusions within recommended dosing limits. However, the actual incidence may be higher in those patients exposed to doses and durations outside these limits and who have additional risk factors. A single-centre, retrospective, observational study by Fashina is the only report providing data on the incidence of PRIS in paediatric patients. Among the 554 critically ill children receiving continuous propofol, the reported incidence of PRIS was 0.2%, even when propofol was administered at doses and durations historically considered high-risk.¹⁵

In critically ill adults, the reported incidence of PRIS ranges between 1.1% and 41%. In 2009, Roberts et al. published the first prospective, multicentre study to determine the incidence of PRIS in a large cohort of critically ill adults receiving propofol for non-procedural sedation in the ICU.¹¹ Among the 1,017 critically ill patients who were administered an infusion of propofol for at least 24 hours, the incidence of PRIS was 1.1%. However, a study by Hwang et al., in patients receiving propofol for refractory status epilepticus showed an incidence of PRIS of around 17% in those receiving doses of at least 5 mg/kg/h, and around 31% in those receiving more than 6mg/kg/h.¹⁶ A retrospective analysis by Diaz et al., of 72 critically ill adult patients receiving propofol for longer than 72 hours in a trauma hospital ICU identified a PRIS incidence of 4.1%.¹⁷ In a study by Schroepel the incidence of PRIS was 2.9% among the 207 adult trauma patients who received propofol for greater than 24 hours.¹⁸ However, following implementation of a prospective clinical screening protocol in a further cohort of 1,038 patients to identify those at risk for PRIS, the rate dropped to only 0.19%. In a more recent retrospective study by Li et al., of 654 critically ill adult patients reported an incidence of PRIS of 2.9%.¹⁹

The overall incidence of PRIS in both children and adults appears to be decreasing over time,¹⁴ and as previously discussed, some more recent studies have reported few if any cases of PRIS in large paediatric populations.^{15,20} The historic surge in cases likely reflect increasing awareness or initial overdiagnosis, and subsequent reduction in cases due to stricter compliance with dosing recommendations, and early detection of biochemical markers indicative of PRIS. The lack of recently published case reports may simply reflect a lack of interest of journals in publishing further case reports of a previously well-described condition, or a reluctance to publish reports in which recommended infusion rates have been exceeded.

Mortality associated with PRIS

Once PRIS develops, it is invariably associated with a high mortality rate. In paediatric patients, mortality rates in excess of 50% have been reported. Among the 44 paediatric case reports of PRIS analysed in the review by Hemphill et al., the overall mortality rate was 52%.⁶ Krajcova et al.,

analysed 153 case reports of PRIS published up to 2014, of which 56 were children.¹⁴ The overall reported case mortality across both children and adults was 51%. However, numerous published case reports and case series have documented only fatal instances of PRIS.

In adults, mortality rates ranging from 18% to 52% have been widely reported. But again, frequent case reports and case series have described only fatal cases of PRIS. Of the 11 patients who developed PRIS, in the multicentre prospective study by Roberts et al., the mortality rate was 18%.¹¹ A mortality rate of 50% was observed among the six adult trauma patients who developed PRIS in the study by Schroepel.¹⁸ Among 153 documented PRIS case reports published up to 2014, of which 97 occurred in adults, the overall reported case mortality was 51%.¹⁴ The review also noted a decline in reported PRIS mortality rates, dropping from 74% prior to 2001, to 64% between 2001 and 2006, and to 32% after 2006. This is likely due to earlier recognition, prompt discontinuation of propofol, and advances in supportive care. Among the 124 adult case reports of PRIS analysed in the review by Hemphill et al, the overall mortality rate was 48%.⁶ In a later study by Li et al., PRIS was identified in 19 out of 654 patients, with an associated mortality rate of 36.8%.¹⁹

