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Central Fever in Critically Ill Adults: A Narrative Review

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Abstract

Fever affects about a quarter of patients in the neurological intensive care unit, and in up to half of them, no infection is found. Such fevers are often labelled central or neurogenic and attributed to disordered thermoregulation after brain injury, but the term "central fever" has no agreed-upon definition and remains a diagnosis of exclusion. This narrative review summarises the evidence on the definition, epidemiology, mechanisms, diagnosis, prognostic significance, and management of central fever in critically ill adults. Central fever is most common after subarachnoid, intraventricular, and intracerebral haemorrhage and severe traumatic brain injury. It typically begins within 72 hours, and negative cultures, a clear chest radiograph, and a high-risk diagnosis make it more likely. Intraventricular blood, hypothalamic injury, sterile inflammation, and autonomic dysregulation are the main proposed mechanisms. Drain-related ventriculitis is the most important mimic because blood in the cerebrospinal fluid makes routine indices unreliable. Fever is consistently associated with poor outcomes, but lowering temperature has not been shown to improve them. Antipyretics have modest, inconsistent effects and can reduce cerebral perfusion pressure, whereas feedback-controlled devices reliably control fever; in the Intensive Care Bundle With Temperature Reduction in Patients With Acute Brain Injury (INTREPID) trial, however, preventing fever did not improve three-month functional outcomes. Current guidelines support treating fever but recommend against prophylactic fever prevention after ischemic stroke. A thorough search for infection, timely discontinuation of empirical antibiotics once infection is excluded, and controlled normothermia (36.0-37.5 °C), with meticulous attention to shivering, remain the most sensible approach.

Categories: Neurology, Internal Medicine, Neurosurgery
Keywords: central fever, neurocritical care unit, neurogenic fever, targeted normothermia, targeted temperature management

Introduction And Background

Fever is common after acute brain injury. Around one in four patients in a neurological intensive care unit (NICU) develops a temperature of 38.3 °C or more, and in up to half of these patients, no infection is found despite a thorough search [1-3]. This matters because elevated temperature is consistently associated with longer stays, higher mortality, and poorer recovery [4,5], and because its cause is often uncertain. "Central" or "neurogenic" fever is defined as fever attributed to disordered thermoregulation within the brain rather than to infection, drugs, or another inflammatory process. The underlying mechanism is thought to involve dysfunction of hypothalamic thermoregulatory pathways, often triggered by direct injury, haemorrhage, or sterile neuroinflammation following acute brain injury. Central fever is diagnosed by exclusion, and errors in either direction can have serious consequences: misclassifying an infection as central fever leaves sepsis untreated, whereas treating central fever as an infection exposes patients to unnecessary antibiotics [3].

This narrative review summarises the evidence on the definition, epidemiology, mechanisms, predictors, diagnosis, prognostic significance, and management of central fever in adults (18 years and older). It concentrates on aneurysmal subarachnoid haemorrhage (SAH), intraventricular haemorrhage (IVH), intracerebral haemorrhage (ICH), traumatic brain injury (TBI), and ischaemic stroke.

Review

Literature search

We searched PubMed/MEDLINE and Europe PMC for English-language studies in adults, combining terms for central, neurogenic, and noninfectious fever, hyperthermia, normothermia, and temperature management with terms for SAH, ICH, TBI, stroke, and neurocritical care. The Cochrane Library was searched on October 15, 2026 (Appendices), and reference lists of key papers were screened. We specifically included randomised controlled trials (RCTs), meta-analyses, prospective cohorts, and various society guidelines, which were reviewed by both authors (SAR and AN). Pediatric studies were excluded; cohorts that also enrolled some patients younger than 18 years were retained only if adults made up the large majority, and this is noted where relevant. As this is a narrative review, no formal risk-of-bias assessment or pooling was performed. The search was last updated in October 2026.

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Definition and terminology

There is no validated or consensus definition of central fever. Most studies use a core temperature of 38.3 °C or higher, the threshold used by the Society of Critical Care Medicine (SCCM) and the Infectious Diseases Society of America (IDSA) for new fever in the intensive care unit (ICU) [6], and label fever as central when it follows acute brain injury and a complete evaluation finds no infection or other cause. Cohorts differ in the duration of fever required and in how rigorously infection was excluded (Table *1*).

Study	Population	Fever definition	Central/non-infectious criterion
Commichau et al., 2003 [1]	387 NICU patients aged 17–98 y (mean 54.1), prospective	First T ≥ 38.3 °C	"Unexplained" after complete diagnostic evaluation
Rabinstein et al., 2007 [2]	93 febrile NICU patients (age criteria not reported), prospective	T ≥ 38.3 °C on ≥ 2 consecutive days	No proven infection; ≥ 2 body-site cultures before antibiotics
Hocker et al., 2013 [3]	526 febrile NICU patients, retrospective	Core T > 38.3 °C on ≥ 2 consecutive days	Negative cultures and no clinically treated infection; other non-infectious causes excluded
Thompson et al., 2003 [7]	76 adults (> 18 y) with severe TBI surviving ≥ 2 weeks, retrospective	T ≥ 38.5 °C, or ≥ 1 °C above baseline	Negative cultures, other sources excluded, plus relative bradycardia and no diurnal variation

TABLE 1: Operational definitions of fever and central fever in key cohorts

NICU: neurological intensive care unit, T: temperature, TBI: traumatic brain injury

"Noninfectious fever" is broader than "central fever" and includes drug fever, venous thromboembolism, transfusion reactions, and postoperative inflammation, whereas central fever implies a hypothalamic or thermoregulatory mechanism that cannot be demonstrated at the bedside [8]. Some authors reserve "hyperthermia" for a rise in temperature without a change in the hypothalamic set point; the distinction matters because antipyretics act only on set-point-driven fever.