To identify clinical predictors of mortality in patients with suspected PRIS, Fong et al., conducted a retrospective review of the FDA MedWatch database from 1989 to 2005.²¹ Applying clinical manifestations based on all the published case reports as clinical criteria, they identified 1,139 suspected PRIS cases, of which 342 (30%) were fatal. After comparing demographic and clinical manifestations between survivors and non-survivors, they found that death from PRIS was more likely if a patient was younger than 18 years of age (OR 2.30, $p < 0.0001$), received a vasopressor (OR 1.76, $p < 0.0001$), or if one of the following PRIS manifestations were present: cardiac symptoms (3.76), metabolic acidosis (3.66), dyslipidaemia (1.98), impairment in renal function (1.92), hypotension (1.78), or rhabdomyolysis (1.76). The propofol infusion dose exceeded 5 mg/kg/h in 88 (68%) of the 129 cases, where dose was reported. Duration of therapy exceeded 48 hours in 74 (54%) of the 136 cases where duration was reported. Because dose-related data were not available for almost 90% of the study sample, these data were not explored as markers for mortality. This study also highlighted the need for raised awareness regarding PRIS-related symptoms, given that only 4% of the MedWatch reports identified PRIS by name in the report.

Risk factors associated with the development of PRIS

Dose and duration of propofol

Propofol doses exceeding 4 mg/kg/h or an infusion duration of more than 48 hours

The influence of propofol infusion rate and duration on the development of PRIS have been widely researched. Numerous reports provide clear evidence of a strong correlation between the development of PRIS in paediatric patients and propofol doses exceeding 4 mg/kg/h or an infusion duration of more than 48 hours.

The first reported death associated with high-dose propofol and the clinical features of PRIS occurred in a child in Denmark in 1990.^{22,23} The case involved a previously healthy two-year-old girl admitted to the ICU with croup. Following a propofol infusion at 10 mg/kg/h for four days, she developed metabolic acidosis, hypotension, and multiorgan failure. In 1992, Parke et al., reported five cases of metabolic acidosis, bradyarrhythmias and fatal myocardial failure in children following the use of propofol for the management of upper respiratory tract infections in a PICU.²⁴ The patients aged four weeks to six years were ventilated and sedated with propofol infusions of 7–10 mg/kg/h for between 66 and 115 hours.

In 1998, Bray et al retrospectively reviewed the reported cases of 18 children who had received propofol infusions and suffered serious adverse events.²⁵ All but three of these cases were fatal. After noting that all 18 children who received propofol infusions experienced similar serious adverse effects, he proposed the term 'propofol infusion syndrome' to describe this clinical state. To further

investigate the relationship between propofol and the occurrence of this 'syndrome' Bray examined admission data from one ICU where propofol infusions had occasionally been used to provide long-term sedation. Of the 44 patients intubated for at least 48 hours, 18 were sedated with propofol. Of these, PRIS was considered to have occurred in three of the nine children who had received propofol at a mean dose greater than 4 mg/kg/h for at least 48 hours. All three of these patients, who were previously described in a separate publication,²⁴ developed progressive myocardial failure and died. These children received propofol in doses of 4.5, 8, and 8.1 mg/kg/h for 72, 74, and 104 hours, respectively. None of the children who received a propofol infusion for less than 48 h, or in a mean dose lower than 4mg/kg/h, developed the syndrome or died.

Extensive evidence demonstrates that continuous propofol infusion rates exceeding 4 mg/kg/h and durations lasting longer than 48 hours are the primary risk thresholds for developing PRIS in paediatric patients. Krajcova et al., analysed 153 case reports of PRIS published up to 2014, in which 78 (51%) had a fatal outcome.¹⁴ In 138 cases (90%) patients developed PRIS as a complication of non-procedural sedation in the ICU. In total, 56 (36%) of the patients were children <18 years of age. Among all patients, dose-related signs of PRIS were found to occur more frequently with infusion rates greater than 4 mg/kg/h, irrespective of the duration of infusion. This includes cardiac failure, metabolic acidosis, fever, and possibly hypotension. With respect to duration, arrhythmia and other ECG changes occur more frequently after 48 hours of infusion, irrespective of dose. The incidence of rhabdomyolysis and hypertriglyceridaemia occur most frequently with high doses of propofol after 96 hours of administration.

Similarly, another structured literature review and analysis of published case reports by Hemphill et al in 2019 suggested that the cumulative dose of propofol is the primary risk factor in the aetiology of PRIS, driven by high infusion rates (>4 mg/kg/h), and/or prolonged duration (>48 h).⁶ This study examined 168 cases of PRIS (44 paediatric cases and 124 adult cases). Of these cases, 23 paediatric and 59 adult patients died. Although most of these cases were previously evaluated in the study by Krajcova, this study analysed paediatric and adult cases separately. The median mean infusion rate of propofol was higher in children (7.75 mg/kg/h) than in adults (5.1 mg/kg/h), as was the median cumulative dose of propofol received (494 vs 380 mg kg, respectively). There was no single clinical feature common to all reported cases in children. The most common being metabolic acidosis (80%) and ECG changes (75%). Lipidaemia, fever, and hepatomegaly occurred more frequently in children than in adults, whilst rhabdomyolysis and hyperkalaemia were more frequent in adults. In the multivariate analysis of 38 children with sufficient data, fever, hepatomegaly, and cumulative dose of propofol >240 mg/kg were associated with an increased risk of mortality in children. In adults, mean propofol infusion rate >5 mg/kg/h, duration of infusion >48 hours, and cumulative dose >240 mg/kg was associated with an increased risk of death. Propofol exposure (dose and duration), laboratory data, and hemodynamic outcomes were further evaluated in a single centre, retrospective review of 104 children admitted to the PICU or paediatric cardiac ICU who had received continuous propofol for non-procedural sedation.²⁶ Although no patient in the study cohort met the full criteria for PRIS, laboratory abnormalities associated with the syndrome were observed more often in those receiving therapy for longer than 48 hours than those exposed for 24 to 48 hours. Hypertriglyceridemia was the most common laboratory value associated with PRIS and was experienced by 43% of patients for whom triglyceride concentrations were monitored.

In agreement with paediatric studies, a dose dependent association between long-term, high-dose, propofol infusion and the occurrence of PRIS was also reported in retrospective cohort study of adult neurosurgical ICU patients.²⁷ Out of 67 patients who received propofol infusion for sedation, seven showed signs of PRIS and died. The syndrome did not occur in those receiving mean propofol doses of less than 5 mg/kg/h but occurred in three of 18 patients (17%) receiving 5 - 6 mg/kg/h, and in four of 13 patients (31%) receiving more than 6 mg/kg/h ($p=0.002$). The authors estimated that the odds ratio for the occurrence of PRIS increased by 1.93 (CI 1.12–3.32) for every 1 mg/kg/h of propofol administered above 4.98 mg/kg/h ($p=0.018$).

Conversely, there are also reports in which continuous propofol infusions have been safely used in paediatric patients at higher than recommended doses and durations with appropriate protocol-driven monitoring. In a retrospective cohort analysis evaluating the safety of prolonged, high-dose propofol infusions in 173 critically ill children in a PICU, no patient developed PRIS.²⁸ Patients were categorized and compared based on infusion duration: those receiving propofol for less than 48-hours versus those receiving it for greater than 48-hours. Both groups received mean doses of propofol greater than 4 mg/kg/h. Despite both cohorts receiving high mean doses of propofol, no cases of PRIS were observed in either group. Among the 554 children included in the study by Fashina et al., no cases of PRIS occurred even when propofol was administered at doses and durations usually considered high-risk.²⁰ In total, 156 patients (28%) received median doses >4 mg/kg/h, and 12 patients (2%) received doses >8 mg/kg/h. Additionally, 119 patients (21%) received propofol infusions for durations of greater than 48 hours, and 40 patients (7%) exceeded 96 hours.