Epidemiology

Fever is common throughout the NICU, but the proportion labelled central varies with the population and the rigour of the workup (Table *2*). Because cohorts did not all exclude every noninfectious cause, these proportions are best interpreted as upper estimates of true central fever.

Study	Population	Fever	Central or non-infectious fever
Commichau et al., 2003 [1]	387 consecutive NICU admissions, prospective	23%	28% of fevers unexplained; 52% infectious
Rabinstein et al., 2007 [2]	93 febrile NICU patients, cultures before antibiotics, prospective	All febrile	33% non-infectious overall; 58% of febrile SAH vs 26% of febrile TBI
Hocker et al., 2013 [3]	526 febrile NICU patients, retrospective	All febrile	46.8% central; onset within 72 h in 76.4% of central vs 60.7% of infectious fevers
Oliveira-Filho et al., 2001 [9]	92 patients with SAH, prospective	41%	26% of febrile patients without an infectious source
Rocha Ferreira da Silva et al., 2016 [10]	55 patients with SAH, database analysis	58% in the first 7 days	No bacterial infection identified during the first week
Gillow et al., 2017 [11]	351 patients with ICH, retrospective	39%	71% of fevers non-infectious
Honig et al., 2015 [12]	95 patients with spontaneous ICH, prospective registry	41%	Central 32% vs infectious 9% of all patients
Hess et al., 2026 [13,14]	547 patients with spontaneous ICH, retrospective [13,14]: same cohort	39%	54 central (10% of the cohort) vs 156 infectious fevers (3 other causes); central fever began earlier (median day 2 (IQR 1-3) vs day 6 [13]; Of first fever episodes: pneumonia 52%, central 25%, catheter-associated infections 17%; median onset day 2 (central), 5 (pneumonia), 8 (catheter-associated infection) [14]
Thompson et al., 2003 [7]	76 adults with severe TBI surviving ≥ 2 weeks, retrospective	Not reported	Neurogenic fever 11.8%

TABLE 2: Frequency of fever and of central or non-infectious fever in key cohorts

NICU: neurological intensive care unit, SAH: subarachnoid haemorrhage, TBI: traumatic brain injury, ICH: intracerebral haemorrhage.

Noninfectious fever in SAH has been linked to vasospasm [15], and the 2026 American Heart Association/American Stroke Association (AHA/ASA) stroke guideline recommends treating hyperthermia and identifying its source [16]. SAH carries the heaviest burden: it independently increased the risk of both infectious and unexplained fever [1], was the strongest predictor of noninfectious fever (odds ratio (OR) 11.8) in a cohort that required cultures before antibiotics [2], and its noninfectious fever is closely linked to vasospasm [15]. Central fever is also common after ICH, particularly with intraventricular extension and larger haematomas [11,12]. After TBI, infection accounts for a larger share of fever [2], and because the main TBI cohort included only patients who survived two weeks, early central fever may have been missed [7]. After ischaemic stroke, central hyperthermia is relatively uncommon, and infection is the usual cause [16]. Timing is the most consistent clue: noninfectious fever usually begins within 72 hours of admission [2,3,14].

Pathophysiology

The mechanism of central fever is incompletely understood, and most hypotheses centre on the hypothalamic thermoregulatory centre [8,17]. Normally, the preoptic area of the anterior hypothalamus integrates thermoreceptor input and defends a set point; in infection, pyrogenic cytokines induce cyclooxygenase-2 and prostaglandin E2, which raise the set point [8]. Four routes may affect this system after brain injury. First, blood in the cerebrospinal fluid (CSF): the association of central fever with SAH, IVH, and ventricular drains suggests that intraventricular blood acts on periventricular structures, directly or

through local cytokine and prostaglandin release [1,3,18], and intraventricular haemoglobin raises CSF prostaglandin E and temperature in rabbits [8]. Second, direct injury: diffuse axonal and frontal injury, raised intracranial pressure, and ischaemia can disrupt thermoregulatory pathways [7,8], and hypothalamic lesions were found in 42.5% of brains in a classic autopsy series of fatal closed head injury [7,8,19]. Third, sterile inflammation is driven by damage-associated molecular patterns and cytokines [17,20]. Fourth, sympathetic overactivity, which at its extreme becomes paroxysmal sympathetic hyperactivity (PSH) [21].

Fever harms the injured brain. Brain temperature exceeds core temperature by about 0.3 °C, more so during fever, and rises in brain temperature were accompanied by increases in intracranial pressure from 14.9 to 22 mm Hg [22]. Experimental hyperthermia aggravates excitotoxicity, free-radical injury, inflammation, apoptosis, and blood-brain barrier disruption [17,20], and each 1 °C rise increases metabolic rate by about 13% [7]. In SAH with refractory fever, induced normothermia reduced cerebral metabolic crisis on microdialysis [23]. Central fever is therefore probably heterogeneous. Prostaglandin-mediated fever driven by blood products should respond at least partly to cyclooxygenase inhibitors [8,24], whereas fever from damaged thermoregulatory pathways behaves like true hyperthermia and needs physical cooling [25]. This may explain why central fever is often resistant to antipyretics [18,25].

Risk Factors and Predictors

The most reproducible predictors of central fever are SAH or IVH, early onset, and negative cultures (Table 3).