Doses up to 4 mg/kg/h for up to 48 hours duration

Several reports have demonstrated the therapeutic efficacy and safety of propofol sedation in paediatric patients when limited to a maximum rate of 4 mg/kg/h for up to 48 hours. A prospective study of 174 children aged two months to 16 years concluded that propofol can be safely used for short-term sedation in a PICU with no metabolic or circulatory adverse effects.²⁹ The median dose of propofol was 2.9 mg/kg/h (range: 0.3–6.5 mg/kg/h), with a negative correlation between dose and duration, indicating that when the duration of treatment was shorter, higher doses were given. The median duration was 13 hours (range: 1.6–179 h), with the majority (80%) receiving treatment for less than 24 hours. None of the children in this cohort developed signs of PRIS. A retrospective review of case series in 142 critically ill children who were sedated with continuous propofol infusion at doses less than 3 mg/kg/h for less than 24 hours found no evidence of metabolic acidosis or hemodynamic instability attributed to propofol.³⁰ Another retrospective cohort study by Koriyama et al., assessed the presence of signs and symptoms of PRIS in 210 children who received a continuous propofol infusion for non-procedural sedation in a tertiary care PICU.³¹ In total 195 patients with none of the symptoms associated with PRIS in the 12 hours preceding administration of propofol were included in the analysis. Local practice was to limit the maximum infusion rate to 4mg/kg/h plus up to 1mg/kg/h of bolus doses and the infusion duration to 24 hours. With an 87% compliance with those guidelines, the median propofol dose including boluses was 2.7mg/kg/h (maximum 7.8mg/kg/h) and the mean duration was 10.3 hours (maximum 41.3 h). In 98% cases the duration of infusion was under 24 hours. None of the patients developed any of the symptoms associated with PRIS.

In a retrospective study of 30 children who received continuous propofol in the PICU or PCICU, none of the patients demonstrated findings consistent with PRIS, even those receiving infusion durations of greater than 100 hours.³² The median initial propofol infusion was 3 mg/kg/h (0.9 – 6.0 mg/kg/h) with a peak dose of 4.2mg/kg/h (0.9 – 12.0 mg/kg/h) over an average of 8 hours (1– 222 h). Similarly, there were no confirmed cases of PRIS reported in a retrospective study involving 127 children who received a continuous infusion of propofol for non-procedural sedation in the PICU.³³ The median infusion rate was 4.1 (2.9 - 5.6) mg/kg/h, with a median duration of 18 (10 - 28) hours. Seventy-three patients (56%) had an average propofol infusion dose exceeding 4 mg/kg/h with inclusion of boluses. The majority of patients (91, 70%) received propofol for less than 24 hours, and a small proportion (14, 11%) received propofol for more than 48 hours. The longest reported infusion duration was 103 hours. Although no definitive cases of PRIS were identified during the study period, altered laboratory values that are commonly associated with PRIS were frequently observed in patients whose labs were monitored. Two patients receiving a propofol dose exceeding 4 mg/kg/h had a documented concern for PRIS, which prompted the immediate cessation of the therapy. However, neither of these patients were reported to experience dysrhythmias nor hemodynamic instability. Moreover, in a 25-year, single centre, retrospective study of 641 children in a PCICU, continuous propofol infusion at median infusion rate of 1.2 (0.7 – 2.1) mg/kg/h and median duration of 22.7 (16.8 – 47.0) hours was not associated with any cases of PRIS.¹⁵ The median cumulative dose, (including additional 1 mg/kg

boluses), was 30 mg/kg. In a second long-term study by the same group, only one case of PRIS was observed amongst 554 children aged receiving continuous propofol infusions for non-procedural sedation in a non-cardiac PICU.²⁰ Patients had received a median dose of 3 mg/kg/h (max 54 mg/kg/h) for a median duration of 22.8 hours (max 203.8). In total, around 70% of patients received doses of ≤ 4 mg/kg/h and for ≤ 48 hours duration. The median cumulative dose (including boluses) was 73.9 mg/kg. The single case of PRIS occurred in a patient who received propofol at a rate of 1.0 mg/kg/h for 42 hours.