Predictor	Association	Source
SAH, IVH, or brain tumour	OR 6.33 (95% CI 3.72-10.77) for central fever	Hocker et al., 2013 [3]
SAH (vs other diagnoses)	OR 11.8 (3.0-59.4) for non-infectious fever	Rabinstein et al., 2007 [2]
Blood transfusion	OR 3.06 (1.63-5.76) for central fever	Hocker et al., 2013 [3]
No infiltrate on chest radiograph	OR 3.02 (1.81-5.05) for central fever	Hocker et al., 2013 [3]
Fever onset within 72 h of admission	OR 2.20 (1.23-3.94) for central fever; OR 2.21 (1.22-4.34) for non-infectious fever	Hocker et al., 2013 [3]; Rabinstein et al., 2007 [2]
Intraventricular catheter	Independent risk factor for unexplained fever (p = 0.004)	Commichau et al., 2003 [1]
Ventriculostomy (SAH)	OR 8.5 (2.4-29.7) for fever	Oliveira-Filho et al., 2001 [9]
Symptomatic vasospasm (SAH)	OR 5.0 (1.03-24.5) for fever	Oliveira-Filho et al., 2001 [9]
Poor Hunt-Hess grade and IVH (SAH)	Strongest predictors of refractory fever (both p < 0.001)	Fernandez et al., 2007 [18]
Hunt-Hess grade > 2 and leucocytosis on admission (SAH)	Predicted early central fever	Rocha Ferreira da Silva et al., 2016 [10]
Intraventricular extension and haematoma volume (ICH)	Adjusted OR 4.67 (1.66-13.14) for IVH and OR 1.013 (1.004-1.021) per mL of haematoma for central fever	Honig et al., 2015 [12]
Left hypothalamic involvement (ICH)	OR 9.7 (1.6-58.8) for central fever on lesion mapping	Hess et al., 2026 [13]
External ventricular drain, surgical evacuation, IVH (ICH)	OR 3.7, 6.78 and 2.0 for fever of any cause	Gillow et al., 2017 [11]
Diffuse axonal injury (TBI)	OR 9.06 (0.99-82.7) for neurogenic fever	Thompson et al., 2003 [7]
Frontal lobe injury (TBI)	OR 6.68 (1.1-39.3) for neurogenic fever	Thompson et al., 2003 [7]

TABLE 3: Independent predictors of central, non-infectious or unexplained fever

SAH: subarachnoid haemorrhage, IVH: intraventricular haemorrhage, OR: odds ratio, CI: confidence interval, ICH: intracerebral haemorrhage, TBI: traumatic brain injury.

Hocker and colleagues combined negative cultures, a clear chest radiograph, a diagnosis of SAH, IVH, or tumour, and onset within 72 hours into a model that predicted central fever with a probability of 0.90 [3], but it was derived retrospectively at a single centre and has not been validated prospectively. Persistent fever was also more common with central fever [3], whereas daily fever duration, the number of febrile days,

and invasive catheters did not discriminate in a prospective cohort [2]. After open craniotomy, fewer than half of late postoperative fevers were infectious; older age, ventricular drainage, transfusion, and longer stay favoured infection, and a machine-learning classifier from that study awaits external validation [26].

Clinical Features and Differential Diagnosis

No feature is pathognomonic. Classic descriptions emphasise a high, plateau-like temperature without diurnal variation, relative bradycardia, little sweating, and resistance to antipyretics [7,8], but none of these is specific. The differential diagnosis is broad (Table *4*).

Category	Conditions to exclude	Clues
Infection	Ventilator-associated pneumonia, aspiration, ventriculitis or meningitis (external ventricular drain, post-craniotomy), bloodstream and catheter infection, urinary tract infection, surgical site infection, Clostridioides difficile, sinusitis	New infiltrate, purulent secretions, positive cultures, rising procalcitonin; for ventriculitis, a rising CSF white cell count or raised CSF lactate or procalcitonin (CSF indices unreliable with intraventricular blood) [27]
Thrombosis	Deep vein thrombosis, pulmonary embolism	Immobility, leg asymmetry, hypoxaemia; duplex ultrasound, CT pulmonary angiography
Drugs	Drug fever (β-lactams, anticonvulsants such as phenytoin), transfusion reactions	Temporal relation to a new drug or transfusion; rash, eosinophilia
Hypermetabolic drug syndromes	Neuroleptic malignant syndrome, serotonin syndrome, malignant hyperthermia, withdrawal (alcohol, baclofen, benzodiazepines)	Rigidity, clonus, raised creatine kinase, recent dopamine antagonist or serotonergic drug
Autonomic	Paroxysmal sympathetic hyperactivity (PSH)	Episodic, simultaneous tachycardia, hypertension, tachypnoea, hyperthermia, sweating and posturing [21]
Inflammatory	Post-operative fever, chemical (aseptic) meningitis, haematoma resorption, acalculous cholecystitis, pancreatitis, adrenal insufficiency, thyrotoxicosis	Timing after surgery; CSF findings; abdominal imaging; endocrine tests

TABLE 4: Differential diagnosis of fever after acute brain injury

CSF: cerebrospinal fluid, CT: computed tomography, PSH: paroxysmal sympathetic hyperactivity.

PSH overlaps most closely with central fever. A 2014 consensus defined PSH as simultaneous, paroxysmal increases in sympathetic and motor activity following severe acquired brain injury and introduced the PSH Assessment Measure (PSH-AM), which combines a Clinical Feature Scale and a Diagnostic Likelihood Tool to improve diagnostic consistency and estimate the probability of PSH [21]. Fever confined to discrete episodes of tachycardia, hypertension, sweating, and posturing favours PSH.

Diagnostic approach

Central fever should be diagnosed only after a structured and systematic search for infection and other causes. The 2023 SCCM/IDSA guideline recommends central temperature measurement where a suitable device is in place (otherwise oral or rectal), imaging and rapid microbiological testing, and biomarkers to guide antimicrobial discontinuation; all of its recommendations are weak [6].

In practice, fever should be confirmed with a reliable core temperature measurement and followed by a review of lines, drains, wounds, drugs, transfusions, and the neurological course. At least two sets of blood cultures should be taken before antibiotics, with further samples directed based on the clinical course, including CSF when an external ventricular drain is present or after recent craniotomy [2,6]. Culturing very early fever has a low yield: in one ICH study, 90% of patients met systemic inflammatory response syndrome criteria within 24 hours, yet blood cultures were positive in 0.1% [28]. Chest imaging usually comes first, whereas leg duplex ultrasound triggered by fever alone adds little [29]. Unstable patients should receive empirical antibiotics, reviewed at 48-72 hours, when negative cultures and a compatible picture support stopping them [3] (Figure *1*).