Two further retrospective studies using propofol as a bridge to extubation in paediatric patients found that propofol was safe and effective when limiting doses to 4 mg/kg/h, and for less than 48 hours.^{34,35} The 2022 Society of Critical Care Medicine's 2022 PANDEM guidelines suggests that continuous propofol for less than 48 hours and at doses less than 4 mg/kg/h may be a safe sedation alternative in the paediatric ICU to minimize the risk of PRIS.³⁶

However, other studies indicate that PRIS can manifest within established dose thresholds and during relatively short-term infusions, highlighting the necessity for clinical vigilance and proactive prevention across all patient populations receiving propofol. The aforementioned review by Krajcova of 153 published case reports of PRIS, including 53 in children, concluded that PRIS can occur following a short duration of infusion and at infusion rates below the established threshold of 4 mg/kg/h.¹⁴ A more recent retrospective, multihospital, observational cohort study of 654 critically ill adults admitted to the ICU also showed that PRIS can occur at lower infusion dose and lower cumulative dose.¹⁹ In the 19 patients who developed PRIS, the median dose and duration of propofol was 2.18 mg/kg/h, and 147.0 h respectively, with a median time to development of PRIS at 125.0 h post propofol infusion, and a cumulative dose of 276.5 mg/kg. Similarly, a prospective observational study in 1,017 critically ill adults found that PRIS occurred in patients receiving propofol at lower dose than previously considered high-risk in this age group.¹¹ Of the 11 patients who developed PRIS, only two had been exposed to a propofol dose exceeding 5mg/kg/min at any point over the course of therapy.

Other risk factors associated with the development of PRIS

As many studies have shown, propofol doses exceeding 4 mg/kg/h and durations of greater than 48 hours are the primary risk factor for the development of PRIS. However, it is evident that not all patients who receive high-dose, long duration propofol develop PRIS, and isolated cases have also occurred with lower doses and shorter durations.⁷ These findings suggest that other additional factors may also play a role in PRIS pathogenesis, highlighting the importance of careful patient selection in the PICU.

Beyond the primary variables of infusion rate and duration, the literature identifies several secondary predisposing and triggering factors for the development of PRIS. These include young age (notably paediatric populations), severe ongoing critical illness, concomitant administration of catecholamine and corticosteroids, low carbohydrate and high fat intake, and subclinical or pre-existing inborn errors of metabolism, such as β -oxidation defects or mitochondrial disorders.^{6,12,13,17,37} However, it remains to be established whether these factors directly play a role in the development of PRIS, or if they merely represent a marker of a severe illness. Furthermore, many of these proposed risk factors lack direct clinical validation, especially within paediatric populations.

Concomitant Medications

Several reports have proposed that concomitant administration of vasopressors or corticosteroids with propofol may be risk factors for development of PRIS.^{10–13,18,37–39} In critically ill patients, the neuroendocrine stress response sharply increases circulating catecholamines and glucocorticoids.¹² Increased catecholamine levels can enhance the metabolic clearance of propofol, which may lead to insufficient sedation and the need for higher propofol infusion rates, subsequently increasing the risk

of PRIS.^{12,38,40} A similar effect may occur when patients receive high-dose inotropic or vasopressor infusions concurrently. The negative inotropic effect of propofol can lead to a vicious cycle in which a decreased level of sedation prompts an increase in propofol infusion rate, resulting in hypotension, which prompts an increase in rate of catecholamine infusion.^{12,38} Furthermore, the metabolic acidosis associated with PRIS may further decrease vasomotor tone, increasing the need for vasopressor and inotrope support.³⁷

Smith et al., reported that the concomitant use of vasopressors in adults with severe head trauma receiving propofol infusions is strongly associated with an increased risk of developing PRIS.³⁹ Furthermore, among the 11 critically ill adults who developed PRIS in the study by Roberts et al., ten (91%) had received concomitant vasopressor therapy, but only two had been exposed to propofol doses exceeding 5 mg/kg/h.¹¹ This is further supported by an observational study by Schroeppel et al., involving 207 adult trauma patients who underwent sedation with continuous propofol for greater than 24 hours.¹⁸ Among the six patients who developed PRIS, there was a significantly higher requirement for concomitant vasoactive support. Specifically, patients developing PRIS had a significantly higher usage of inotropes (50 vs. 9%, $p = 0.02$) and vasopressors (67 vs. 5%, $p < 0.001$) compared to those who did not develop the syndrome.

In the setting of critical illness, propofol paired with supportive catecholamines, and glucocorticoids may potentiate protein degradation in both skeletal and cardiac muscle cells, which manifests as rhabdomyolysis and cardiac failure, followed by metabolic acidosis and acute renal failure.^{6,38} Moreover, both glucocorticoids and catecholamines accelerate the conversion of triglycerides into glycerol and free fatty acids, increasing the circulating free fatty-acid load, which is a key pathogenic mechanism of PRIS. There is also evidence that steroids reduce mitochondrial energy production by altering gene transcription. When paired with propofol's direct inhibition of mitochondrial respiratory function, this can severely disrupt cellular energy production, leading to oxidative stress, cell death, and ultimately to multi-organ failure.^{37,41,42}

Critical illness

Critical illness markedly elevates the risk of PRIS, as these patients typically exhibit a hypermetabolic, catecholamine-driven state coupled with baseline mitochondrial dysfunction.^{6,11,13} This risk is further exacerbated in the intensive care setting by the frequent requirement for prolonged sedation, the concurrent administration of corticosteroids or vasopressors, and elevated endogenous stress hormones. Together, these factors intensify metabolic demand and severely compromise mitochondrial resilience, thereby precipitating lactic acidosis, cardiac dysfunction, and the characteristic metabolic derangements of PRIS.

Inborn Errors of Metabolism

There are a number of genetic factors which are thought to predispose individuals to PRIS.^{7,43} Since PRIS appears to mimic mitochondrial myopathies, particularly those characterized by functional defects within the mitochondrial respiratory chain, individuals with pre-existing mitochondrial diseases may be more prone to PRIS.^{2,43–45} It is possible that certain phenotypes of mitochondrial disorders may be more vulnerable to the mitochondrial toxicity of propofol than others.¹ In two such cases, patients who developed PRIS were found to have genetic mitochondrial defects, which put them at a greater susceptibility to mitochondrial dysfunction.⁴³ In the first patient, an adult receiving postoperative sedation with propofol for 88 hours the mitochondrial disorder was detected only after the occurrence of PRIS.⁴⁶ In the second adult patient, PRIS developed shortly after receiving propofol for the management of refractory epilepsy, and a mitochondrial disorder was suspected, which was subsequently confirmed by detection of a mutation in the POLG1 gene.⁴⁷

Younger Age

Paediatric patients may be more susceptible to PRIS due to various factors.¹⁰ Children have a larger volume of distribution and faster drug clearance, meaning they require higher relative doses and blood concentrations of propofol compared to adults to achieve adequate sedation. They also have proportionally higher metabolic demands, lower physiological reserves, and greater reliance on fatty acid oxidation for energy production making them more vulnerable to energy failure when exposed to mitochondrial toxins like propofol. Moreover, they also have less mature mitochondrial respiratory chain functions and lower baseline reserves of coenzyme Q than adults.^{10,43} Additionally, paediatric patients may have a higher prevalence of undiagnosed or subclinical metabolic and mitochondrial diseases, further elevating their risk.^{43,44}