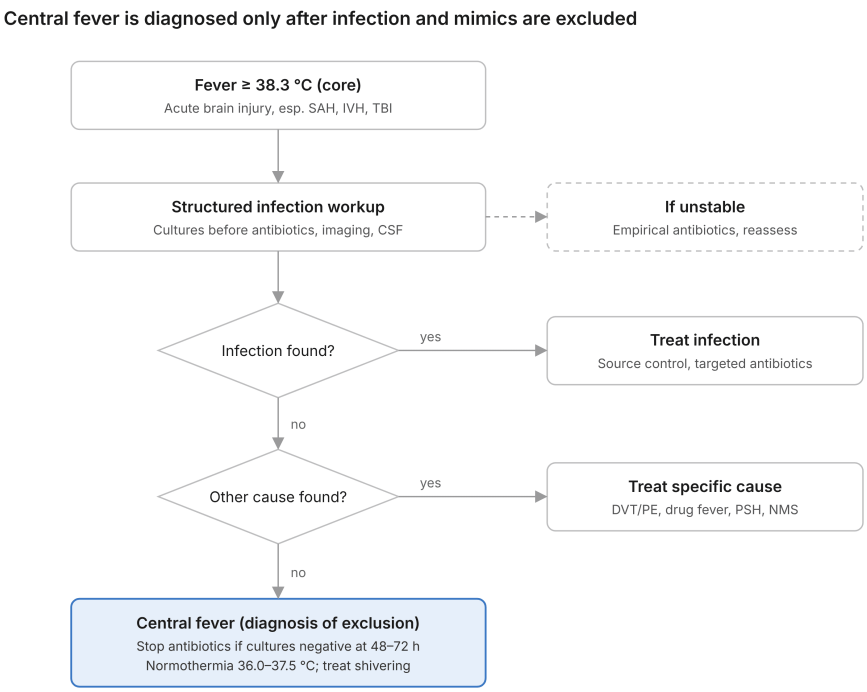


FIGURE 1: Diagnostic approach to fever in the brain-injured patient

Diagnostic approach to fever in the brain-injured patient: Infection and non-infectious mimics are excluded in sequence; only then is fever labelled central, antibiotics stopped, and normothermia maintained [3,6,30-32].

SAH: subarachnoid haemorrhage, IVH: intraventricular haemorrhage, TBI: traumatic brain injury, CSF: cerebrospinal fluid, DVT: deep vein thrombosis, PE: pulmonary embolism, PSH: paroxysmal sympathetic hyperactivity, NMS: neuroleptic malignant syndrome, esp.: especially, h: hour.

Drain-related ventriculitis is the most important mimic. It occurs in 0-22% of patients with an external ventricular drain (pooled incidence 11.4 per 1,000 catheter-days), and because blood in the CSF confounds cell count, glucose, and protein, abnormal values do not reliably indicate infection and normal values do not exclude it [27]. New fever with a rising CSF white cell count or worsening mental status should raise suspicion; CSF lactate or procalcitonin, serum procalcitonin, and the cell index may help, and CSF should be sampled from the drain port rather than the bag [27].

Serum procalcitonin is of limited value in this scenario. Studies in neurocritical care conflict [33,34], although inflammatory markers were higher with infection in a large ICH cohort [13]. A low value supports, but cannot establish, a central cause. No diagnostic criteria are validated; in practice, central fever is diagnosed when fever of 38.3 °C or more follows a high-risk brain injury and infection, drugs, transfusion, thromboembolism, PSH, and drug-induced hyperthermia syndromes have been excluded [1-3,7].

Impact on Outcomes

The association between fever and poor outcome is one of the most consistent findings in neurocritical care (Table *5*). Two meta-analyses, the larger including more than 460,000 adults, linked fever to worse neurological outcome and higher mortality, although with very high heterogeneity [4,35]. The substantial heterogeneity reported in these meta-analyses (I^2: 92-93%) suggests considerable variation in patient populations, brain injury types, definitions of fever, and management strategies across included studies. Consequently, pooled estimates should be interpreted with extreme caution given the above-mentioned heterogeneity, and their applicability to individual patients with suspected central fever may therefore be limited. In SAH, both the degree and the duration of fever predict poor outcome [9,18], and temperatures below 36 °C were also harmful [36]. Whether central fever is worse than infectious fever is unclear. After ICH, central fever carried a high mortality, but outcomes were similar to those of infectious fever, suggesting that fever itself, rather than its cause, drives prognosis [12]. All of these data are observational, and fever may simply mark larger haemorrhage, more intraventricular blood, or vasospasm [15]; the neutral fever-prevention trials reinforce this caution [37].

Study	Population	Main findings
Greer et al., 2008 [4]	Meta-analysis: 39 studies, 14,431 patients (mostly adults)	Fever associated with worse results on every outcome: mortality RR 1.5, poor modified Rankin Scale score RR 2.2, prolonged ICU stay RR 2.8, prolonged hospital stay RR 3.2
Diringer et al., 2004 [5]	4,295 NICU patients	Elevated temperature independently prolonged ICU stay by 3.2 days and hospital stay by 4.3 days
Oliveira-Filho et al., 2001 [9]	92 patients with SAH	Each febrile day: poor outcome OR 1.4
Honig et al., 2015 [12]	95 patients with spontaneous ICH	Central fever: mortality 80% vs 29% without fever; HR for death 3.26 (1.67–6.37); outcomes similar to infectious fever
Lai et al., 2019 [15]	44 patients with SAH	Non-infectious fever associated with radiographic vasospasm (OR 2.2–2.4) but not with delayed cerebral ischaemia or outcome
Fernandez et al., 2007 [18]	353 patients with SAH	Each 1 °C of daily temperature excess: death or severe disability OR 3.0 (1.6–5.8)
Gouvêa Bogossian et al., 2024 [35]	Meta-analysis: 180 studies, 460,846 adults	Unfavourable neurological outcome OR 2.37 (2.08–2.71); death OR 1.31 (1.28–1.34); delayed cerebral ischaemia after SAH OR 1.96; heterogeneity I^2 92–93%
Wasilewski et al., 2025 [36]	287 patients with SAH (EARLYDRAIN trial)	Temperature > 39 °C (OR 2.60) and < 36 °C (OR 3.82) associated with unfavourable 180-day outcome

TABLE 5: Fever and outcome after acute brain injury

RR: relative risk, ICU: intensive care unit, NICU: neurological intensive care unit, SAH: subarachnoid haemorrhage, OR: odds ratio, ICH: intracerebral haemorrhage, HR: hazard ratio.

Antibiotic Stewardship

Empirical antibiotics are often prescribed in sick patients while investigations are underway. In such circumstances, culture results and clinical reassessment should be reviewed within 48-72 hours. In patients with negative cultures, no evidence of infection, and clinical features consistent with central fever, discontinuation of empirical antimicrobial therapy should be strongly considered. Such an approach may reduce antimicrobial misuse and subsequent resistance, adverse drug effects, and overall healthcare costs [3,6].

Management

Current practice aims for controlled normothermia once infection has been sought, using antipyretics first and feedback-controlled devices when these fail. This rests on consensus and physiology; no trial has shown improved functional outcome.

Pharmacological Antipyresis

Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) lower the set point by inhibiting prostaglandin E2 synthesis and are usually ineffective when fever reflects failed thermoregulation [8,25]. Most randomised evidence for paracetamol comes from stroke and concerns prevention (Table *6*): doses of up to 6 g/day lowered temperature by only 0.1-0.4 °C, and neither Paracetamol (Acetaminophen) in Stroke (PAIS), Paracetamol (Acetaminophen) in Stroke 2 (PAIS 2), nor Prevention of Complications to Improve Outcome in Elderly Patients With Acute Stroke (PRECIOUS) improved functional outcome [38-41]. The only traumatic brain injury (TBI) trial found a non-significant 0.3 °C reduction [42,43]. Treating established fever is more promising: in NEUROTHERM, a single 1 g intravenous dose lowered brain temperature by 0.6 °C over 6 hours, although about a third of patients did not respond [24]. The 6 g/day used in several trials exceeds the 4 g/day usually regarded as the maximum in critically ill adults, so hepatic function should guide dosing.

Trial	Population	Regimen	Effect on temperature	Clinical outcome
Koennecke et al., 2001 [44]	42 normothermic patients with ischaemic stroke, within 24 h	Paracetamol 4 g/day vs placebo	Fever > 37.5 °C in 5.0% vs 36.4% (p = 0.014)	Not assessed (pilot)
Dippel et al., 2001 [45]	75 patients with ischaemic stroke	Paracetamol 3 or 6 g/day vs placebo, 5 days	6 g/day: 0.4 °C lower at 24 h (95% CI 0.1–0.7); 3 g/day no effect	Not powered
Kasner et al., 2002 [46]	39 afebrile patients with stroke, NIHSS ≥ 5	Paracetamol 3.9 g/day vs placebo, 24 h	0.22 °C lower (95% CI −0.08 to 0.51; p = 0.14)	No change in NIHSS at 48 h
PISA, Dippel et al., 2003 [47]	75 patients with ischaemic stroke	Paracetamol 6 g/day vs ibuprofen 2.4 g/day vs placebo, 5 days	Paracetamol 0.3 °C greater fall (95% CI 0.0–0.6); ibuprofen no significant effect	Not adequately powered
PAIS, den Hertog et al., 2009 [38]	1,400 patients with ischaemic stroke or ICH, within 12 h	Paracetamol 6 g/day vs placebo, 3 days	0.26 °C lower at 24 h (95% CI 0.18–0.31)	No overall benefit (adjusted OR 1.20, 0.96–1.50); post hoc benefit at baseline 37–39 °C
PAIS 2, de Ridder et al., 2017 [39]	256 patients with ischaemic stroke or ICH (stopped early)	Paracetamol 6 g/day vs placebo, 3 days	Not reported in the main results	No effect (adjusted common OR 1.15, 0.74–1.79)
PRECIOUS, de Jonge et al., 2023 [40,41]	1,493 patients with stroke aged ≥ 66 y (factorial trial)	Paracetamol 1 g four times daily for 4 days vs none	0.1 °C lower at 24 h; fever or subfebrile temperature 8.3% vs 15.8%	No effect (adjusted common OR 1.19, 0.96–1.47)
Chen et al., 2018 [48]	Meta-analysis: 6 stroke trials, 1,836 patients	Paracetamol vs placebo	0.21 °C lower at 24 h	No effect on function; lower 7–14-day mortality (RR 0.62)
Saxena et al., 2015 [43]	41 adults with TBI	Paracetamol 1 g IV every 4 h vs saline, 72 h	37.4 vs 37.7 °C (−0.3 °C, 95% CI −0.6 to 0.0; p = 0.09)	Not powered; no excess hypotension
NEUROTHERM, de Mesmay et al., 2026 [24]	99 sedated, ventilated brain-injured adults with brain temperature > 38.5 °C	Single 1 g IV dose of paracetamol vs saline	Brain temperature 38.4 vs 39.0 °C over 6 h; about 30% non-responders	Pharmacodynamic trial; moderate fall in systolic pressure and heart rate
Cormio and Citerio, 2007 [49]	22 comatose patients with TBI or SAH (aged 14–75 y)	Continuous diclofenac 0.004–0.08 mg/kg/h vs intermittent NSAID boluses, 3-10 days	Time > 38 °C 4% vs 34% (p < 0.0001)	Higher MAP and CPP; no bleeding