Excess Carbohydrates or Lack of Lipids

Low carbohydrate intake and depleted glycogen reserves are further risk factors for PRIS.^{7,38,45} In the critically ill patients, where systemic metabolic stress induces a primary reliance on lipid substrates for energy production, the exhaustion of carbohydrate reserves precipitates excess lipolysis within adipose tissue.^{13,48} This process leads to an accumulation of free fatty acids that cannot undergo adequate beta-oxidation, contributing to the pathogenesis of PRIS.^{7,37,38} In addition parenteral feeding and the propofol (lipid emulsion) infusion itself, may also contribute to excess free fatty acid levels.^{2,37,45,49}

Paediatric patients have significantly lower baseline carbohydrate reserves and limited glycogen storage capacity compared to adult populations, which may explain the relatively higher prevalence of PRIS in children.⁵⁰ In critically ill children there may be insufficient calorific intake to balance the increased metabolic demands, and in susceptible children the diversion of metabolism to fat substrates may lead to PRIS. This specific paediatric vulnerability is illustrated by a case report of a child with epilepsy who developed fatal PRIS following the initiation of a ketogenic diet during propofol sedation.⁵¹ The authors suggested that the exogenous high-fat load, compounded by propofol-mediated inhibition of mitochondrial fatty acid oxidation, lead to metabolic acidosis. It has further been suggested that supplementary carbohydrate administration at 6-8 mg/kg/m could suppress fat metabolism in critically ill children and thus mitigate the risk of PRIS,⁵⁰ but this has not been routinely implemented in practice.

Obesity

Although obesity has not been definitively established as an independent risk factor for PRIS, it may increase the likelihood of circumstances that predispose individuals to its development. If propofol is dosed using actual body weight rather than lean body weight, patients with obesity may receive unnecessarily high absolute propofol doses.^{6,52} Furthermore, patients with obesity in critical care settings frequently require higher sedative doses, prolonged mechanical ventilation, and increased catecholamine support, all of which may increase propofol exposure.¹ Moreover, obesity is also associated with altered lipid metabolism and mitochondrial dysfunction, both of which are thought to increase susceptibility to PRIS, particularly in those exposed to prolonged or high-dose propofol infusions.

Monitoring

Ultimately, optimising patient safety during propofol administration within the PICU necessitates a rigorous, individualised risk–benefit assessment coupled with comprehensive daily clinical and laboratory monitoring. Maintaining a high index of clinical suspicion is essential, and all patients receiving propofol should be closely monitored for complications suggestive of PRIS.^{6,7,10,18,53} However, the early identification of PRIS is challenging, as its initial manifestations are largely non-specific and often overlap with the confounding clinical presentations frequently encountered in critically ill patients. Surveillance focuses on the early detection of metabolic, cardiac, and muscular

abnormalities that signal emerging mitochondrial dysfunction. Regular assessment of arterial lactate is central, as rising lactate is often the earliest biochemical indicator of metabolic stress. Creatine kinase should be monitored to detect the onset of rhabdomyolysis, while serum triglycerides help identify excessive lipid load. Continuous ECG monitoring is crucial for recognising characteristic conduction abnormalities. Renal function, electrolytes and acid–base status should be checked frequently to identify evolving renal injury, hyperkalaemia, or metabolic acidosis. In patients considered at increased risk of PRIS, more intensive and frequent monitoring is warranted.

Treatment of PRIS

The lack of universally accepted diagnostic criteria and the inevitable overlap of confounding clinical manifestations common in critical illness means that there are no established guidelines for the treatment of PRIS. Management strategies focus on early recognition, immediate discontinuation of propofol, commencing alternative sedation, and rapid correction of the severe metabolic and cardiovascular derangements associated with the syndrome.^{6–8,10,12,13,44,53} Aggressive supportive therapy is essential, including optimisation of haemodynamics with vasopressors or inotropes, management of arrhythmias, and correction of metabolic acidosis with intravenous fluids and bicarbonate when indicated. Hemofiltration and extra-corporeal membrane oxygenation (ECMO) have both been used with success in the treatment of PRIS.^{54,55}

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