TABLE 6: Trials of paracetamol and NSAIDs for temperature control after stroke and acute brain injury

CI: confidence interval; NIHSS: National Institutes of Health Stroke Scale; PISA: Paracetamol (Acetaminophen) In Stroke; PAIS: Paracetamol (Acetaminophen) In Stroke; ICH: intracerebral haemorrhage; PRECIOUS: Prevention of Complications to Improve Outcome in Elderly Patients With Acute Stroke; OR: odds ratio; RR: risk ratio; TBI: traumatic brain injury; IV: intravenous; SAH: subarachnoid haemorrhage; NSAID: nonsteroidal anti-inflammatory drug; MAP: mean arterial pressure; CPP: cerebral perfusion pressure.

Intravenous antipyretics can compromise cerebral perfusion (Table 7). Half of ICU patients had a fall in mean arterial pressure (MAP) of at least 15% after intravenous paracetamol [50], and in brain-injured patients, paracetamol and diclofenac lowered MAP and cerebral perfusion pressure (CPP), increased vasopressor requirements and, in poor-grade SAH, were followed by brain-tissue hypoxia after 35% of diclofenac doses [51-53]. The randomised trial by Cormio and Citerio evaluated continuous low-dose intravenous diclofenac infusion versus intermittent NSAID boluses for fever control over a treatment period ranging from 3 to 10 days. The mean treatment duration was 6.6 ± 2.3 days in the diclofenac group and 5.9 ± 1.9 days in the control group [49]. NSAIDs carry bleeding and renal risks after haemorrhage or craniotomy, and their use should follow an individual risk-benefit assessment [8,31].

Study	Population drug	Effects	
Cantais et al., 2016 [50]	160 ICU adults (not specific to brain injury)	IV paracetamol	MAP fell by ≥ 15% in 51.9%, a median of 30 min after infusion (nadir 64 mm Hg); 34.9% of episodes needed fluids or vasopressors
Picetti et al., 2014 [51]	32 adults in a neuro-ICU	IV paracetamol 1 g	Temperature 37.8 to 37.4 °C at 2 h; MAP 96.6 to 87.2 and CPP 81.9 to 73.0 mm Hg; norepinephrine use 47% to 75%
Picetti et al., 2016 [53]	30 adults with acute brain injury	IM diclofenac 12.5 mg	Temperature 37.8 to 37.5 °C at 2 h; MAP 102.3 to 89.5 and CPP 86.8 to 74.1 mm Hg; noradrenaline started or increased
Schiefecker et al., 2013 [52]	21 patients with poor-grade SAH and multimodal monitoring	IV diclofenac infusion over about 34 min	Temperature −0.8 °C; MAP and CPP −10%; brain-tissue oxygen −13%, with brain-tissue hypoxia after 35% of doses

TABLE 7: Haemodynamic and cerebral effects of parenteral antipyretics

ICU: intensive care unit, IV: intravenous, MAP: mean arterial pressure, CPP: cerebral perfusion pressure, IM: intramuscular, SAH: subarachnoid haemorrhage.

Other agents have weak evidence. A 2025 scoping review found mostly case reports for baclofen, dantrolene, and bromocriptine and rated continuous diclofenac as the best-supported drug [54]. Bromocriptine has modest, slow effects in retrospective cohorts and a non-significant effect in the only RCT, with occasional hepatotoxicity (Table *8*) [55-58]; it may be considered as an adjunct for persistent central fever but not as prophylaxis. In PSH, β-blockers and clonidine are the mainstay [8], although in a recent TBI cohort, propranolol reduced heart rate and PSH features but not maximum temperature [59].

Study	Design and population	Regimen	Result
Perez et al., 2023 [55]	Retrospective, 33 adults with suspected central fever	Median 7.5 mg/day for a median of 13 days	Adjusted temperature fall of 0.3 °C at 24 h, 0.5 °C at 48 h and 0.7 °C at 72 h
Rajesh et al., 2025 [57]	Double-blind RCT, 88 adults (18–65 y) with severe TBI analysed	Prophylactic 5 mg twice daily vs placebo	Neurogenic fever 41.9% vs 55.6% (p = 0.199); lower peak temperature on day 5; no difference in mortality
Rhodes et al., 2026 [56]	Retrospective, 67 adult neuro-ICU patients	5 mg every 8 h plus paracetamol vs paracetamol alone	Temperature fall at 72 h −0.86 vs −0.39 °C (p = 0.017); baseline maximum temperature higher with bromocriptine (38.9 vs 38.6 °C), which may exaggerate the difference
Amin et al., 2024 [58]	Retrospective, 30 adults in neuro- or trauma ICUs (47% TBI), started at a median of day 7	Median 8 mg/day (IQR 5–15)	Mean temperature 37.8 °C before vs 37.4 °C after initiation (p = 0.005); 4 stopped for adverse effects: hepatotoxicity in 3 (one severe, at 60 mg/day) and bradycardia in 1

TABLE 8: Studies of bromocriptine for central or neurogenic fever

RCT: randomised controlled trial, TBI: traumatic brain injury, ICU: intensive care unit, IQR: interquartile range, SAH: subarachnoid haemorrhage, esp.:especially, h: hour.

In practice, scheduled paracetamol within hepatic dose limits is a reasonable first step, with monitoring of MAP and CPP after intravenous doses; NSAIDs should be used selectively, preferably by continuous infusion; and persistent fever should prompt early device-based cooling rather than escalating drugs [30,31].

Physical and Device-Based Cooling

Feedback-controlled surface and intravascular devices control fever far better than drugs or conventional

blankets (Table 9), measured as fever burden, the area under the temperature curve above a threshold, in °C·h [37]. INTREPID (Intensive Care Bundle With Temperature Reduction in Patients With Acute Brain Injury), the largest trial, halved fever burden with prophylactic automated normothermia after ischaemic stroke, ICH, and SAH, but did not improve 3-month function and was stopped for futility after 686 of a planned 1,176 patients [37]; a smaller trial of prophylactic endovascular normothermia had shown the same pattern [60]. Observational data are mixed: therapeutic normothermia after ICH brought more sedation, ventilation, and tracheostomy without better outcomes [61], whereas in SAH, advanced fever control was independently associated with a lower risk of poor 12-month outcome, at the cost of more hyperglycaemia and arrhythmias [62].

Trial	Design	Comparison	Result
Diringer et al., 2004 [63]	RCT, 296 patients aged ≥ 17 y, 13 NICUs	Intravascular heat-exchange catheter plus conventional care vs conventional care (paracetamol and cooling blankets)	Fever burden 2.87 vs 7.92 °C·h over 72 h (64% reduction); no excess infection
Mayer et al., 2004 [64]	RCT, 47 patients	Hydrogel surface pads vs water-circulating blanket	Fever burden 4.1 vs 16.1 °C·h (75% reduction); time febrile 8% vs 42%; shivering 39% vs 8%
Broessner et al., 2009 [60]	RCT, 102 patients (poor-grade SAH, ICH with GCS ≤ 10, severe infarction), 2 NICUs	Prophylactic endovascular normothermia (36.5 °C) vs stepwise conventional fever management	Median fever burden 0.0 vs 4.3 °C·h ($p < 0.0001$); no excess major adverse events; no difference in mortality or long-term outcome
INTREPID, Greer et al., 2024 [37]	RCT, 677 adults aged 18–85 y (ischaemic stroke, ICH, SAH), 43 ICUs; stopped for futility	Prophylactic automated surface normothermia (37.0 °C, up to 14 days) vs tiered fever treatment at ≥ 38 °C	Daily fever burden 0.37 vs 0.73 °C·h ($p < 0.001$); no difference in 3-month mRS (OR 1.09, 0.81–1.46); major adverse events 82.2% vs 75.9%

TABLE 9: Randomised trials of device-based fever control in neurocritical care

RCT: randomised controlled trial, NICU: neurological intensive care unit, °C·h: degree-hours, SAH: subarachnoid haemorrhage, ICH: intracerebral haemorrhage, GCS: Glasgow Coma Scale, ICU: intensive care unit, mRS: modified Rankin Scale, OR: odds ratio.

Devices have their own costs: intravascular catheters need central venous access and carry a risk of thrombosis, surface pads can injure the skin, and both provoke shivering [8,65]. Controlled normothermia also removes fever as a warning sign of infection, so surveillance must continue through examination, inflammatory markers, cultures, and imaging [31].

Shivering Management

Shivering is the main adverse effect of cooling and raises metabolic demand. Nearly two-thirds of cerebrovascular patients shivered during temperature modulation; the Bedside Shivering Assessment Scale correlates with oxygen consumption and energy expenditure, and low serum magnesium predicts shivering [66]. Stepwise protocols start with paracetamol, buspirone, and skin counter-warming and escalate through magnesium, dantrolene, meperidine, dexmedetomidine, and propofol; neuromuscular blockade has no place in fever control [25].

Guideline and Consensus Positions

Table *10* summarises the main guidelines and consensus statements. All agree that infection should be sought first and fever treated, but they differ in emphasis. The consensus statements favour early, continuous, feedback-controlled normothermia (36.0-37.5 °C) with shivering management in patients at risk of secondary injury [30-32], and the Neurocritical Care Society guideline addresses how to deliver it [67]. The AHA/ASA guidelines are more cautious: treating elevated temperature is a weak recommendation after ICH, the effectiveness of temperature management for refractory fever after SAH is uncertain, and the 2026 ischaemic stroke guideline strongly recommends treating hyperthermia but recommends against prophylactic fever prevention, in line with INTREPID and PRECIOUS [16,28,37,40,65].

Source	Population	Key recommendations
SCCM/IDSA 2023 [6]	Adult ICU, new fever	Central or oral/rectal temperature measurement; imaging and rapid microbiology; biomarkers to guide antibiotic discontinuation
AHA/ASA 2026 [16]	Acute ischemic stroke	Hyperthermia: target normothermia, including nurse-initiated fever protocols (class 1, LOE B-R); identify and treat the source, such as infection (class 1, LOE C-EO); induced hypothermia or prophylactic fever prevention in normothermic patients not recommended (class 3: no benefit, LOE B-R)
AHA/ASA 2022 [28]	Spontaneous ICH	Pharmacological treatment of elevated temperature may be reasonable to improve functional outcome (class 2b, LOE C-LD); usefulness of therapeutic hypothermia (< 35 °C) to reduce peri-hematomal oedema unclear (class 2b, LOE C-LD)
Andrews et al. 2018 [30]	ICH, SAH, ischemic stroke with assumed neurogenic fever	Start temperature management above 37.5 °C after an infection work-up if antipyretics fail within 1 h; target 36.5–37.5 °C; continuous measurement and precise control
NTCR (Lavinio et al.) 2023 [31]	ICH, SAH, ischemic stroke in critical care	Continuous core temperature monitoring (bladder or oesophageal preferred); maintain 36.0–37.5 °C with automated feedback devices; start within 1 h of fever; continue while the brain is at risk; controlled rewarming at about 1 °C per day; NSAIDs only after individual risk–benefit assessment; monitor and treat shivering
ESICM/NACCS (Lavinio et al.) 2024 [32]	Severe TBI	Continuous temperature monitoring; prompt fever management; controlled normothermia 36.0–37.5 °C as an option in intracranial pressure tiers 1–2; individualise targets to the risk of secondary injury and fever aetiology
AHA/ASA 2023 [65]	Aneurysmal SAH	For fever refractory to antipyretics, the effectiveness of temperature management in the acute phase is uncertain (class 2b, LOE C-LD)

TABLE 10: Guideline and consensus recommendations relevant to central fever

SCCM/IDSA: Society of Critical Care Medicine/Infectious Diseases Society of America, ICU: intensive care unit, AHA/ASA: American Heart Association/American Stroke Association, LOE: level of evidence (B-R: randomised, C-EO: expert opinion, C-LD: limited data), ICH: intracerebral haemorrhage, SAH: subarachnoid haemorrhage, NTCR: Neuroprotective Therapy Consensus Review, NSAIDs: nonsteroidal anti-inflammatory drugs, ESICM/NACCS: European Society of Intensive Care Medicine/Neuro Anaesthesia and Critical Care Society, TBI: traumatic brain injury.

Colder is not better. In TBI, hypothermia to 32-35 °C for raised intracranial pressure worsened outcome in the Eurotherm3235 trial [68], prolonged hypothermia was no better than fever control in the Brain Hypothermia (B-HYPO) trial (patients aged 15-69 years) [69,70], and a Cochrane review found no high-quality evidence of benefit [71]. Together with the harm associated with temperatures below 36 °C after SAH [36], these data support a target of normothermia rather than hypothermia.

Controversies and future directions

The central puzzle is the gap between consistent observational associations and neutral interventional trials [4,35,37-40]. Fever may be a marker rather than a mediator of injury, or the benefit of normothermia may be offset by the burden of achieving it: sedation, ventilation, shivering, and infection [37,61]. If benefit exists, it is probably concentrated in particular patients. INTREPID reduced fever burden most after ICH and SAH [37], and patients with high fever burden, intracranial hypertension, or delayed cerebral ischaemia may be better candidates than unselected populations. Whether rapid control of established fever, rather than prophylaxis, improves outcome has not been tested definitively. In cardiac arrest, the Targeted Temperature Management 2 (TTM2) trial found no advantage of hypothermia over normothermia with early fever treatment, shifting attention to fever avoidance [72]. The organisation of care also matters: nurse-initiated protocols for fever, hyperglycaemia, and swallowing reduced death or dependency after stroke in the Quality in Acute Stroke Care (QASC) cluster trial, although the effect of the fever component cannot be isolated [73]. Diagnosis remains the weakest link. No validated criteria or biomarker identify central fever prospectively [33,34], and prospective validation of the Hocker model and profiling of CSF and serum cytokines are needed [3]. Better diagnosis would support antibiotic stewardship: in one SAH cohort, 31 febrile patients without an identified infection received 1,000 antibiotic doses [74]. Finally, core temperature underestimates brain temperature by about 0.3 °C [22,24], and whether brain-temperature-guided management improves outcome is unknown.

Conclusions

Central fever accounts for up to half of fevers in the NICU and is most common after SAH, IVH, ICH, and

severe TBI. It remains a diagnosis of exclusion, made most confidently when fever starts early in a high-risk patient with negative cultures and a clear chest radiograph, and after drain-related ventriculitis has been considered. Fever is consistently associated with worse outcomes, and devices achieve normothermia reliably, yet fever prevention has not improved functional recovery, and current AHA/ASA guidelines support treating hyperthermia but not prophylactic fever prevention. Until better evidence is generated and published, we suggest a thorough search for infection, prompt withdrawal of unneeded antibiotics, and controlled normothermia (36.0-37.5 °C) with active shivering management in patients at continuing risk of secondary brain injury.

Appendices

Cochrane Library search strategy

The Cochrane Library (Cochrane Database of Systematic Reviews and CENTRAL, Issue 10 of 12, October 2026) was searched on 15 October 2026 using Search Manager (Table *11*). Line #1 returned 16 reviews (all screened; two relevant [42,71]) and 927 trials; line #3 returned 79 trials, all of which were screened.

Line	Search	Records
#1	([mh Fever] OR [mh "Body Temperature Regulation"] OR (fever* OR hyperthermi* OR pyrexi* OR normotherm* OR antipyretic* OR "central fever" OR "neurogenic fever" OR "temperature control" OR "temperature management"):ti,ab,kw) AND ([mh "Brain Injuries"] OR [mh Stroke] OR [mh "Subarachnoid Hemorrhage"] OR [mh "Cerebral Hemorrhage"] OR ((brain NEXT injur*) OR (head NEXT injur*) OR TBI OR subarachnoid OR intracerebral OR intraventricular OR stroke OR neurocritical OR neurointensive):ti,ab,kw)	943 (16 reviews, 927 trials)
#2	("central fever" OR "neurogenic fever" OR "non-infectious fever" OR "noninfectious fever" OR normotherm* OR "fever control" OR "fever prevention" OR antipyretic* OR paracetamol OR acetaminophen):ti	5,154
#3	#1 AND #2	79 (0 reviews, 79 trials)

TABLE 11: Cochrane Library search strategy

mh: Medical Subject Headings (MeSH) term, ti: title, ab: abstract, kw: keyword, NEXT: adjacency operator, *: truncation

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Abhijit Nair, Sulaiman Al Rahbi

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In preparing this manuscript, the authors used an artificial intelligence (AI) assistant, Claude (Anthropic; model Claude Opus 5.5), for literature searching in PubMed and Europe PMC, screening of Cochrane Library search exports, extraction of data from full-text articles, drafting and revision of the text, preparation of tables and Figure 1, and formatting of references. We checked every reference against PubMed and verified cited figures against full-text articles where accessible. All AI-assisted content was reviewed, edited, and approved by the authors, who take full responsibility for the accuracy, originality, and integrity of the work. The AI tool does not meet authorship criteria and is not listed as an author. No patient data or other confidential information was entered into the AI tool.

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